SOCIETY FOR NEUROSCIENCE

ABSTRACTS

VOLUME 19, PART 3

23RD ANNUAL MEETING

WASHINGTON, D.C.

NOVEMBER 7–12, 1993

Made in the United States of America.
International Standard Book Numbers:
Part 1 ISBN 0–916110–40–0
Part 2 ISBN 0–916110–41–9
Part 3 ISBN 0–916110–42–7
All parts ISSN 0190–5295
Library of Congress Catalog Card Number 75-7761

Proper citation form for this volume:
Soc. Neurosci. Abstr., Vol. 19, Part 3, p. xxx, 1993.

Published by:
Society for Neuroscience
11 Dupont Circle, N.W.
Suite 500
Washington, D.C. 20036

CONTENTS—PART 3

* 10,975 volunteer abstracts, 18 symposia abstracts, 17 history of neuroscience abstracts, and 56 teaching of neuroscience abstracts.

Please note that due to the increase in abstract submissions this year, the *Abstracts* Volume 19 is printed in **three** parts. The three parts will be mailed, one part at a time, starting in mid-August. The *Abstracts* Volume 19 Part 3, the last part to be mailed, includes the Key Word Index and the Author Index.

1993 Program Committee

Dennis W. Choi, M.D., Ph.D.
Chairperson
Washington University School of Medicine

Irwin B. Levitan, Ph.D.
Incoming Chairperson
Brandeis University

David G. Amaral, Ph.D.
The Salk Institute

Andrew G. Bulloch, Ph.D.
University of Calgary Health Science Center

Marc G. Caron, Ph.D.
Duke University Medical Center

Michael E. Goldberg, M.D.
National Eye Institute, NIH

Mark W. Hamblin, M.D., Ph.D.
University of Washington
Seattle VA Medical Center

Harvey J. Karten, M.D.
University of California, San Diego

Darcy B. Kelley, Ph.D.
Columbia University

James E. Krause, Ph.D.
Washington University School of Medicine

Jean M. Lauder, Ph.D.
University of North Carolina School of Medicine

James O. McNamara, M.D.
Duke University Medical Center
and VA Medical Center

Charles B. Nemeroff, M.D., Ph.D.
Emory University School of Medicine

Mary L. Oster-Granite, Ph.D.
University of California, Riverside

John L.R. Rubenstein, M.D., Ph.D.
University of California, San Francisco

Clifford B. Saper, M.D., Ph.D.
Beth Israel Hospital

Gary Charles Schoenwolf, Ph.D.
University of Utah School of Medicine

S. Murray Sherman, Ph.D.
SUNY, Stony Brook

Roger P. Simon, M.D.
University of California, San Francisco

W. Thomas Thach, Jr., M.D.
Washington University School of Medicine

Leslie G. Ungerleider, Ph.D.
National Institutes of Health

Charles J. Vierck, Ph.D.
University of Florida Health Science Center

Monte Westerfield, Ph.D.
University of Oregon

Richard E. Zigmond, Ph.D.
Case Western Reserve University
School of Medicine

Ira B. Black, M.D., *ex officio*
UMDNJ/RWJ Medical School

Lynn T. Landmesser, Ph.D., *ex officio*
University of Connecticut

Larry R. Squire, Ph.D., *ex officio*
VA Medical Center, San Diego

CHRONOLOGICAL LIST OF SESSIONS

(See page xv for Thematic List of Sessions)

TUESDAY, NOVEMBER 9

WEDNESDAY, NOVEMBER 10

THURSDAY, NOVEMBER 11

FRIDAY, NOVEMBER 12

THEMATIC LIST OF SESSIONS

(Includes slide and poster sessions, and symposia only)

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
THEME A: DEVELOPMENT AND REGENERATION							
192.	Aging processes I	Poster		tAM			
371.	Aging processes II	Poster			wAM		
717.	Aging processes III	Poster					fAM
25.	Axon guidance mechanisms and pathways I	Poster	mAM				
26.	Axon guidance mechanisms and pathways II	Poster	mAM				
103.	Axon guidance mechanisms and pathways III	Slide	mPM				
450.	Axon guidance mechanisms and pathways IV	Poster			wPM		
451.	Axon guidance mechanisms and pathways V	Poster			wPM		
536.	Axon guidance mechanisms and pathways VI	Poster				thAM	
608.	Axon guidance mechanisms and pathways VII	Slide				thPM	
707.	Axon guidance mechanisms and pathways VIII	Poster					fAM
356.	Cell lineage and determination: cellular and molecular specification	Slide			wAM		
21.	Cell lineage and determination: gene expression and growth factors	Poster	mAM				
256.	Cell lineage and determination: immortalization, transplants, cortex	Slide		tPM			
269.	Cell lineage and determination: neural crest	Poster		tPM			
268.	Cell lineage and determination: telencephalon	Poster		tPM			
534.	Cell lineage and determination: visual system	Poster				thAM	
22.	Cell migration and motility: cell-surface molecules	Poster	mAM				
362.	Cell migration and motility: neural plate and crest derivative	Poster			wAM		
361.	Cell migration and motility: olfactory neurons	Poster			wAM		
23.	Cell shape and differentiation: activity	Poster	mAM				
107.	Cell shape and differentiation: immortalized cells and cell lines	Poster	mPM				
705.	Cell shape and differentiation: morphogenesis	Poster					fAM
281.	Cerebral cortex and limbic system	Poster		tPM			
30.	Cerebral cortex and limbic system: molecular determinants and molecular markers	Poster	mAM				
526.	Formation and specificity of synapses	Slide				thAM	
270.	Formation and specificity of synapses: motor neuron muscle interaction	Poster		tPM			
272.	Formation and specificity of synapses: motor neuron to muscle	Poster		tPM			
271.	Formation and specificity of synapses: neuronal target interaction	Poster		tPM			
537.	Formation and specificity of synapses: receptor localization	Poster				thAM	
273.	Formation and specificity of synapses: telencephalon	Poster		tPM			
27.	Formation and specificity of synapses: visual system	Poster	mAM				
516.	**GABA as a Developmental Signal**	**SYMP**				**thAM**	
20.	Genesis of neurons and glia I	Poster	mAM				
360.	Genesis of neurons and glia II	Poster			wAM		
533.	Genesis of neurons and glia III	Poster				thAM	
704.	Genesis of neurons and glia IV	Poster					fAM
28.	Glia and other non-neuronal cells: CNS development	Poster	mAM				
113.	Glia and other non-neuronal cells: PNS development	Poster	mPM				
190.	Glia and other non-neuronal cells: microglia/macrophage	Poster		tAM			
280.	Glia and other non-neuronal cells: neurotransmitters and ion channels	Poster		tPM			
189.	Glia and other non-neuronal cells: response to injury	Poster		tAM			
367.	Hormones and development: androgens	Poster			wAM		
365.	Hormones and development: estrogens	Poster			wAM		
366.	Hormones and development: glucocorticoids	Poster			wAM		
542.	Hormones and development: neuroanatomical finding	Poster				thAM	
712.	Hormones and development: other	Poster					fAM

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
112.	Molecular and pharmacological correlates of development I	Poster	mPM				
262.	Molecular and pharmacological correlates of development II	Slide		tPM			
457.	Molecular and pharmacological correlates of development III	Poster			wPM		
714.	Molecular and pharmacological correlates of development IV	Poster					fAM
621.	Motor systems	Poster				thPM	
187.	Neuronal death I	Poster		tAM			
266.	Neuronal death II	Slide		tPM			
279.	Neuronal death III	Poster		tPM			
368.	Neuronal death IV	Poster			wAM		
620.	Neuronal death V	Poster				thPM	
452.	Neurotransmitters and channels: acetylcholine, amines, peptides, G-proteins	Poster			wPM		
708.	Neurotransmitters and channels: channels	Poster					fAM
274.	Neurotransmitters and channels: glutamate and GABA	Poster		tPM			
175.	Neurotrophic factors: biological effects I	Slide		tAM			
275.	Neurotrophic factors: biological effects II	Poster		tPM			
276.	Neurotrophic factors: biological effects III	Poster		tPM			
277.	Neurotrophic factors: biological effects IV	Poster		tPM			
278.	Neurotrophic factors: biological effects V	Poster		tPM			
453.	Neurotrophic factors: biological effects VI	Poster			wPM		
454.	Neurotrophic factors: biological effects VII	Poster			wPM		
455.	Neurotrophic factors: biological effects VIII	Poster			wPM		
690.	Neurotrophic factors: biological effects IX	Slide					fAM
8.	Neurotrophic factors: expression and regulation I	Slide	mAM				
108.	Neurotrophic factors: expression and regulation II	Poster	mPM				
109.	Neurotrophic factors: expression and regulation III	Poster	mPM				
110.	Neurotrophic factors: expression and regulation IV	Poster	mPM				
111.	Neurotrophic factors: expression and regulation V	Poster	mPM				
538.	Neurotrophic factors: receptors and cellular mechanisms I	Poster				thAM	
539.	Neurotrophic factors: receptors and cellular mechanisms II	Poster				thAM	
540.	Neurotrophic factors: receptors and cellular mechanisms III	Poster				thAM	
541.	Neurotrophic factors: receptors and cellular mechanisms IV	Poster				thAM	
606.	Neurotrophic factors: receptors and cellular mechanisms V	Slide				thPM	
713.	Nutritional and prenatal factors	Poster					fAM
709.	Other factors and trophic agents I	Poster					fAM
710.	Other factors and trophic agents II	Poster					fAM
711.	Other factors and trophic agents III	Poster					fAM
94.	Pattern formation, compartments, and boundaries I	Slide	mPM				
188.	Pattern formation, compartments, and boundaries II	Poster		tAM			
456.	Pattern formation, compartments, and boundaries III	Poster			wPM		
24.	Process outgrowth, growth cones, and sprouting I	Poster	mAM				
185.	Process outgrowth, growth cones, and sprouting II	Slide		tAM			
259.	Process outgrowth, growth cones, and sprouting III	Slide		tPM			
363.	Process outgrowth, growth cones, and sprouting IV	Poster			wAM		
364.	Process outgrowth, growth cones, and sprouting V	Poster			wAM		
448.	Process outgrowth, growth cones, and sprouting VI	Poster			wPM		
449.	Process outgrowth, growth cones, and sprouting VII	Poster			wPM		
535.	Process outgrowth, growth cones, and sprouting VIII	Poster				thAM	
706.	Process outgrowth, growth cones, and sprouting IX	Poster					fAM
178.	Regeneration I	Slide		tAM			
282.	Regeneration II	Poster		tPM			
283.	Regeneration III	Poster		tPM			
543.	Regeneration IV	Poster				thAM	
622.	Regeneration V	Poster				thPM	
715.	Regeneration VI	Poster					fAM
344.	**Regulation of Oligodendrocyte Development**	**SYMP**			**wAM**		

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
257.	Sensory and motor systems	Slide		tPM			
29.	Sensory systems I	Poster	mAM				
369.	Sensory systems II	Poster			wAM		
32.	Transplantation I	Poster	mAM				
284.	Transplantation II	Poster		tPM			
357.	Transplantation III	Slide			wAM		
544.	Transplantation IV	Poster				thAM	
623.	Transplantation V	Poster				thPM	
716.	Transplantation VI	Poster					fAM
105.	Visual system	Slide	mPM				
370.	Visual system: LGN and cortex	Poster			wAM		
191.	Visual system: optic tectum/superior colliculus	Poster		tAM			
31.	Visual system: retina	Poster	mAM				
	THEME B: CELL BIOLOGY						
288.	Blood-brain barrier: permeability/transport	Poster		tPM			
287.	Blood-brain barrier: structure/function	Poster		tPM			
34.	Cytoskeleton transport and membrane targeting I	Poster	mAM				
436.	Cytoskeleton transport and membrane targeting II	Slide			wPM		
35.	Gene structure and function I	Poster	mAM				
97.	Gene structure and function II	Slide	mPM				
289.	Gene structure and function III	Poster		tPM			
461.	Gene structure and function IV	Poster			wPM		
520.	Gene structure and function V	Slide				thAM	
699.	Gene structure and function VI	Slide					fAM
718.	Gene structure and function VII	Poster					fAM
115.	Membrane composition and cell-surface macromolecules I	Poster	mPM				
193.	Membrane composition and cell-surface macromolecules II	Poster		tAM			
286.	Membrane composition and cell-surface macromolecules III	Poster		tPM			
372.	Membrane composition and cell-surface macromolecules IV	Poster			wAM		
33.	Neuroglia and myelin I	Poster	mAM				
114.	Neuroglia and myelin II	Poster	mPM				
176.	Neuroglia and myelin III	Slide		tAM			
285.	Neuroglia and myelin IV	Poster		tPM			
460.	Neuroglia and myelin V	Poster			wPM		
517.	**Neuronal Functions of Calmodulin-dependent Protein Kinase II**	**SYMP**				**thAM**	
459.	Staining, tracing, and imaging techniques I	Poster			wPM		
545.	Staining, tracing, and imaging techniques II	Poster				thAM	
458.	Staining, tracing, and imaging techniques: confocal microscopy	Poster			wPM		
	THEME C: EXCITABLE MEMBRANES AND SYNAPTIC TRANSMISSION						
291.	Calcium channel pharmacology and modulation I	Poster		tPM			
607.	Calcium channel pharmacology and modulation II	Slide				thPM	
720.	Calcium channel pharmacology and modulation III	Poster					fAM
721.	Calcium channel pharmacology and modulation IV	Poster					fAM
549.	Calcium channel physiology	Poster				thAM	
11.	Calcium channel structure, function, and expression I	Slide	mAM				
548.	Calcium channel structure, function, and expression II	Poster				thAM	
463.	Calcium channels: effects of transmitters and hormones	Poster			wPM		
464.	Chloride and other ion channels	Poster			wPM		
295.	Ion channel modulation and regulation I	Poster		tPM			
521.	Ion channel modulation and regulation II	Slide				thAM	
629.	Ion channel modulation and regulation III	Poster				thPM	
722.	Ion channel modulation and regulation IV	Poster					fAM

Session Number	Session Title	Type	Day and Time: Mon.	Tue.	Wed.	Thu.	Fri.
723.	Ion channels: cell function	Poster					fAM
119.	Ligand-gated ion channels: glutamatergic	Poster	mPM				
120.	Ligand-gated ion channels: non-glutamatergic	Poster	mPM				
106.	Long-term potentiation I	Slide	mPM				
183.	Long-term potentiation II	Slide		tAM			
374.	Long-term potentiation III	Poster			wAM		
375.	Long-term potentiation IV	Poster			wAM		
376.	Long-term potentiation V	Poster			wAM		
546.	Long-term potentiation VI	Poster				thAM	
547.	Long-term potentiation VII	Poster				thAM	
703.	Long-term potentiation VIII	Slide					fAM
118.	Pharmacology of synaptic transmission I	Poster	mPM				
627.	Pharmacology of synaptic transmission II	Poster				thPM	
117.	Postsynaptic mechanisms I	Poster	mPM				
626.	Postsynaptic mechanisms II	Poster				thPM	
294.	Potassium channel modulation	Poster		tPM			
293.	Potassium channel pharmacology	Poster		tPM			
550.	Potassium channel physiology	Poster				thAM	
292.	Potassium channel structure, function, and expression I	Poster		tPM			
438.	Potassium channel structure, function, and expression II	Slide			wPM		
255.	Presynaptic mechanisms I	Slide		tPM			
373.	Presynaptic mechanisms II	Poster			wAM		
462.	Presynaptic mechanisms III	Poster			wPM		
625.	Presynaptic mechanisms IV	Poster				thPM	
719.	Presynpatic mechanisms V	Poster					fAM
170.	**Role of Calcium in Stimulus-secretion Coupling**	**SYMP**		**tAM**			
121.	Sodium channels I	Poster	mPM				
628.	Sodium channels II	Poster				thPM	
116.	Synaptic structure and function I	Poster	mPM				
290.	Synaptic structure and function II	Poster		tPM			
445.	Synaptic structure and function III	Slide			wPM		
624.	Synaptic structure and function IV	Poster				thPM	

THEME D: NEUROTRANSMITTERS, MODULATORS, TRANSPORTERS, AND RECEPTORS

377.	Acetylcholine	Poster			wAM		
10.	Acetylcholine receptors	Slide	mAM				
551.	Acetylcholine receptors: expression of muscarinic receptors	Poster				thAM	
725.	Acetylcholine receptors: muscarinic	Poster					fAM
194.	Acetylcholine receptors: muscarinic antagonists and agonists	Poster		tAM			
465.	Acetylcholine receptors: muscarinic subtypes	Poster			wPM		
552.	Acetylcholine receptors: muscle	Poster				thAM	
726.	Acetylcholine receptors: mutagenesis of muscarinic and nicotinic receptors	Poster					fAM
195.	Acetylcholine receptors: neuronal and α-bungarotoxin-sensitive	Poster		tAM			
123.	Acetylcholine receptors: neuronal nicotinic I	Poster	mPM				
630.	Acetylcholine receptors: neuronal nicotinic II	Poster				thPM	
631.	Acetylcholine receptors: nicotinic antagonists and agonists	Poster				thPM	
466.	Acetylcholine receptors: nicotinic receptor expression	Poster			wPM		
378.	Acetylcholine: ChAT and AChE	Poster			wAM		
122.	Acetylcholine: neuroanatomy	Poster	mPM				
724.	Acetylcholine: release	Poster					fAM
310.	Behavioral pharmacology I	Poster		tPM			
311.	Behavioral pharmacology II	Poster		tPM			
486.	Behavioral pharmacology III	Poster			wPM		

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
569.	Behavioral pharmacology IV	Poster				thAM	
101.	Catecholamine receptors	Slide	mPM				
733.	Catecholamine receptors: α- and ß-adrenergic	Poster					fAM
39.	Catecholamine receptors: dopamine I	Poster	mAM				
439.	Catecholamine receptors: dopamine II	Slide			wPM		
562.	Catecholamine receptors: dopamine receptor localization and regulation	Poster				thAM	
302.	Catecholamine receptors: dopamine receptors—molecular biology	Poster		tPM			
38.	Catecholamine receptors: dopaminergic agonists and antagonists	Poster	mAM				
40.	Catecholamines I	Poster	mAM				
203.	Catecholamines II	Poster		tAM			
695.	Catecholamines III	Slide					fAM
382.	Catecholamines: anatomical and developmental aspects	Poster			wAM		
303.	Catecholamines: biosynthesis and degradation	Poster		tPM			
304.	Catecholamines: dopamine release	Poster		tPM			
563.	Catecholamines: electrophysiology	Poster				thAM	
479.	Catecholamines: release	Poster			wPM		
196.	Excitatory amino acids: anatomy and physiology I	Poster		tAM			
379.	Excitatory amino acids: anatomy and physiology II	Poster			wAM		
18.	Excitatory amino acids: excitotoxicity I	Slide	mAM				
553.	Excitatory amino acids: excitotoxicity II	Poster				thAM	
554.	Excitatory amino acids: excitotoxicity III	Poster				thAM	
555.	Excitatory amino acids: excitotoxicity IV	Poster				thAM	
619.	Excitatory amino acids: excitotoxicity V	Slide				thPM	
698.	Excitatory amino acids: excitotoxicity VI	Slide					fAM
727.	Excitatory amino acids: excitotoxicity VII	Poster					fAM
728.	Excitatory amino acids: excitotoxicity VIII	Poster					fAM
729.	Excitatory amino acids: excitotoxicity IX	Poster					fAM
124.	Excitatory amino acids: pharmacology I	Poster	mPM				
197.	Excitatory amino acids: pharmacology II	Poster		tAM			
296.	Excitatory amino acids: pharmacology III	Poster		tPM			
380.	Excitatory amino acids: pharmacology IV	Poster			wAM		
556.	Excitatory amino acids: pharmacology V	Poster				thAM	
730.	Excitatory amino acids: pharmacology VI	Poster					fAM
36.	Excitatory amino acids: receptors I	Poster	mAM				
125.	Excitatory amino acids: receptors II	Poster	mPM				
198.	Excitatory amino acids: receptors III	Poster		tAM			
261.	Excitatory amino acids: receptors IV	Slide		tPM			
297.	Excitatory amino acids: receptors V	Poster		tPM			
381.	Excitatory amino acids: receptors VI	Poster			wAM		
467.	Excitatory amino acids: receptors VII	Poster			wPM		
557.	Excitatory amino acids: receptors VIII	Poster				thAM	
558.	Excitatory amino acids: receptors IX	Poster				thAM	
731.	Excitatory amino acids: receptors X	Poster					fAM
472.	GABA receptors: development	Poster			wPM		
523.	GABA receptors: function—*in vivo* studies	Slide				thAM	
468.	GABA receptors: function—$GABA_A$	Poster			wPM		
471.	GABA receptors: function—$GABA_B$, $GABA_C$	Poster			wPM		
633.	GABA receptors: function—anesthetics	Poster				thPM	
470.	GABA receptors: function—benzodiazepines	Poster			wPM		
351.	GABA receptors: function—molecular modeling I	Slide			wAM		
469.	GABA receptors: function—molecular modeling II	Poster			wPM		
632.	GABA receptors: function—neurosteroids	Poster				thPM	
199.	GABA receptors: structure	Poster		tAM			
3.	**Gender and the Brain**	**SYMP**	**mAM**				
128.	Interactions between neurotransmitters I	Poster	mPM				

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
205.	Interactions between neurotransmitters II	Poster		tAM			
484.	Interactions between neurotransmitters III	Poster			wPM		
566.	Interactions between neurotransmitters IV	Poster				thAM	
343.	**Molecular Biology of Neuropeptide Receptors: How Different Are They?**	**SYMP**			**wAM**		
171.	**Molecular Plasticity to Psychotropic Drugs**	**SYMP**		**tAM**			
602.	**Neurotransmitter Transporters**	**SYMP**				**thPM**	
202.	Opioids: anatomy and physiology I	Poster		tAM			
477.	Opioids: anatomy and physiology II	Poster			wPM		
478.	Opioids: anatomy and physiology III	Poster			wPM		
732.	Opioids: behavior	Poster					fAM
348.	Opioids: receptor molecular biology	Slide			wAM		
177.	Opioids: receptor physiology and sigma sites	Slide		tAM			
37.	Opioids: receptors I	Poster	mAM				
475.	Opioids: receptors II	Poster			wPM		
476.	Opioids: receptors III	Poster			wPM		
638.	Opioids: receptors IV	Poster				thPM	
41.	Other biogenic amines and purines: histamine and melatonin	Poster	mAM				
42.	Other biogenic amines and purines: purines	Poster	mAM				
301.	Peptides: anatomical localization I	Poster		tPM			
473.	Peptides: anatomical localization II	Poster			wPM		
474.	Peptides: anatomical localization III	Poster			wPM		
559.	Peptides: biosynthesis, metabolism, and biochemical characterization I	Poster				thAM	
560.	Peptides: biosynthesis, metabolism, and biochemical characterization II	Poster				thAM	
561.	Peptides: biosynthesis, metabolism, and biochemical characterization III	Poster				thAM	
200.	Peptides: physiological effects I	Poster		tAM			
201.	Peptides: physiological effects II	Poster		tAM			
636.	Peptides: physiological effects III	Poster				thPM	
637.	Peptides: physiological effects IV	Poster				thPM	
441.	Peptides: posttranslational processing	Slide			wPM		
104.	Peptides: receptor molecular biology	Slide	mPM				
525.	Peptides: receptor physiology	Slide				thAM	
298.	Peptides: receptors I	Poster		tPM			
299.	Peptides: receptors II	Poster		tPM			
300.	Peptides: receptors III	Poster		tPM			
634.	Peptides: receptors IV	Poster				thPM	
635.	Peptides: receptors V	Poster				thPM	
181.	Receptor modulation, up- and down-regulation I	Slide		tAM			
207.	Receptor modulation, up- and down-regulation II	Poster		tAM			
487.	Receptor modulation, up- and down-regulation III	Poster			wPM		
43.	Regional localization of receptors and transmitters I	Poster	mAM				
129.	Regional localization of receptors and transmitters II	Poster	mPM				
308.	Regional localization of receptors and transmitters III	Poster		tPM			
17.	Second messengers I	Slide	mAM				
130.	Second messengers II	Poster	mPM				
386.	Second messengers III	Poster			wAM		
568.	Second messengers IV	Poster				thAM	
309.	Second messengers: PKC, calcium, and IP3	Poster		tPM			
485.	Second messengers: nitric oxide and calcium	Poster			wPM		
639.	Serotonin receptors: cell biology and effector mechanisms	Poster				thPM	
265.	Serotonin receptors: molecular biology I	Slide		tPM			
480.	Serotonin receptors: molecular biology II	Poster			wPM		
564.	Serotonin receptors: ontogeny and regulation	Poster				thAM	
481.	Serotonin receptors: pharmacology and localization	Poster			wPM		

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
93.	Serotonin receptors: pharmacology, localization, regulation	Slide	mPM				
565.	Serotonin receptors: physiology and behavior	Poster				thAM	
437.	Serotonin: anatomy, regulation, and clinical studies	Slide			wPM		
305.	Serotonin: electrophysiology	Poster		tPM			
126.	Serotonin: neurochemistry	Poster	mPM				
482.	Serotonin: neurotoxins, behavior and physiology	Poster			wPM		
640.	Serotonin: other	Poster				thPM	
384.	Storage, secretion, and metabolism I	Poster			wAM		
567.	Storage, secretion, and metabolism II	Poster				thAM	
527.	Transmitters in invertebrates	Slide				thAM	
306.	Transmitters in invertebrates: acetylcholine	Poster		tPM			
204.	Transmitters in invertebrates: amino acids	Poster		tAM			
127.	Transmitters in invertebrates: biogenic amines	Poster	mPM				
483.	Transmitters in invertebrates: nitric oxide	Poster			wPM		
383.	Transmitters in invertebrates: peptides	Poster			wAM		
4.	**Unraveling the Serotonergic System: Insights from Molecular Biology**	**SYMP**	**mAM**				
7.	Uptake and transporters I	Slide	mAM				
95.	Uptake and transporters II	Slide	mPM				
206.	Uptake and transporters III	Poster		tAM			
307.	Uptake and transporters IV	Poster		tPM			
385.	Uptake and transporters V	Poster			wAM		
	THEME E: ENDOCRINE AND AUTONOMIC REGULATION						
393.	Autonomic regulation: central gastrointestinal control	Poster			wAM		
212.	Autonomic regulation: genital innervation	Poster		tAM			
394.	Autonomic regulation: peripheral gastrointestinal control	Poster			wAM		
135.	Autonomic regulation: spinal and peripheral mechanisms	Poster	mPM				
134.	Autonomic regulation: supraspinal control	Poster	mPM				
213.	Autonomic regulation: urinary system innervation	Poster		tAM			
446.	Cardiovascular regulation: brainstem integration	Slide			wPM		
391.	Cardiovascular regulation: descending control	Poster			wAM		
392.	Cardiovascular regulation: hypothalamic control	Poster			wAM		
610.	Cardiovascular regulation: spinal and peripheral control	Slide				thPM	
184.	Cardiovascular regulation: supramedullary control	Slide		tAM			
132.	Cardiovascular regulation: sympathetic system	Poster	mPM				
133.	Cardiovascular regulation: vagal system	Poster	mPM				
390.	Cardiovascular regulation: ventrolateral medulla	Poster			wAM		
312.	Hypothalamic-pituitary-adrenal axis regulation: CRF	Poster		tPM			
488.	Hypothalamic-pituitary-adrenal axis regulation: POMC and steroid receptor studies	Poster			wPM		
387.	Hypothalamic-pituitary-adrenal axis regulation: basic and clinical studies	Poster			wAM		
174.	Hypothalamic-pituitary-adrenal axis regulation: focus on CRF and glucocorticoid receptors	Slide		tAM			
349.	Hypothalamic-pituitary-gonadal regulation: cellular and molecular aspects	Slide			wAM		
258.	Hypothalamic-pituitary-gonadal regulation: control of GnRH secretion	Slide		tPM			
131.	Hypothalamic-pituitary-gonadal regulation: control of LH secretion	Poster	mPM				
572.	Hypothalamic-pituitary-gonadal regulation: gonadotropins, neuropeptides, steroids	Poster				thAM	
570.	Hypothalamic-pituitary-gonadal regulation: neuropeptides and transmitters	Poster				thAM	
734.	Hypothalamic-pituitary-gonadal regulation: regulatory aspects	Poster					fAM
571.	Hypothalamic-pituitary-gonadal regulation: releasing hormones	Poster				thAM	

Session Number	Session Title	Type	Day and Time: Mon.	Tue.	Wed.	Thu.	Fri.
641.	Hypothalamic-pituitary-gonadal regulation: steroid receptors	Poster				thPM	
696.	Hypothalamus and autonomic regulation	Slide					fAM
250.	**Integration in Central Somato-visceral Processing**	**SYMP**		**tPM**			
210.	Neural-immune interactions: CNS effects on immune response	Poster		tAM			
98.	Neural-immune interactions: cytokine effects on the nervous system	Slide	mPM				
211.	Neural-immune interactions: endocrine effects on immune response	Poster		tAM			
45.	Neural-immune interactions: immune mediators in normal CNS	Poster	mAM				
46.	Neural-immune interactions: nervous system pathology	Poster	mAM				
208.	Neural-immune interactions: neurochemical effects of immune stimulation	Poster		tAM			
691.	Neural-immune interactions: neuroendocrine control of immune response	Slide					fAM
209.	Neural-immune interactions: neurophysiological response to immune stimulation	Poster		tAM			
389.	Neural-immune interactions: other neurotransmitters in immune tissues	Poster			wAM		
388.	Neural-immune interactions: sympathetic regulation of immune response	Poster			wAM		
489.	Neuroendocrine regulation: CRF, gonadal and adrenal steroids	Poster			wPM		
573.	Neuroendocrine regulation: catecholamine and GABA	Poster				thAM	
442.	Neuroendocrine regulation: gene expression and co-localization	Slide			wPM		
642.	Neuroendocrine regulation: miscellaneous	Poster				thPM	
735.	Neuroendocrine regulation: oxytocin, vasopressin, fluid balance, and the pineal	Poster					fAM
44.	Osmotic regulation	Poster	mAM				
530.	Osmotic regulation/chemical senses: central pathways	Slide				thAM	
613.	Respiratory regulation	Slide				thPM	
574.	Respiratory regulation: carotid body, pons, hypothalamus, miscellaneous	Poster				thAM	
490.	Respiratory regulation: medullary and spinal cord mechanisms	Poster			wPM		
47.	Thermoregulation and fever	Poster	mAM				
THEME F: SENSORY SYSTEMS							
739.	Auditory behavior	Poster					fAM
581.	Auditory cortex I	Poster				thAM	
582.	Auditory cortex II	Poster				thAM	
693.	Auditory system	Slide					fAM
494.	Auditory system: central anatomy—brainstem	Poster			wPM		
583.	Auditory system: central anatomy—midbrain, thalamus, and cortex	Poster				thAM	
580.	Auditory system: cochlea	Poster				thAM	
649.	Auditory, vestibular, and lateral line: hair cells	Poster				thPM	
585.	Chemical senses: central gustatory mechanisms	Poster				thAM	
55.	Chemical senses: central olfactory mechanisms	Poster	mAM				
54.	Chemical senses: olfactory bulb	Poster	mAM				
584.	Chemical senses: peripheral gustatory mechanisms	Poster				thAM	
12.	Chemical senses: peripheral mechanisms	Slide	mAM				
53.	Chemical senses: peripheral olfactory mechanisms	Poster	mAM				
431.	**Cortical Oscillatory Responses and Feature Binding**	**SYMP**			**wPM**		
90.	**Functional Organization of Human Visual Cortex**	**SYMP**	**mPM**				
141.	Invertebrate sensory systems I	Poster	mPM				
142.	Invertebrate sensory systems II	Poster	mPM				
219.	Lateral geniculate nucleus: biophysics and pharmacology	Poster		tAM			
218.	Lateral geniculate nucleus: structure and function	Poster		tAM			
530.	Osmotic regulation/chemical senses: central pathways	Slide				thAM	
577.	Pain modulation: pharmacology IV	Poster				thAM	
736.	Pain modulation: pharmacology V	Poster					fAM

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
50.	Pain modulation: anatomy and physiology I	Poster	mAM				
102.	Pain modulation: anatomy and physiology II	Slide	mPM				
216.	Pain modulation: anatomy and physiology III	Poster		tAM			
395.	Pain modulation: anatomy and physiology IV	Poster			wAM		
576.	Pain modulation: anatomy and physiology V	Poster				thAM	
51.	Pain modulation: pharmacology I	Poster	mAM				
217.	Pain modulation: pharmacology II	Poster		tAM			
396.	Pain modulation: pharmacology III	Poster			wAM		
444.	Pain: pathways I	Slide			wPM		
575.	Pain: pathways II	Poster				thAM	
646.	Pain: pathways III	Poster				thPM	
493.	Retina: choroid, pigment epithelium, and photoreceptors	Poster			wPM		
578.	Retina: functional organization	Poster				thAM	
519.	Retina: ganglion cells I	Slide				thAM	
579.	Retina: ganglion cells II	Poster				thAM	
52.	Retina: immunocytochemistry	Poster	mAM				
492.	Retina: invertebrate	Poster			wPM		
100.	Retina: photoreceptors and interneurons	Slide	mPM				
48.	Somatic and visceral afferents I	Poster	mAM				
136.	Somatic and visceral afferents II	Poster	mPM				
214.	Somatic and visceral afferents III	Poster		tAM			
49.	Somatosensory cortex and thalamocortical relationships I	Poster	mAM				
313.	Somatosensory cortex and thalamocortical relationships II	Poster		tPM			
644.	Somatosensory cortex and thalamocortical relationships III	Poster				thPM	
645.	Somatosensory cortex and thalamocortical relationships IV	Poster				thPM	
702.	Somatosensory cortex and thalamocortical relationships V	Slide					fAM
491.	Spinal cord I	Poster			wPM		
643.	Spinal cord II	Poster				thPM	
737.	Striate cortex: development and plasticity	Poster					fAM
139.	Striate cortex: functional organization I	Poster	mPM				
140.	Striate cortex: functional organization II	Poster	mPM				
179.	Striate cortex: functional organization III	Slide		tAM			
359.	Striate cortex: plasticity	Slide			wAM		
263.	Striate cortex: response properties I	Slide		tPM			
647.	Striate cortex: response properties II	Poster				thPM	
648.	Striate cortex: response properties III	Poster				thPM	
221.	Subcortical auditory pathways I	Poster		tAM			
222.	Subcortical auditory pathways II	Poster		tAM			
223.	Subcortical auditory pathways III	Poster		tAM			
137.	Subcortical somatosensory pathways: spinal cord and brainstem	Poster	mPM				
215.	Subcortical somatosensory pathways: thalamus	Poster		tAM			
220.	Subcortical visual pathways: retinofugal and retinopetal systems	Poster		tAM			
314.	Subcortical visual pathways: superior colliculus	Poster		tPM			
13.	Subcortical visual systems	Slide	mAM				
138.	Subcortical visual systems: pretectum and pulvinar	Poster	mPM				
397.	Visual cortex: extrastriate—anatomy	Poster			wAM		
19.	Visual cortex: extrastriate—cognitive mechanisms I	Slide	mAM				
398.	Visual cortex: extrastriate—cognitive mechanisms II	Poster			wAM		
618.	Visual cortex: extrastriate—functional architecture	Slide				thPM	
531.	Visual cortex: extrastriate—motion processing	Slide				thAM	
315.	Visual cortex: extrastriate—unit properties	Poster		tPM			
316.	Visual psychophysics and behavior I	Poster		tPM			
738.	Visual psychophysics and behavior II	Poster					fAM

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
THEME G: MOTOR SYSTEMS AND SENSORIMOTOR INTEGRATION							
56.	Basal ganglia and thalamus I	Poster	mAM				
57.	Basal ganglia and thalamus II	Poster	mAM				
58.	Basal ganglia and thalamus III	Poster	mAM				
320.	Basal ganglia and thalamus IV	Poster		tPM			
399.	Basal ganglia and thalamus V	Poster			wAM		
586.	Basal ganglia and thalamus VI	Poster				thAM	
587.	Basal ganglia and thalamus VII	Poster				thAM	
650.	Basal ganglia and thalamus VIII	Poster				thPM	
651.	Basal ganglia and thalamus IX	Poster				thPM	
400.	Cerebellum I	Poster			wAM		
401.	Cerebellum II	Poster			wAM		
499.	Cerebellum III	Poster			wPM		
529.	Cerebellum IV	Slide				thAM	
652.	Cerebellum V	Poster				thPM	
146.	Circuitry and pattern generation I	Poster	mPM				
231.	Circuitry and pattern generation II	Poster		tAM			
406.	Circuitry and pattern generation III	Poster			wAM		
656.	Circuitry and pattern generation IV	Poster				thPM	
700.	Circuitry and pattern generation V	Slide					fAM
63.	Control of posture and movement I	Poster	mAM				
64.	Control of posture and movement II	Poster	mAM				
226.	Control of posture and movement III	Poster		tAM			
227.	Control of posture and movement IV	Poster		tAM			
228.	Control of posture and movement V	Poster		tAM			
229.	Control of posture and movement VI	Poster		tAM			
230.	Control of posture and movement VII	Poster		tAM			
404.	Control of posture and movement VIII	Poster			wAM		
405.	Control of posture and movement IX	Poster			wAM		
655.	Control of posture and movement X	Poster				thPM	
692.	Control of posture and movement XI	Slide					fAM
657.	Invertebrate motor function	Poster				thPM	
616.	Motor cortex	Slide				thPM	
498.	Motor cortex: neuropharmacology	Poster			wPM		
65.	Muscle: fiber types	Poster	mAM				
66.	Muscle: gene transfer, contractile properties, fatigue	Poster	mAM				
322.	Oculomotor system: eye-head control	Poster		tPM			
653.	Oculomotor system: neuroanatomy	Poster				thPM	
180.	Oculomotor system: physiology and psychophysics of saccades	Slide		tAM			
144.	Oculomotor system: pursuit and optokinetic nystagmus	Poster	mPM				
321.	Oculomotor system: saccades and superior colliculus	Poster		tPM			
354.	Oculomotor system: superior colliculus and brainstem	Slide			wAM		
145.	Oculomotor system: vergence and accommodation	Poster	mPM				
654.	Oculomotor system: vertical movements, integration, torsion	Poster				thPM	
61.	Reflex function I	Poster	mAM				
62.	Reflex function II	Poster	mAM				
318.	Sensorimotor cortex: behavioral correlates of neuronal discharge	Poster		tPM			
496.	Sensorimotor cortex: functional imaging	Poster			wPM		
495.	Sensorimotor cortex: functional stimulation, models, and behavior	Poster			wPM		
497.	Sensorimotor cortex: neuroanatomy	Poster			wPM		
319.	Sensorimotor cortex: neuronal interactions	Poster		tPM			
317.	Sensorimotor cortex: plasticity	Poster		tPM			
224.	Spinal cord and brainstem I	Poster		tAM			
225.	Spinal cord and brainstem II	Poster		tAM			

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
402.	Spinal cord and brainstem III	Poster			wAM		
403.	Spinal cord and brainstem IV	Poster			wAM		
588.	Spinal cord and brainstem V	Poster				thAM	
614.	Vestibular system	Slide				thPM	
59.	Vestibular system: anatomy and pharmacology	Poster	mAM				
60.	Vestibular system: neurophysiology	Poster	mAM				
143.	Vestibular system: psychophysics	Poster	mPM				
	THEME H: OTHER SYSTEMS OF THE CNS						
590.	Association cortex and thalamocortical relations I	Poster				thAM	
591.	Association cortex and thalamocortical relations II	Poster				thAM	
524.	Brain metabolism and blood flow I	Slide				thAM	
615.	Brain metabolism and blood flow II	Slide				thPM	
502.	Brain metabolism and blood flow: PET	Poster			wPM		
501.	Brain metabolism and blood flow: blood flow	Poster			wPM		
500.	Brain metabolism and blood flow: miscellaneous	Poster			wPM		
503.	Brain metabolism and blood flow: nitric oxide	Poster			wPM		
68.	Comparative neuroanatomy I	Poster	mAM				
407.	Comparative neuroanatomy II	Poster			wAM		
67.	Hypothalamus	Poster	mAM				
147.	Limbic system I	Poster	mPM				
148.	Limbic system II	Poster	mPM				
149.	Limbic system III	Poster	mPM				
352.	Limbic system IV	Slide			wAM		
589.	Limbic system V	Poster				thAM	
	THEME I: NEURAL BASIS OF BEHAVIOR						
159.	Aging	Poster	mPM				
75.	Aging: functional anatomy	Poster	mAM				
247.	Aging: memory and cognition	Poster		tAM			
235.	Biological rhythms and sleep I	Poster		tAM			
236.	Biological rhythms and sleep II	Poster		tAM			
434.	Biological rhythms and sleep III	Slide			wPM		
612.	Biological rhythms and sleep IV	Slide				thPM	
662.	Biological rhythms and sleep V	Poster				thPM	
701.	Biological rhythms and sleep VI	Slide					fAM
742.	Biological rhythms and sleep VII	Poster					fAM
254.	Drugs of abuse: alcohol, barbiturates, benzodiazepines	Slide		tPM			
333.	Drugs of abuse: amphetamine and other stimulants—amphetamine	Poster		tPM			
335.	Drugs of abuse: amphetamine and other stimulants—amphetamine derivatives	Poster		tPM			
334.	Drugs of abuse: amphetamine and other stimulants—amphetamine: behavior	Poster		tPM			
336.	Drugs of abuse: amphetamine and other stimulants—nicotine	Poster		tPM			
337.	Drugs of abuse: amphetamine and other stimulants—phencyclidines and other	Poster		tPM			
617.	Drugs of abuse: cocaine	Slide				thPM	
751.	Drugs of abuse: cocaine—behavior	Poster					fAM
752.	Drugs of abuse: cocaine—cell membrane	Poster					fAM
753.	Drugs of abuse: cocaine—glutamate	Poster					fAM
754.	Drugs of abuse: cocaine—locomotor	Poster					fAM
755.	Drugs of abuse: cocaine—microdialysis	Poster					fAM
762.	Drugs of abuse: cocaine—miscellaneous	Poster					fAM
756.	Drugs of abuse: cocaine—monoamines	Poster					fAM
757.	Drugs of abuse: cocaine—neonatal	Poster					fAM

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
758.	Drugs of abuse: cocaine—neurophysiology	Poster					fAM
759.	Drugs of abuse: cocaine—nucleus accumbens	Poster					fAM
760.	Drugs of abuse: cocaine—other drugs	Poster					fAM
761.	Drugs of abuse: cocaine—self-administration	Poster					fAM
595.	Drugs of abuse: ethanol and benzodiazepines—tolerance, dependence, withdrawal	Poster				thAM	
74.	Drugs of abuse: ethanol, benzodiazepines, barbiturates I	Poster	mAM				
157.	Drugs of abuse: ethanol, benzodiazepines, barbiturates II	Poster	mPM				
245.	Drugs of abuse: ethanol, benzodiazepines, barbiturates—GABA	Poster		tAM			
749.	Drugs of abuse: ethanol—development	Poster					fAM
750.	Drugs of abuse: ethanol—monoamines	Poster					fAM
512.	Drugs of abuse: opioids and others—developmental effects	Poster			wPM		
596.	Drugs of abuse: opioids and others—miscellaneous	Poster				thAM	
418.	Drugs of abuse: opioids and others—opioids: behavior	Poster			wAM		
417.	Drugs of abuse: opioids and others—opioids: neurochemistry	Poster			wAM		
511.	Drugs of abuse: opioids and others—opioids: withdrawal	Poster			wPM		
72.	Hormonal control of reproductive behavior: hormones and metabolites	Poster	mAM				
416.	Hormonal control of reproductive behavior: immediate early gene expression	Poster			wAM		
241.	Hormonal control of reproductive behavior: male/female/parental	Poster		tAM			
744.	Hormonal control of reproductive behavior: neuroanatomy	Poster					fAM
665.	Hormonal control of reproductive behavior: neuropeptides and transmitters	Poster				thPM	
332.	Hormonal control of reproductive behavior: receptors	Poster		tPM			
233.	Human cognition: attention	Poster		tAM			
532.	Human cognition: attention and memory	Slide				thAM	
347.	Human cognition: audition and language I	Slide			wAM		
740.	Human cognition: audition and language II	Poster					fAM
659.	Human cognition: electrophysiology	Poster				thPM	
232.	Human cognition: hemispheric laterality, gender differences	Poster		tAM			
323.	Human cognition: memory, other	Poster		tPM			
658.	Human cognition: vision, methods	Poster				thPM	
239.	Ingestive behaviors I	Poster		tAM			
240.	Ingestive behaviors II	Poster		tAM			
331.	Ingestive behaviors III	Poster		tPM			
508.	Ingestive behaviors IV	Poster			wPM		
522.	Ingestive behaviors V	Slide				thAM	
697.	Ingestive behaviors VI	Slide					fAM
743.	Ingestive behaviors VII	Poster					fAM
14.	Invertebrate learning and behavior I	Slide	mAM				
238.	Invertebrate learning and behavior II	Poster		tAM			
330.	Invertebrate learning and behavior III	Poster		tPM			
440.	Invertebrate learning and behavior IV	Slide			wPM		
660.	Learning and memory: models	Poster				thPM	
741.	Learning and memory: pharmacology—acetylcholine	Poster					fAM
412.	Learning and memory: pharmacology—benzodiazepines	Poster			wAM		
413.	Learning and memory: pharmacology—excitatory amino acids	Poster			wAM		
153.	Learning and memory: pharmacology—monoamines	Poster	mPM				
154.	Learning and memory: pharmacology—opioids	Poster	mPM				
234.	Learning and memory: pharmacology—other I	Poster		tAM			
507.	Learning and memory: pharmacology—other II	Poster			wPM		
173.	Learning and memory: physiology I	Slide		tAM			
324.	Learning and memory: physiology II	Poster		tPM			
325.	Learning and memory: physiology III	Poster		tPM			
326.	Learning and memory: physiology IV	Poster		tPM			
411.	Learning and memory: physiology V	Poster			wAM		

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
150.	Learning and memory: systems and functions I	Poster	mPM				
151.	Learning and memory: systems and functions II	Poster	mPM				
152.	Learning and memory: systems and functions III	Poster	mPM				
186.	Learning and memory: systems and functions IV	Slide		tAM			
408.	Learning and memory: systems and functions V	Poster			wAM		
409.	Learning and memory: systems and functions VI	Poster			wAM		
410.	Learning and memory: systems and functions VII	Poster			wAM		
447.	Learning and memory: systems and functions VIII	Slide			wPM		
504.	Learning and memory: systems and functions IX	Poster			wPM		
505.	Learning and memory: systems and functions X	Poster			wPM		
506.	Learning and memory: systems and functions XI	Poster			wPM		
592.	Learning and memory: systems and functions XII	Poster				thAM	
747.	Monoamines and behavior: dopamine and movement	Poster					fAM
748.	Monoamines and behavior: electrophysiology	Poster					fAM
243.	Monoamines and behavior: gene expression	Poster		tAM			
745.	Monoamines and behavior: nucleus accumbens	Poster					fAM
244.	Monoamines and behavior: serotonin	Poster		tAM			
242.	Monoamines and behavior: sexual behavior	Poster		tAM			
509.	Monoamines and behavior: stimulants	Poster			wPM		
510.	Monoamines and behavior: stress and depression	Poster			wPM		
746.	Monoamines and behavior: transmitter release	Poster					fAM
155.	Motivation and emotion I	Poster	mPM				
329.	Motivation and emotion II	Poster		tPM			
661.	Motivation and emotion III	Poster				thPM	
328.	Neural plasticity I	Poster		tPM			
414.	Neural plasticity II	Poster			wAM		
69.	Neural plasticity: cerebral cortex	Poster	mAM				
327.	Neural plasticity: hippocampus	Poster		tPM			
237.	Neuroethology: audition	Poster		tAM			
663.	Neuroethology: behavioral strategies	Poster				thPM	
415.	Neuroethology: bird vocalization	Poster			wAM		
156.	Neuroethology: electroreception	Poster	mPM				
70.	Neuroethology: invertebrate	Poster	mAM				
73.	Neuropeptides and behavior: CCK, CRF, vasopressin, and somatostatin	Poster	mAM				
6.	Neuropeptides and behavior: CRF, oxytocin, and other peptides	Slide	mAM				
594.	Neuropeptides and behavior: vasopressin, NPY, neurotensin, and others	Poster				thAM	
603.	**Prefrontal Mechanisms of Disordered Cognition: Relevance to Schizophrenia**	**SYMP**				**thPM**	
246.	Psychotherapeutic drugs: antipsychotics	Poster		tAM			
666.	Psychotherapeutic drugs: antipsychotics and other agents	Poster				thPM	
763.	Psychotherapeutic drugs: anxiolytics and antidepressants	Poster					fAM
158.	Psychotherapeutic drugs: clozapine	Poster	mPM				
353.	Psychotherapeutic drugs: effects on neurotransmitter systems	Slide			wAM		
664.	Stress: behavioral studies	Poster				thPM	
358.	Stress: from molecular biology to behavior	Slide			wAM		
593.	Stress: neurochemistry	Poster				thAM	
71.	Stress: neuroendocrine mechanisms	Poster	mAM				
688.	**The Contribution of Identified Neurons to Neuroscience: A 25-Year Retrospective**	**SYMP**					**fAM**
687.	**View of a Neural System in the Blink of an Eye: The Eyeblink Reflex—Control, Learning, and Cellular Mechanisms**	**SYMP**					**fAM**

THEME J: DISORDERS OF THE NERVOUS SYSTEM

15.	Degenerative disease: Alzheimer's—ß-amyloid I	Slide	mAM				

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
77.	Degenerative disease: Alzheimer's—ß-amyloid II	Poster	mAM				
162.	Degenerative disease: Alzheimer's—ß-amyloid III	Poster	mPM				
182.	Degenerative disease: Alzheimer's—ß-amyloid IV	Slide		tAM			
338.	Degenerative disease: Alzheimer's—ß-amyloid V	Poster		tPM			
355.	Degenerative disease: Alzheimer's—ß-amyloid VI	Slide			wAM		
421.	Degenerative disease: Alzheimer's—ß-amyloid VII	Poster			wAM		
422.	Degenerative disease: Alzheimer's—ß-amyloid VIII	Poster			wAM		
513.	Degenerative disease: Alzheimer's—ß-amyloid IX	Poster			wPM		
528.	Degenerative disease: Alzheimer's—ß-amyloid X	Slide				thAM	
600.	Degenerative disease: Alzheimer's—ß-amyloid XI	Poster				thAM	
669.	Degenerative disease: Alzheimer's—ß-amyloid XII	Poster				thPM	
79.	Degenerative disease: Alzheimer's—cognitive function: imaging and neuropathology	Poster	mAM				
78.	Degenerative disease: Alzheimer's—cognitive function: neuropsychology	Poster	mAM				
96.	Degenerative disease: Alzheimer's—neuropathology and neurotransmitters	Slide	mPM				
80.	Degenerative disease: Alzheimer's—neuropharmacology and neurotransmitters I	Poster	mAM				
163.	Degenerative disease: Alzheimer's—neuropharmacology and neurotransmitters II	Poster	mPM				
423.	Degenerative disease: Alzheimer's—neuropharmacology and neurotransmitters III	Poster			wAM		
514.	Degenerative disease: Alzheimer's—neuropharmacology and neurotransmitters IV	Poster			wPM		
81.	Degenerative disease: Alzheimer's—other I	Poster	mAM				
99.	Degenerative disease: Alzheimer's—other II	Slide	mPM				
260.	Degenerative disease: Alzheimer's—other III	Slide		tPM			
424.	Degenerative disease: Alzheimer's—other IV	Poster			wAM		
425.	Degenerative disease: Alzheimer's—other V	Poster			wAM		
515.	Degenerative disease: Alzheimer's—other VI	Poster			wPM		
601.	Degenerative disease: Alzheimer's—other VII	Poster				thAM	
670.	Degenerative disease: Alzheimer's—other VIII	Poster				thPM	
264.	Degenerative disease: Parkinson's	Slide		tPM			
164.	Degenerative disease: Parkinson's—free radicals	Poster	mPM				
427.	Degenerative disease: Parkinson's—functional morphology	Poster			wAM		
426.	Degenerative disease: Parkinson's—human neuropharmacology and pathology	Poster			wAM		
428.	Degenerative disease: Parkinson's—human performance and primate models	Poster			wAM		
165.	Degenerative disease: Parkinson's—neurotoxicity I	Poster	mPM				
166.	Degenerative disease: Parkinson's—neurotoxicity II	Poster	mPM				
429.	Degenerative disease: Parkinson's—transplantation and glia	Poster			wAM		
82.	Degenerative disease: other I	Poster	mAM				
167.	Degenerative disease: other II	Poster	mPM				
339.	Degenerative disease: other III	Poster		tPM			
346.	Degenerative disease: other IV	Slide			wAM		
76.	Developmental disorders of the nervous system I	Poster	mAM				
597.	Developmental disorders of the nervous system II	Poster				thAM	
668.	Epilepsy: anticonvulsant drugs	Poster				thPM	
16.	Epilepsy: basic mechanisms I	Slide	mAM				
249.	Epilepsy: basic mechanisms II	Poster		tAM			
420.	Epilepsy: basic mechanisms III	Poster			wAM		
599.	Epilepsy: basic mechanisms IV	Poster				thAM	
764.	Epilepsy: basic mechanisms V	Poster					fAM
161.	Epilepsy: human studies and animal models I	Poster	mPM				

Session Number	Session Title	Type	Day and Time Mon.	Tue.	Wed.	Thu.	Fri.
248.	Epilepsy: human studies and animal models II	Poster		tAM			
419.	Epilepsy: human studies and animal models III	Poster			wAM		
598.	Epilepsy: human studies and animal models IV	Poster				thAM	
160.	Genetic models of nervous system disorders I	Poster	mPM				
667.	Genetic models of nervous system disorders II	Poster				thPM	
694.	Genetic models of nervous system disorders III	Slide					fAM
684.	Infectious diseases	Poster				thPM	
267.	Ischemia I	Slide		tPM			
350.	Ischemia II	Slide			wAM		
435.	Ischemia III	Slide			wPM		
671.	Ischemia: acidosis	Poster				thPM	
672.	Ischemia: calcium	Poster				thPM	
673.	Ischemia: drug treatment I	Poster				thPM	
674.	Ischemia: drug treatment II	Poster				thPM	
675.	Ischemia: glia	Poster				thPM	
676.	Ischemia: heat shock protein	Poster				thPM	
677.	Ischemia: models	Poster				thPM	
678.	Ischemia: molecular biology/immunocytochemistry	Poster				thPM	
679.	Ischemia: neonatal	Poster				thPM	
680.	Ischemia: neurochemistry I	Poster				thPM	
681.	Ischemia: neurochemistry II	Poster				thPM	
682.	Ischemia: neurophysiology	Poster				thPM	
683.	Ischemia: temperature	Poster				thPM	
9.	Mental illness I	Slide	mAM				
84.	Mental illness II	Poster	mAM				
340.	Mental illness III	Poster		tPM			
769.	Mental illness IV	Poster					fAM
251.	**Microglia and Neuronal Injury**	**SYMP**		**tPM**			
443.	Neuro-oncology I	Slide			wPM		
773.	Neuro-oncology II	Poster					fAM
83.	Neuromuscular disease	Poster	mAM				
609.	Neurotoxicity I	Slide				thPM	
686.	Neurotoxicity II	Poster				thPM	
770.	Neurotoxicity III	Poster					fAM
771.	Neurotoxicity IV	Poster					fAM
772.	Neurotoxicity V	Poster					fAM
685.	Neurotoxicity: metals	Poster				thPM	
89.	**Phosphorylation Cascades, Neurofibrillary Tangles, and Alzheimer's Disease**	**SYMP**	**mPM**				
430.	**Thalamocortical Mechanisms Underlying Generalized Absence Seizures**	**SYMP**			**wPM**		
611.	Trauma	Slide				thPM	
765.	Trauma: cord	Poster					fAM
767.	Trauma: miscellaneous I	Poster					fAM
768.	Trauma: miscellaneous II	Poster					fAM
766.	Trauma: treatment	Poster					fAM
OTHER							
85.	History of neuroscience	Poster	mAM, PM	tAM, PM	wAM, PM	thAM, PM	fAM
86.	Teaching of neuroscience I	Poster	mAM, PM	tAM, PM	wAM, PM	thAM, PM	fAM
87.	Teaching of neuroscience II	Poster	mAM, PM	tAM, PM	wAM, PM	thAM, PM	fAM
88.	Teaching of neuroscience III	Poster	mAM, PM	tAM, PM	wAM, PM	thAM, PM	fAM

736.5

MORPHINE FAILS TO PRODUCE TOLERANCE AND NALOXONE-PRECIPITATED WITHDRAWAL WHEN ADMINISTERED IN THE PRESENCE OF FORMALIN PAIN IN RATS. Anthony L. Vaccarino* and Leland C. Couret, Jr., Department of Psychology, University of New Orleans, LA 70148.

Clinical studies have reported that patients who take morphine for pain relief do not show a high degree of tolerance or dependence. The present study examined the development of tolerance to morphine analgesia and naloxone-precipitated withdrawal under conditions in which morphine was administered in the *presence* or *absence* of pain induced by injection of formalin (50 ul/2.5%, s.c.) into the hind-paw of rats. To examine the development of tolerance, rats were injected with morphine (25 mg/kg, i.p.) or saline for 3 consecutive days either in the presence of pain (10 min after formalin) or in the absence of pain (6 h prior to formalin). On the 4th day, tolerance to the analgesic effect of test doses of morphine (6 or 10 mg/kg) was assessed in the formalin and tail-flick tests, respectively. Significant tolerance was observed in both test in animals receiving morphine in the absence of pain during the tolerance induction period, but not in animals receiving morphine in the presence of pain. To examine withdrawal, morphine (10 mg/kg) or saline were administered for 4 consecutive days in the presence of pain (10 min after formalin) or in the absence of pain (10 min after saline). On the 5th day, rats were injected with naloxone (1 mg/kg, i.p.) and observed for signs of precipitated withdrawal. Withdrawal symptoms were significantly greater in rats that received morphine in the absence of pain than in rats that received morphine in the presence of pain.

736.6

TOLERANCE AND IRREVERSIBLE ANTAGONISM STUDIES DIFFERENTIATE μ OPIOIDS IN AN ANALGESIC ASSAY. E.A. Walker*, J.D. House, and A.M. Young, Department of Psychology, Wayne State University, Detroit, MI 48202.

Opioids are differentially sensitive to receptor inactivation by either chronic opioid treatment or irreversible antagonism. The notion that these differences are related to efficacy was tested using etorphine (ET), morphine (MR), buprenorphine (BP), and GPA 1657 (GP) in an analgesic assay. Rats were placed in restrainers and the latency for tail withdrawal from 55°C water was measured. Repeated treatment of 20 mg/kg/day MR for 2 wks increased the doses of ET, MR, BP, and GP required for 100% maximum possible effect (MPE) 2 to 6-fold. When the MR treatment dose was increased to 40 mg/kg/day for 1 wk, the dose of ET remained unchanged, the dose of MR required for 100% MPE increased 3-fold further, and no dose of BP or GP produced 100% MPE. Repeated treatment of 0.2, 0.4, or 0.8 mg/kg/day BP for 1-3 wks, respectively, increased the doses of ET and MR required for 100% MPE 8 to 80-fold. After treatment of 0.2 mg/kg/day BP for 1 wk, no dose of BP or GP produced 100% MPE. Repeated treatment of 0.05 mg/kg/day BP for 1 wk increased the dose of GP required for 100% MPE 30-fold. Acute administration of the irreversible antagonist clocinnamox (3.2 mg/kg) slightly increased the MR dose required for 100% MPE, whereas no BP or GP dose produced 100% MPE. After 10 mg/kg clocinnamox, no MR dose produced 100% MPE whereas the ET dose required for 100% MPE was increased 6-fold. These data suggest each agonist requires a different fraction of the receptor population to produce analgesia. (Supported by DA03796 and K02 DA00132)

736.7

CONTEXTUAL CONTROL OF WITHDRAWL TO COLD-WATER SWIM INDUCED OPIOID ANALGESIA S. Pierce, J.E. Blustein & P.J. Hand* Beaver Coll, Glenside, PA, 19038 and Univ Penna School of Vet Med*, Philadelphia, PA, 19104.

The present study was conducted to determine if the development of withdrawal to cold water swim induced analgesia is contextual mediated. Twelve rats were exposed to daily, five minute cold water swims in a distinct context until tail-curl latencies returned to baseline. The subjects were then divided into two equal groups with half of the subjects swimming in the original context while the other animals swam in a novel environment. One hundred and five minutes after the last swim subjects were injected with naltrexone and placed in the context of their last swim. Twenty minutes following the injection of naltrexone, withdrawal behaviors were scored for a 14 minute observation period. Results indicated that the rats who remained in the same context exhibited significantly more wet dog shakes (a prominent opiate withdrawal behavior) than the animals place in the novel context. These data support the concept that withdrawal behaviors to opiate stress induced analgesia are mediated by the context.

736.8

BLOCKADE OF MORPHINE TOLERANCE BY NITRIC OXIDE SYNTHASE INHIBITOR: BEHAVIORAL AND BIOCHEMICAL DATA.

Y. Kolesnikov[1]*, A.M. Babey[1], J. Cheng[1], R.R. Trifiletti[2], and G. W. Pasternak[1,2,3]. [1]Cotzias Laboratory of Neuro-Oncology, Memorial Sloan-Kettering Cancer Center, [2]Dept. Neurology and Neuroscience, [3]Dept. Pharmacology, Cornell University Medical College. New York, NY 10021

We have previously reported that N-nitro-L-arginine (NO_2Arg) prevents the development of tolerance to morphine analgesia but not to κ drugs. Since NO_2Arg is an inhibitor of nitric oxide synthase (NOS), we investigated the role of NO and NOS in the mediation of tolerance to morphine in mice. In behavioral studies, morphine treatment alone reduces the analgesic response from 60% to 0% by day 5. NO_2Arg maintains the analgesic response for at least 28 days when co-injected with morphine. In biochemical studies, chronic morphine treatment had no effect on either NOS enzymic levels or NOS mRNA levels in cerebellum on brain stem. NO_2Arg, at doses used, decreased NOS activity *in vivo* by 61% in cerebellum and 53% in brain stem. The mechanism by which NO_2Arg restores analgesic responsiveness in animals treated chronically with morphine appears to be complex and remains to be elucidated.

736.9

ANALGESIC AND HYPOTHERMIC CROSS-TOLERANCE BETWEEN CONTINUOUS AND INTERMITTENT COLD-WATER SWIMS IN RATS. Z. Pavlovic and R.J. Bodnar*. Dept. of Psychology, Queens Col., CUNY, Flushing, NY 11367.

Analgesic responses induced by continuous (CCWS, 2°C, 3 min) and intermittent (ICWS, 2°C, 18 10-s swims) cold-water swims differ in their sensitivity to opioid antagonists and cross-tolerance with morphine. The present study examined whether CCWS and ICWS analgesia and hypothermia displayed cross-tolerance in rats. Jump thresholds were significantly increased following acute exposure to CCWS and ICWS. CCWS analgesia displayed tolerance (90% reduction following repeated (14 day) exposure to CCWS and cross-tolerance (100% reduction) following repeated exposure to ICWS. ICWS analgesia displayed tolerance (74% reduction following repeated (14 day) exposure to ICWS and cross-tolerance (81% reduction) following repeated exposure to CCWS. Although CCWS and ICWS hypothermia displayed tolerance to the same stressor and cross-tolerance to the other stressor, the changes in the analgesic and hypothermic responses failed to correlate with each other.

736.10

SUPRASPINAL ANALGESIC SYNERGY IN RATS AND OPIOID RECEPTOR SUBTYPE AGONISTS. G.C. Rossi*, G.W. Pasternak, M.L. Cooper and R.J. Bodnar. Psychology Depts., Queens and Hunter Col., CUNY; Neurol. Dept., Mem. Sloan-Kettering Cancer Ctr., NY, NY.

Multiplicative analgesic interactions occur for simultaneous morphine administration in the periaqueductal gray (PAG) and rostro-ventral medulla (RVM) (Brain Res., 1993). The present study examined supraspinal analgesic interactions by using agonists of mu (DAMGO), kappa (U50488H), $delta_1$ (DPDPE) and $delta_2$ (deltorphin) receptors. DAMGO (10-20ng) increased tail-flick latencies in the PAG and RVM. Supraspinal multiplicative interactions occurred following simultaneous administration of sub-analgesic DAMGO doses. Deltorphin (20 ug) produced a mild analgesia in the PAG and RVM. Simultaneous administration of deltorphin (10ug) produced a small interaction, and produced more pronounced effects when paired with DAMGO (3ng). Neither U50488H (20ug) nor DPDPE (20ug) altered latencies in the PAG and RVM, or interacted with DAMGO or deltorphin. Thus, mu, and to a lesser degree, $delta_2$, opioid receptor subtypes mediate analgesic synergy in the PAG and RVM, confirming the sensitivity of supraspinal morphine synergy to mu_1 antagonism.

736.11

POTENTIATION OF CONTINUOUS AND INTERMITTENT COLD-WATER SWIM ANALGESIA BY NITRIC OXIDE SYNTHASE INHIBITION IN RATS. M. Spinella* and R.J. Bodnar. Psych. Dept., Queens Col., CUNY, NY, NY 11367.

Intermittent (ICWS, 2°C, 10 10-s swims) and continuous (CCWS, 2°C, 3 min) cold-water swim analgesia are respectively sensitive and insensitive to mu-opioid manipulations (Crit. Rev. Biol. 6: 39-49, 1990). Nitric oxide (NO) has been implicated in analgesia through the use of its synthase inhibitor, N_w-nitro-L-arginine (L-NA; e.g., Neurosci. 50: 7-10, 1992). The present study examined whether CCWS and ICWS analgesia and hypothermia were altered by either L-NA or by its inactive isomer, N^w-nitro-D-arginine methyl ester (D-NAME). L-NA significantly potentiated the magnitude and duration of CCWS analgesia on the tail-flick (39%; 64%) and jump (100%; 249%) tests while reducing CCWS hypothermia (36%). L-NA significantly potentiated the duration of ICWS analgesia on the tail-flick (36%) and jump (34%) tests while reducing ICWS hypothermia (21%). In contrast, D-NAME failed to alter either CCWS or ICWS analgesia, but comparably reduced hypothermia. L-NA's failure to alter basal nociception indicates that NO synthase inhibition appears to be acting specifically upon analgesic processes.

736.12

SYNERGISTIC ANALGESIA PRODUCED BY LOW DOSES OF D-AMPHETAMINE AND MORPHINE IN THE FORMALIN TEST. S. Dalal* and R. Melzack. Department of Psychology, McGill University, 1205 Dr. Penfield Ave., Montreal, Quebec, Canada, H3A 1B1.

A number of experimental and clinical studies have shown that amphetamine coadministered with an opioid can synergistically increase the effectiveness of opioid analgesia and alleviate some opioid-induced side effects. We investigated the analgesic effects of combined sub-analgesic doses of these drugs in the formalin test, as well as the time of drug administration in relation to phase of formalin pain.

Male Long-Evans rats were administered morphine (0.0-2.5 mg/kg) and d-amphetamine (0.0-1.0 mg/kg) subcutaneously to obtain dose-response curves. To preferentially affect the early phase (0-5 minutes) and late phase (20-50 minutes) of formalin pain, morphine and amphetamine were administered at different times relative to formalin injection. We confirm that d-amphetamine can potentiate morphine analgesia in a dose-dependent manner. In addition, earlier coadministration of the drugs at optimal doses can produce analgesia in both the early and late phases of formalin pain. This study provides additional support for the use of amphetamine as an adjunct to morphine in the treatment of pain.

Supported by NSERC grant A7896.

736.13

ANTINOCICEPTIVE INTERACTION BETWEEN ALPRAZOLAM AND OPIOIDS: GENETIC DIFFERENCES. C. G. PICK* Dep. of Anatomy, Sackler Sch. of Med.Tel Aviv Univ. Tel Aviv, 69978, Israel.

Benzodiazepines (BZ) have been shown to interact with the antinociceptive effects of opioid drugs. This study was designed to investigate the antinociceptive effects of the most prescribed BZ i.e. alprazolam, administrated alone or in combination with morphine in genetically distinct strains of mice. Groups of CD-1, BALB/C, C57/BL and SWISS mice were treated with different drugs. Analgesia was assayed using the radiant heat tailflick. Alprazolam (1 mg/kg, i.p.) elicited analgesia in BALB/C mice (50%). However, its analgesic potency in additional strains varied considerably. In fact, no tailflick analgesia was observed in CD-1 or C57/Bl mice. The sensitivity of SWISS (20%) was intermediate. Intrathecally administered Alprazolam (10μg) elicited analgesia in BALB/C mice (40%), no tailflick analgesia was observed in C57/Bl mice. The sensitivity in SWISS (30%) and CD-1 (20%) were intermediate. We found a synergistic increase in analgesia when a subthreshold dose of alprazolam was given with morphine and vice versa. This interaction was antagonized by naloxone. Our results demonstrate that injections of alprazolam can produce analgesia under different genetic controls and modify morphine-induced antinociception in mice as assessed in the tailflick assay. No effect was found when alprazolam was coadministrated with other specific opioid agonists.

736.14

IMIPRAMINE AND FENTANYL ANTINOCICEPTION IN THE RABBIT TOOTH PULP MODEL. K.Asher, L.Alvarez, R.Wynn, N.Myslinski, R.Meszler.* Depts. of Physio. and Pharm., Univ. of Maryland, Baltimore, MD 21201.

Fentanyl(F) produces rapid and effective antinociception but has the dangerous side effect of respiratory depression. Recent reports indicate that the tricyclic antidepressant imipramine(IMI) may produce antinociception in mice. The purpose of this study was to determine the antinociceptive properties of IMI, its effect on F antinociception, and its effect on respiratory depression in the rabbit tooth pulp model. Eight New Zealand white rabbits(1.5-3.0 kg) were prepared according to the method of Wynn et al. An electrical stimulus was applied to the tooth pulp of each rabbit and the voltage that evoked a lick-chew response was recorded. Control volts(CV) were recorded before IV administration of IMI, and test volts(TV) were recorded after. It was considered effective if TV were more than twice CV. IMI doses used were 2.5 mg/kg and 7.5 mg/kg. It was shown to be effective in antinociception and produced a graded dose response. The ED50 value of IMI(4.3 mg/kg) was calculated using the method of Litchfield and Wilcoxon. The ED50 value of F was calculated as above. Three more ED50 values for F were then determined 15 mins after pretreating 8 different rabbits with 1/4, 1/2, and 3/4 the ED50 dose of IMI. The ED50 values were plotted on an isobologram for drug combination, and the points fell well within the area for super additivity. The effect of IMI on respiration was determined by measuring the blood PCO2 and counting the number of breaths per minute(BPM) 5 minutes after IV administration of IMI. No significant change in PCO2 or BPM was found. This study showed that IMI produces analgesia, is super additive with F, and does not depress respiration in the rabbit model. (Supported in part by Designated Research Initiative Funds from the University of Maryland)

736.15

INTRATHECAL BENZODIAZEPINES MODULATE THE ANALGESIA PRODUCED BY INTRATHECAL ISOGUVACINE BUT NOT BY INTRATHECAL MUSCIMOL IN THE RAT. M.K. McGowan* and D.L. Hammond. Department of Anesthesia & Critical Care, University of Chicago, Chicago IL 60637.

This study examined whether the antinociception produced by intrathecal (i.t.) administration of the prototypic $GABA_A$ agonists isoguvacine or muscimol is modulated by i.t. administration of the benzodiazepine receptor agonist diazepam or the inverse agonist DMCM. Rats were prepared under general anesthesia with an i.t. catheter. After a one-week recovery period, baseline nociceptive sensitivity was determined using the tail flick test. Rats were then injected i.t. with either diazepam (40 μg) or DMCM (10 μg) in combination with either isoguvacine (15 μg) or muscimol (0.5 μg), and TFL was redetermined at fixed intervals thereafter. Injection of isoguvacine or muscimol significantly increased TFL ($p < 0.05$). Coadministration of diazepam significantly enhanced the increase in TFL produced by i.t. isoguvacine ($p < 0.05$), but not the increase in TFL produced by i.t. muscimol. Conversely, i.t. DMCM significantly attenuated the increase in TFL produced by i.t. isoguvacine ($p < 0.05$), but not that produced by i.t. muscimol. These results provide further evidence that spinal $GABA_A$ receptors are involved in the production of antinociception. They also suggest that not all spinal $GABA_A$ receptors are coupled to benzodiazepine receptors. Supported by PHS Grant DA07004.

736.16

CORTICAL POTENTIALS EVOKED BY TOOTH PULP STIMULATON DISTINGUISH ANALGESIA FROM CHANGES IN AROUSAL. P.J. Danneman*. ULAM, Univ. of Michigan, Ann Arbor, MI 48109.

Many analgesic drugs induce changes in arousal which may influence results in behavioral tests of antinociception. Previous studies in this laboratory showed that the cortical potential (CEP) evoked by electrical stimulation of the rat tooth pulp (TPS) effectively distinguishes between the analgesic and sedative effects of morphine. This model was used to study the analgesic effects of several drugs which cause sedation or increased arousal. Ten male Sprague-Dawley rats were anesthetized and instrumented for TPS and CEP recording as described previously. Testing of awake rats started 1 week later. Drugs were administered subcutaneously and each was tested in 5-8 rats. Latency, amplitude, and area under the curve (AUC) of pre-treatment and post-treatment CEPs were compared by t-test analyses. Significant decreases in the amplitude and AUC of the earliest CEP components showed that the following drugs were analgesic: fentanyl (0.1 mg/kg), hydromorphone (1.5 mg/kg), cocaine (15 mg/kg), D-amphetamine sulfate (3 mg/kg), buprenorphine (0.4 mg/kg), diazepam (5 mg/kg), and midazolam (2.15 mg/kg). Ketamine (60 mg/kg), phencyclidine (1 mg/kg), and pentobarbital (30 mg/kg) showed no antinociceptive activity. The analgesic activity demonstrated by both the sedative and excitatory drugs was generally consistent with previous reports. **These results strongly support the controversial contention that benzodiazepines are antinociceptive.** (Supported by #RR00052)

736.17

DIFFERENTIAL DISTRIBUTION OF $GABA_A$ AND $GABA_B$ RECEPTORS IN THE TRIGEMINAL NUCLEUS. G.H. Fromm* and K.Q. Sun. Dept. of Neurology, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA 15261.

Previous experiments showed that trigeminal neuralgia drugs (baclofen, carbamazepine) facilitate segmental inhibition (SI) of low-threshold mechanoceptive (LTM) neurons in the trigeminal nucleus, while postherpetic neuralgia drugs (amitriptyline) enhance SI of wide dynamic range (WDR) neurons. We have now investigated the effect of the iontophoretic of application of $GABA_A$ and $GABA_B$ antagonists on LTM, WDR and nociceptive specific (NS) neurons in the spinal trigeminal nucleus caudalis.

In rats anesthetized with α-chloralose/urethane, the iontophoretic administration of the $GABA_A$ antagonist bicuculline decreased SI of LTM, WDR and NS neurons, but the iontophoresis of the $GABA_B$ antagonist CGP 35348 only had a small depressant effect on SI of LTM neurons. The iontophoresis of GABA increased SI of LTM, WDR and NS neurons to approximately the same degree, and this action of exogenous GABA was also blocked by bicuculline. CGP 35348 only blocked the effect of exogenous GABA on SI of LTM neurons.

Our experiments indicate that SI of LTM neurons is mediated by both $GABA_A$ and $GABA_B$ receptors, but that SI of WDR and NS neurons is due to $GABA_A$ receptors. Furthermore, CGP 35348's greater effectiveness against exogenous than endogenous GABA suggests that $GABA_B$ receptors respond to paroxysmal releases of GABA evoked by high levels of activity while $GABA_A$ receptors mediate tonic as well as phasic GABAergic inhibition. These observations, and the effectiveness of the $GABA_B$ agonist baclofen against trigeminal neuralgia, provide further support for the hypothesis that the pathogenesis of trigeminal neuralgia involves paroxysmal discharges of LTM neurons in the trigeminal nucleus. (Supported by NS-19889).

736.18

PERIPHERAL JOINT INFLAMMATION AND HEAT HYPERALGESIA ARE BLOCKED BY SPINAL ADMINISTRATION OF A $GABA_A$ BUT NOT BY A $GABA_B$ RECEPTOR ANTAGONIST. K.A. Sluka*, W.D. Willis and K.N. Westlund. Marine Biomedical Institute, UTMB, Galveston, TX 77555-0843.

The injection of kaolin and carrageenan (3%) into the knee joint cavity of rats results in: 1) localized joint inflammation; 2) heat hyperalgesia of the ipsilateral paw; and 3) increased release of amino acids in the dorsal horn. Amino acid release was monitored and GABA receptor antagonists (bicuculline ($GABA_A$) or CGP35.348 ($GABA_B$)) were infused through a microdialysis fiber implanted into the spinal cord dorsal horn. As expected, the increased release of amino acids occurring at the time of knee joint injection in arthritic animals was also measurable in arthritic animals treated with either GABA receptor antagonist.

Joint circumferences, thermographic readings, and paw withdrawal latencies to radiant heat were assessed following 8 hr of arthritis. Pretreatment of the spinal cord with the $GABA_A$ antagonist, bicuculline, impeded the development of the joint inflammation (i.e. joint circumferences were 50% less than in arthritic animals). No heat hyperalgesia developed in bicuculline-treated animals. On the other hand, if animals were pretreated with the $GABA_B$ antagonist, CGP35.348, the inflammation and hyperalgesia were similar to that of the untreated arthritic animals.

Therefore, direct spinal administration of bicuculline ($GABA_A$) blocks the development of joint inflammation and heat hyperalgesia. This implies that $GABA_A$ mediated spinal events influence joint inflammation. These $GABA_A$ receptor events might include depolarization of primary afferent fibers producing dorsal root reflexes which could enhance the peripheral release of inflammatory neuropeptides. Supported by NIH grant NS11255, NS28064, and NS01445 (RCDA to KNW).

736.19

SPINAL $GABA_B$ INVOLVEMENT IN PARENTERAL NICOTINE-INDUCED ANTINOCICEPTION. D. T. Rogers* and E. T. Iwamoto, Dept. of Pharmacol., Univ. of Kentucky Coll. of Med., Lexington, KY 40536.

The role of γ-amino butyric acid (GABA)type B receptors in the mechanism of of s.c. nicotine antinociception was examined in intrathecally catheterized (i.t.), male Sprague-Dawley rats, using the hot-plate and tail-flick tests. The $GABA_B$ receptor agonist baclofen (BAC) produced 100% inhibition of hot-plate and tail-flick test responses 10-15 min following 47 nmol i.t. administration. Test latencies remained elevated relative to controls for up to two hours after i.t. BAC administration. Pretreatment with 50 nmol (i.t.) of the selective $GABA_B$ receptor antagonist phaclofen (PHAC) completely reversed the antinociception produced by 47 nmol i.t. BAC. Nicotine, 0.375 mg/kg, produces 100% inhibition of test responses 10 min after injection, and test responses remain elevated above controls for up to 30 min. Pretreatment with 50 nmol i.t. PHAC 12 min before 0.375 mg/kg s.c. nicotine prolonged the duration of nicotine antinociception in both tests. Test responses remained maximally elevated (>90 sec, hot-plate; >15 sec, tail-flick) for up to 30 min after s.c. nicotine administration. Injection of s.c. nicotine (0.125, 0.375, 0.5 mg/kg) 5 min after i.t. BAC dose-dependently attenuated BAC antinociception. Pretreatment with 0.375 mg/kg nicotine 30 min minutes before 47 nmol i.t. BAC injection also attenuated BAC antinociceptiom. I.t. nicotine (10-30 μg) pretreatment produced no changes in BAC antinociception. I.t. baclofen antinociception was blocked by prior microinjection of the rostral ventral medulla(RVM) with the the high-affinity choline uptake inhibitor hemicholinium-3. These data indicate that nicotine antinociception may involve presynaptic and/or postsynaptic $GABA_B$ components. Nicotine may functionally antagonize baclofen antinociception by producing desensitization of lumbar spinal antinociceptive mechanisms. This study also suggests that i.t. BAC antinociception is dependent upon cholinergic transmission in the RVM. (Supported by NIH NS-28847 and the KTRB).

STRIATE CORTEX: DEVELOPMENT AND PLASTICITY

737.1

ZINC COLUMNS IN PRIMARY VISUAL CORTEX OF ADULT VERVET MONKEYS: TOPOGRAPHIC DISTRIBUTION AND EFFECTS OF MONOCULAR IMPULSE BLOCKADE. Richard H. Dyck*, Avi Chaudhuri and Max S. Cynader. Department of Ophthalmology, University of British Columbia, Vancouver, British Columbia, Canada, V5Z 3N9.

A subset of glutamatergic neurons in the mammalian telencephalon contain a pool of histochemically-reactive zinc (Zn) within vesicles of their terminal boutons. Here we describe the laminar and tangential distribution of Zn in the primary visual cortex of normal adult monkeys (*Cercopithicus aethiops*), and monkeys deprived of monocular visual input for 24 hours by an intraocular injection of tetrodotoxin. The topographic distribution of Zn, was compared to the neuronal activity markers cytochrome oxidase (CO) and Zif 268. In normal animals, the laminar and tangential distributions of Zn and CO were found to be precisely complementary. In general, the highest density of Zn was localized to laminae staining least densely for CO. In the tangential domain, a Zn-stained matrix formed a precisely interdigitated mosaic with CO-blobs in laminae II/III; while in sublamina IVA the honeycomb-like CO-staining surrounded Zn-dense islets. Although 24 hours of monocular impulse blockade was insufficient to clearly reveal the ocular dominance pattern with CO staining, eye-specific reductions in the levels of Zn-staining dramatically revealed the ocular dominance bands in all cortical laminae. When compared with levels of Zif 268 expression (known to be reduced in deprived-eye stripes) in serially adjacent sections, levels of Zn were found to be reduced in ocular dominance stripes innervated by the **open eye**. These results suggest that synaptic zinc demarcates anatomical and functional columnar domains complementary to those of cytochrome oxidase and, furthermore, indicate that levels of synaptic zinc are extremely susceptible to activity-dependent modifications within a time frame of less than 24 hours.

737.2

Patterns of gene expression as determinants of cortical specificity in the monkey visual system

A. Chaudhuri,* S.S. Prasad, and M.S. Cynader

Dept. of Ophthalmology, Univ. of British Columbia, Vancouver, B.C. CANADA

The visual cortex of the monkey is divided into a number of areas that appear to be dedicated to specific roles in information processing. It is believed that these various areas are anatomically linked and separated into two processing streams, the M- and P-pathways. In order to elucidate the molecular basis for the observed phenotypic differences among the different cortical areas and the two pathways, we have initiated a search to identify genes and gene products that are preferentially expressed within neurons that belong to these areas.

The initial phase of this study involves the construction and evaluation of cDNA libraries from several specific cortical areas of the monkey, including V1, V2, V4, MT, IT, and FEF. We have now isolated mRNAs specfic to each area, e.g. MT clones were selected using subtractive hybridization with V1 as the control tissue. The issue of pathway specificity has been approached at the LGN level where neurons belonging to the two processing streams are more easily separated thereby producing a pure population of M- and P- neurons for cDNA library construction. Our approach is to obtain subtracted clones at the LGN level and then screen the various cortical libraries to determine which mRNAs are also expressed at the higher levels.

We are proceeding with the characterization of the subtracted clones at the nucleotide level and evaluation of the spatial expression of these mRNAs in various specific brain regions.

737.3

IDENTIFICATION OF VISUAL CORTEX cDNA CLONES WHOSE DEVELOPMENTAL EXPRESSION IS INPUT-DEPENDANT. S.S. Prasad*[1], F. Lepore[2], M. Ptito[2] and M.S. Cynader[1] [1]Dept. of Ophthalomology, Univ. of British Columbia, Vancouver, B.C. Canada V5Z3N9 and [2]Dept of Psychology, Univ. of Montreal, P.Q. Canada H2V 2S9.

Abundant evidence has shown that the visual exposure history of the organism can markedly influence the course of future cortical development. The experience-dependant modifications of cortical connectivity and physiology in kittens have a well defined critical period which peaks at about 30 days of age and studies at the protein level have documented transient elevation of several important molecules within cortical cell populations at this age. This critical period is itself input-dependant and can be prolonged into adulthood by restricting visual input to the cortex.

Previously we reported the characterization of about 200 cDNA clones which were found by subtractive hybridization to be expressed at much higher levels in the kitten visual cortex compared to the adult visual cortex. Further examination of twenty of these differentially expressed cDNA clones by northern blot hybridization to RNAs from cerebellum and frontal cortex revealed that many of these clones are related to aging in general, and probably not specifically related to the critical period. Therefore we have constructed a subtracted cDNA library comparing the visual cortex from the two hemispheres of adult cats whose optic tracts had been sectioned on one side before the critical period. In such animals the visual cortex in the operated hemisphere is expected to retain the plasticity of the critical period. We anticipate that this approach should allow us to identify only the mRNAs that are involved in the activity-dependant plasticity mechanism. We are now screening this subtracted library with the subtracted probes derived from normal 30 day old kitten visual cortex. The results of these multiple subtractions should enable us to isolate and focus on a small, rather specific set of genes, whose differential expression underlies the plastic capabilities of the visual cortex.

737.4

OPTICAL IMAGING OF THE REVERSE SUTURING EFFECT IN KITTEN VISUAL CORTEX DURING THE CRITICAL PERIOD. Tobias Bonhoeffer†, Dae-Shik Kim, Wolf Singer*. Max-Planck-Institute for Brain Research., 6000 Frankfurt, FRG. †Present adress: Max-Planck-Institute for Psychiatry, 8033 München-Martinsried, FRG.

In kittens the layout of the orientation map converges to an equilibrium state before the age of 3 weeks and remains unchanged under normal conditions. However, this state can be disturbed during a critical period. In the present study we examined whether the reorganization of geniculo-cortical connections that occurs in response to reverse monocular deprivation affects the orientation map in area 18. After recording the orientation maps for each eye, kittens were monocularly deprived for $\sim$ 1 week by lid suture, and the orientation maps for both eyes were re-examined. Our results indicate an almost complete loss of responses to stimuli presented to the deprived eye, whereas the orientation map visualized by stimulating the normal eye remained unchanged. Subsequently, the eyes were reverse-sutured for $\sim$ 1 week. Following this period, responses to the newly deprived eye had vanished completely, and responses to the other eye had recovered. The orientation map obtained by stimulating the newly opened eye closely ressembled that observed prior to deprivation. We conclude that the basic layout of iso-orientation domains is determined before the age of 3 weeks and is not altered by the reversible weakening and strengthening of thalamic input connections that results from reverse monocular deprivation.

737.5

CHRONICAL OBSERVATION OF THE EMERGENCE OF ISO-ORIENTATION DOMAINS IN KITTEN VISUAL CORTEX. Dae-Shik Kim and Tobias Bonhoeffer*†. Max-Planck-Inst. for Brain Research, 6000 Frankfurt, FRG. †Present adress: Max-Planck-Inst. for Psychiatry, 8033 München-Martinsried, FRG.

In the present study we used optical imaging to investigate how iso-orientation domains emerge in the cortex of young kittens. Chronical recordings were performed in kittens from the age of postnatal day 17 on. To ensure the constancy of the recording site over the period of several weeks, identified blood vessels and silver wires placed below the skull were used as landmarks. Our results show that domains of orientation preference are present already at the age of 2 $\frac{1}{2}$ weeks. However, they are much more irregular in form and in size than those of adult animals. In our chronical recordings we could observe how these irregular structures are transformed into the patchy domains of orientation preference of more adult kittens. In general, the position of the clusters does not seem to change markedly during this period. But most of these initially fuzzy structures are shaped and segregated into patches of orientation preference very similar to those in adult animals. Between postnatal weeks three and eight we could not observe the emergence of any new iso-orientation domains in those cortical regions from which we recorded. Taken together, our data suggest that in normal kittens the basic layout of the orientation preference map is present already shortly after eye-opening at 2 $\frac{1}{2}$ weeks. The initially fuzzy map is sharpened over the course of a few days such that it converges to an equilibrium state around the age of 3 weeks.

737.6

OCULAR DOMINANCE COLUMN (ODC) DEVELOPMENT IN RHESUS MONKEYS RAISED WITH BINOCULAR, UNEQUAL DEPRIVATION. D.V. Bradley* and M. Tigges. Departments of Psychology, Ophthalmology, Anatomy & Cell Biology, and Yerkes Regional Primate Research Center, Emory Univ., Atlanta, GA 30322.

We reported previously the results of competition for cortical territory between aphakic and occluded fellow eyes (J.C.N. 316, 1992) in monkey models simulating unilateral infantile aphakic amblyopia. Here we present data from 4 aphakic monkeys reared under 2 additional types of visual deprivation. In 2 monkeys, the aphakic eye was optically corrected to a near point (ANP), while the phakic fellow eye was undercorrected (UC). In the other 2 monkeys, the aphakia was corrected to a far point (AFP), while the phakic fellow eye was corrected to a near point (NP). To label ODCs by their reduced cytochrome oxidase (CytOx) reactivity, one eye was enucleated 2 weeks prior to perfusion of the brain for routine CytOx histochemistry. After ANP combined with UC, ODCs related to the UC eye were wider than those related to the ANP eye. After AFP combined with NP, ODCs related to the NP eye were wider than those related to the AFP eye. Thus, neither type of optical correction gives an aphakic eye an advantage in its competition for cortical space against phakic UC and NP fellow eyes. We will compare these results with those from the previous study. Supported by T32EY-07092, EY-05975, and RR-00165.

737.7

THE STATE OF THE GLYCINE SITE AT THE NMDA RECEPTOR IN THE VISUAL CORTEX OF INTACT CATS

D. Czepita, S. Reid and N.W. Daw*. Ophthalmology Department, Yale University Medical School, New Haven, CT 06510.

Between 3 and 6 weeks of age, the number of NMDA receptors in the cat's visual cortex increases, while their contribution to the visual response decreases. We decided to test whether this is due to a change in the state of activation of the NMDA receptor by glycine. As a preliminary test we have observed the level of saturation of the glycine in older animals. We recorded single units using carbon fiber microelectrodes surrounded by two barrels containing 7-chlorokynurenic acid and D-serine. Cells were characterised for the best length, width, orientation, velocity and direction of movement of the stimulus. We set up a stimulus moving with the preferred parameters, and observed the effect of 7-chlorokynurenic acid and D-serine on the response. 7-chlorokynurenic acid reduced the response and spontaneous activity by a variable amount. D-serine, however, rarely increased the visual response by more than 40%. The effect on spontaneous activity was sometimes much larger, but usually only when the control level was quite small. Application of D-serine in the presence of 7-chlorokynurenic acid was used to show that the D-serine was active. We conclude that the glycine site at the NMDA receptor is usually saturated by endogenous glycine. However, we have not yet recorded enough cells to say whether this is true of all cells in all layers at all ages.

737.8

VISUAL DEPRIVATION ALTERS GABA-A BUT NOT NMDA RECEPTOR DISTRIBUTION IN MACAQUE VISUAL CORTEX.

D. March*, H. Goodwin, C.A. Shaw, and A. Hendrickson. Depts. of Ophthalmology and Physiology, University of British Columbia, Vancouver, Canada & Dept. of Biological Structure, University of Washington, Seattle.

Receptor immunostaining and radioligand binding in macaque monkey visual cortex provide evidence that inhibitory GABA-A receptor distributions are sensitive to visual deprivation at particular stages in development. GABA-A R density decreased in layer 4C bands innervated by the deprived eye, suggesting a correlation between GABA-mediated intracortical inhibition and visual cortex plasticity (Hendry et al., *J. Neurosci.*10:2438 - 2450,1990; Hendrickson et al., unpublished). Since the excitatory NMDA receptors are co-localized to the same laminae in macaque visual cortex (March et al., *Soc. Neurosci. Abstr.* 18: 299, 1992), we have examined the distributions of NMDAR in adult normal (n=3) vs animals monocularly eye-lid sutured (n=7) or enucleated (n=3) at various ages. [3H]-MK801, a NMDA channel antagonist, was used to label NMDAR. In all cases, the distribution of NMDAR in deprived animals matched that of controls, with the highest receptor densities located in layer 4C and the supragranular laminae. Overall no differences in receptor distribution or number were seen in any lamina; layer 4C was homogeneous with no hint of any banding pattern. These results show that NMDAR are unaffected by the same sensory stimuli which severely alter GABA-AR, suggesting that inhibitory, rather than excitatory mechanisms, are key features in the cortical modifications which follow sensory deprivation.

737.9

SPATIAL FREQUENCY TUNING OF CELLS IN AREA 17 OF CHIASMATOMIZED AND/OR CALLOSOTOMIZED UNILATERAL ESOTROPIC CATS.

S. Quessy, F. Lepore, M. Ptito*, J.-P.Guillemot. Dép. de Psychologie and Dép. de Kinanthropologie Université de Montréal et Université du Québec, Montréal, Québec, H3C 3P8

Unilateral esotropia induced early in life results in amblyopia and changes in the spatial frequency tuning of cells in the visual cortex of cats. These functional changes are attributed to competitive interactions between the eyes. In order to assess the effects of a modification of these interactions, we measured the spatial frequency sensitivity of cells in area 17 of 4 groups of cats: 1-Induced unilateral esotropia (Eso), 2-Eso+early chiasmatomy (EsoXy), 3-EsoXy+early callosotomy (EsoXyCC), 4-Eso+adult chiasmatomy (EsoXa). The manipulations added to esotropia reduce the possibility of binocular competition. Recordings in the visual cortex were carried out when the animals were at least 8 months of age. Preparatory surgery for recording was carried out using Halothane-N_2O anesthesia and single cell activity was measured under paralysis, low level anesthesia and N_2O. Visual stimuli consisted of sinusoidal gratings of various spatial frequencies, swept in the optimal direction. Compared to normal cats, neurons of Eso cats showed an important loss in their spatial resolution. However, after the reduction of the possibilities of developmental binocular competition (EsoXy, EsoXyCC) neurons showed a less severe loss. EsoXa cells had the most important reduction in their visual acuity and sensitivity to gratings stimulation. These results will be compared with behavioral studies.

737.10

COMPARISON OF RESIDUAL VISUAL FUNCTION AFTER DAMAGE TO STRIATE CORTEX IN INFANCY AND ADULTHOOD.

T. Moore*, H.R. Rodman, A.B. Repp, C.G.Gross. Dept. of Psychology, Princeton University, Princeton, N.J. 08544.

Greater functional sparing after early as compared to late damage has been found for primate somatosensory and motor cortices, but is less clear for visual cortex. We have tested the ability of macaque monkeys to detect and localize visual targets with saccadic eye movements 1.5 to 5 years after large unilateral subtotal lesions of striate cortex made either in infancy or adulthood. Monkeys were trained to fixate and make visually guided saccades to a target (0.5 degree diameter, 3 log. contrast) which appeared at an unpredictable time and location within the central 30°. The monkey was rewarded for all saccades ending in an error window around the target. Within several weeks of the first testing session, the animal with the infant lesion could detect and make accurate saccades to virtually all target positions in the central 24°. No detection errors were present at the innermost points (6°) even on the first session. By contrast, the monkey with the adult lesion could not detect stimuli (i.e., did not initiate saccades) at the vast majority of tested contralateral points until the perimetry paradigm was altered to cue the animal when to respond. The preliminary results suggest that early damage to monkey striate cortex results in relatively greater sparing of function.

Supported by NSF BNS-9109743, an NSF pre-doctoral fellowship and the NERPRC .

737.11

REORGANIZATIONAL PLASTICITY IN THE PRIMARY VISUAL CORTEX (V1) OF ADULT CATS OCCURS FOLLOWING MONOCULAR RETINAL LESIONS.

L. M. Schmid, M. G. P. Rosa, and M. B. Calford*. Vision, Touch and Hearing Research Centre, Depart. Physiol. and Pharm., The University of Queensland, Queensland, Australia 4072.

Discrete lesions of the retina (5°-20° in size; 10°-30° above the optic disc) created using an argon laser were placed in one eye of adult cats, 2 weeks to 3 months prior to electrophysiological recording. Retinal histology revealed that the lesions obliterated the photoreceptor layer but left the ganglion cell layer largely undamaged. This produced a region in visual cortex (2-4 mm in diameter) that was deafferented for the lesioned eye in the affected part of the visual field but that received a normal input from the other eye. We found that the affected region of visual cortex responded to the lesioned eye with receptive fields being displaced onto regions of normal retina around the edge of the lesion. In some cases receptive fields were split into two or even three distinct parts. The affected region of cortex was unresponsive at some recording sites, but these were not restricted to the centre of the deafferented region. Instead, the unresponsive sites (10-25%) seemed to be scattered through the whole extent of the affected region. A shift in ocular dominance towards the normal eye in the affected cortex occurred. Receptive fields for the intact eye corresponded to the normal topographic representation. In some cases, on the same day as the initial laser lesioning, the other eye was totally deafferented. No cortical responses were elicited from stimulation of this eye. The reorganization which occurred in these cases was similar to that reported by others using binocular lesions and to our monocularly lesioned cases. Our findings show that the representation of the two eyes in visual cortex, even in binocular neurons, are capable of independent reorganization of the normal topographic representation of the visual field.

737.12

DEAFFERENTED CELLS IN V1 FOVEAL PROJECTION AREA SHOW MODERATE RECOVERED ORIENTATION SPECIFICITY IN MONKEY WITH LONG-TERM CENTRAL VISION LOSS.

C.M. Acocella*, A.A. Witkofsky and A.A. Skavenski. Northeastern University, Boston, MA 02115.

Recent studies have shown that V1 cells which are unresponsive following removal of their normal retinal input acquire new receptive fields on intact retina (Heinen and Skavenski, ARVO, 1988). The present study examined the extent to which "recovered" V1 foveal cells were orientation specific in an animal with long-term central vision loss. A macaque monkey with bilateral foveal lesions had a stainless-steel chamber surgically mounted over V1 cortex corresponding to the foveal projection area, which allowed single cell recording in an awake, behaving animal over long periods of time. Three years after foveal lesions, receptive fields were mapped using retinally stabilized small spots or bars of light (0.1 X 0.1 to 2.0 X 0.5 deg arc). Orientation specificity was tested using bars (2.0 X 0.5 and 8.0 X 0.5 deg arc) presented at different angles. Unlike normal V1 cells, most recovered cells did not require visual stimuli of specific orientation to elicit responses. We found that less than half of recovered cells showed orientation specificity even after prolonged recovery. Gilbert and Wiesel (ARVO, 1991) stated that there was recovery of orientation specificity after parafoveal retinal lesions were made. This raises the possibility that different mechanisms may mediate recovery in foveal and peripheral V1.

737.13

EXAMINATION OF RECOVERY OF FOVEAL V1 NEURONS AFTER COMPLETE DEAFFERENTATION.

A.A. Witkofsky*, C.M. Acocella and A.A. Skavenski. Northeastern University, Boston, MA 02115

Deafferented foveal V1 neurons have been shown to recover response to visual stimulation on intact eccentric retina 75 days after laser lesion of the fovea (Hienen and Skavenski,Exp Brain Res,1988). Recovered neurons and receptive fields differed from normal V1 units in that reported latency to peak response (mean=285ms) was longer than normal cells. Receptive fields were oddly shaped, and large, as long as five deg arc. The prior study was designed to establish that recovery occurs at all and used crude methods. We recorded from over 100 cells in the foveal representation of V1 in a macaque monkey and mapped receptive fields, using fine stimuli with good time resolution. Mean response latency to first activity was 110ms for recovered cells, compared to the mean of 92ms for normal cells, not a statistically significant difference. Fifty three percent of normal cells and 45% of recovered cells had latencies under 75ms from stimulus onset. In addition, receptive fields were in general smaller than those previously reported. We found no recovered receptive fields longer than four deg arc, and 50% of the receptive fields were smaller than 2.5 deg arc. Twenty percent were one deg arc or less. These data show characteristics of the recovered neurons are similar to those of normal V1 neurons which receive normal input from intact retina.

738.1

CONTRAST MATCHING IN THE RED-GREEN CHANNEL: FLATTENING EFFECT AND COLOR-CONTRAST-CONSTANCY

R.L.P. Vimal* and R. Pandey The New England College of Optometry, Boston, MA 02115

Achromatic contrast matching functions [CMF: reciprocal of contrast needed to match the standard vs spatial frequency (SF)] have been shown to be much flatter at higher contrasts than the achromatic bandpass contrast sensitivity function (CSF) [Georgeson and Sullivan (1975), J. Physiol. 252, 627]. Our interest was to investigate the behavior of the CMFs of the Red-Green Channel that had lowpass CSF. CMFs were measured by a randomized double-staircase procedure and a 2-interval forced choice technique on 2 normal observers. The Red-Green Channel was isolated by the minimum flicker (red: 11.7 cd/m^2) and hue cancellation techniques. We presented spatially localized vertical color patterns (SFs: 0.063 to 8 cpd in 1 octave steps; contrast: 3% - 80%) under sustained (Gaussian) conditions on an ATVista System with a color monitor. We found that CMFs showed lowpass behavior at lower contrasts, but were flatter than CSF, showed a slight bandpass at intermediate contrasts, and were flatter at higher contrasts. We conclude that CMFs exhibit a flattening effect as contrast increases finally leading to partial SF-color-contrast-constancy (CMF independent of SF) at high contrast.

738.2

ORIENTATION CONTRAST SENSITIVITY IN THE RED-GREEN CHANNEL: ATTENUATION OF THRESHOLD-OBLIQUE-EFFECT AT SUPRATHRESHOLD COLOR CONTRASTS

R. Pandey* and R.L.P. Vimal The New England College of Optometry, Boston, MA 02115

The oblique effect [lower contrast sensitivity (CS) to oblique gratings than to vertical and horizontal gratings] is well documented in the achromatic channel [Campbell et al (1966), J. Physiol. 187, 427-436]. Our interest was to find if it occurred in the Red-Green Channel at threshold and suprathreshold contrasts. CS was measured as a function of orientation by the method of constant stimuli and a 2-interval forced choice (2IFC) technique on 2 normal observers. The suprathreshold oblique effect was investigated by color contrast matching experiments using a randomized double-staircase procedure with 2IFC. The Red-Green Channel was isolated by the hue cancellation and the minimum flicker (red: 11.7 cd/m^2) techniques. We presented spatially localized color patterns [spatial frequencies (SFs): 0.063, 0.125, 0.5, 2, 4, 8 cpd; orientations: 0^0 - 90^0 in 15^0 steps; contrasts: 12% - 80%] under sustained (Gaussian) conditions on an ATVista system with a color monitor. We found that for all SFs: (1) CSs to oblique patterns were usually lower than that to vertical and/or horizontal patterns, (2) at suprathreshold color contrasts, orientation contrast matching functions [CMF: reciprocal of contrast needed to match the standard vertical pattern vs orientation] were flatter than orientation CS functions. We conclude that the oblique effect in the Red-Green channel that occurs at threshold level is reduced at suprathreshold color contrasts, leading to partial orientation-color-contrast-constancy (CMF independent of orientation) at high contrast.

738.3

COLOR FILLING IN FOVEAL VISION. M. Fujita* Communications Research Laboratory, Koganei-shi, Tokyo 184, Japan.

Perceptual filling-in of artificially induced scotomas during steady eccentric fixation is well-known. We found that humans also perceive color filling-in of foveated figures during fixation.

Subjects were asked to fixate the central mark of a circle of five degree radius on a display. When the color of the circle was equiluminant with the background color, subjects perceived filling-in. The central circle color and the background color merged across their border, decreasing in saturation. The whole image became homogeneous in color within several seconds, if the two colors had exactly the same luminance. As the eye position was set closer to the display, the color of the central figure became dominant in the merged homogeneous color. As the display was set further from a subject, the filling-in process became unstable. When the central circle was viewed as less than two degrees in radius, filling-in was hardly observed. Adding a smaller circle of three degree radius of an equiluminant third hue, superimposed centrally, the subjects perceived filling-in and the three colors merged into a homogeneous color.

We examined a stereoscopic view of two above-mentioned images in which the central figures had disparity. As the filling-in progressed, the stereoscopic view disappeared. We investigated not only the case of equiluminant color combination but also the case of textured patterns and motion patterns under equiluminant conditions. The filling-in was not as complete as in the color filling-in.

Our model of color filling-in has two edge detectors, one for color and another for brightness. When the color edge detector signals no sign, having been not activated by the brightness edge detector for several seconds, then color information is transmitted across the boarder from each side.

738.4

ELECTROPHYSIOLOGICAL RESPONSES SUGGEST SEPARATION OF COLOR AND MOTION PROCESSING IN HUMANS. L. Anllo-Vento*, S. J. Luck, T. C. Rubin and S. A. Hillyard. Department of Neurosciences, 0608, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093.

In order to characterize and localize color and motion processing subsystems in humans, we recorded multichannel event-related brain potentials during an adaptation paradigm in which the stimuli were designed to activate selectively either the parvocellular or the magnocellular processing stream. The stimuli consisted of isoluminant, colored, high spatial frequency checkerboards in one experiment, and of gray, low spatial frequency, low contrast moving stimuli in another. In both experiments, a 1000-ms adapting stimulus was followed by a 100-ms test stimulus of either the same color or direction of motion or a different color or direction of motion.

Color stimuli evoked a prominent negativity peaking at 90 ms, which was sensitive to stimulus wavelength and visual field location and exhibited wavelength-specific adaptation; topographic maps of current source density for this component were consistent with an origin in striate cortex. A subsequent positivity (P1 at 100-130 ms) included subcomponents that differed in scalp distribution, sensitivity to wavelength, and effects of adaptation; its surface topography was consistent with sources in extrastriate cortex. In contrast, moving stimuli did not evoke N90 or P1 responses like those obtained for colored stimuli, but instead produced a waveform dominated by later negative (170 ms) and positive (250 ms) components that did not vary as a function of motion direction but exhibited clear direction-specific adaptation effects. These results suggest that there are functionally segregated visual areas in humans akin to the parvocellular and magnocellular streams that have been previously described in non-human primates.

738.5

FEEDBACK AND REWARD EFFECTS ON THE TILT AFTEREFFECT (TAE)

R. S. Pauly, M. A. Berkley,* & R. Vogels.[1] Program in Neuroscience, Florida State University, Tallahassee, FL; [1]Katholieke Universiteit, Leuven, Belgium

Investigations of the TAE in awake behaving monkeys yield much smaller magnitude TAEs than comparable human psychophysical data. Four explanations are possible: 1) erratic sequences of trials reduced levels of adaptation; 2) feedback (FB) from the delivery of rewards influenced judgments; 3) rewards motivated the monkeys to misreport perceptions or 4) monkeys experience a smaller TAE. To study the effects produced by FB and reward on the TAE, 3 naive human subjects made judgments of the verticality of a test grating after adapting to blank, 0° or 15° tilted gratings under different instructions, levels of FB and reward. Each test trial consisted of a 6 s adaptation period, a 300 ms blank period, a 250 ms test stimulus, and a 1 s intertrial interval. The FB conditions were: 1) no FB; 2) FB on every trial; and 3) FB on a random 50% of all trials. The instructions were: 1) Base response only on the appearance of the test stimulus; 2) Maximize correct judgments using FB signal; and 3) Maximize correct judgments for a cash prize. All subjects showed large TAEs (3-4°) after adaptation to 15° gratings relative to their control performance in all the FB-without-cash conditions. However, the size of the TAE was diminished by 50-100% under the FB-on-every-trial-cash-reward condition and by roughly 25-50% under the FB-on-half-the-trials-cash-reward condition. The results demonstrate that motivational variables have a significant effect on the TAE, but FB per se has little influence. The findings also account for the modest (1-2°) TAE observed in previously reported monkey studies. These results suggest that direct comparisons between monkey and human psychophysical experiments must consider the influence of the rewards used to maintain behavior in animal studies.

Supported by NATO Grant CRG920511 and NIH Grant EY00953

738.6

MULTISENSORY INTEGRATION INFLUENCES PERCEPTION OF VISUAL INTENSITY.

L.K. Wilkinson*[1], D.D. Price[2], N. London[3], and B.E. Stein[3] Departments of Psychology[1], Anesthesiology[2], and Physiology[3], Medical College of Virginia/Virginia Commonwealth University, Richmond, VA, 23298

Visual neurons in the central nervous system are of two varieties: unimodal (unaffected by nonvisual stimuli) and multisensory. Perception of visual intensity is, in part, dependent on the firing frequency of visual neurons. However, the responses of multisensory neurons, unlike those of their unimodal counterparts, are affected by nonvisual cues in highly predictable ways. If multisensory neurons play a role in the perception of visual intensity, this perception should also be altered in the same ways by the presence of a nonvisual stimulus. Five subjects were tested in an apparatus consisting of pairs of LEDs and speakers. With the subject fixating directly ahead, a faint visual stimulus was presented either alone (at 0°, 30° right, or 30° left) or paired with a brief low-intensity sound. The sound was either spatially coincident with, or disparate (by 45°) to, the visual stimulus. During testing, the subject rated visual intensity on a visual analogue scale. A significant enhancement of perceived visual intensity was evident when an auditory stimulus was spatially coincident or lateral to the visual stimulus. However, a medially disparate auditory stimulus resulted in little change of perceived visual intensity. These data are consistent with multisensory ERP responses in humans, and with single neuron data from various CNS structures in animals. The results suggest that multisensory neurons do indeed play a role in judgements of visual intensity, and that these judgements are governed by a common set of rules that also apply to very different multisensory functions involving many structures at different levels of the neuraxis. Supported by a grant from the McDonnell-Pew Program.

738.7

SENSORIMOTOR ADAPTATION TO MUSCLE VIBRATION-INDUCED ILLUSIONS. W.T. Clower*, D.M. Clower, G.E. Alexander. Neurology Dept., Emory University, Atlanta, GA 30322.

Vibration applied to the cervical musculature results in the apparent displacement of a fixated point of light in an otherwise dark room (Biguer et.al. 1988). We have found that by simply observing apparent target displacement caused by cervical vibration, normal subjects developed shifts in perceived visual, proprioceptive, ocular, and auditory midlines similar to the effects observed in prism adaptation. Further, if permitted to reach to the illusory target location and to perceive their pointing errors, subjects were able to adapt to the perceptual distortion and eventually could reach accurately to the actual target. Following adaptive exposure, subjects showed pointing errors in the direction opposite to the illusory target displacement. Although measures of midline shifts and pointing errors varied widely across subjects, when effects caused solely by observing target displacement (vibration without reaching) were subtracted from the effects of adapting to the displaced target (vibration with reaching), we found consistent shifts in perceived proprioceptive, ocular, visual, and auditory midlines. This indicates that the adaptation to muscle vibration-induced visual illusions may be analogous to the type of visuomotor adaptation that occurs with exposure to laterally displacing prisms. This in turn suggests that both forms of sensorimotor adaptation may share some of the same neural substrates.

738.8

ALTERATIONS IN SPATIAL REPRESENTATION RESULTING FROM PRISM ADAPTATION. D.M. Clower*, W.T. Clower, G.E. Alexander. Neurology Dept., Emory University, Atlanta, GA 30322

Adaptation to laterally displacing prisms has been shown to result from a combination of alterations in a subject's perceived proprioceptive and visual midlines. We examined visual, proprioceptive, ocular, and auditory components of prism adaptation in normal volunteers. Three exposure conditions were tested in which each subject was provided with variable visual feedback while reaching to small targets located on a vertical display. The conditions involved a) vision of both the target and the limb, b) vision of the target but not the limb, and c) vision of neither the target nor the limb. In the final two conditions, error feedback of the limb position relative to the target was provided after each reach was completed. It was determined that the visual component of prism adaptation could be attributed almost completely to an alteration in the perceived position of the eyes in the orbit. In addition, we found that adaptation to prisms induced consistent shifts in each subject's perceived auditory center, even though care was taken to ensure that auditory processes played no direct role in the sensorimotor adaptation observed in this study. These results suggest that there may be adaptive and interactive linkages between the neural representations of visual, proprioceptive and auditory space.

738.9

IMPAIRED PERCEPTION OF SUBJECTIVE CONTOURS.
Russell Mast, Robert Fox, & Stephen Orosz III*. Department of Psychology, Vanderbilt University, Nashville, TN 37240.

Interpolative processes compensate for missing information across a variety of stimulus conditions. Examples include perceiving partly occluded real objects, subjective contours, surfaces specified by stereograms or kinematograms of low element density, and completion across the blind-spot or scotomas. A number of theories have been proposed that attempt to describe the underlying neural mechanisms that drive interpolation. Previously, we have found that mildly mentally retarded adults (MR) are impaired at perceiving low density stereograms and kinematograms. In this study we compare the ability of MR and nonretarded adults to perceive subjective contours. To objectively assess subjective contour perception, induction of a visual illusion (Poggendorf) was measured for three conditions: luminance-defined contours, subjective contours, and a non-contour control condition. Transveral angle (30, 45, and 60 deg) and distance between parallel lines (4 and 6 cm) were varied factorially. Luminance-defined contours induced the illusion for both groups similarly across all levels of angle and distance. In contrast, the subjective contours induced the illusion for the nonretarded group but not the MR group. However, an inspection of individual data suggests that a minority of the MR do perceive subjective contours. These results, and those from studies currently in progress, will be discussed with respect to various theories of interpolation and the existence of subgroups within the MR group.

Supported by HD15051, HD27706, HD29556

738.10

3-D PERCEPTION AND SEARCH OF BOUNDARIES AND SURFACES IN VISUAL CORTEX. S. Grossberg*. Center for Adaptive Systems and Department of Cognitive and Neural Systems, Boston University, Boston, MA 02215.

A neural model of 3-D vision by the parvocellular cortical streams of visual cortex is developed. The model's stereopsis mechanisms predict how cells sensitive to multiple spatial frequencies, disparities, and orientations are combined by filtering, competition, and cooperation to form coherent 3-D boundary segmentations within the Interblob-V4 stream. Model properties clarify why small disparities are not selectively coded by high spatial frequencies and few discrete spatial frequency tuned mechanisms exist, yet a size-disparity correlation can occur. Boundary segmentations interact at several processing stages with luminance and color signals to fill-in visible surface representations within the model Blob-V4 stream. Boundary-surface interactions are used to analyze such data as 3-D neon color spreading, closer and brighter appearance of Kanizsa squares, and spatial frequency dependent figure-ground reversals. Area V4 is predicted to support figure-ground separation and to play a key role in visual search. Adaptive Resonance Theory (ART) mechanisms model how prestriate cortical areas interact reciprocally with a visual object recognition system in inferotemporal cortex (IT) to carry out attentive object binding and categorization. Object attention mechanisms of this What cortical processing stream are distinguished from spatial attention mechanisms of the parietal Where cortical processing stream. Model parvocellular boundary and surface signals interact with the model What stream. Model parvocellular and magnocellular motion signals interact with the model Where stream. Reciprocal interactions between these systems are used to analyze data about visual search and saccadic eye movements, including fast search of conjunctive targets, search of 3-D surfaces, selective search of like-colored targets, attentive tracking of multi-element groupings, and recursive search of simultaneously presented targets.

Supported in part by AFOSR F49620-92-J-0499, ARPA ONR N00014-92-J-4015, and ONR N00014-91-J-4100.

738.11

A SCHEMATIC REPRESENTATION OF THE SENSORY INTEGRATION PROCESS. Kenichiro Mogi* Laboratory for Neural Networks, RIKEN, Hirosawa 2-1, Wako-shi, Saitama, 351-01 Japan

The problem of sensory integration in the brain (the 'binding' problem) is one of the most important problems in cognitive neuroscience still unresolved today. We formulate a schematic representation of the integration of sensory perception. We argue that it is advantageous to divide the sensory integration process into two different modes, namely the 'basic' binding process and the 'higher' (functional) binding process. Our assumptions are based on the experimental evidence in human psychophysics that there are two distinct modes of texture discrimination (Julesz 1981). In particular, it has been shown that there is a pre-attentive texture discrimination process that functions in a short time (<160 ms). The 'basic' binding process is assumed to be independent of attention, whereas the 'higher' (functional) binding process is assumed to depend on attention. We argue that the basic binding process works to formulate the 'reference field', against which the higher features of an object are projected through the higher (functional) binding process. We postulate that in the visual perception, the LGN of the thalamus and the primary visual cortex work as the locus of the basic binding process. The sensory integration process is then represented as a graph dynamics, where the vertices represent a neuron, a subpopulation of neurons, or a cortical area representing the various features that are integrated. The edges represent a correlation between the features. The sensory integration process can the be formulated as the dynamics of the connectivity of the vertices representing the integrated features. We argue that the identity of a sensory unit is represented by the connectivity in the basic binding set, which is a subset of the whole sensory area. In our scheme, the thalamus is expected to play a double role. The first role is to provide the reference field, and the second role is to modulate the attention-dependent integration of higher features.

738.12

BINOCULAR RIVALRY MODEL USING MULTIPLE HABITUATING NONLINEAR RECIPROCAL CONNECTIONS.
K. F. Arrington*. Cognitive & Neural Systems, Boston University, Boston, MA, 02215

Binocular rivalry is the alternation of perception that occurs when stimuli to the two eyes are sufficiently different that they cannot be combined into a single visual percept. Binocular rivalry was mathematically modeled using a reciprocal inhibition oscillator network that is based on the gated pacemaker model of Carpenter & Grossberg (1983). The model uses multiple gating of recurrent signals by slowly habituating chemical transmitters at nonlinear interneurons. These slowly habituating gates drive switches between competing populations. The model was evaluated by computer simulation. The results show that the model performs well with respect to psychophysical data including all of Levelt's (1965) propositions, the constant depth-of-suppression criteria of Fox & Check (1972), and under the binocular rivalry stimulus paradigm employed by Mueller & Blake (1989). It is concluded that this biologically plausible neural network can accurately predict the temporal dynamics of binocular rivalry.

Carpenter, G. & Grossberg S., (1983). *Biol. Cybernetics*, **48**, 35-59.
Fox, R. & Check, R. (1972). *Journal of Exper. Psychology*, **93**, 283-289.
Levelt, W. J. M. (1965). *On binocular rivalry*. Ph.D. thesis, Netherlands.
Mueller, T. J. & Blake, R. (1989). *Biol. Cybernetics*, **61**, 223-232.

738.13

PLASTICITY OF EGOCENTRIC LOCALIZATION, BINOCU LAR CORRESPONDENCE AND STEREOPSIS IN ADULT HUMANS. S. Cobb and V. S. Ramachandran*, UCSD, La Jolla, CA 92130.

Binocular fusion and stereopsis are usually thought to arise from confluence of neural signals from the two eyes on to single neurons in area 17. But is this the whole story? To find out we studied two intermittent exotropes that could either fixate binocularly or allow the left eye to deviate outward by 60°. Most patients "suppress" the image in the deviant eye, but we found that our two patients could continuously "remap" binocular correspondence and egocentric localization as the eye deviated -- a syndrome that we have dubbed "dynamic anamolous retinal correspondence." We showed this using three procedures: a) With his left eye shut, the subject fixated the top of a slit mounted on a flash gun to generate a retinal afterimage. He then looked at the bottom of the slit with the left eye to create another afterimage. The two afterimages were perfectly lined up when he looked straight but when the left eye deviated the afterimage in that eye also deviated outward by 40-60°. Hence a continuous remapping of egocentric space occured selectively for the left eye based on reafference signals from the left eye. B) Using a ballistic presented pointing task we found that they could accurately point to briefly presented spots (>150 msec) of light presented to the deviated left eye. C) Surprisingly, stereopsis was present even when the left eye was deviating by 15° (so that the two half images are exciting non-corresponding retinal point separated by 15°) in spite of the fact that the disparity range was only 20 min of arc! We conclude that the "remapping" occurs not only for egocentric localization, but also for binocular correspondence and stereopsis.

738.14

VISUALLY PITCHED LINEAR POINT ARRAYS, CONTINUOUS LINES, AND VISUALLY PERCEIVED EYE LEVEL. Leonard Matin* and Wenxun Li, Dept. Psychol., Columbia Univ., New York, NY 10027

Each of 4 subjects set a 20' circular target to appear at eye level (VPEL) while viewing two 64°-long parallel linear arrays of equally-spaced 18' points in darkness. The arrays were symmetrically-placed relative to the median plane (25° horizontal eccentricity) and vertical when erect. The arrays were viewed at each of seven pitch angles (-30° to +30° in 10° steps). At each pitch the number of points in each array (NOP) was systematically varied from 1 to 25 in 9 steps. The slope of the VPEL-vs-Pitch function was linear at each NOP and increased with NOP along a negatively accelerated exponential that asymptotes at the value measured for two continuous, 64°-long, pitched-from-vertical lines. The space constant derived from the slope-vs-separation function (12.7°) was similar to that for the slope-vs-line-length function with the continuous lines (15.1°) (Matin & Li, JEPHPP, 18:257, 1992; Vis. Res., in press). These results imply summation far beyond the receptive fields of individual orientationally-selective neural units in V1; they are closely comparable to what would be expected from the extent of excitatory interaction from the long horizontal connections in layer 6 of V1 (Gilbert & Wiesel, J. Neurosci, 3:1116, 1983) or from space constants measured in V7a of posterior parietal cortex (Zipser & Andersen, Nature, 331:679, 1988).

(Supported by AFOSR 91-0146).

738.15

RECOGNITION POTENTIAL LATENCY AND RT FOR CLEAR AND DEGRADED IMAGES. A.P. Rudell* and J. Hua. Dept. of Physiology, SUNY-Hlth. Sci. Ctr., Brooklyn, NY 11203.

The recognition potential (RP) is an electrical response of the brain that occurs when a subject views a recognizable image. Compared to event-related potentials (ERP's) like N2 and P3, it has shorter latency, different scalp distribution, less sensitivity to probability of occurrence, and greater sensitivity to the region of the visual field in which an image appears. The RP was thought to occur only when a subject viewed a recognizable image. If so, factors that delayed image recognition should produce a corresponding increase in the latency of the RP. We used the rapid stream stimulation technique[1] and measured reaction time (RT) for recognition of clear and degraded word images. RT and RP latency were both about 40 ms longer for degraded than for clear word images. Peak RP latency was about 150-200 ms less than RT. It was also substantially less than for N2 and P3. Thus a brain response reflecting the recognition process occurred well before the customary ERP's used to index mental chronometry. The shorter latency provided some advantages for psychophysical studies, especially greater freedom from interference by eye artifacts and problems with overlap of ERP components like N2 and P3. (Supported by NIH Grant 412-9375 B.)

[1]Rudell, A.P. Electroenceph. clin. Neurophysiol, 83: 77-82, 1992.

738.16

SPATIAL DEFICITS IN DEAF BRAIN DAMAGED SIGNERS. Rita Venturini, Ursula Bellugi* and Mark Kritchevsky** Salk Institute, La Jolla, CA 92138-9216 , ** VA medical Center, UCSD, La Jolla, CA,USA.

Spatial relations and linguistic relations are intimately intertwined in American Sign Language. Deaf Signers represent a valuable opportunity to explore the effect of an highly visual language experience on visual spatial cognition and its impairments following focal brain lesions. We documented visual spatial abilities in 10 left (LHD) and 9 right (RHD) hemisphere damaged signers, using a test battery composed of both visual perceptive and visual constructive tasks. Hearing subjects present deficit in integrating parts in a coherent whole after right hemisphere lesions, while following left lesions they show deficit in analytic perception and reproduction. Similarly, RHD signers were impaired in processing and reproducing global configural elements of drawings and visual constructs, while LHD signers showed a stronger impairment in dealing with featural elements of drawings and constructs. Copies of the Rey-Osterreith complex figure made by RHD patients showed a significant loss of configural elements ($p < 0.05$) compared to the one from the LHD group, and a significant impairment in placing of Cluster elements ($p< 0.05$). Copies of hierarchical forms present a double dissociation between global/local accuracy in RHD vs LHD ($p < 0.005$). WAIS-R blocks design presented a dissociated set of errors between the two groups. Error analysis was also able to separate the performance of LHD and RHD signers in the Benton lines orientation judgment test, revealing very different approaches to the task between the two groups. Our data suggest that the brain structures underlying spatial cognition in deaf signers are organized similarly to hearing subjects, and that they maintain strong hemispheric specialization.

AUDITORY BEHAVIOR

739.1

INTERICTAL CHANGES IN CENTRAL AUDITORY PROCESSING. D. M. Daly*. Box 210855, Dallas, TX 75211.

Disordered functioning manifest in seizures can also give rise to subtle, pervasive interictal changes. We have used sets of synthesized acoustic stimuli to evaluate changes in auditory perception[1]; we report aspects of two cases.

Case 1, a 10 yr. girl who had undergone right hemispherectomy, developed seizures which involved frontotemporal structures with spread to auditory areas. On inter-ictal auditory testing she could perform consistently with right ear (AD), she remained at chance levels with left ear (AS). During and immediately following two spontaneous seizures she performed at chance with AD; she described the sounds as 'buzzes'. Within 8 min. performance resolved toward normal ($p<0.001$, $p < 0.01$, re 16 a/s matched seizure-free controls). Throughout, AS continued at chance. Over a 20 min. interval she reported and later recalled brief (20-50 sec) episodes when sounds to AD were clearly the same stop (***b*** or ***g***); she denied comparable episodes with AS.

Case 2, a 14 yr. boy with a left hemiatrophy and refractory seizures, underwent excision of right temporal and inferior Rolandic and parietal structures, sparing most primary auditory cortex. In pre-op tests (lasting >2 hr.) he had reported sounds in each set as identical, save briefly following 'spells'. Post-op AD performance improved ($p<0.001$) more than AS ($p<0.015$). He now reported episodes (<6 min.) when stimuli to AS sounded identically; he was unaware when AD ***ge-ye*** or ***be-we*** boundary increased 20-40 msec.

Given the anatomic residuals in each case, the lateralized improvement in Case 2 must involve callosal-accessible cortical structures. If 'buzzes' reflect disinhibition, prolonged and 'clear and identical' episodes must reflect enhanced GABA-ergic inhibition. These changes, as well as more obvious ictal events, must be controlled to restore auditory processing and comprehension.

[1]J Neurophysiol (44:1, 200, 1980); *Kindling II* (219, 1981) Testing contributed by inventor who retains all proprietary rights and interests.

739.2

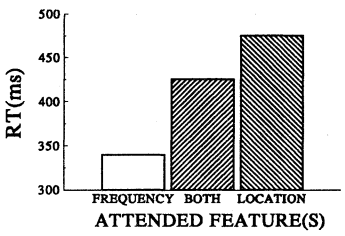
ABNORMAL MISMATCH NEGATIVITY IN CHILDREN WITH SPECIFIC LANGUAGE IMPAIRMENT. I.Holopainen*, P.Korpilahti, H.Lang and M.Sillanpää. Dep. of Pediatric Neurology and Clinical Neurophysiology, Univ.Hospital of Turku, and Centre for Hearing,Cognition and Communication, Univ. of Turku, Finland.

The basic neural mechanism of language development and the factors leading to impairment of normal language learning are still unknown. We have studied an attention-independent negative component termed 'mismatch negativity' (MMN) of the auditory event-related potentials (ERP) in children with specific language impairment (SLI, 3-13 years) and compared the responses with those obtained from control children (3-13 years) with normal speech and language development. The grand average of peak amplitude of the MMN to pitch differences (500/553 Hz) was significantly decreased in the SLI group as compared with the control group. The latency of pitch peak MMN decreased with age in the control group, but not in the SLI children. The results suggest that SLI children have a defect in the automatic central auditory processing of at least pitch differences. Supported by Arvo and Lea Ylppö Foundation.

739.3

AUDITORY FEATURE CONJUNCTION: PRIMACY OF FREQUENCY OVER LATERALIZATION CUES. David L. Woods*, Claude Alain, Keith H. Ogawa, and Diego Covarrubias, Dept. of Neurology and Neurosciences Center, UC Davis, Northern California System of Clinics, Martinez, CA 94553.

The processing of tone frequency and location was examined in an auditory feature conjunction task in which subjects attended to randomized sequences of 60 ms tone bursts presented at high rate (150-450 ms stimulus onset asynchronies). In different conditions they responded to tones of a designated frequency (250, 612 or 1500 Hz), a designated location (left, binaural or right), or a designated conjunction of frequency and location (e.g., left 250). Subjects were 85 ms *faster* in responding to frequency than to frequency+location. In contrast, they were 50 ms *slower* in responding to location than frequency+location. The results suggest that in environments with multiple sound sources, subjects must analyze sound frequency before processing sound location. Supported by the NIDCD, VA Research Service and FCAR.



739.4

MINIMUM AUDIBLE ANGLES IN NORMAL AND MONAURALLY DEAFENED FERRETS. A.J. King, R.L. Martin, Z.D. Jiang and D.R. Moore*. Lab. of Physiology, Parks Road, Oxford OX1 3PT, U.K.

Monaural human subjects can localize broad-band sounds, although less well than if binaural cues are also available. We have compared the auditory spatial acuity of normal ferrets and of animals that had received a unilateral cochlear ablation in infancy or as adults. An associative conditioning method was used to measure minimum audible angles (MAA's) in the horizontal plane around 0°, -45° and +45°. Three durations (500, 100 and 40 ms) of digitally-synthesized broad-band noise were used. The MAA's obtained for the normal ferrets were similar to those reported in previous studies: performance declined slightly with decreasing stimulus duration and the lateral field MAA's were larger than the midline values. In the monaural ferrets a small but consistent increase in the MAA's was observed for 500 ms stimuli at the midline and in the hemifield ipsilateral to the intact ear. Much larger MAA's were obtained with the shorter duration stimuli and performance fell close to that expected by chance at 40 ms. The monaural ferrets also performed at or near chance at all stimulus durations when the speakers were separated by 80° in the contralateral hemifield. These data indicate that auditory localization in ferrets is impaired under monaural hearing conditions, particularly at stimulus durations that are too short for head movements to allow the sound to be sampled multiple times.

739.5

GAP DETECTION FOLLOWING BILATERAL LESIONS OF AUDITORY CORTEX IN THE FERRET. B.J. Rooney*, J.B. Kelly and D.P. Phillips. Laboratory of Sensory Neuroscience and Psychology Departments, Carleton University, Ottawa, Canada K1S 5B6 and Dalhousie University, Halifax, Nova Scotia B3H 4J1.

Several lines of evidence, including clinical reports of patients with temporal lobe damage, suggest that auditory cortex is important for processing temporal features of sounds. Gap detection, the ability to perceive a brief silent interval between two sounds, is a simple test of auditory temporal resolution. Ferrets (Mustela putorius) were trained in a gap detection paradigm to discriminate an interruption in an otherwise continuous noise signal. Band pass noise (8 kHz) was presented from a loudspeaker and the ferrets had to execute an observing response by contacting a water spout located in the center of a two choice apparatus. To receive a water reward, the animals were required to go left if they detected a gap and right if they did not. The size of the gap was then reduced until discrimination was no longer possible. Normal ferrrets were capable of discriminating gaps as small as 4-5 ms, which compares favorably with gap detection thresholds for humans and other mammals under similar conditions. Following bilateral lesions of the middle ectosylvian gyrus, a region that corresponds to the physiologically defined primary auditory cortex in the ferret, the animals had difficulty detecting small silent intervals in continuous noise. Deficits were seen as elevations in threshold for gap detection. The results support the idea that auditory cortex is important for temporal resolution and that cortical damage results in impairments in auditory gap detection.

Research supported by the Ontario Mental Health Foundation.

739.6

SOUND LOCALIZATION IN HEMISPHERECTOMIZED PATIENTS. P. Poirier*, M. Lassonde, A. Schiavetto, S. Caillé, F. Lepore, Groupe de Rech. en Neuropsy. Exp., Univ. de Montréal, Mtl., Qc, Canada, H3C-3J7.

In order to precisely evaluate the consequences of cortical damage on free-field sound localization in humans, the present study examined response accuracy to auditory targets in three hemispherectomized patients and IQ-matched controls. Listeners reported sound location by pointing with their dominant hand to the apparent sound location in an anechoic chamber. Two conditions were tested: (i) localization of a fixed-sound source and (ii) localization of the beginning and the end of a simulated moving stimulus. In both conditions, the responses of the patients were less accurate than those of the controls in the hemifield contralateral to their removed hemisphere. Moreover, the single-case analyses revealed that the performances obtained with fixed sources were generally more precise than those obtained with moving sources. This result is discussed in terms of a differential involvement of cortical and subcortical pathways in the processing of stationary and moving sounds. Finally, the age at surgery and the post-surgical interval were correlated with the magnitude of the deficits, suggesting the possible influences of functional reorganization and cerebral plasticity. (*supported by FCAR and CRSNG*).

739.7

EFFECTS OF UNILATERAL AND BILATERAL DNLL LESIONS ON MIDLINE SOUND LOCALIZATION IN THE ALBINO RAT. J.B. Kelly* and L. Li, Laboratory of Sensory Neuroscience, Psychology Department, Carleton University, Ottawa, Canada K1S 5B6.

Albino rats were tested for their ability to localize sounds in space before and after large lesions of the dorsal nucleus of the lateral lemniscus (DNLL). The animals were trained to approach a sound source in a two choice test apparatus in order to obtain a water reward. Minimum audible angles were determined for midline (left vs. right) sound localization using the method of descending limits to define thresholds for auditory spatial acuity. All critical tests were conducted with a single broad-band noise burst, 45 ms in duration, presented at the beginning of each trial. Lesions were made by local injection of kainic acid (1.2-1.6 µl of 1mg/ml KA in Locke's solution) into DNLL through a glass micropipette inserted into the brain according to stereotaxic coordinates. The micropipette was also used as a recording electrode to monitor physiological responses to sound prior to, during and after injection of kainic acid. Following a postoperative recovery period of at least two weeks the rats were retrained and again tested for sound localization ability. Both unilateral and bilateral DNLL lesions resulted in elevated thresholds for midline localization. Minumum audible angles were increased but the ability to localize brief sounds was not totally abolished by either unilateral or bilateral lesions. The results suggest that the DNLL plays a role in the enhancement of auditory spatial perception.

This research was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada.

739.8

AZIMUTH FUNCTIONS OF INFERIOR COLLICULUS NEURONS OF C57BL/6J MICE WITH AND WITHOUT SENSORINEURAL HEARING LOSS. S.L. McFadden* and J. F. Willott. Northern Illinois University, DeKalb, IL 60115.

In order to begin to examine the effects of sensorineural hearing loss (SNHL) on the neural coding of sound source location, azimuth functions (discharge rates as a function of stimulus azimuth) were obtained from inferior colliculus (IC) neurons of C57BL/6J (C57) mice of three age groups (2, 7, and 12 months). The C57 strain exhibits a progressive loss of high-frequency sensitivity and basal cochlear pathology beginning after 2 months of age; by 7 months of age, substantial SNHL has occurred. Stimuli were characteristic frequency tones of levels up to 80 dB SPL, delivered from seven azimuthal locations in the frontal free-field. Comparisons between age groups revealed a significant age-related increase in the proportion of neurons exhibiting maximal firing in response to tones delivered from azimuths ipsilateral to the IC recording site, suggesting that SNHL can alter the excitatory-inhibitory binaural interactions of IC neurons. Changes in neural binaural processing mechanisms could contribute to the decreased ability of C57 mice with SNHL to perform a sound localization task, as shown by Heffner and Donnal (ARO, 1993). It is possible that similar changes could contribute to the decline in the ability of many humans with presbycusis to localize sounds in space.

739.9

BEHAVIORAL CHANGES PARALLEL PHYSIOLOGICAL PLASTICITY IN THE CENTRAL AUDITORY SYSTEM OF C57BL/6J (C57) MICE WITH HEARING LOSS. J.F. Willott*, S. Carlson, J.T. Jacobson, and L. L. Miller. N. Illinois Univ., DeKalb, IL 60115.

By 6 mos. of age, absolute thresholds of C57 mice become elevated greatly for 24 kHz (and higher) tones, moderately for 16 kHz tones, and minimally for 4-12 kHz tones. Physiological studies have demonstrated plasticity in the inferior colliculus and auditory cortex (AI) of these mice: as high frequency sensitivity is lost, neurons become increasingly responsive to unaffected frequencies (especially 10-13 kHz in AI).

The saliency of tones was assessed in 1-2 and 5-6 mo.-old mice using the startle modification paradigm. Modifer stimuli were tone pips (2 ms rise-fall, 10 ms duration) of 4, 8, 12, 16, or 24 kHz at 50 - 80 dB SPL presented 100 ms before a standard startle-eliciting stimulus (100 dB SPL noise burst). The 24 kHz tones were effective modifiers (they reduced startle amplitude) in young, but not older mice, as expected from threshold elevations. However, the other tones (especially 12 kHz) were significantly more effective in middle-aged mice. This was the case even for modifier intensities of 50-60 dB: SPLs close to absolute thresholds in middle-aged mice. The data suggest that 12kHz and other middle-to-low frequency tones have enhanced behavioral saliency as well as enhanced representation in the central auditory system.

739.10

NEURONS IN THE INFERIOR COLLICULUS AND AUDITORY CORTEX OF THE LITTLE BROWN BAT SELECTIVELY PROCESS AMPLITUDE-MODULATED SIGNALS THAT MIMIC ECHOES FROM FLUTTERING INSECT TARGETS. C.J. Condon*, K.R. White, and A.S. Feng. Neurosci. Prog. & Dept. of Physiol., Univ. of Illinois, Urbana, IL 61801.

Behavioral studies have shown that bats are capable of using echolocative cues to discriminate their fluttering prey. The wingbeat pattern and frequency of an insect are species-specific; they produce echoes that have specific amplitude and frequency modulations which are readily encoded in the brain. While bats that emit long constant-frequency (CF) echolocation pulses are thought to be better-suited for detecting fluttering targets, FM bats that emit brief (<10 ms) frequency-modulated (FM) echolocation pulses are known to have a capacity to discriminate fluttering targets with a resolution approaching that of CF bats. However, the mechanism by which these FM bats detect and discriminate fluttering targets is not fully understood. Single pulses are too short to register the slow wingbeat frequencies of most insects. In order for FM bats to extract wingbeat frequency, they might have to integrate such information *across* several pulse-echo cycles. To determine how well auditory neurons in the FM bat represent amplitude change across echoes, single-unit recordings were made from the inferior colliculus (IC) or auditory cortex (AC) of tranquilized or lightly anesthetized bats (*M. lucifugus*) in response to trains of acoustic signals that simulated "echoes" returning from a fluttering target. The train of echoes were sinusoidally amplitude-modulated (5-110 Hz) across echoes. The trains were repeated at five different base repetition rates (25, 50, 100, 200 & 400 pps) encompassing the range of emission rates for the different stages of target directed flight. We measured both the units' response magnitude and ability to synchronize their firing to the modulation frequency of the stimulus.

The results show that neurons in both the IC and AC can accurately represent complex stimuli that mimic echoes returning from fluttering prey. While neurons in the IC could more faithfully represent the modulation envelope of the signal, neurons in both IC and AC showed response selectivities for specific "wingbeat" frequencies. The repetition rate of the signals influenced the ability of neurons in both structures to extract the "wingbeat" modulation frequency suggesting that the encoding of fluttering targets may be accomplished by the neural integration of echo information from a sequence of echolocation signals.

HUMAN COGNITION: AUDITION AND LANGUAGE II

740.1

A SINGLE CASE STUDY OF A PATIENT WITH A SELECTIVE LEXICAL PROCESSING DEFICIT FOLLOWING A LEFT INFERIOR PREFRONTAL LESION. M. Corbetta*, R.L. Buckner, M.E. Raichle, J. Schatz, and S.E. Petersen. Washington Univ. Sch. of Med., Box 8111, St. Louis, MO 63110.

A 72 y/o man (LF1) had a sudden onset of speech difficulty. MRI revealed a left inferior frontal lesion consistent with ischemic infarction. He scored in the top decile on the WAIS-R (information and block design) and the WMS visual reproduction tasks. He could read words aloud, even at a delay, and scored high on the Boston Diagnostic Aphasia Exam (> 90% except complex ideational material = 85%). He was impaired on some tasks that required speech production (WAIS-R vocabulary, 16%; WMS paragraph recall no delay, 17%; delay, 10%; Thurstone's word fluency, 13 with impaired being <45) and on the Stroop task. He was not impaired on a non-verbal analog to the Thurstone word fluency task. Inspired by PET findings showing involvement of regions in left lateral prefrontal cortex in verb generation (Nature 331:585-589), we tested and found that he was unable to generate verbs to visually-presented nouns, and couldn't generate synonyms, rhymes, or words beginning with the same syllable as another word. He generated words when only presented with word stems (given **STR**___ he could say street), unique individual letters (given **L** he could say lost), or auditorily presented syllables (given **"pur"** he could say purchase). In contrast, he couldn't generate a word that began with the same three letters as a presented word (given **STRAIGHT** he could not say street) or when asked to come up with a **second** response to a word stem (after saying straight to **STR**___, he could not say street). These tests show that LF1 has difficulties with tasks that require him to produce a word that is different from a presented word or a word that has been recently accessed. This suggests a lexical processing deficit beyond simple access, generation, and output of lexical items.

740.2

NEURAL MODULARITY IN LANGUAGE: EVIDENCE FROM ALZHEIMER'S AND PARKINSON'S DISEASES. M. Ullman, S. Corkin*, S. Pinker, M. Coppola, J. Locascio and J.H. Growdon. Dept. of Brain and Cognitive Sciences and the Clinical Research Center, MIT. Cambridge, MA 02139.

What neural systems subserve language computation? One way to address this question is to examine a simple linguistic system whose characteristics show promise of being generalizable to other language systems. Inflectional morphology, the transformation of grammatically related words (*talked-talked*) is ideal in this respect. Its key asset is computational modularity of the sort one finds in other linguistic systems: Regular verbs (*talk-talked*) are generated by the type of productive rule implicated in other grammatical operations; whereas the idiosyncratic irregulars (*sing-sang*) are stored in associative memory together with uninflected words (see Pinker, 1991). To see whether this modularity extends to a double dissociation across neural systems, we administered a past tense generation task ("Every day I *drive* a Ford. Yesterday I _____ a Ford.") to three groups (age and education matched): subjects with Alzheimer's disease (AD) or Parkinson's disease (PD), and normal control subjects (NCS).

AD impairs lexical memory, and should therefore impair irregulars. But AD spares grammar, and so should spare regulars. We found that ADs produced regulars almost perfectly (mean=99.1%), but were impaired in producing irregulars (85%). The lexical nature of irregulars was confirmed by a correlation between deficits in irregular production and an independent object naming task, (r=.85, p=.004); however, this correlation did not hold for regulars.

Evidence exists that PD impairs grammar, and so should impair regulars. We found that PDs were significantly worse than ADs and NCSs in producing regulars, but not irregulars. We also found a correlation between deficits in regular production and an independent motor activity task (r=-.61, p=.037); however, the correlation did not hold for irregulars. This supported our hypothesis that the basal ganglia mediate the processing of regulars, but not irregulars.

740.3

AN EVENT-RELATED BRAIN POTENTIALS STUDY OF CROSS-MODAL SEMANTIC PRIMING USING PICTURES AND WORDS E.M. Kouri*, W.B. McPherson, & P.J.Holcomb. Psychology Department, Tufts University, Medford, MA 02155

Two cross-modal experiments investigated the effects of semantic priming on auditory word and visual image processing. Experiment 1, a lexical decision task with picture primes and auditory word targets, obtained significant differences in the N400 component between words that were semantically related to the priming pictures and those words that had no relationship to the prime. These difference were similar for both 0 and 800 msec target stimulus onset asynchronies (SOAs). Experiment 2, an identification task with auditory word primes and picture targets, also obtained differences in the 800 SOA condition between related and unrelated targets for the N400 component, however, the onset for these differences were much earlier and had a stronger frontal distribution than the word differences of Experiment 1. In Experiment 2 differences in the 0 SOA condition occurred much later and did not reach significance. The results of Experiment 1 are similar to those of previous word-word priming studies and the results of Experiment 2 are similar to those of previous picture-picture priming studies. Thus even though there are differences in picture and word processing as evidenced by the modality specific priming distributions, words and pictures appear to be tapping a common semantic network since the priming effect between modalities is consistent with previous within modality studies.

740.4

EVENT-RELATED POTENTIALS REFLECT REPETITION PRIMING EFFECTS FOR WORDS AND PICTURES. H. T. Morehouse, T. B. O'Rourke, R. A. Chechile and P. J. Holcomb*. Psychology Department, Tufts University, Medford, MA, 02155.

While initial sensory and cognitive processes are generally accepted as being modality specific, there is still some question as to the degree of modality specificity in higher level cognition processing. Several resent studies have examined this issue by comparing and contrasting word and picture processing. Although somewhat controversial, some evidence has been found that words and pictures share a common conceptual system. The current study used event-related potentials (ERPs) to compare repetition priming between pictures and between pictures and words. Memory sets of line drawings were followed by one of two types of probe stimuli, a line drawing or word. Subjects were instructed to indicate whether this probe was or was not part of the memory set. It was predicted that repetition priming effects would be found for both words and pictures. Difference waves between foil and target pictures, and foil and target words revealed that words and pictures produced similar N400-like components. Words and pictures also produced a similar scalp distribution, being somewhat larger over the right hemisphere and at midline sites. The only significant difference for words and pictures was seen in the time course of an N400-like component (onset of 200 ms for pictures and 300 ms for words). The later onset for words is consistent with previous research comparing spoken and written word priming. The similarity of the N400-like component found for both words and pictures would appear to be most consistent with the common conceptual system model.

740.5

EVENT-RELATED POTENTIALS AND THE TIME COURSE OF SPOKEN WORD RECOGNITION. S. A. Kotz*, T. B. O'Rourke and P. J. Holcomb. Psychology Department, Tufts University, Medford, MA, 02155.

The Cohort Model of spoken word recognition (Marslen-Wilson and Welsh, 1978) argues that the temporal nature of spoken language, coupled with the proficiency of listeners, requires that spoken words be recognized at the first point in the acoustic signal where a lexical representation is uniquely specified. An alternative hypothesis is that listeners wait until all available information in the acoustic signal is present to proceed with word recognition. Uniqueness points in words (UPs), where a lexical representation is uniquely specified, and deviation points (DPs) in pronounceable nonwords, where a stimulus can be rejected as a word, have been manipulated in behavioral studies designed to test the Cohort Model. The results have been mixed. This study used event-related potentials (ERP) to investigate this issue. UPs and DPs were manipulated to occur either early or late in the acoustic signal. EEG was recorded at 13 scalp locations while subjects made speeded lexical decisions. The results showed that latency of negativity in the N400 region of the ERP is sensitive to the latency of UPs and DPs. Specifically, stimuli with early UPs and DPs produced negativity which began sooner in the ERP epoch than stimuli with late UPs and DPs. This finding demonstrates the value of ERPs for evaluating spoken word recognition and suggest that listeners use UPs and DPs during lexical processing.

740.6

AN ELECTROPHYSIOLOGICAL STUDY OF CROSS-MODAL REPETITION PRIMING EFFECTS. J.E. Anderson* & P.J. Holcomb. Psychology Department, Tufts University, Medford, MA, 02155.

Repetition priming effects were examined in a cross-modal lexical decision task (auditory prime and visual target) at three stimulus onset asynchronies (SOAs) using event-related brain potentials and behavioral measures. The purpose was to examine the time course of repetition priming in order to determine if common processes and/or representations are shared between the two modalities. Twelve subjects made speeded lexical decisions to visual targets which were paired with auditory primes. The stimulus list consisted of 360 word pairs, each third of which was made up of either repeated, unrepeated, or word/pronounceable nonword pairs. Three stimulus onset asynchronies (0, 200, and 800 msec) were randomly mixed across the experiment. Reaction times were significantly faster to repeated words at all three SOAs, but were largest at the 800 SOA. The N400 effect (i.e., a reduction in the negativity for repeated targets) was absent at the 0 SOA, but present at the 200 and 800 SOAs. Compared to a similar study using semantic priming, the effects were larger and had an earlier onset, but had a somewhat similar scalp distribution indicating that similar cognitive mechanisms may underlie repetition and semantic priming. The results favor a model in which the visual and auditory modalities share a common set of relatively early information processes.

740.7

VISUAL EVENT-RELATED POTENTIALS AND SEMANTIC PRIMING:SUPERORDINATE CATEGORIZATION OF PICTURES AND WORDS. L.M.Lisk*,D.S.O'Leary and M.Seidenberg. Univ. of Health Sci./The Chicago Med. Sch., N.Chicago,IL 60064.

The aim of this study was to investigate the VERP concommitants of semantic priming of pictures and words during a superordinate categorization task. VERPs were collected from left and right hemisphere scalp electrodes for 9 male and 9 female right handed adults. Peak amplitude and latency data for four negative and positive VERP peak components (P2,N2,N3,P4)were analyzed for picture and word stimulus conditions primed and unprimed target conditions, and left and right hemisphere electrodes. It was hypothesized that VERPs for pictures and words would show differences in the early peak components and hemispheric specialization would also be evident. Late VERP components' peak amplitudes were hypothesized to show differences for primed and unprimed pictures and words. VERP components' latencies were postulated to show decreased peak latencies for primed picture and word targets. The results supported these hypotheses and additionally demonstrated facilitation for a late positive peak for categorizing pictures consistent with behavioral RT findings in the literature.

740.8

REPETITION EFFECTS IN PROCESSING VISUAL WORDS: A HIGH DENSITY ERP STUDY OF LATERALIZED STIMULI. B. D. McCandliss, T. Curran, and M. I. Posner.* Psychology Dept., Univ. of Oregon, Eugene, OR 97403.

Repeated words are processed more rapidly and accurately than non-repeated words. Previous Event Related brain Potential (ERP) studies suggest ERPs to repeated words first differ from non-repeated words over posterior sites by about 250 milliseconds. To better understand the neural substrates of word repetition effects, we presented repeated or non-repeated words to left or right visual fields (LVF, RVF) and asked subjects to detect repetitions. ERPs were recorded in a High Density (64 channel) electrode array. Early positive ERP components occurring at about 100 milliseconds over lateral occipital regions were identical for repeated and non-repeated words, but occurred earlier for words presented to the contralateral field than for words presented to the ipsilateral field. Differences between repeated and non-repeated words first occurred at about 200 milliseconds in several posterior sites in the left and right hemispheres. This difference appeared strongest in posterior temporal sites, and may be somewhat left lateralized. This effect of word repetition appeared virtually identical in amplitude, latency, and spatial distribution over its entire timecourse for stimuli presented to either left or right visual fields. Our data suggest that although some computations sensitive to word repetitions may be left lateralized, these computations are uninfluenced by the visual field in which repeated stimuli occur.

This research supported by J. S. McDonnell Foundation and Pew Memorial Trust.

740.9

LEFT LATERALIZED SCALP POTENTIALS EVOKED BY LEXICAL TASK PERFORMANCE A.Z. Snyder and T.O. Videen*, Departments of Neurology and Radiology, Box 8225, Washington University School of Medicine, St. Louis, MO 63110 USA

Whereas language function is known to be strongly left lateralized in normal right handed individuals, the evoked potential correlates of this asymmetry are uncertain. The best known electrophysiologic correlate of semantic access, i.e., the N400 potential, is generally reported as having a slightly right lateralized distribution over the central and parietal scalp

We recorded scalp potentials in 27 normal right handed volunteers performing a lexical task known to produce strongly left lateralized regional cerebral blood flow (rCBF) activation (Petersen et al., Nature, 1988 331: 585-589). The subjects viewed single nouns tachistoscopically presented on a CRT screen and, in response to a visual cue, either said the presented word (repeat condition) or generated a semantically related verb (generate condition). In both task conditions, the responses recorded in phase with the word presentation included strongly left lateralized inferior frontal and parietal positive potentials, the latter being greatly enhanced in the generate condition. Early right lateralized P1 and P2 components (Kutas et al., Electroenceph. clin. Neurophysiol. 1988, 69: 218-233) were also recorded. The generate-repeat difference potentials demonstrated left anterior temporal and inferior frontal positivity peaking at 230 msec and right mid-temporal negativity peaking at 700 msec. These responses bear a remarkable correspondence both in sign and topography with results obtained by positron emission tomography (Raichle et al., Cerebral cortex, in press).

SUPPORTED by NS06833

740.10

MAGNETIC RESONANCE IMAGING STUDIES OF VISUAL WORD RECOGNITION: WORDS VERSUS FALSE FONT STRINGS. [1,2]R.R. Benson, [1]K.K. Kwong, [1]J.W. Belliveau*, [1]J.R. Baker, [1]M.S. Cohen, [1]C.E. Stern, [2]N. Hildebrandt, [2]D. Caplan, [1]B.R. Rosen. Massachusetts General Hospital Dept. of [1]Radiology and [2]Neurology, Boston, MA, 02114.

Positron Emission Tomography (PET) has made use of the correlation between rCBF and neuronal activity to investigate cognitive functions including language. Petersen (1988) and Wise (1991) in PET studies of word recognition using similar paradigms came to different conclusions regarding the localization of semantic processing. Both of these studies, however, had similar limitations which are attributable to limitations of PET: 1) relatively low sensitivity requiring intersubject averaging, and 2) relatively low spatial and temporal resolution. Functional Magnetic Resonance Imaging (fMRI), by contrast, has higher spatial (millimeter) and temporal (subsecond) resolution, and allows for single subject studies and finer distinction between experimental conditions. Here, we used fMRI to investigate word recognition in strongly right-handed normal male volunteers (n=2) ages 24 and 33, while simultaneously measuring responses and reaction times (n=1). The task was a counterbalanced, blocked physical matching task using words and false font strings matched for letter properties (Bouma, 1971). Postulated processing differences include activation of visual letter units, activation of the visual input lexicon, activation of semantic processing and assembled phonology (Henderson, 1982) Analysis of results showed several regions of activation in common for the two conditions, including motor and visual cortex; however, only two regions--inferior frontal (Area 45) and inferior parietal cortex (Area 39, 40) bilaterally--showed differential activity for words compared with false font strings. Reaction times were significantly faster for words ($p<.001$). These results, not unlike those of Peterson and Wise, suggest that networks involving bilateral inferior frontal and inferior parietal regions may be involved in the differential processing of words and false font strings, including semantic processing. Additional stimuli, i.e., non-legal nonwords and pseudowords, will be used to further constrain the range of cognitive processes under study.

740.11

ACTIVATION OF BRAIN AREAS DURING A LANGUAGE TASK USING CONVENTIONAL MRI A.C. Nobre*, R.T Constable, G. McCarthy, J.C. Gore, Neuropsychology Laboratory, VAMC, West Haven, CT 06516 and Yale University School of Medicine, Depts. of Neurosurgery and Diagnostic Radiology, New Haven, CT 06510.

The ability to localize language areas in an individual's brain using non invasive techniques would have tremendous positive consequences for clinical neurology and neurosurgery and for basic language research. The localization of receptive language areas was studied in normal volunteers using conventional gradient-echo (CGE) MRI sequences at 1.5T.

Three axial slices were chosen that covered the middle and superior temporal gyri. Typical image parameters were: field strength = 1.5T, TR = 150ms, TE = 40ms, slice thickness = 7mm, α = 40°, field of view = 40cm, and matrix size = 256x128x2nex. Twenty CGE images were acquired of each axial slice for an experimental and a control condition. In the experimental condition, subjects viewed a line drawing headed by a word, and made a rhyming judgement between the name of the object and the word. The task involved implicit naming, phonological processing, and reading. In the control condition, subjects viewed abstract line drawings headed by unpronounceable letter strings. Visual and motor-response aspects were closely matched in the control and experimental conditions.

T-test comparisons of individual-pixel intensities across task conditions revealed three brain regions that were significantly ($p<0.05$) more activated by the rhyming task: (1) the left middle or superior temporal gyrus, suggesting activation of Wernicke's area, (2) the visual cortex surrounding the collateral sulcus, and (3) the inferior frontal area. The magnitude of signal change in the present language task was smaller than measured in visual and motor tasks using CGE imaging (Constable, McCarthy, Allison et al, *Magnetic Reson Imag*, 11(4), 1993), and thus the data is more prone to motion or pixel-misregistration artifacts. In face of these possible sources of false activation, the reliability of the findings is continuing to be assessed. The present results suggest that it is feasible to study the neural organization of language in humans non invasively with accessible MR technology.

740.12

CORTICAL STIMULATION DURING A LANGUAGE TASK WITH KNOWN BLOOD FLOW CHANGES. J.G. Ojemann, G.A. Ojemann*, E. Lettich. Dept. of Neurological Surgery, University of Washington, Seattle, WA 98195.

Previous PET studies (Soc Neurosci Abstr 17:21) have shown increase in blood flow in left frontal and left posterior temporal cortex during verb generation in normal right-handed subjects. We sought to identify areas in posterior, dominant, left temporal cortex where this task could be interrupted by electrical stimulation of cortex during awake craniotomies for surgical treatment of epilepsy. As in the PET studies, patients said aloud an appropriate verb for each visually presented nouns and read the word. Cortical sites were electrically stimulated during these two tasks and picture naming. Inability to perform word reading or naming during stimulation identified any general block of speech function.

Of 4 patients studied, three, all right-handed males, had sufficient baseline performance to assess the effects of stimulation. All three had at least one left posterior site in which verb generation (V) was blocked during stimulation but both word reading (R) and naming (N) were preserved. In Case 1, a posterior superior temporal gyrus site involved task V only with adjacent sites involving, respectively, task N alone and both tasks N and V. Case 2 had two V sites, in middle and posterior superior temporal gyrus, distinct from a third site, adjacent to the V site in middle gyrus, which blocked all speech tasks (V, N and R). Another N site was in anterior temporal lobe. Case 3 had one parietal site involving V with an incomplete block of R and an adjacent site interrupting both V and R. There were no posterior naming sites. Only non-specific blocks of speech output were seen in the frontal sites tested in these three cases.

Areas essential for the generation of verbs from nouns can be identified in posterior left temporal cortex in regions similar to those identified by PET. These areas are discreet, may vary across subjects, and are distinct from areas involved in picture naming or word reading.

Supported by NIH Grant NS 21724.

740.13

THE EFFECTS OF WORD FREQUENCY AND SPELLING-TO-SOUND REGULARITY ON THE FUNCTIONAL ANATOMY OF READING. J.A.Fiez*, D.A.Balota, M.E.Raichle, and S.E.Petersen. Washington Univ. Sch. of Med., Box 8111, St. Louis, MO, 63110 and Univ. of Iowa Col. of Med., Iowa City, IA, 52242

Several models have been proposed for word reading based, in part, on studies of the effects of word frequency (the number of times a word appears in normal reading) and spelling-to-sound regularity in word processing tasks. Functional neuroimaging studies of these variables were conducted in order to provide information pertaining to the different models. Separate PET measures were taken while subjects read aloud 4 sets of words presented at .67 Hz below a fixation point: high-frequency regular words (HF-R)(e.g., name),high-frequency irregular, exception words (HF-E)(have), low frequency regular words (LF-R)(deed), and low frequency exception words (LF-E)(pint). Two sets of nonwords were also used. A fixation control was subtracted from each condition. Areas activated by these tasks included motor and premotor frontal cortex bilaterally, cerebellar regions, several regions in occipital and temporal cortex, and bilateral thalamus. Analyses of variance at these loci revealed: 1)a frequency effect at or near right temporal area 41/42 (HF>LF), and a trend at left posterior temporal cortex (LF> HF); 2) a regularity effect in left buried frontal/insular cortex and a trend at lateral frontal cortex (E>R); and 3) an interaction effect in right motor cortex. The most striking effect was in the buried frontal region where activation was lacking for regular words, moderate for HF-E words, and powerful for LF-E words. While these data do not critically exclude any of the currently proposed classes of models, they are most consistent with multiple route models that propose several separate routes by which word inputs can reach output.

740.14

PET ACTIVATION STUDIES OF OBJECT NAMING IN NORMAL SUBJECTS. H. A. Buchtel* (1), T. R. Henry (2) S. Minoshima (3) and R. A. Koeppe (3). (1) Ann Arbor VA Medical Center and University of Michigan Departments of (2) Neurology, (1) Psychiatry and (1) Psychology, and (3) The Division of Nuclear Medicine, Ann Arbor MI 48105

Functional activation PET scan studies with verbal fluency and text reading have shown task-related changes in blood flow in the expected left hemisphere brain regions (Broca's Area, Wernicke's Area), and in other areas presumably involved in looking and talking but not necessarily required for language functions per se. In order to identify brain regions specifically involved with word generation in a task of oral naming of animal drawings (e.g., "That's a mountain lion"), we carried out O-15-H2O blood flow studies on ten normal control subjects. The activation pattern elicited by a control task (oral report of a size judgement of complex nonsense "Attneave" figures, e.g. "That's a small figure") was subtracted from the activation pattern elicited by the naming task, and the resulting parametric t statistical map, corrected for multiple comparisons, was examined. This analysis shows a significant activation of left inferior temporal lobe regions (fusiform gyrus), especially in the male subjects. Results with the female subjects were more variable and individual differences were seen in both sexes. The findings are consistent with notions of the functions of inferior temporal lobe areas at the border between picture identification and the generation of names of objects, and with hypotheses about sex differences in brain organization of language functions. Supported by the Ann Arbor VAMC.

740.15

INTERHEMISPHERIC TRANSFER OF BILATERAL LINGUISTIC STIMULI. K. E. LUH.*Dept. of Psychology, University of Wisconsin, Madison, WI, 53706.

Previous work has shown that there are differences in both accuracy and error patterns for linguistic stimuli presented in the left and right visual fields (LVF, RVF). Error pattern differences can be used to determine how stimuli presented simultaneously to both visual fields (bilateral presentation-BVF) are processed.

A tachistoscopic syllable identification task was given to 40 right-handed men and women. Double redundant syllables were presented in the LVF, RVF, and BVF with font sizes adjusted to control for reduced visual acuity at greater eccentricity from fovea. Accuracy was equal in RVF and BVF, and greater than in LVF. However, when error rates were normalized to 100% for each field, error patterns did not differ in the three fields, with LVF/right hemisphere (RHEM) error patterns being much more like the RVF/LHEM pattern than has been found previously. One interpretation of these findings is that, for all visual fields, the more leftward stimulus is processed by the RHEM, whereas the more rightward is processed by the LHEM.

To test this interpretation, a second study (n = 24) was done with double nonredundant syllables. Overall performance was low as the task was very difficult, but was greatest in the BVF, and greater for BVF-rightward than BVF-leftward syllables. Analyses of error patterns indicated that, for all three fields, the more leftward syllable yielded a more LVF/RHEM error pattern, and the more rightward yielded a more RVF/LHEM pattern. In addition, BVF-rightward error patterns correlated with RVF error patterns, and BVF-leftward error patterns correlated with LVF patterns.

Thus, it appears that, regardless of visual field of presentation, when two stimuli are presented simultaneously, processing of the more leftward stimulus is dominated by the right hemisphere, whereas processing of the more rightward stimulus is dominated by the left hemisphere. When there are heavy processing demands, processing appears to be allocated on the basis of body-defined hemispatial coordinates rather than retinotopic coordinates.

740.16

BILATERAL PRESENTATION OF WORDS FASCILITATES LEXICAL PROCESSING IN NORMALS BUT NOT IN SPLIT-BRAIN PATIENTS. F. Pulvermüller, B. Mohr, J. Rayman, E. Zaidel & A. Aertsen*. Dpts. of Psychology and of Applied Linguistics, UCLA, Los Angeles, CA 90024

If two copies of a meaningful word are tachistoscopically presented simultaneously in both visual half-fields the word will be processed more rapidly and more accurately than after unilateral presentation (bi gain). Matched pseudowords do not lead to any bi gain. It has been hypothesized that the word specific bi gain is due to excitatory neuronal connections within interhemispheric cell assemblies corresponding to words. Such positive connections must be absent in split-brain patients. Therefore, such a patient was tested in a lexical decision task with words and pseudowords presented in the LVF, the RVF, or in both simultaneously. Whereas typical patterns of lexical processing (e.g., RVF advantage for words) could be observed, the bi gain was absent as predicted by our hypothesis. These results suggest (i) that both hemispheres contribute to lexical processing, and (ii) that callosal connections play a significant role in lexical processing. If word specific cell assemblies are distributed over both hemispheres they must be held together through positive callosal connections.

740.17

EMERGENCE OF ACCESS TO SPEECH IN A DISCONNECTED RIGHT HEMISPHERE. K. Baynes†, C.M. Wessinger‡, M.S. Gazzaniga‡ and R. Fendrich‡*. †Department of Psychiatry, Dartmouth Medical School, Lebanon, NH 03756; ‡Center for Neuroscience, University of California, Davis, CA 95616.

Callosotomized patient JW has a well-documented history of right hemisphere language abilities. Previously reported characteristics of this subject's right hemisphere language include an auditory and visual lexical-semantic system with limited phonology and syntax. However, JW's right hemisphere has previously not demonstrated the ability to control motor speech. We now report the emergence of this ability.

A series of experiments were conducted in which pictures and text were presented to the subject's left visual field. Retinal stabilization ensured that these stimuli remained correctly lateralized. JW was able to correctly name these stimuli approximately one quarter of the time under a variety of presentation conditions. Subsequent matching experiments discounted the possibility that this speech was based on the transfer of semantic or phonological information from the right to the left hemisphere. Thus, 13 years post-callosotomy, the right hemisphere of this patient appears to have developed the ability, albeit limited in nature, to access speech.

Supported by NIH/NIDCD grant R29 DC00811 to K.B. and NIH/NINDS grant PO1 NS 17778-11 and the McDonnell-Pew Foundation to M.S.G.

740.18

AUDITORY EVOKED POTENTIALS AS AN INDEX OF INFANTS' ABILITY TO DISTINGUISH THEIR NATIVE FROM NON-NATIVE LANGUAGES.

V.L. Shafer and D.W. Shucard* Departments of Neurology and Linguistics, SUNY @ Buffalo, 100 High Street (D-6), Buffalo, NY 14203.

Recently, psycholinguists have begun to recognize that prosodic, as well as segmental/phonetic information may play an important role in the acquisition of language in infants. Prosodic information, such as intonation contours, stress and accent patterns, and syllable duration may serve as sources of information to aid in segmenting speech into functional units, such as words and phrases. Previous behavioral studies by P. Jusczyk and J. Mehler suggest that 2-month-old American infants were able to discriminate English from Italian on the basis of prosodic information. Their research also indicates that prosodic information is exploited in language acquisition earlier in an infant's development than segmental/phonetic information. In the present study, we attempted to investigate this phenomenon in infants using electrophysiological techniques. Auditory Evoked Potentials (AEPs) to task-irrelevant pairs of tone probes were obtained to investigate the ability of 3-month-old infants to discriminate English from Italian and Dutch. English and Italian differ in prosodic characteristics, but share similar segmental inventories, while English and Dutch are very similar in prosodic information, but have a different segmental inventory. The pattern of AEP fast habituation and changes in amplitude response to the tone pairs across conditions were examined. A pattern indicating less habituation to the tone probes during the Foreign Language Conditions than the English Condition was found, suggesting that infants attended more to the novel conditions. This finding supports the notion that 3-month-old infants can discriminate both Italian and Dutch from English. Thus, it appears that 3-month-old infants may use both prosodic and segmental information to discriminate English from a foreign language.

740.19

LOSS OF LEXICAL IMAGERY IN AN INFANTILE CASE OF ASSOCIATIVE VISUAL AGNOSIA

Maryse Lassonde*, Alessandra Schiavetto, and André Roch Lecours
Department of Psychology, Université de Montréal, and Centre de Recherche du Centre Hospitalier Cote-des-Neiges, Montréal, Qué. CANADA

The aim of this project was to investigate reading and writing deficits in a case of associative visual agnosia. The patient, A.R., developed a herpetic encephalitis at age 9. As a result of this illness, the patient became prosopagnosic, color agnosic and presented evidence of associative visual agnosia accompanied by dyslexia and dysgraphia. Recent MRI revealed a right temporal atrophy, affecting the hippocampal region. Prior to her illness, A.R. could read and write without difficulty. However, immediately following her encephalitis, she was no longer able to recognize or produce letters or words. Following an intensive 6 month rehabilitation, A.R. re-learned to read, but only through graphophonemic conversion. Similarly, her written productions have improved. However, her writing is characterized by phonographemic productions and she is unable to write irregular words (abundant in French) that must be "visualized" in order to be either read or written. These specific reading and writing deficits, as well as her difficulties in recognizing visual percepts suggest that this patient may have lost access to a common visual register of global representations of words and objects. In fact, it appears that A.R.'s reading and writing difficulties reflect a dysfunction in her logographic lexicons, thereby suggesting that she has a surface dyslexia, which, to our knowledge has never been reported in a child.

740.20

ELECTROPHYSIOLOGICAL INDICANTS OF LETTER PROCESSING IN DEVELOPMENTAL READING DISABILITY. S.L. Miller*. Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, NJ 07102.

Developmental reading disabled (RD) and non-reading disabled (NRD) control subjects were compared on event-related potentials (ERPs) and behavioral measures. ERPs were recorded during a series of black/white, letter/non-letter, and rhyme/non-rhyme discrimination tasks of visually presented black and white letter and non-letter stimuli (stimulus duration = 50 ms). Results indicated an increase in latency for reaction time and for ERPs recorded at 200-240 msec (N220) after stimulus presentation across the three tasks suggesting a sequential hierarchy for stimulus feature selection. Group differences indicated a general reduction in N220 amplitude for the RD group, as compared to NRD group, with this reduction being more pronounced: (a) over the left than right hemisphere, and (b) for the rhyme/non-rhyme discrimination task. Observer sensitivity (d') similarly indicated that the RD group was less sensitive in performing the discriminations, particularly for the letter rhyming task. These findings are considered to reflect a basic perceptual deficit(s) in RD which is more pronounced when stimulus feature selection is based on phonological information. Supported by NIH Grant RO1 NS19413

740.21

PATTERNS OF COGNITIVE ABILITY AND AUDITORY EVOKED POTENTIAL ASYMMETRY IN NORMAL READERS: WHY AREN'T THEY READING DISABLED? **E.L. Sargent*, C.P. Schaeffer, D.W. Shucard Department of Neurology, SUNY @ Buffalo School of Medicine and Biomedical Sciences, 100 High Street (D-6), Buffalo, New York 14203**

One possible subtype of dyslexia was first proposed by Bannatyne in 1971. The basis of this "genetic dyslexia" subtype was a regrouping of nine of the subtests of the Wechsler Intelligence Scale for Children, Revised (WISC-R) into three composite measures: conceptual, spatial and sequential abilities. Bannatyne proposed and others have shown, as well, that approximately 30% of children with reading disabilities (r-d) are characterized by a particular ordering of these abilities: Spatial > Conceptual > Sequential. Bannatyne observed a greater incidence of r-d among biological relatives of these children leading him to conclude that this pattern of abilities constituted a "genetic dyslexia" subtype. More recent studies, however, have tended to question this conclusion (e.g. Decker and Corley, 1984).

Previous work in our laboratory has shown a different pattern of auditory evoked potential (AEP) amplitude asymmetry to probe stimuli between r-d and normal readers during the performance of cognitive tasks. In this study, we examined the AEP asymmetry in two groups of normal readers: those with the Bannatyne profile (n=20) and those without (n=90). Results indicated that (1) Bannatyne-profile normal readers had an AEP amplitude asymmetry similar to that of r-d children and opposite to that of normal readers; (2) there was a higher reported incidence of reading difficulties among family members of normal readers with the Bannatyne profile. These findings suggest that patterns of electrophysiological measures of cerebral organization coupled with patterns of cognitive abilities may provide an index of risk for r-d, but that in normal readers other factors such as the availability of cognitive resources may influence the phenotype. Supported in part by NICHD Grant HD11681.

740.22

MULTIDIMENSIONAL SCALING ANALYSIS OF MUSICAL TIMBRE PERCEPTION AFTER UNILATERAL TEMPORAL-LOBE RESECTION. S. Samson*, R.J. Zatorre and J.O. Ramsay. Montreal Neurological Institute and Psychology Dept., McGill University, Montreal, Quebec, Canada H3A 2B4.

Musical timbre is related to both the spectral shape and temporal envelope of a periodic tone. The temporal neocortex is known to subserve auditory perceptual function, but relatively little is known about its possible role in processing these features of timbre. We studied timbre perception of single tones and melodic sequences in 30 patients who had undergone resection of the anterior right temporal (RT) or left temporal (LT) lobe, and in 15 matched normal control (NC) subjects. The stimuli consisted of synthetic tones, derived from crossing three levels of spectral content (1, 4 or 8 harmonics), with three levels of onset times (1, 100, or 190 ms), to create a matrix of nine hybrid sounds. All combinations of pairs of stimuli were presented to subjects for judgment of perceived dissimilarity. Multidimensional scaling analyses were performed on the subjects' pairwise judgments using an 8-point rating scale. These analyses produced a two-dimensional perceptual space for the NC and LT groups in which the two dimensions correspond closely to the spectral and temporal dimensions inherent to the stimuli. These results indicate that subjects in the LT and NC groups based their perceptual judgments on both spectral and time information in a systematic fashion. In comparison with the NC and LT groups, the analysis of the RT group's ratings revealed a different, distorted perceptual space. The subjects in the RT group relied primarily on the spectral cues, and tended to neglect the temporal information that contributes to musical timbre. The findings are in agreement with our previous data suggesting an important role for the right temporal neocortex in perception of timbre. In addition, these data provide qualitative information about the perceptual abilities of patients with RT lobe lesions.

740.23

AUDITORY PROCESSING FOLLOWING UNILATERAL TEMPORAL LOBE SURGERY. P. C. Lebby*, R. B. Ivry & J. A. Walker. Psych. Dept., Univ. of Calif., Berkeley, CA. 94720.

The present study investigated auditory processing following unilateral temporal lobe resection. All patients underwent the surgery as a treatment for intractable epilepsy. Previous research using normal subjects has shown a right ear - left hemisphere advantage for the processing of relatively high auditory frequencies, and a left ear - right hemisphere advantage for the processing of relatively low auditory frequencies. The present study examined whether this frequency by hemisphere interaction would be present in a population with unilateral temporal lobe lesions. It was hypothesized that right hemisphere damaged patients would show a relatively high frequency processing advantage, and left hemisphere damaged patients would show a relatively low frequency processing advantage. The interaction was predicted for relative differences in frequency but not absolute differences. Previous studies have shown the frequency by hemisphere interaction for relative frequency differences, but not for the absolute frequency range attended. Presented are the results of two experiments that support the present hypothesis. The first experiment used duplex auditory stimuli similar to those used with normal subjects. The second study used phonemic stimuli differing in either their high or low frequency components. Patients that had undergone right temporal lobe resection demonstrated a relatively high frequency processing advantage. Conversely, left temporal lobe patients showed a relatively low frequency processing advantage.

740.24

IN VIVO MORPHOMETRY OF INTERHEMISPHERIC ASYMMETRY AND CONNECTIVITY IN EMINENT MUSICIANS. Gottfried Schlaug*, Lutz Jäncke, Yanxiong Huang, Helmuth Steinmetz. Depts. of Neurology and General Psychology , University of Düsseldorf , Germany.

Early autoptic descriptions in eminent musicians and results of electrophysiological and functional imaging studies suggest differences in hemispheric lateralization and connectivity between musicians and nonmusicians. Since the planum temporale (PT) is an anatomical correlate of functional laterality it was investigated whether musicians would differ in PT asymmetry from nonmusicians. Additionally, since increased interhemispheric transfer can be assumed to be an important neurophysiological characteristic of key and string players, the midsagittal size of the corpus callosum (CC) was measured. In 27 professional right-handed musicians (19 men + 8 women, age range 21-34) and matched nonmusicians 3-D FLASH magnetic resonance images with 128 contiguous slices (thickness: 1.17 mm, pixel size: 1x1 mm) were obtained. Morphometric evaluation of the PT was performed by two blinded observers (interobserver reliability: r = 0.93) according to published criteria. The midsagittal size of the CC was determined by a semiautomatic method after segmentation. In musicians with a commencement of musical training ≤ 6 years of age (n=17) as well as in musicians with a perfect pitch (n=9) a significant difference in PT asymmetry (larger left PT) comparing each group to other musicians and nonmusicians was found (ANOVA, $p<0.05$ for both groups). Similarly, early beginning musicians showed a larger midsagittal size of the anterior CC (ANOVA, $p=0.01$). The latter is interpreted as a morphological substrate of an increased interhemispheric transfer required for performing complicated bimanual motor sequences. On the other hand, the extreme degree of PT asymmetry points to a strongly lateralized pattern of temporo-parietal brain functions in eminent musicians.

740.25

LAUGHTER: VARIATIONS ON A THEME. R.R. Provine*
Dept. of Psychology, UMBC, Baltimore, MD 21228.

Laughter is a stereotyped human vocalization (Ethology, 89 (1991) 115-124) that is contagious, occurs almost exclusively in social contexts (Ethology, 83 (1989), 295-305), punctuates and is subservient to speech, is only sometimes associated with jokes or other formal efforts at humor, and shows gender differences. Speakers, especially females, laugh more than their audiences, and audiences of both males and females laugh more to male than female speakers.

Laughter has stereotyped, but not invariant, note duration ("ha," X = 75 ms) and internote intervals ("ha-ha," X = 210-218 ms), strong harmonic structure and a decrescendo. Variations of this basic structure usually involve the vowel sound of laugh notes (i.e., "ha-ha," "ho-ho," "he-he") and the duration of the terminal note of a series (i.e., "ha-ha-haaa") but not the underlying laugh structure that is the basis for laugh recognition. Although the vowel sounds of laugh notes vary, they are not mixed within a given laugh episode. (There are no "ha-ho-ha-ho" laughs.) The species-typical character and strong neurological programming of laughter provides insights into the evolution, development and neural basis of human vocal production and recognition of which speech is a special case.

LEARNING AND MEMORY: PHARMACOLOGY—ACETYLCHOLINE

741.1

AN OPERANT TASK FOR RAPIDLY TRAINING RATS AND ASSESSING THE MNEMONIC EFFECTS OF DRUGS. P. E. Mallet* and R. J. Beninger. *Dept Psychol, Queen's Univ, Kingston, Canada, K7L 3N6.*

In tasks designed to test memory in animals, it is often difficult to determine whether a change in performance can be attributed unequivocally to mnemonic functioning. That is, some tasks are equally sensitive to non-mnemonic variables such as motivation, perception, and motor functioning. One method of eliminating non-mnemonic confounds is to devise a task which consists of two components: one which requires the use of working memory (WM) and one reference memory (RM). It can be argued that a treatment which has affected only one component can be attributed to an alteration of mnemonic functioning since factors affecting non-mnemonic variables should be reflected in both components. We describe here a rapid operant task for assessing memory in rats in which each trial consists of a conditional discrimination (requiring RM) and a delayed non-match-to-position (requiring WM). Rats received 60 training trials/day in a two-retractable-lever operant chamber. A trial began by extending both levers and presenting either a light or white noise. Pressing one lever was rewarded with a food pellet only when one stimulus was present, while the other lever was rewarded only when the other stimulus was present. Both levers were retracted following a press and were re-extended 4s later, and the lever opposite the one pressed during the first component was rewarded. Rats reached the acquisition criterion (80% correct over 3 consecutive days) after a mean of 15.83 training sessions. Supporting the notion that memory was being assessed were the observations that various delays (4-16s) imposed between the RM and WM components revealed a WM-specific delay-dependent decrease in performance, and the observation that scopolamine hydrobromide (0.2-0.8 mg/kg i.p.) produced a WM-specific dose-dependent decrease in performance. Supported by NSERC.

741.2

SCOPOLAMINE IMPAIRS ACQUISITION AND FACILITATES CONSOLIDATION OF FEAR CONDITIONING: DIFFERENTIAL EFFECTS FOR TONE VS CONTEXT CONDITIONING. S. L. Young*, D. L. Bohenek, M. S. Fanselow. Department of Psychology, University of California, Los Angeles, CA 90024.

Acetylcholine contributes to the production of hippocampal theta rhythm. Hippocampal damage, as well as administration of cholinergic antagonists, will impact selected learning tasks. Perhaps, learning deficits or enhancements produced by cholinergic antagonism result from the blockade of atropine-sensitive theta rhythm impairing hippocampal functioning. Hippocampal lesions prevent context fear conditioning without effect on tone conditioning. These lesions also produce a time-dependent retrograde deficit in context conditioning. To examine the possibility that cholinergic antagonism mimics hippocampal damage, rats were given scopolamine (ip) either before or after fear conditioning. In the fear conditioning procedure, rats received tone-footshock pairings. Evidence of conditioning to the tone and the context was provided by observation of freezing. When given prior to training, scopolamine blocked fear conditioning to the tone in a dose dependent fashion. Scopolamine prior to training did not impair context conditioning. The impairment of conditioning did not occur with methlyscopolamine indicating the central action of the drug. Rats given scopolamine immediately following fear conditioning and tested 24 hours later in a drug-free state, froze more to the tone than rats given a control injection. The effect of scopolamine on freezing to the context was not reliable. The present results suggests that scopolamine's impact on fear conditioning is mediated by some mechanism other than impaired hippocampal functioning.

741.3

DOSE-DEPENDENT DISRUPTION BY SCOPOLAMINE OF SPATIAL WORKING MEMORY PERFORMANCE OF RATS IN A PHI(ϕ)-MAZE. W. J. Wilson* and N. C. Steinbronn. Dept. of Psychological Sciences, Indiana University - Purdue University Fort Wayne, Fort Wayne IN 46805 USA.

Ten experimentally naive female Sprague-Dawley rats were trained in a spatial alternation task in a phi(ϕ)-maze. On each trial the rat was required to leave the Start/Goal Box via a central alley, and return to it through either the Left or Right Arm of the maze. A reinforcer consisting of one-quarter of a Froot Loop was delivered in the S/G Box if the rat returned to the S/G Box through the arm that was not used on the previous trial. Each session continued until the rat received 40 reinforcers. Rats were trained to criterion before drug testing was started.

Each rat was tested following the intraperitoneal injection of five different doses (0.0, 0.15, 0.30, 0.60, or 1.20 mg/kg) of scopolamine hydrobromide and scopolamine methyl bromide. Injection days alternated with non-injection days, and the order of dose and drug administration for each rat followed a 10 x 10 Latin-Square design.

Scopolamine, but not the peripherally acting methyl scopolamine, caused a dose-dependent increase in the number of errors (failures to alternate). After initiating a trial and selecting an arm of the maze, rats on scopolamine tended to wander throughout the maze rather than returning to the feeder in the S/G Box. Rats initiated a trial, and ran through the central alley as quickly when given scopolamine as when given saline or methyl scopolamine, and they were equally willing to eat the reinforcer. Therefore, we do not believe that the increase in errors represents a motivational or motor deficit. The results reflect an impairment of spatial working memory, and perhaps some concordant reference memory problems, following central muscarinic blockade.

741.4

SCOPOLAMINE-INDUCED RECOVERY OF PASSIVE AVOIDANCE RESPONDING AFTER EXTINCTION IN RATS. G. Roldán, G. L. Quirarte and R. A. Prado-Alcalá* Dept. Physiol., Fac. Med., Natl. Univ. México, México, D.F., México.

Several lines of evidence strongly suggest that acetylcholine (ACh) is importantly involved in memory consolidation and in retrieval of instrumentally conditioned behaviors. However, its role in extinction has not been determined. In the present work the effect of scopolamine (SCOP) on retrieval after extinction was investigated. Rats were trained in a one-trial passive avoidance task, and tested for extinction during 14 daily sessions. Ten min before sessions 10-14 each animal was treated with saline, SCOP, no treatment, SCOP, and saline, respectively. SCOP was injected in doses of 0, 1, 2, 4, and 8 mg/kg to independent groups. A dose-related recovery of the extinguished avoidance response was found after SCOP administration. It is suggested that 1) ACh is differentially involved in memory consolidation and in retrieval of information, and 2) extinction represents a special case of learning.

Supported by PADEP (MED-0293 and MED-9210).

741.5

SCOPOLAMINE BUT NOT METHYL-SCOPOLAMINE REDUCES LATENT LEARNING AND MAZE-LEARNING IN RATS. H.Sundberg. Inst. Biol. Med. Psychology, Univ. of Bergen, Bergen, NORWAY. (Spon: European Brain and Behaviour Society)

Alzheimer's disease is characterised by a substantial loss of cholinergic neurones in the basal forebrain. Furthermore, there is a substantial decrease in the activity of *choline acetyltransferase (CAT)* mainly in the cortex and in the hippocampus. It is also well known that anti-muscarinic drugs like scopolamine can interfere with a variety of learning and memory tasks. We exposed 3 groups of rats to a Lashley-III maze under 3 conditions with no reinforcement. Either under the influence of 0.3 mg/kg, ip scopolamine hydrobromide (SCOP), 0.3 mg /kg, ip. scopolamine methylbromide (MSCOP) or saline. The first two groups were then divided into two subgroups learning the maze either under the influence of SCOP or MSCOP. The saline control group was tested under saline. The rats which had explored the maze under SCOP showed no latent learning in terms of reduced number of errors when compared to MSCOP or saline-controls. The latter two groups were indistinguishable. However, the rats trained under SCOP made significantly more errors than the other two groups. This study indicates that blocking central muscarinic neurons interferes with the memory of places explored as well as the subsequent reinforced aquisition of the same maze

741.6

METHYLATROPINE BLOCKS THE CENTRAL EFFECTS OF CHOLINERGIC ANTAGONISTS RD Smith*, ME Grzelak & VL Coffin. *Schering-Plough Research Institute, Kenilworth NJ 07033.*

Reports on the effects of quaternary amines in rodent cognition have produced conflicting results. A series of behavioral studies were conducted in order to establish the dose-dependency and relative peripheral versus central activity of four prototypical cholinergic antagonists on the rodent passive-avoidance response, a *widely-used animal model of retention.* Subcutaneous administration from 0.1 to 100 mg/kg, revealed a potency profile of scopolamine>atropine>> methylscopolamine≥methylatropine for the impairment of passive-avoidance responding. A series of neurological assessements of the doses used, indicated that side-effects alone were not sufficient to impair passive-avoidance responding. Although inactive when delivered peripherally, methylatropine was able to produce retention deficits at 10 nmols when administered intracerebrally. To further evaluate whether systemic methylatropine could enter the central nervous system, either scopolamine or atropine was administered subcutaneously in mice and rats pretreated with 10 to 100 mg/kg methylatropine. This was done since entry of methylatropine into the CNS may result in potentiation of the deficit producing effects of scopolamine or atropine. However, the deficit-producing effects of scopolamine and atropine were abolished with methylatropine. Thus methylatropine is an exclusive peripheral antagonist; its ability to block the deficit-producing effects of scopolamine and atropine may occur through a change in blood-brain barrier permeability, or through uncharacterized pharmacokinetic properties.

741.7

192 IgG-SAPORIN INDUCED IMMUNOTOXIC LESIONS OF BASAL FOREBRAIN CHOLINERGIC NEURONS: EFFECTS ON SPATIAL AND NON-SPATIAL LEARNING. L.F. Kromer,* N. Vnek,[1] T.C. Gleason,[1] R.G. Wiley,[2] and L.A. Rothblat[1]. Dept. of Anat. & Cell Biol., Georgetown Univ., Washington, DC, 20007, [1]Dept. of Psychology, George Washington Univ., Washington, DC 20052 and [2]DVAMC, Vanderbilt Univ., Nashville, TN 37212.

Current clinical and experimental data implicate the basal forebrain cholinergic system in a wide array of cognitive functions. However, it has been difficult to confirm the cholinergic hypothesis of learning and memory since, until recently, it has not been possible to produce selective cholinergic cell loss without disrupting other neuronal connections. In the present study we utilized the immunotoxin 192 IgG-saporin (3.0μg injected intraventricular) to produce selective lesions of only those forebrain cholinergic neurons which possess low affinity NGF receptors. Beginning at 3 weeks postlesion, rats were trained on a discrete trial rewarded alternation on a T-maze to assess spatial function. Non-spatial learning was then evaluated by training rats on a visual task involving a series of individual object discriminations. Lesioned rats were severely impaired on both tasks compared with sham lesioned and normal controls. Lesioned rats made significantly fewer correct responses (63%) than did controls (89%) on the alternation task and required nearly twice the amount of training to learn the object discriminations (56 vs 31 days). Histological evaluation of lesioned specimens stained for acetylcholinesterase indicated that there was a bilateral depletion of the cholinergic innervation to the hippocampus and neocortex. These results suggest that the forebrain cholinergic-hippocampal/cortical system is important for both spatial and non-spatial cognitive functions. Supported by GWU Facilitating Fund and NIH grant NS-23522.

741.8

QUINPIROLE DOES NOT REDUCE THE SPATIAL MEMORY DEFICITS INDUCED BY MEDIAL SEPTAL LESIONS. C.P.J. Dokla*, J.J. Boitano,+ S.A. Belanger,+ A. Deraney,+ & C. Laflamme. Depts. of Psychology, Saint Anselm College, Manchester, NH 03102 and +Fairfield Univ., Fairfield, CT 06430.

Medial septal (MS) lesions induce cholinergic loss in the hippocampus and spatial memory deficits in the Morris water maze task, but the deficits are not reversed by physostigmine (Dokla et al, Soc. Neurosci. Abstr., 17: 138, 1991). The present study examined activation of the D-2 receptor subtype on the MS-lesion deficits. F-344 rats received electrolytic lesions of the MS at one (MS-1; n=7) or two (MS-2; n=7) sites, while a control group (CONT; n=6) was given sham-operations. All rats received 4 days of predrug testing in a water maze using a working memory procedure in which the location of the escape platform was changed daily. Each daily training trial was followed 5 min later by two retention trials. During the next 4 days, quinpirole (1 mg/kg, i.p.) was given using a crossover design in which all rats received either drug or saline (2 days each). Both MS groups had over 40% reduction of cholineacetyltransferase in hippocampus. During drug testing, the MS groups had significantly longer swim latencies and distances than the CONT group during retention but not training trials, and the MS-2 group was more impaired than the MS-1 group. However, quinpirole produced no significant effects between the groups on any of the dependent measures.

741.9

EFFECTS OF MUSCIMOL ON SCOPOLAMINE-INDUCED AMNESIA. S. E. Cruz-Morales* and R. A. Prado-Alcalá. Psychol., ENEP-Iztacala and Dept. Physiol., Fac. Med., Natl. Univ. México, México, D.F., México 04510.

The objective of this experiment was to evaluate the interaction of GABAergic and cholinergic systems in memory processes. Rats were trained in inhibitory avoidance and tested for retention 24 hours later. The rats were assigned to one of 11 groups: two groups were injected with 4 or 8 mg/kg of scopolamine (SCP); three groups with 0.125, 0.5 or 2.0 mg/kg of muscimol (MU); three groups received 8 mg/kg of SCP in combination with 0.125, 0.5 or 2.0 mg/kg of MU; three groups served as controls: not-treated, injected with isotonic saline and a not-footshocked group. All injections were administered 5 minutes post-training. SCP induced amnesia in a dose-dependent manner; MU had no effects on consolidation but reversed the amnesia induced by SCP.

Supported by DGAPA (IN202791) and PADEP (MED-9210).

741.10

BASAL FOREBRAIN INJECTIONS OF BACLOFEN AND MUSCIMOL SELECTIVELY IMPAIR WORKING MEMORY IN RATS IN THE DOUBLE Y-MAZE. N.J. DeSousa, R.J. Beninger*, K. Jhamandas° and R.J. Boegman°. Depts. Psychol and °Pharmacol & Toxicol, Queen's Univ., Kingston, ON, Canada.

This study was designed to evaluate the possible contribution to memory of GABAergic inputs to the basal forebrain in the region of the nucleus basalis magnocellularis (NBM). In two experiments (exp), rats implanted with bilateral intra-NBM guide cannulae were placed in one of two start arms of the first 'Y' and the reference memory (RM) task was to travel to its central stem for food. Access to the second 'Y' was then given and the working memory (WM) task for exp 1 was to travel to the goal arm diagonally opposite the start arm in the first 'Y' of that trial. In exp 2, the WM task was to travel to the goal arm opposite the goal arm entered in the second 'Y' on the preceding trial, with delays of 0 and 15 s inserted between trials. In exp 1, rats (n=8) received the $GABA_A$ agonist muscimol (0.1 µg/0.5 µL), the $GABA_B$ agonist R(+)-baclofen (0.01, 0.05 and 0.1 µg) and its less active enantiomer S(-)-baclofen (0.1 µg) in a counterbalanced order with retraining to criterion (≥ 85% correct) between injections. In exp 2, rats (n=9) received R(+)-baclofen (vehicle and 0.1 µg), the $GABA_B$ antagonist phaclofen (0.1 µg) and R(+)-baclofen + phaclofen (0.1 + 0.1 µg). Results of exp 1 revealed that intra-NBM muscimol and, in a dose-dependent manner, R(+)-baclofen affected WM but not RM. In exp 2, the differential mnemonic impairment produced by R(+)-baclofen was replicated and co-injection with phaclofen reversed this effect. Results also demonstrated that a delay of 15 s between trials impaired WM but not RM. These results suggest that both $GABA_A$ and $GABA_B$ receptors may be involved in modulating the mnemonic functions of NMB cholinergic neurons.

(Funded by a grant from OMHF)

741.11

EFFECTS OF SCOPOLAMINE ON MEMORY IN RATS PRETREATED WITH THE SEROTONERGIC DEPLETER PCA. A.C. Santucci*, E. Moody and J. Demetriades. Dept. of Psychology, Manhattanville College, Purchase, NY 10577.

The present study investigated the mnemonic consequences of muscarinic blockade in rats pretreated with the serotonergic depleter p-chloroamphetamine (PCA). Subjects were initially injected (ip) with either PCA (2.5 mg/kg) or saline (SAL) six to seven days prior to testing on a working memory version of the Morris water maze. Testing consisted of administering 4 daily trials with the escape platform located in one of the four pool quadrants. Testing continued for 4 days with the location of the escape platform changing daily. PCA and SAL pretreated subjects were injected (ip) with either one of three doses of scopolamine HCL (SCOP; 0.0, 0.5, 1.0 mg/kg) 15 min prior to each daily test session (n = 8 per group). Latency to find the platform on each trial served as the measure of memory. Results indicated that SCOP impaired task performance ($p < .05$). However, the particular dose of SCOP that impaired performance differed depending on whether or not subjects were pretreated with PCA: 1.0 mg/kg impaired SAL pretreated subjects while 0.5 mg/kg impaired PCA pretreated subjects (ps < .05). This pattern of results did not generalize to another memory test (passive avoidance) wherein only a significant dose-dependent effect of SCOP was observed ($p < .05$). These data suggest that muscarinic blockade does impair spatial working memory but that the degree of muscarinic blockade necessary to produce this effect is dependent upon the status of the serotonergic system. These results imply that the cholinergic and serotonergic systems interact in a functionally important, as of yet, undetermined manner.

741.12

CHARACTERISTICS OF NEUROPHARMACOLOGICAL EFFECTS OF TAK-147, A NOVEL ACETYLCHOLINESTERASE INHIBITOR, IN VITRO. K. Hirai, K.Kato*, T. Nakayama, H. Murakoshi, Y. Ishihara, G. Goto and M. Miyamoto. Pharmaceutical Res. Lab. I, Pharmaceutical Res. Div., Takeda Chem. Ind. Ltd., Osaka 532, Japan.

It has been demonstrated that TAK-147, a novel acetylcholinesterase (AChE) inhibitor, ameliorates impaired learning and memory without affecting the peripheral nervous systems. In the present study, we investigated the effects of TAK-147 on AChE and butyrylcholinesterase (BuChE) activities and on uptake of monoamines in synaptosomal fractions. TAK-147 showed a potent inhibition of AChE activity in homogenate of the rat cerebral cortex with IC50 value of 51.2 nM. The inhibition of AChE activity induced by TAK-147 was 3.0- and 2.4-fold more potent than those of THA and physostigmine, respectively, and a half potency of E2020. In contrast, TAK-147 was the least potent inhibitor of BuChE activity in rat plasma, the IC50 value being 19.0 µM. E2020 also showed a similar weak inhibition of BuChE activity with IC50 value of 6.5 µM. THA and physostigmine inhibited BuChE activity at the concentration of 100 nM. TAK-147 inhibited uptake of noradrenaline and serotonin in synaptosomal fractions of the rat cerebral cortex and hippocampus with IC50 values of 4.02 and 1.35 µM, respectively. Although E2020 and THA also inhibited uptake of monoamines, the effects were less potent than TAK-147. Physostigmine had no significant effect on uptake of monoamines. These results suggest that TAK-147 inhibits AChE activity without affecting peripheral BuChE activity, and activates the monoaminergic systems via inhibition of monoamine uptake.

741.13

EFFECTS OF TAK-147, A NOVEL ACETYLCHOLINESTERASE INHIBITOR, ON IMPAIRED LEARNING AND MEMORY IN ANIMAL MODELS. M. Miyamoto*, H. Takahashi, Mitsuyo Nishiyama, Yuji Ishihara and Giichi Goto. Pharmaceutical Res. Lab. I, Pharmaceutical Res. Div., Takeda Chem. Ltd., Osaka 532, Japan.

We examined the effects of TAK-147, a novel acetylcholinesterase (AChE) inhibitor, on impaired learning and memory in animal models. TAK-147 ameliorated scopolamine-induced impairment of delayed matching to sample task assessed by a 3-lever operant behavior and diazepam-induced passive avoidance deficit in a dose-dependent manner at doses of 0.3-3 mg/kg, p.o., in which TAK-147 had no significant effect on general behavior. THA improved these impaired learning and memory at doses of 10-30 mg/kg, p.o. which caused side effects such as miosis and fasciculation. E2020 ameliorated the impairments at doses of 1-3 mg/kg. TAK-147 improved impaired DRL (differential reinforcement at low rate) performance in AF64A-treated rats at 1 mg/kg and THA and E2020 ameliorated the impairment at 10 and 3 mg/kg, respectively. TAK-147 had no significant effect on the duration of immobility in a forced swimming test in rats at doses of 2-10 mg/kg. However, THA (5-20 mg/kg) and E2020 (2-10 mg/kg) prolonged the duration of immobility, indicating that THA and E2020 but not TAK-147 may increase behavioral depression at nearly doses showing improvement of impaired learning and memory in rats. Furthermore, TAK-147 reversed reserpine-induced hypothermia and ptosis at doses of 3-10 mg/kg in mice. These results suggest that TAK-147 is a brain selective AChE inhibitor and produces an apparent improvement of impaired learning and memory in animal models without affecting the peripheral nervous systems.

741.14

DuP 996 (LINOPIRDINE), AN ACETYLCHOLINE RELEASER, IMPROVES PERFORMANCE OF RATS AND MICE IN SOME BEHAVIORAL TESTS OF LEARNING AND MEMORY. A. Buxton, C. A. Henderson, G. T. Inouye, R. M. Johnson*, and D. J. Fontana. Department of Neurosciences, Institute of Pharmacology, Syntex Discovery Research, Palo Alto, CA 94304, U.S.A.

We evaluated the action of DuP 996 (linopirdine), 3,3-bis(4-pyrindinylmethyl)-1-phenylindolin-2-one, on cognition in rats and mice in several behavioral tests, and we measured its effects on hippocampal acetylcholine (ACh) overflow in rats. Using mice treated with scopolamine, a muscarinic receptor antagonist, we studied the effects of DuP 996 on retention of a passive avoidance task. DuP 996 (0.1 & 1.0 mg/kg, i.p.) reversed the scopolamine-induced deficit partially. Furthermore, in a scopolamine-induced hyperactivity test, DuP 996 (1.0 mg/kg, i.p.) decreased the motoric stimulation associated with the cholinergic hypofunction. Using rats, we studied the effects of DuP 996 on performance in the Morris Water Maze (MWM). Young rats treated with atropine (30 mg/kg, i.p.), a muscarinic receptor antagonist, took significantly longer to locate the submerged platform. DuP 996 (0.01 & 0.1 mg/kg, i.p.) ameliorated the atropine-induced deficit. In addition, DuP 996 (0.1 mg/kg, i.p.) ameliorated the deficit in cognition-impaired aged rats (24-25 months), but did not affect non-impaired aged rats. In delayed matching to position (DMTP) and delayed non-matching to position (DNMTP) paradigms, DuP 996 (0.25, 0.50, & 1.0 mg/kg, i.p.) did not increase the rats' accuracy. In terms of neurochemical action, DuP 996 (1, 10, & 100 uM) produced a concentration-dependent increase in tritiated-ACh release from rat hippocampal tissue. Also, DuP 996 (10 uM) increased ACh release in young control rats and cognition-impaired and non-impaired aged rats similarly. Our results confirm and extend findings from other studies that demonstrate the cognition-enhancing action of DuP 996 in rodent models. Furthermore, our results suggest that the ACh-releasing action of DuP 996 may be beneficial only when cholinergic function is compromised.

741.15

THE SELECTIVE HISTAMINE H_3 RECEPTOR ANTAGONIST THIOPERAMIDE IMPROVES COGNITION AND ENHANCES HIPPOCAMPAL ACETYLCHOLINE RELEASE *IN VIVO*. J.C. Barnes, J. Clapham, R.P. Dennes, G.J. Kilpatrick, F.H. Marshall., C.T. O'Shaughnessy and E. Cavicchini*≈. Dept. Neuropharmacology., Glaxo Group Research Ltd., Ware, Herts., SG12 0DP, U.K. ≈ Dept. Pharmacology. Glaxo SpA., 37100 Verona, Italy.

It has recently been shown that the selective H_3 receptor antagonist thioperamide can increase the release of acetylcholine (Ach) from slices of rat entorhinal cortex *in vitro* (Clapham & Kilpatrick, 1992, Br.J. Pharmacol. 107, 919-923). In view of the link between central cholinergic function and learning and memory, this finding highlights a possible modulatory role for H_3 receptors in cognition. Thus, the ability of thioperamide to improve spatial learning and memory in different tasks was studied in the rat. Also, *in vivo* microdialysis was used to measure the ability of thioperamide to increase extracellular hippocampal Ach levels in the conscious rat. In a delayed non-matching to position task, a model of short term memory, thioperamide (0.2 - 2 mg/kg ip) dose-dependently improved performance. Following 2 mg/kg ip, accuracy across delays up to 16s was increased above control ($P<0.05$). This effect was seen from day 1 of treatment and was maintained on subsequent days of testing. In a serial reversal learning task in the T-maze, thioperamide (2mg/kg ip) reduced the number of trials to criterion of the reversal task on days 2 and 3 of testing ($P<0.05$). Thioperamide also improved performance on the retention task on day 3 ($P<0.05$). These data implicate the involvement of central H_3 receptors in the modulation of cognition. In the microdialysis experiments, thioperamide increased Ach levels in the dialysate (5mg/kg sc: 195± 10% of basal, $P<0.05$ vs saline, 97.3±11.4% of basal). These findings highlight the ability of H_3 receptors to modulate Ach release *in vivo* and thereby provide a possible mechanism underlying the cognitive-enhancing actions of thioperamide.

741.16

EFFECTS OF THE SELECTIVE M2 RECEPTOR ANTAGONIST, BIBN-99, ON ACETYLCHOLINE RELEASE IN AGED RATS AND SPATIAL MEMORY PERFORMANCE IN SCOPOLAMINE TREATED RATS. A. Wilson*, W. Rowe, M. Meaney, N.M. White, & R. Quirion. Douglas Hospital Research Center and Department of Psychology, McGill University, Montreal, Quebec, Canada, H3A 1B1.

We have recently reported that a selective new M2 receptor antagonist, BIBN-99, enhanced acquisition rates of aged cognitively-impaired rats in the Morris water maze task. The extent to which BIBN-99 modulates release of ACh in the CA1 region of the hippocampus was examined using an in vivo microdialysis technique. 24 month old male Long-Evans rats were categorized as impaired or unimpaired using the swim maze task. These animals were dialyzed using Ungersted ringer buffer containing physostigmine and ACh levels were determined using GC-MS. Subcutaneous injections of BIBN-99 which improved performance in the swim maze (0.5 mg/kg) increased hippocampal ACh release differentially in impaired vs unimpaired rats; 27.60% in unimpaired animals, as opposed to 86.73% in impaired animals. BIBN-99 was able to reverse performance deficits induced by scopolamine in young rats in the radial arm maze task. Male Long-Evans rats were subcutaneously administered scopolamine (0.1 mg/kg) 30 minutes before the test session. These animals made significantly more revisits to previously baited arms ($p=0.027$) than saline controls. Rats pretreated with BIBN-99 (0.5 mg/kg) 30 minutes before scopolamine (60 minutes before the test session) performed similarly to saline controls. These results indicate that the cholinergic M2 receptor antagonist BIBN-99 is able to potentiate ACh release in animals whose cholinergic system is made dysfunctional with age. Furthermore, the drug is able to improve memory performance in animals whose cholinergic system is made dysfunctional by an acute pharmacological manipulation. Supported by funds from MRCC and Karl Thomae, Gmbh, Germany.

741.17

WITHDRAWN

741.18

NOOTROPIC EFFECT OF NICOTINE ON CARBON MONOXIDE (CO)-INDUCED DELAYED AMNESIA IN MICE. M. Hiramatsu[1]*, H. Satoh[1], T. Kameyama[1] and T. Nabeshima[2]. [1]Dept. of Chem. Pharmacol., Meijo Univ., Nagoya 468, Japan and [2]Dept. of Neuropsychopharmacol. & Hospital Pharmacy, Nagoya Univ. Sch. of Med., Nagoya 466, Japan.

The involvement of nicotinic mechanisms in learning and memory is suggested by memory-enhancing effects of nicotine observed in both humans and experimental animals. In the present study, effects of nicotine on the carbon monoxide (CO)-induced amnesia in mice were investigated using a step-down type passive avoidance task. Male ddY strain mice (30-40 g) were exposed to CO 3 times with 1 hour interval at the rate of 10 cc/min 7 days before the first training and retention test was done 24 hr after the first training. Memory deficiency occurred in mice when training was commenced more than 3 days after CO exposure (delayed amnesia). The median step-down latency in the retention test of the CO-exposed group was significantly shorten than that of the control group. Administration of (-)-nicotine (15.6 and 31.3 nmol/kg, i.p.) 15 min before the first training prolonged the step-down latency in the CO-exposed group, but (+)-nicotine did not. To clarify whether the effect of (-)-nicotine was mediated via nicotinic cholinergic receptors, we attempted to block its action by using a nicotinic acetylcholine receptor antagonist, mecamylamine. Mecamylamine (1.25 μmol/kg) blocked the effect of (-)-nicotine (31.3 nmol/kg) on the delayed amnesia. Administration of (-)-nicotine (15.6 - 62.5 nmol/kg) immediately after the first training failed to improve the learning ability in the CO-exposed group. These results suggest that (-)-nicotine potentiates nicotinic cholinergic neuronal system and that it may potentiate acquisition of memory. This work was supported by the Japan Smoking Research Foundation.

BIOLOGICAL RHYTHMS AND SLEEP VII

742.1

DAY-NIGHT CHANGES IN NEUROPEPTIDE Y RECEPTOR BINDING IN THE SUPRACHIASMATIC NUCLEUS OF THE GOLDEN HAMSTER. H.I. Ryer[1]*, D.I. Friedman[1], E.G. Stopa[2] and H.E. Albers[3] [1]SUNY Health Science Center and VAMC, Syracuse NY, [2]Brown University, Providence, RI, [3]Georgia State University, Atlanta, GA.

The suprachiasmatic nucleus (SCN) of the hypothalamus is a circadian pacemaker that receives input from the retinohypothalamic tract (RHT) and the lateral geniculate nucleus via the geniculohypothalamic tract (GHT). Neuropeptide Y (NPY)-containing fibers in the GHT project to the ventrolateral SCN and modulate circadian rhythmicity. Fluctuation of neuropeptide Y within the SCN has been documented in rats, with peak NPY levels occurring during light-dark transitions. In hamsters, local administration of NPY within the SCN produces phase shifts in circadian wheel running rhythms that are similar to the phase shifts produced by pulses of darkness and transitions from light to dark. We evaluated NPY receptor density as a function of the circadian cycle in the golden hamster. NPY receptors were localized with ^{125}I-Peptide YY using receptor autoradiography in golden hamsters sacrificed at specific times during a 14:10 light-dark cycle as follows: 4 hours before onset of darkness ($n=7$), 1 hour before onset of darkness ($n=6$) and 2 hours after the onset of darkness ($n=6$). Peptide YY specific binding within the SCN was significantly higher after the light-dark transition. No similar fluctuations were observed in two other hypothalamic regions adjacent to the SCN. The observed receptor changes are consistent with fluctuations in NPY peptide concentrations within the SCN previously demonstrated in rats and suggest that NPY receptors may be regulated by environmental lighting conditions. Supported by Hendricks Research Fondation, NS25512, AG09301, AG10682.

742.2

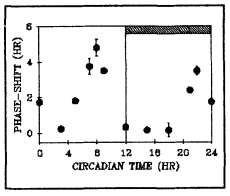
NEUROPEPTIDE Y (NPY) PHASE SHIFTS CIRCADIAN RHYTHMS IN GOLDEN HAMSTERS HOUSED IN CONSTANT DARKNESS. K.L. Huhman* and H.E. Albers. Lab. of Neuroendocrinol. & Beh., Depts. of Biol. & Psychol., GA State Univ., Atlanta, GA 30303.

The suprachiasmatic nucleus (SCN) has been identified as a circadian pacemaker in mammals. Information about environmental lighting reaches the SCN at overlapping terminal fields of a direct (retinohypothalamic tract - RHT) and an indirect (geniculo-hypothalamic tract - GHT) pathway from the retina. The GHT contains NPY immunoreactivity. NPY inhibits spontaneous discharge of SCN neurons *in vitro*, and microinjections of NPY phase shift activity rhythms in hamsters housed in constant light in a manner similar to pulses of darkness. If NPY mimics dark pulses by inhibiting the response of the SCN to light, then NPY should not produce phase shifts in hamsters housed in constant darkness (DD). Male hamsters free-running in DD were implanted with cannulae aimed at the SCN and were injected with NPY (100ng in 100nl saline, $N=17$) or vehicle (100nl saline, $N=13$) at times throughout the circadian cycle. NPY injections given between CT5-9 caused phase advances of 56 ± 20 min (vs. a 6 ± 6 min delay with saline). At CT14-18 NPY caused a 24 ± 9 min delay (vs. 0 ± 9 min with saline). The pattern of phase shifts produced by NPY in DD was very similar to that seen in constant light. These data suggest that NPY does not shift the clock by inhibiting lighting information transmitted by the RHT. Supported by NIH NS30022.

742.3

RAT SUPRACHIASMATIC CIRCADIAN PACEMAKER SHOWS TWO WINDOWS OF SENSITIVITY TO NPY IN VITRO. M. Medanic* & M.U. Gillette. Depts of Physiology & Biophysics, and Cell & Structural Biology, Univ. of Illinois, Urbana, IL, 61801.

Neuropeptide Y (NPY), present in the geniculo-hypothalamic tract to the suprachiasmatic nuclei (SCN), is thought to influence photic as well as behavioral entrainment in the mammalian circadian system. We have examined the role of NPY in rats by studying its effect on the electrical activity rhythm of SCN neurons *in vitro*. The SCN, isolated in hypothalamic brain slices from Long Evans rats (12L:12D), were briefly treated with a microdrop of NPY to the geniculate projection sites, at 11 time points across the circadian cycle. The effects of this treatment on the electrical activity rhythm were assessed extracellularly on day 2 and 3 *in vitro*. Phase shifts were determined by comparing the time-of-peak in NPY vs. vehicle treated slices. A microdrop of 10^{-6} M NPY was found to induce phase-shifts between CT 5-9 and CT 21-24, demonstrating two windows of SCN sensitivity which precede photic transitions in the entrained day-night cycle. (Supported by AFOSR Grant 90-0205).



742.4

HUMAN CHORIONIC GONADOTROPIN AFFECTS SLEEP/WAKE AND BEHAVIORAL PATTERNS IN RATS. P. Toth, H. Lukacs, E.S. Hiatt*, K.H. Reid, V. Iyer and Ch. V. Rao. Depts. OB/GYN, Anatomy/Neurobiology and Neurology, Univ. of Louisville, Louisville KY 40292

We recently demonstrated hippocampus and other rat brain areas contain luteinizing hormone/human chorionic gonadotropin (LH/hCG) receptors and ^{125}I-hCG injected into peripheral circulation can cross the blood brain barrier. In the present studies, we investigated the possible effects of hCG on sleep/wake activity and associated behavioral patterns. Adult cycling female rats (n=5) were prepared with chronic epidural electroencephalographic (EEG) and temporal muscle electromyographic (EMG) electrodes. Each rat was injected on proestrus first with saline and 4 days later with 100 IU hCG (CR-127) i.p. Three hours after saline or hCG injection, EEG, EMG and behavioral patterns such as grooming, rearing, walking, and sleeping were recorded for 3.5 hrs in the regular awake phase of the rat (6:00-9:30 PM). EEG and EMG were visually scored in 30 sec epochs by two different investigators for time spent in active awake (AW), quiet awake (QW) and sleeping (SL) phases. hCG significantly decreased AW with a concomitant increase of QW ($p<0.05$). SL showed a small consistent but nonsignificant increase. While behavioral patterns, grooming, rearing and walking decreased, sleeping increased after hCG administration. In summary, our study demonstrates that hCG decreases the activity of female rats. This pattern of decreased activity resembles that seen in first trimester pregnant women when serum hCG is highest.

742.5

MICROINJECTION OF NITRIC OXIDE SYNTHESIS INHIBITOR INTO THE BRAINSTEM SUPPRESSES SLEEP IN RATS. **L. Kapás*, M. Kimura, J. Fang, J.M. Krueger, Univ of Tennessee, Memphis, TN 38163.**

Our previous experiments indicated that NO may be involved in the regulation of sleep-wake activity. Systemic or intracerebroventricular injection of the NO synthase inhibitor Nω-L-arginine methyl ester (NLA) suppresses rapid-eye-movement sleep (REMS) and non-REMS (NREMS) in rabbits and rats. Several brain regions which are implicated in sleep regulation are rich in NO synthase enzyme. They are possible sites for the sleep suppressive effects of NO synthase inhibitor. In the present experiments we studied the role of one of these structures, the pedunculopontine tegmentum (PPT), in the sleep-suppressive effects of NLA. Cortical EEG electrodes, brain thermistor and intra-PPT guide cannula were implanted to eleven male rats. After a 10-day recovery and habituation period the sleep-wake activity of the rats was recorded under five different conditions. Intra-PPT injection of 1 µl saline did not affect sleep-wake activity compared to the non-injected control. Injection of 0.2 mg (0.3 µl) NLA elicited a significant NREMS suppression in the first two postinjection h. A higher dose of NLA (0.67 mg in 1 µl) suppressed NREMS to a greater extent for 3. REMS was also decreased in the first h, and increased in h 7 after the injection of the higher dose. These results indicate that NO produced in the PPT may be involved in the maintenance of spontaneous sleep.

Supported by NS-25378, NS-27250 and UT Medical Group.

742.6

ANTIDEPRESSANT EFFECTS ON HAMSTER CIRCADIAN ACTIVITY RHYTHMS Harry Klemfuss* & Daniel F. Kripke, Veterans Affairs Medical Center (151), San Diego, 92161, and Dept. of Psychiatry, Univ. of California, San Diego.

We tested whether antidepressant and prodepressant drugs consistently alter the light-synchronized phase and circadian period of the wheelrunning rhythm in adult male golden hamsters. The mood stabilizer lithium and monoamine oxidase (MAO) inhibitor clorgyline have been most thoroughly studied in this regard, but chronobiologic effects of tricyclic antidepressants, other MAO inhibitors, and atypical antidepressants have been reported, as have rhythm effects of drugs that can precipitate depressive symptoms in susceptible patients (e.g., clonidine, propranolol). This evidence is cited to support a relationship between circadian rhythmicity and mood disorders in human patients. However, other reports find no chronopharmacologic activity of some mood-altering drugs.

This study compared 5 antidepressants and 2 prodepressant agents. Of these 7 drugs, only clorgyline delayed light-synchronized wheelrunning rhythms (by 1.4 h compared to control) and increased the circadian period in constant darkness by 0.1 h ($p<.05$, Dunnett's test). Desipramine significantly shortened period by the same amount. However, other drugs (fluoxetine, amitriptyline, propranolol, phenelzine, clonidine) did not alter light-entrained phase or free-running period over a range of doses.

Effective antidepressant drugs may increase or decrease circadian period, but do not necessarily alter the phase or period of circadian rhythms. Therefore, it appears unlikely that antidepressant or depressogenic drugs act primarily by influencing circadian oscillators. However, in affective disorders with a chronobiologic component desipramine or clorgyline may potentially interact with the circadian rhythm disturbance.

Supported by the Dept. of Veterans Affairs and NIMH MH000117.

742.7

CIRCADIAN PHASE-RESPONSE CURVES TO MORPHINE AND ACTIVITY IN THE MOUSE. E. Marchant and R.E.Mistlberger*, Dept. Psychology, Simon Fraser University, Burnaby BC Canada V5A 1S6.

The rodent suprachiasmatic nuclei (SCN) function as a master pacemaker with a primary role in the regulation of circadian rhythms. Recent studies describe L-enkephalin immunoreactivity within the SCN of several rodent species, which in some cases may originate in cells of the intergeniculate leaflet afferent to the SCN. To assess a possible role for endogenous opiates in circadian function, we examined the effects of single morphine injections (25 mg/kg) on circadian wheel running rhythms of male C57BL/6J mice recorded in constant dim red light. Injections were made IP at 2-4 week intervals and 8 different circadian phases. Changes in free-running phase and period were quantified by regression lines fit to daily activity onset or end. Phase shifts were observed following 44 of 89 injections; these included 28 advances (mean=48 ± 39 min; max=200 min) and 16 delays (mean=30 ± 15 min; max=60 min). The phase-response curve (PRC) was of the "dark-pulse" type, with maximum advances (33 ± 49 min) to injections at mid-subjective day (CT6), and maximum delays (but primarily no responses) at mid-to-late subjective night. Bouts (1-4 h) of intense wheel running occurred with variable latency following many injections; phase shifts replotted with respect to the circadian time of drug-induced activity onset resulted in a PRC with advances at CT6-8, 12-14 and 18-20 and that conformed to no recognizable PRC type. Saline injections were without effect in 35/39 cases (max shift=-20 min). Further studies will attempt to assess the phase-shifting effects of morphine independent of drug-induced activity. Circadian phase-dependency of drug-induced activity will also be characterized.

Supported by an NSERC grant (R.E.M.) and Postgraduate Fellowship (E.M.).

742.8

INDUCED DAYTIME MELATONIN LEVELS COMPARABLE TO NORMAL NOCTURNAL LEVELS AFFECT HUMAN MOOD AND PERFORMANCE. A.B. Dollins, I.V. Zhdanova, M.H. Deng, H.J. Lynch, C.J. Watkins* and R.J. Wurtman, Department of Brain and Cognitive Sciences, M.I.T., Cambridge, MA 02139.

We examined the effects of 0.1, 0.3, 1.0, or 10 mg. of melatonin or placebo, administered at 1145 hr., on sleep latency and duration, mood, performance, and oral temperature in 20 healthy male volunteers. Subjects completed a battery of tests designed to assess mood and performance between 930 and 1700 hr.; the sequence and timing of the tests were identical on each day. The sedative-like effects of melatonin were assessed by a simple sleep test: at 1400 hr., subjects were asked to hold a positive pressure switch in each hand and to relax with eyes closed, while reclining in a quiet darkened room. Latency and duration of switch release, an indicator of sleep, were measured. All melatonin doses significantly increased sleep duration, as well as self-reported sleepiness and fatigue, relative to placebo. Sleep onset latency, oral temperature and number of correct responses on the Wilkinson Auditory Vigilance Task were significantly decreased by all melatonin doses. Responses did not differ between the 1 and 10 mg. doses. The 0.1 and 0.3 doses of melatonin produced elevations in circulating melatonin levels comparable in magnitude and time course to normal nocturnal levels. These data suggest that such normal melatonin levels have sleep-inducing properties.

742.9

RESPONSE OF COLLARED LEMMINGS TO MELATONIN IMPLANTS. T.R. Nagy, B.A. Gower*, and M.H. Stetson. School of Life and Health Sciences, University of Delaware, Newark, 19716.

Collared lemmings, *Dicrostonyx groenlandicus*, possess several interesting photoperiod-responsive traits. When transferred from long to short photoperiod, lemmings increase in body mass, molt to a white pelage, and develop a bifid "digging" claw. Since many of the effects of photoperiod are mediated by the pineal hormone melatonin, we tested the hypothesis that the ability to respond to a change in photoperiod is dependent upon detection of an endogenous, circadian melatonin rhythm. Using constant-release melatonin implants to mask the endogenous hormone rhythm, we examined the lemmings' ability to perceive and respond to photoperiod. Female lemmings were reared until weaning under either long (22L:2D) or short (8L:16D) photoperiods. At weaning, animals were given an implant of either beeswax or melatonin. Animals either remained in the preweaning photoperiod, or were transferred to the opposite photoperiod, for 8 weeks. Treatment with melatonin implants had no effect on any parameter measured in animals which remained on the preweaning photoperiod for the duration of the experiment. However, in those animals which experienced a change in photoperiod at weaning, implantation with melatonin prevented the change in pelage color, claw size, and uterine weight exhibited by the animals implanted with beeswax. The change in body mass induced by the change in photoperiod, however, was not blocked by implantation with melatonin. Consequently, we conclude that, whereas most seasonal physiological characteristics of the lemming require perception of the endogenous melatonin rhythm, photoperiod-mediated changes in body mass may be independent of this rhythm, and instead, respond to some other component of the circadian system. (Supported by NSF DCB87-14638 to MHS)

742.10

MELATONIN ATTENUATES LIGHT- INDUCED PHASE SHIFTS IN CIRCADIAN ACTIVITY IN C3H/HeN MICE. S. Benloucif,* M.J. Niblick and M. L. Dubocovich, Dept. of Pharmacology, Northwestern Univ. Medical School, Chicago, IL60611.

Activation of melatonin receptors at the site of the circadian pacemaker, the suprachiasmatic nucleus (Eur. J. Pharmacol.,1990, 180:387) appear to regulate circadian entrainment in mammals. However, a phase shifting effect for melatonin on free running activity has been difficult to demonstrate. While melatonin phase advanced the circadian rhythm of rats when administered at circadian times (CT) 9 - 11 (Adv. Pineal Res., 1991, 5:259), we found that this hormone (1 or 10 mg/kg i.p.) did not alter the circadian phase of C3H/HeN mice. Here we report a modulatory effect of melatonin on light-induced phase shifts. C3H/HeN mice, entrained to a 12:12 L:Dcycle, were placed in DD with activity monitored by running wheels. After a stable free running rhythm was obtained, a phase response curve was generated by applying a 15 min light pulse (300 lux) at various CTs. Delays in activity onset of up to 3 hours were observed when the light pulse occurred between CT 12 and CT 19, and advances in activity onset were observed when light was pulsed between CT 22 and CT 1. Delay and advance regions were used to test the effect of melatonin on light-induced phase shifts. Mice, free running in DD, were injected with either melatonin (3 mg/kg s.c.) or vehicle (10% ethanol/saline) 30 min prior to a light pulse. Melatonin alone did not shift activity onset (n = 5), but it reduced the delay in activity onset induced by a light pulse at CT 14 ($-1.05 \pm .32$ h vs. -2.57 ± 0.19 h for vehicle treated controls, $p < 0.001$, n = 7 - 8). In preliminary results, melatonin also reduced light-induced phase shifts at CT 18 and CT 21 - 1 (n = 4). These results suggest that melatonin affects circadian activity by modifying the action of light on the SCN. Supported by a Glaxo grant and NIH Fellowship T32-NS07140 (S.B.).

742.11

THE SEDATIVE-HYPNOTIC ACTIVITY OF MELATONIN MAY NOT BE MEDIATED BY BENZODIAZEPINE OR MELATONIN RECEPTOR BINDING SITES. K.L. Jorgenson* and A.D. Rotelli. Interneuron Pharmaceuticals Inc., Lexington, MA 02173.

It has been suggested that the benzodiazepine binding site of the GABA receptor may be involved in the sedative-hypnotic effects of melatonin. We have evaluated this possibility using hexobarbital-induced "sleep" and forced motor activity (rotorod) assays in mice. Melatonin (3-100 mg/kg) administered ip or po significantly increased the latency to recover the righting reflex in the hexobarbital "sleep" assay in a dose-dependent fashion. Coadministration of the benzodiazepine antagonist, flumazenil (0-300 mg/kg ip), did not block the effect of melatonin (100 mg/kg ip). However, as expected, flumazenil (1.0 mg/kg ip) did block the sleep-prolonging effect of triazolam (0.1 mg/kg ip). Analogous results were obtained with the rotorod test. Two putative melatonin receptor blockers, luzindole and ML-23, were also tested. Luzindole (30 mg/kg ip) itself increased sleep time and failed to block the effects of melatonin. ML-23 alone did not affect sleep time, and at doses up to 100 mg/kg (ip) did not block melatonin-induced increases in sleep time. Together these findings suggest that the sedative-hypnotic activity of melatonin may not be mediated through an interaction with benzodiazepine or melatonin receptors.

742.12

GLUTAMATE INDUCES LIGHT-LIKE PHASE SHIFTS IN THE RAT SCN IN BRAIN SLICE. J. M. Ding* and M. U. Gillette. Dept. of Cell & Structural Biology and Neuroscience Program, University of Illinois, Urbana, IL 61801.

The suprachiasmatic nucleus (SCN) receives direct visual input via the retino-hypothalamic tract (RHT). A number of behavioral, electrophysiological, and immunocytochemical studies suggest that glutamate (GLU) may play a role in photo-entrainment through the RHT pathway. We examined the effect of GLU on the phase of circadian rhythm of the electrical activity of the SCN in brain slice. Hypothalamic slices containing SCN from 7-10 wk male L-E rats in 12L:12D were treated focally with 1 µl GLU (10^{-7}-10^{-2} M, pH 7.4) for 10 min at different circadian times (CT). The phase of the circadian rhythm was determined by measuring the time-of-peak of the spontaneous discharge rate of the SCN in brain slice. The phase response curve (PRC) induced by GLU resembles the light-induced PRC with a maximum 4 hr ϕ_A at CT 19 and a 3 hr ϕ_D at CT 14-15. No phase shift was induced in the subjective day. This supports a role for GLU in photo-entrainment directly at the SCN. Furthermore, when GLU was applied at CT 17, the potential phase delay or advance transitional zone, multiple peaks of firing rate occurred, suggesting that within this particular time frame, the SCN might be intrinsically programmed to be able to shift to either direction. (Supported by AFOSR grant 90-0205).

742.13

INHIBITORY AMINO ACID NEUROTRANSMISSION IN THE DORSAL RAPHE NUCLEUS DURING SLEEP-WAKE STATES. Douglas Nitz and Jerome Siegel*Departments of Neuroscience and Psychiatry, UCLA School of Medicine, Los Angeles, CA, 90024-1763 and the Sepulveda VAMC.

Serotonergic neurons of the dorsal raphe nucleus (DRN) are tonically active in waking and non-rapid eye movement (NREM) sleep, cease discharge during the transition to REM sleep and are silent throughout the REM sleep period. The technique of microdialysis was employed in this study to investigate the possibility that glycinergic and/or GABAergic neurons mediate inhibition of activity of DRN neurons in REM sleep.

Cats were implanted with two guide cannulas aimed at the DRN and standard recording electrodes for the determination of sleep-wake states. Microdialysis samples were collected during sequential 5 to 10 minute periods of wake, NREM, and REM in three freely-moving cats. Samples were analyzed by high-performance-liquid-chromatography (HPLC) with electrochemical detection (ECD) for content of the inhibitory amino-acid neurotransmitters glycine and GABA.

Histological analysis of nissl-stained sections from 2 cats confirms placement of 2 of the probes on the midline of the central gray in the DRN. Two other probes were located 1.5 mm lateral to the midline in the central gray directly adjacent to the DRN.

GABA levels in the dialysates ranged between 5 and 500 femto-moles/microliter. Glycine levels ranged between 0.3 and 3 picomoles/micro-iter. Results indicate a significant increase in GABA release during REM sleep as compared to wake and NREM sleep. No significant differences were found between wake and NREM. Glycine release was remarkably similar in all three states.

The data is consistent with our hypothesis that REM sleep cessation of DRN serotonergic neurons is mediated by GABA.
(Supported by National Multisite Program for Basic Sleep Research NH18825, Medical Research Service of the VA and PHS grants HS14610 and HL41370.)

742.14

METABOTROPIC GLUTAMATE RECEPTORS REGULATE CALCIUM IN CULTURED NEURONS AND GLIA FROM THE SUPRACHIASMATIC NUCLEUS. K. G. Bina[1]*, A. H. Cornell-Bell[2] and A. N. van den Pol[1]. Depts. of [1]Neurosurgery and [2]Cell Biology, Yale Univ. Sch. of Med., New Haven, CT 06510.

In mammals, the suprachiasmatic nucleus (SCN) is responsible for the generation of circadian rhythms and its synchronization to exogenous cues. Glutamate appears to be the most likely transmitter candidate at the retinohypothalamic terminals in the SCN, thus implicating its role in entrainment. Metabotropic receptor protein is present in the SCN (van den Pol et al, this volume). This study was designed to determine if metabotropic receptors had any functional role in SCN cells. To monitor intracellular calcium (Ca^{2+}) changes in response to trans-ACPD (100 µM), an agonist at the metabotropic receptor, we used cultured cells obtained from late embryonic rat SCN area, time-lapse confocal laser microscopy and Fluo-3. Both neurons (identified by their response to NMDA) and glia responded to trans-ACPD with an increase in Ca^{2+}; some cells responded with ultradian oscillations (period of about 15s) This response was maintained in both calcium-free buffer and in buffer containing nitrendipine (10µM), an antagonist at the voltage sensitive calcium channel, suggesting that the increase in Ca^{2+} was a result of release from internal stores. L-AP3 (1mM), an antagonist at the metabotropic receptor, blocked the Ca^{2+} increase in more than half of the cells responding to trans-ACPD. These results suggest that increases in Ca^{2+} can arise from intracellular stores upon activation of metabotropic glutamate receptors and may contribute to SCN function.

742.15

REM SLEEP DEPRIVATION AND DOPAMINE RECEPTOR BINDING IN THE RAT CEREBRUM. A. Hamdi, J.Brock*, K. Ross, S Payne, and C. Prasad. Pennington Biomed.Res.Ctr., Baton Rouge, LA, 70808; Dept. Medicine, LSUMC, New Orleans, LA, 70112.

REM sleep deprivation (RSD) of rats results in facilitation of dopaminergic (DA) behavior and an increase in striatal DA-D2 receptor density. To determine whether RSD results in changes in D2 in other regions, D2 affinity (Kd) and density (Bmax) were measured in the anteromediofrontal (A) and cingulate (C) cortex in 4 groups of rats: RSD96 (RSD for 96 hrs using small-pedestal/water tank method); RSD24 (resided on large pedestal for 72 hrs then small pedestal for 24 hrs); TC (large pedestal for 96 hrs); and CC (home cages). Bmax and Kd were analyzed using [^{3}H]YM-09151-2 (Bmax in fmol/mg protein; Kd in pM; N = 6 each).

		CC	TC	RSD24	RSD96
(A)	Bmax	13.4±5	5.1±1^	12.8±3*	4.9±1
	Kd	51.6±22	25.4±9^	63.4±21*	36.2±18
(C)	Bmax	10.7±1	16.3±2^	17.3±10	10.4±2
	Kd	76.6±9	103.4±18^	123.4±54	62.2±17

(^ different from group CC; * different from TC)

Conclusion: The data are consistent with an increase in dopamine activity in the cerebrum of REM sleep deprived rats after 24 hrs which was selective for the anteromediofrontal region.

(Supported by the Dept. of Army)

742.16

MODULATION OF CATAPLEXY IN THE NARCOLEPTIC CANINE BY LOCAL PERFUSION WITH DOPAMINERGIC DRUGS M.S.Reid*, J.Geary, S.Nishino, J.M.Siegel, W.C.Dement and E.Mignot, Psychiatry Dept., Stanford University School of Medicine, Palo Alto CA 94304

Studies have shown that dopaminergic and noradrenergic drugs have significant effects on cataplexy in the narcoleptic canine when given systemically. In the present study, we have investigated the effects of monoaminergic drugs on cataplexy in narcoleptic canines when perfused locally, via microdialysis probes. Four different brain regions were studied; amygdala, globus pallidus (GP), nucleus accumbens and ventral tegmental area (VTA), using bilaterally implanted microdialysis probes (5 mm membrane) in awake, freely moving, narcoleptic Dobermans. Cataplexy and arousal state were measured using the Food Elicited Cataplexy Test and electrophysiological recordings of EEG, EOG and EMG. The drugs tested are known to either stimulate cataplexy; quinpirole, 7-OHDPAT, BHT-920, prazosin, or to inhibit cataplexy; raclopride and yohimbine, when given systemically. In the amygdala and nucleus accumbens, none of the above compounds produced any change in cataplexy. In the GP (N=4) and VTA (N=2), quinpirole and 7-OHDPAT (10^{-3}-10^{-2}M) produced a significant increase, while raclopride (10^{-3}M) produced a moderate decrease, in cataplexy. The increase in cataplexy produced by quinpirole and 7-OHDPAT was stronger in the VTA than in the GP, furthermore, the effects in the VTA appeared to be concommitent with an increase in sleepiness. The noradrenergic drugs were ineffective in either of these structures. These results suggest that cataplexy may be modulated by local stimulation of D2 and/or D3 dopaminergic receptors. The effects in the VTA indicate that dopaminergic projection neurons in the mesencephalon may be involved in mediating this effect, perhaps via dopaminergic autoreceptor inhibition. Further studies in the VTA will be performed

742.17

AUTORADIOGRAPHIC LOCALIZATION OF D1-DOPAMINE RECEPTORS IN THE FETAL AND NEONATAL HAMSTER SUPRACHIASMATIC NUCLEUS. W. N. Strother, K.A. Zimmer, A.B. Norman ‡, H.J. Duncan‡‡*, and M.N. Lehman. Departments of Anatomy & Cell Biology, ‡ Psychiatry,‡‡* Otolaryngology, Univ. Cincinnati College of Medicine, Cincinnati, OH 45267.

Recent evidence in rats (Weaver et al., PNAS, 89:9201) indicates the existence of an activatable dopamine system within the fetal suprachiasmatic nucleus (SCN), the site of an endogenous circadian clock. We examined the distribution of D1-dopamine receptors in the fetal and neonatal hamster brain using receptor autoradiography. Golden hamster brains were collected at embryonic days 13, 15, and postnatal days 1, 5, and 10. Adult tissue was used as a positive control. Brains were quick frozen on dry ice and stored at -20°C. Cryostat sections were cut at 10 microns and refrigerated overnight or processed the same day for receptor autoradiography. The slides were incubated in a buffered solution containing the specific D1 antagonist [3H]-SCH 23390 (3nM) for 90 minutes, at room temperature. Some slides were incubated with [3H]-SCH 23390 and1 μM (+) butaclamol for the determination of nonspecific binding. After thorough drying, the slides were juxtaposed to sheets of Amersham hyperfilm in x-ray cassettes and sealed. The cassettes were stored at 2°C for 7 days. Specific D1-dopamine receptor binding was first seen in the striatum of embryonic day 15 animals. Specific binding in the SCN was first seen at postnatal day 1 and persisted up to postnatal day 10. To determine whether there is an endogenous source of dopamine for D1 receptor activation in the developing SCN, we are currently examining fetal and neonatal hamster brains for the presence of tyrosine hydroxylase positive neurons and fibers. [Supported by NIH R01 NS 28175 to M.N.L.]

742.18

CATECHOLAMINE TURNOVER IN BRAIN AND WHITE ADIPOSE TISSUE OF SIBERIAN HAMSTERS EXPOSED TO LONG OR SHORT PHOTOPERIODS. T.G. Youngstrom* and T.J. Bartness. Depts. of Biology & Psychology, Georgia State University, Atlanta, GA 30303.

Siberian hamsters display a number of physiological responses when transferred to a short-day photoperiod (SD), including a reduction in body weight. The loss of body weight is expressed primarily as loss of fat (white adipose tissue; WAT). Internal WAT stores (*e.g.*,-epididymal WAT; EWAT) are lost preferentially during the first several weeks of constant exposure to SD, while peripheral WAT (*e.g.*,-inguinal WAT, IWAT) is depleted subsequently. Lipolysis is mediated, in part, by catecholaminergic (CA) innervation of the WAT. Depletion of lipid stores with SD exposure may result from changes in activity of CA containing nerves within WAT. Animals housed in a long-day photoperiod (LD) or SD for 5 wk were used to examine the turnover (TO) of CA in selected tissues, including medial basal hypothalamus (MBH), EWAT, IWAT and heart (HT). Adult male Siberian hamsters (*Phodopus sungorus sungorus*) were sacrificed at 0 h or received intraperitoneal injections of α-methyl paratyrosine then sacrificed at 2 or 4 h following 5 wk exposure to the selected photoperiod. Norepinephrine (NE) TO in brains of animals exposed to SDs was significantly higher. NE TO also was increased significantly in EWAT of SD-housed animals. In IWAT, NE TO in LD *vs* SD animals were not different from one another. Body weight is lost primarily as internal WAT during the initial few weeks of exposure to SD. The increased TO of NE in the EWAT of SD-housed animals and the similarity of TO of NE in IWAT of LD- and SD-housed animals may reflect the preferential lipolysis of these depots. Supported by NIMH RSDA MH00841 & NIH DK 35254 to TJB.

742.19

Nω-NITRO-L-ARGININE METHYLESTER, A BLOCKER OF NITRIC OXIDE SYNTHASE INHIBITS BRAIN CATALASE ACTIVITY IN RATS. S. Amir, F. Rogan, S.E. Rotzinger, P. Tisio and Z. Amit*. Ctr. Stud. Behav. Neurobiol., Dept. Psychol., Concordia Univ., Montréal, Québec, Canada, H3G 1M8.

Nw-Nitro-L-arginine methylester (L-NAME), a presumed specific inhibitor of nitric oxide synthase was found to also inhibit brain catalse activity in rat brain using both *in vivo* and *in vitro* preparations. We first observed that catalase activity in the hypothalamus was significantly inhibited in rats injected with 50 mg/kg of L-NAME and assayed both 6 and 24 hrs post injection. Assays of tissues from five other brain regions did not reveal any decrease in catalase activity. In an *in vitro* study we also observed that aliquotes of whole brain homogenates treated with five doses of L-NAME yielded a dose dependent reduction in catalase activity which was maintained, at least, over a six hour period. Finally, male Long Evans rats injected with 100 mg/kg of L-NAME were sacrificed at 0, 6, 24, 48, and 72 hrs post injection and their brains assayed for catalase activity at 1, 4, and 12 hrs after homogenization. These assays revealed a time dependent decrease in brain catalase activity with a maximal reduction at 48 hrs. The significance of these findings for the proposal that L-NAME is a specific blocker of nitric oxide synthase as well as its potential role as an inhibitor of catalase activity will be discussed. In addition, the potential role of L-NAME in studies on the involvement of brain catalase activity in the control of voluntary ethanol intake will be assessed.

742.20

SEROTONIN AGONIST AND MELATONIN EFFECTS ON PHOTIC RESPONSES OF HAMSTER SUPRACHIASMATIC NUCLEUS (SCN) AND INTERGENICULATE LEAFLET (IGL) CELLS. S.-W. Ying and B. Rusak*, Dept. of Psychology, Life Sciences Center, Dalhousie Univ., Halifax, N.S., Canada B3H 4J1

Neurons in the SCN and IGL are involved in mediating photic entrainment of mammalian circadian rhythms. Both serotonin (5-HT) and its derivative melatonin are known to affect circadian rhythms. We investigated the effects of 5-HT agonists and melatonin on spontaneous and photically evoked activity of SCN and IGL cells in hamsters. Hamsters were anesthetized with urethane, and single cells showing sustained responses to retinal illumination were recorded with a multibarrel micropipette to permit iontophoretic application of drugs.

5-HT agonists (5-HT, and the $5HT_{1A}$ agonists 8-OH-DPAT and 5-CT) suppressed both photic responses and spontaneous activity in a dose-dependent manner. The depressant effects could be antagonized by a non-selective 5-HT antagonist, metergoline, and a $5HT_{1A}$-directed antagonist, pindobind-$5HT_{1A}$. However, other drugs with $5HT_{1A}$ antagonist properties were weak (propranolol), or ineffective (pindolol and spiperone) in blocking agonist-induced responses, as were $5\text{-}HT_2$ antagonists (ketanserin and ritanserin). Melatonin generally mimicked the effects of 5-HT, but its effects were not attenuated by the 5-HT antagonist metergoline. The results indicate: 1. Photic responses of SCN and IGL neurons are regulated by serotonergic input and melatonin; 2. The effects of 5-HT are mediated by a receptor resembling the $5HT_{1A}$ receptor; 3. Melatonin acts through a non-5-HT receptor. Supported by grants from the US AFOSR and NSERC of Canada.

742.21

EFFECT OF LIGHTING CONDITIONS ON THE PHASE-SHIFTS CAUSED BY QUIPAZINE IN RATS. Jones BJ., Sidey FM* SmithKlineBeecham Pharmaceuticals, Coldharbour Rd., The Pinnacles, Harlow, Essex CM19 5AD, U.K.

The effect of saline or quipazine injection on the free running rhythms of rats was investigated under two experimental conditions. In the first experiment, animals were maintained in complete darkness and experimental manipulations were performed under dim red light. Injection of saline produced a phase reponse curve (PRC) in activity rhythms, with maximum advance at circadian time (CT) 21 (median phase-shift 69 min., interquartile range 0 to 110 min.) and maximum delay of 120 min. (96 to 140 min.) at CT15 (where CT12 is defined as activity onset). The timing of the phase-shifts was different from that seen in hamsters (Mead et al 1992) but was similar to that caused by exposure to light. In addition to this, quipazine caused a significant phase advance of 78 min. at CT3 (54 to 120 min., p=0.034 vs saline analysed by a permutation test of ANOVA), and a significant delay of 139 min. (84 to 168 min., p=0.05 vs saline) at CT21.

When animals were maintained and manipulated under constant dim red light the PRC caused by saline injection in the previous experiment was absent. Under these constant light conditions saline injection did not cause a phase-shift at any of the CTs tested (3,9,15 and 21). Injection of quipazine caused a phase **advance** of 60 min.at CT21 (24 to 102 min) rather than the delay seen at this time point in the first experiment. Thus the "saline" PRC observed in the first experiment was due to exposure of the animals to dim light at the time of injection, and the phase delay caused by quipazine was due to an interaction between the drug itself and exposure to dim light. These results reinforce the importance of experimental conditions in circadian research, and suggest that serotonin can interact with the circadian system at different levels.

Mead S, Ebling FJP, Maywood ES, Humby T, Herbert J, Hastings MH. (1992) J Neuroscience *12(7)* 2516-2522

742.22

A K^+ CHANNEL MEDIATES SEROTONERGIC- AND cAMP-INDUCED PHASE ADVANCES OF THE SUPRACHIASMATIC CIRCADIAN CLOCK. R.A. Prosser*, J.D. Miller, and H.C. Heller. Dept. of Biological Sciences, Stanford University, Stanford CA 94305.

We have previously shown that serotonin (5-HT) and the 5-HT agonists quipazine and 8-OH-DPAT (DPAT) phase-advance the suprachiasmatic (SCN) circadian clock through stimulating a 5-HT_{1A}-like receptor and activating the cAMP-dependent protein kinase PK-A. Also, the patterns of phase advances induced by 5-HT and cAMP analogs are similar. Here we investigated whether the mechanism through which these advances occur also involves the opening of a K^+ channel.

Coronal brain slices were prepared from male Wistar rats, maintained in a slice chamber, and continuously warmed, oxygenated, and perifused as described previously (Brain Res. 534,336). At circadian time (CT) 6 (CT 0=lights-on) slices were treated with DPAT (10 uM) or 8-benzylamino-cAMP (BA-cAMP; 10 uM) with or without a K^+ channel blocker ($BaCl_2$, 2 mM or apamin, 0.5 uM). $BaCl_2$ blocks all K^+ channels, while apamin selectively blocks a small conductance, Ca^{2+}-dependent K^+ channel. Single cell recordings were made on day 2 *in vitro*. The firing rates of single cells were averaged into 2 h means using 1 h lags to determine the time of peak activity, the phase marker used to determine shifts. DPAT and BA-cAMP induced shifts of 3-4 h when applied alone. The phase advances induced by DPAT and BA-cAMP were completely blocked by $BaCl_2$ (0.88 $\pm$ 0.35 h shift, n=3 and 0.13 $\pm$ 1.24 h shift, n=2, respectively) and apamin (0.5 $\pm$ 0.35 h shift, n=3 and 0.42 $\pm$ 0.1 h shift, n=3, respectively). Also, preliminary data suggest that these shifts are mimicked by valinomycin, a K^+ ionophore. These data support the conclusion that 5-HT- and cAMP-induced phase advances of the SCN circadian clock occur through opening a K^+ channel.

742.23

ELICITED PONTINE WAVES IN RATS: LACK OF EVIDENCE FOR $5HT_{1A}$ INHIBITORY MECHANISM. L.D. Sanford, S.M. Tejani-Butt, R.J. Ross and A.R. Morrison.* Depts. Anim. Biol. and Psychiatry, Univ. Penna., Phila., PA. 19104

Auditory stimuli elicit waves from the pontine site that yields spontaneous ponto-geniculo-occipital (PGO) waves during REM sleep in rats. The generation of PGO waves, and possibly elicited PGO waves (PGO_E), has been traced to "burst" neurons in the pedunculopontine (PPT) and lateral dorsal tegmental (LDT) nuclei of the pons in cats. Serotonin (5HT) likely is an inhibitory modulator of PGO wave generation. Bursting neurons of rat LDT are inhibited in vitro by a $5HT_1$ agonist. However, lesions of PPT, not LDT, eliminate PGO waves in cats. We investigated the inhibition in vivo of PGO_E by a $5HT_{1A}$ agonist, administered systemically or locally into PPT. Rats (N=8) were implanted with electrodes with the tip in the vicinity of the locus coeruleus for recording PGO_E. Subcutaneously administered (N=3) 8-OH-DPAT (0.3, 1.0, 3.0 mg/kg) produced no change in PGO_E amplitude but did increase response frequency in 8 blocks of 40 white noise stimuli (90 ms, 100 dB, 0.2-50 kHz, 2 s ISI). Microinjections of 8-OH-DPAT (0.01, 0.1, 1.0 μg/0.5 μl) into PPT (N=5) did not alter PGO_E response frequency or amplitude across 6 blocks of 40 tones (90 ms, 110 dB, 4 kHz, 2 s ISI). Quantitative autoradiographic ^{3}H-cyanoimipramine analysis of presynaptic uptake sites for 5HT indicated moderate 5HT innervation in PPT, but there was little ^{3}H-8-OH-DPAT binding (1 Nm) to $5HT_{1A}$ receptor sites in this region. We conclude that inhibitory modulation of PGO_E in rats does not involve $5HT_{1A}$ receptors in PPT. We speculate that systemic 8-OH-DPAT may have been operating at $5HT_{1A}$ autoreceptors in the dorsal raphe nucleus to decrease serotonergic cell firing and thereby increase the response frequency of PGO_E. Supported by MH42903 and D.V.A. Med. Res. Serv.

742.24

BLOCKADE OF MUSCARINIC M_2 RECEPTORS IN THE MEDIAL PREOPTIC AREA: EFFECTS ON THE SLEEP-WAKE CYCLE. L. Imeri*, S. Bianchi, P. Angeli▪ and M. Mancia. Istituto di Fisiologia Umana II, Università di Milano, Milano and ▪Dip. di Scienze Chimiche, Università di Camerino, Camerino, Italia.

The aim of this study was to evaluate the role played by muscarinic M_2 receptors of the Medial Preoptic Area (MPA) in the regulation of the sleep-wake cycle. Microinjections of methoctramine (MET), a highly selective M_2 antagonist, were performed in the MPA of freely moving rats, instrumented for chronic recordings of EEG, EOG and EMG. A stainless steel guide cannula was stereotaxically implanted (tip 3 mm above the MPA). MET (1, 5 and 10 μg) was dissolved in sterile isotonic saline (0.1 μl). The site of the injection was histologically verified. After MET microinjection, a dose-dependent decrease in slow wave sleep (SWS) and an increase in wakefulness were observed during 6 hour recordings. 5 and 10 μg MET also induced a significant reduction of desynchronized sleep (DS) amount. DS and SWS latencies were increased only by the highest dose tested (10 μg). The results suggest that MPA muscarinic M_2 receptors are involved in sleep control.

742.25

CHOLINERGIC DEVELOPMENT IN THE HUMAN LATERAL GENICULATE NUCLEUS (LGN) ACROSS EARLY LIFE. DD Seilhean, HC Kinney*. Children's Hospital and Harvard Medical School, Boston, MA.

The neurochemical basis for the marked developmental changes in sleep-wake states occuring during early human life remains little known. We examined development of cholinergic receptors and terminals over early life within the LGN, a structure extensively used as a model for arousal pathways. We studied ^{3}H-nicotine binding to nicotinic receptors (nAChRs) and ^{3}H-quinuclidinyl benzilate (QNB) binding to muscarinic receptors (mAChRs) in adjacent tissue sections using quantitative receptor autoradiography; the distribution of cholinergic terminals was determined by acetylcholinesterase (AChE) histochemistry. Cholinergic parameters in the LGN from 4 midgestational fetuses (21 weeks gestation), 2 newborns, and 5 infants (from 2 to 15 postnatal months) were compared to those from 2 adults. For all ages, ^{3}H-nicotine binding in the LGN was relatively high, and contrasted with very low levels of binding in the other sensory relay nuclei. ^{3}H-QNB binding in the LGN was low in the fetal period and increased over the first year of life, with adult levels attained around 15 postnatal months. AChE staining was low in fetuses, and moderate-to-high from birth to 15 postnatal months. ^{3}H-nicotine and ^{3}H-QNB binding, and AChE staining were uniform throughout the LGN laminae. The heterogeneous distribution of nAChR and mAChR binding among thalamic nuclei suggests differential effects of ACh. The increase in ^{3}H-QNB binding between midgestation and infancy further suggests that developmental changes related to the cholinergic modulatory effect in the LGN are, at least in part, secondary to changes in mAChRs. (Supported by NICHD 20991, National SIDS Alliance, and Fondation de France.)

742.26

Excitatory effects of histamine on nucleus basalis cholinergic neurones in guinea-pig brain slices. A. Khateb*, P. Fort, A. Pegna, B.E. Jones°, M. Mühlethaler *Dept. of Physiology, CMU, 1211 Geneva 4, Switzerland and °Montreal Neurological Inst., McGill University, Canada H3A 2B4*

With afferent input from the brainstem reticular formation and widespread efferent projections to the cerebral cortex, the cholinergic neurones of the nucleus basalis are thought to represent an important component of cortical activating systems. Histaminergic neurones situated in the posterior hypothalamus within the tuberomamillary nuclei are also believed to play an important role in cortical activation, in part by direct cortical projections. The interaction in between the histaminergic hypothalamic and the cholinergic basalis systems could thus be of importance in the coordinated function of ascending activating systems. We therefore examined whether identified cholinergic neurones of the nucleus basalis were sensitive to histamine in the guinea-pig brain slice. Using intracellular recordings, we found that such neurones were usually strongly depolarized by histamine. This effect was accompanied by an increase in membrane resistance and in firing rate. The depolarizing effect of histamine persisted in presence of either TTX or a high Mg^{2+}/low Ca^{2+} solution and is therefore most certainly postsynaptic. The effect of histamine could be mimicked by impromidine, a very specific H2 agonist which is devoid of any agonist activity on the H1 receptor. Neither agonists (alpha-methyl histamine) nor antagonists (thioperamide) of the H3 receptor had any effect on the membrane potential. Our results suggest that the involvement of histamine in cortical activation and arousal may be mediated not only by direct cortical projections but also by recruitment of other activating systems including the basalo-cortical system. (Swiss NSF, Canadian MRC, Fondation Fyssen and Lyonnaise des Banques).

742.27

STATE-DEPENDENT RELEASE OF THALAMIC ACETYLCHOLINE MEASURED BY *IN VIVO* MICRODIALYSIS. J.A. Williams*, H.C. Fibiger and P.B. Reiner Kinsmen Laboratory of Neurological Research, Dept. of Psychiatry, University of British Columbia, Vancouver, B.C. Canada, V6T 1Z3.

Brainstem cholinergic neurons have been suggested to play a key role both in EEG desynchrony and rapid-eye-movement sleep (REM) generation. However, the state-dependent activity of brainstem cholinergic neurons remains unclear. In an attempt to resolve this issue, we carried out experiments using *in vivo* microdialysis, in which acetylcholine release was measured across behavioral states in the rat thalamus, a major projection site of brainstem cholinergic neurons. In each rat, a transverse dialysis probe was stereotaxically implanted in the thalamus (AP= -3.3; DV= -5.6 from bregma) with 6 mm active surface exposed to all but the reticular thalamic nuclei. Electrodes for recording cortical EEG and either hippocampal theta or nuchal EMG were also implanted for monitoring behavioral states. Because REM periods in rats are short-lived, we developed a method to collect and accumulate dialysate samples from each of the individual behavioral states of wake, slow-wave sleep (SWS) and REM that were large enough for off-line analysis via HPLC-ECD. Probe placement and the source of cholinergic input to the microdialysis probe were verified with retrograde tracing by fluorogold and ChAT immunohistochemistry. The preliminary results from these experiments suggest that extracellular concentrations of acetylcholine in the thalamus are highest in REM, intermediate in wake, and low during SWS.

742.28

MUSCLE ATONIA CAN BE GENERATED BY CARBACHOL IN CATS ANESTHETIZED WITH α-CHLORALOSE. F. López-Rodríguez*, K. Kohlmeier, F. R. Morales and M. H. Chase. Dept. of Physiology, Dept. of Anatomy and Cell Biology, and the Brain Research Institute. UCLA School of Medicine, Los Angeles, CA 90024.

Cholinergic excitation of structures in the pontine reticular formation appears to be a key step in the induction of active sleep *(for review, see Jones et al., Neuroscience, 1990, 40:637-656)*. For example, muscle atonia which occurs as a result of postsynaptic inhibition of motoneurons during active sleep is also present after carbachol is injected into the pontine reticular formation *(Morales et al., J. of Neurophysiology, 1987, 57, 4: 1118-1129)*. In the present study, in order to obtain information regarding the mechanisms that generate atonia during active sleep and to provide a paradigm for studying atonia in anesthetized cats, we determined whether cholinergically-induced atonia could be generated in an animal that was anesthetized with α-chloralose. Experiments were performed in cats that were chronically implanted to monitor states of sleep and wakefulness. Cats anesthetized with α-chloralose (40 mg/kg, I.V.) exhibited spikes in the EEG, hippocampus and LGN. Muscle atonia occurred after carbachol (200mM) was injected by microiontophoresis (300-500 nA) into the laterodorsal portion of the pontine reticular formation; the spikes in the EEG and hippocampus were still present. In the same cats when they were not anesthetized with α-chloralose, carbachol injections in the same sites induced active sleep, with its accompanying pattern of muscle atonia; this suggests that the atonia induced by carbachol in chloralose-anesthetized cats is mediated by the same mechanisms that operate in the unanesthetized animal. We conclude that the cholinergically-induced processes that initiate and maintain muscle atonia are not blocked by the action of α-chloralose. In further experiments we will explore the mechanisms that are utilized to suppress motoneuron activity in the carbachol-chloralose-anesthetized animal and determine whether they are similar to the glycinergic postsynaptic processes that are employed during active sleep. Supported by NS 09999.

742.29

SENSORY RESPONSES OF "POSSIBLY" CHOLINERGIC NEURONS IN THE RAT LATERODORSAL TEGMENTAL NUCLEUS. Y. Kayama* and Y. Koyama. Dept. of Physiol., Fukushima Med. Col., Fukushima 960-12, Japan.

Cholinergic neurons in the laterodorsal tegmental nucleus are proved to have a pivotal role in neural machanism of paradoxical sleep. They may also function in some aspect of waking mechamism. To clarify the latter role, we recorded from the putative cholinergic neurons, distinguished with their "broad spikes" (Kayama et al., Brain Res. 569:210,'92), in undrugged, head-restrained rats, and their sensory responses were evoked by light touch to the tail, air puff to the face, and auditory tone. Sensory responses evoked by different stimuli were the same in quality in a neuron. The sensory response most commonly observed was composed of a short duration of high-frequency firing, which attenuated strongly by repetition of the stimulation. Some neurons having this type response were most active during paradoxical sleep and inactive during wakefulness, and the on-going discharges suddenly stopped when a sensory stimulus was given during sleep. Another type response was initiation or increase of tonic discharges, in which response to each of repeated stimuli was not clear. Neurons with the latter response may be concerned in waking mechanism to elevate vigilance level, while those with the former in transient elevation of global excitatory level to cause attention to a novel stimulus.

742.30

DISCRIMINATIVE STIMULUS EFFECTS OF MELATONIN (M) IN THE RAT. K.W. Locke* and T.R. Levesque. Interneuron Pharmaceuticals Inc., Lexington, MA 02173.

To evaluate the mechanism(s) underlying the sedative-hypnotic properties of M, rats were trained to discriminate M (150 mg/kg, ip) from saline in a discrete-trial avoidance paradigm. Stimulus generalization curves for M were steep; complete generalization with M occurred at 100-150 mg/kg. Triazolam generalized completely with M (n=7). However, flurazepam generalized completely with M in only 2 out of 6 rats; partial generalization was produced in the remaining 4 animals. The M-appropriate responding produced by triazolam was antagonized completely (in 6 out of 7 rats) by 0.3-10 mg/kg of flumazenil. In contrast, the dose of flumazenil necessary to completely block the M-like discriminative effects of triazolam failed to block the stimulus effects of the training dose of M. These results suggest that the discriminative effects of M may not be mediated through benzodiazepine receptors. Pentobarbital produced primarily M-appropriate responding, with complete generalization with M in 5 out of 7 rats. Diphenhydramine generalized completely with M in 2 out of 7 rats, however, little or no partial generalization was observed in the remaining 5 rats. Together, these results suggest that although M shares discriminative effects to some degree with a variety of sedative-hypnotics, the mechanisms underlying these effects may be different.

INGESTIVE BEHAVIORS VII

743.1

FEEDING INDUCED BY MERCAPTOACETATE (MA) BUT NOT BY 2-DEOXY-D-GLUCOSE (2DG) IS SUPPRESSED BY FOURTH VENTRICLE (4V) INJECTION OF THE GALANIN RECEPTOR ANTAGONIST, M40. F.H. Koegler*, S. Ritter. Department of VCAPP, Washington State University, Pullman, WA 99164-6520.

2DG and MA stimulate feeding by blocking glucose and fatty acid metabolism, respectively. MA- but not 2DG-induced feeding requires vagal sensory neurons that terminate in the area postrema/nucleus of the solitary tract (AP/NTS). However, 2DG-induced feeding also requires neurons in the AP/NTS region. The chemical mediators of 2DG- and MA-induced feeding are not known. However, we recently found that galanin (GAL), a peptide which stimulates feeding when injected into the PVN and amygdala, is present in rat vagal sensory neurons and NTS terminals. Therefore, we assessed the potential participation of GAL in 2DG- and MA-induced feeding. We found that 4V GAL stimulates feeding. In addition, 4V injection of M40 supresses feeding induced by systemic MA, but not by 2DG, in 60 min tests. Thus, GAL terminals, possibly in the NTS, may mediate MA-induced feeding.

ip/sc	4V	food intake(g)	*p<.05	N
	sal	0.0 ± 0.0		
	GAL	1.1 ± 0.4	*vs sal	8
sal	sal	0.2 ± 0.1		
MA	sal	1.5 ± 0.0	*vs sal/sal	5
MA	M40	0.8 ± 0.2	*vs MA/sal	5
sal	sal	0.2 ± 0.1		
2DG	sal	1.4 ± 0.4	*vs sal/sal	7
2DG	M40	1.2 ± 0.2	n.s. vs 2DG/sal	7

743.2

DIFFERENTIAL EFFECTS OF INFUSED NUTRIENTS ON 2DG-AND MA-INDUCED FEEDING. L.K. Singer* and S. Ritter. Department of VCAPP, Washington State University, Pullman, WA 99164-6520.

Previously we reported that 2-deoxy-D-glucose (2DG)-induced feeding can be reversed by intravenous infusion of glucose but not by equicaloric infusion of lipid. Mercaptoacetate (MA)-induced feeding, on the other hand, can be reduced by either intravenous glucose infusion or lipid infusion. (Soc. Neurosci. Abstr. #514.4, 1992). We have extended these results by examining the effect of intravenous infusion of fructose on 2DG- and MA-induced feeding. Fructose, a sugar that is not an energy substrate for the brain, did not significantly reduce 2DG-induced feeding. Rats injected with 2DG (200 mg/kg) and infused with saline ate 12.35±1.14 kcal while rats injected with 2DG and infused with fructose ate 9.63±2.3 kcal (p>.05). MA-induced feeding was significantly reduced by fructose infusion. Rats injected with MA (600 μmol/kg) and infused with saline ate 13.28±1.99 kcal while rats injected with MA and infused with fructose ate 5.24±1.59 kcal (p<.05). Together these results suggest that 2DG-induced feeding is mediated by receptor cells which are selectively responsive to glucose availability while receptors mediating MA-induced feeding are responsive to a wider range of metabolic fuels.

743.3

HYPOTHALAMIC DYNORPHIN EXPRESSION DURING FOOD DEPRIVATION. J.D. White*, X. Lu and P. Camp. Div. Endocrinology SUNY Stony Brook, Stony Brook, NY 11794

The opioid peptides have long been suspected to play a role in the regulation of food intake. In particular, dynorphin (DYN), and other kappa receptor ligands, are thought to act in the hypothalamic paraventricular nucleus (PVN) to stimulate the intake of fatty foods. In the present study, we used *in situ* hybridization methods to test the hypothesis that hypothalamic DYN expression will be increased by food deprivation (FD). Adult male Sprague-Dawley rats were fed *ad libitum* or FD for 72hr, with free access to water, and then perfused with 4% paraformaldehyde. 30μm coronal tissue sections were processed for *in situ* hybridization using a ^{35}S-labeled cRNA probe to rat proDYN. Hybridization was assessed from film autoradiograms, using an MCID image analysis system, over 7 brain regions: ventromedial nucleus (VMN), dorsomedial hypothalamus (DMH), arcuate nucleus (ARC), supraoptic nucleus retrochiasmatic (SOR), supraoptic nucleus (SON), PVN and hippocampal dentate gyrus (DG). In both fed and FD animals, hybridization signal was readily apparent and corresponded well with immunohistochemical localization of DYN-containing neurons. A complex regulation of DYN expression was observed in hypothalamus following FD. In SON and ARC, no change in hybridization was measured. In VMN, DMH and PVN, DYN expression was diminished with FD. Finally, in SOR DYN expression was increased with FD. DG DYN expression was unaffected by FD. These data suggest that hypothalamic DYN expression is modulated by the metabolic and hormonal status of the animal. However, the complex nature of the data does not permit simple interpretation in the context of DYN's role in food intake.

743.4

THE KAPPA-AGONIST, U-50,488, INCREASES THE INTAKE OF SUCROSE SOLUTIONS AT HIGH CONCENTRATIONS: EVIDENCE FOR AN EFFECT ON SATIATION. J. Stewart * and A. Badiani. Center for Studies in Behavioral Neurobiology, Dept. Psychology, Concordia University, Montréal, Canada, H3G 1M8.

Kappa-opioid agonists enhance feeding and depress drinking. It has been reported that they also increase intake of a 20% sucrose solution or of sweetened condensed milk, a finding attributed to an increase of the hedonic properties of sweet solutions by the kappa-opioid. An alternative explanation is that kappa agonists delay satiation by reducing the effect of post-ingestive factors.

In sham-feeding rats where post-ingestive factors are minimized, the intake of sucrose solutions increases monotonically with increasing concentrations, whereas in normal-feeding rats, intake follows an inverted U-shaped curve, with reduced intake at the higher concentrations. A manipulation that delayed the development of satiation would be expected to increase intake of high concentration sucrose solutions, but not of low concentration solutions. On the contrary, one that enhanced the hedonic properties of sucrose would be expected to increase the intake only at lower concentrations.

We tested the effect of U-50,488 (U50) on the intake of 1, 4, 16,32 and 40% sucrose solutions in 30-min tests in normal-feeding rats. U50 increased intake of the 32 and 40% solutions and depressed the intake of the 1% solution. This finding supports the view that U50 increases feeding by delaying satiation.

743.5

ONTOGENY OF OPIOID MEDIATION OF SUCROSE INTAKE IN THE RAT. J. Philopena and G.P. Smith*. E.W. Bourne Behavioral Research Laboratory, New York Hospital-Cornell Medical Center, White Plains, NY 10605.

To investigate the ontogeny of opioid mediation of sucrose intake, we administered naloxone (1mg/kg,ip) 15 min before pups (n=8-40) ingested 10% sucrose for 20 min from the floor of a beaker (Independent Ingestion, II) or from a continuous intraoral infusion through an anterior, sublingual catheter (OC). Pups were tested on postnatal (PN) days 7,9,11, and 14. Each pup was tested once without prior experience with 10% sucrose or the test conditions. Naloxone (NX) inhibited intake significantly in II as early as PN11, but NX did not inhibit intake in OC until PN14. On PN14, the threshold dose for inhibition of intake in II and OC was 0.1mg/kg. These results demonstrate that endogenous opioid mechanisms become necessary for the normal ingestion of 10% sucrose by PN11. The apparently equivalent efficacy of NX in II and OC tests on PN14 contrasts with the efficacy of D_1 and D_2 antagonists in II, but not in OC, at the same age (Tyrka and Smith, 1991; Tyrka et al., 1992). This difference in the efficacy of NX and DA antagonists demonstrates that endogenous opioids are necessary for ingestion in OC at this age, but endogenous DA mechanisms are not.

Supported by MH15455.

743.6

EFFECTS OF OPIATE RECEPTOR BLOCKADE IN THE NUCLEUS ACCUMBENS ON FEEDING BEHAVIOR. E.P. Bless, A.E. Kelley and H. Mahut*. Department of Psychology, Northeastern University, Boston, MA 02115.

It is well established that peripheral injections of morphine, an opiate agonist, induce feeding in satiated rats. There is also evidence that peripheral injections of the opiate antagonist naloxone can reduce food intake. The nucleus accumbens, a subregion of the striatum, contains a high concentration of opiate receptors. In the first experiment, food-deprived rats were given microinjections of methyl naloxonium bromide (MN, 0, 0.05, 0.5, 5.0 µg/1 µl), into the nucleus accumbens. Various aspects of feeding behavior and general motor activity were recorded for a 30 minute session by an observer blind to treatment. MN caused a dose-dependent decrease in total food intake which did not reach statistical significance ($p<0.06$). MN also significantly decreased the total time spent feeding; however, number of feeding bouts was increased by MN. The highest dose of MN also elicited an increase in locomotion and rearing. In the second experiment the effects of intra-accumbens infusion of MN (0, 0.5, 2.5 µg/1µl) and naloxone (20 µg/1µl) on palatable food intake (Froot Loops) were examined in non-deprived animals. Naloxone significantly decreased gram intake of palatable food, feeding bouts, and feeding duration. Naloxone also significantly decreased locomotor activity but had no effect on rearing. In contrast, MN had no effect on any aspect of feeding or activity. These results suggest that the opiate receptors in the nucleus accumbens mediate certain aspects of feeding behavior, and that naloxone may be better suited than MN in revealing these effects. Moreover, the opiate system in this region may play a specific role in the rewarding aspects of feeding.

743.7

EFFECTS OF DIET COMPOSITION AND DIET PREFERENCE ON PAIN SENSITIVITY AND MORPHINE ANALGESIA. B.A. Gosnell*, D.D. Krahn, S.M. Bell and K.E. Lane. Dept. of Psychiatry, University of Wisconsin and W.S. Middleton VA Hospital, Madison, WI 53792.

Opioids appear to be involved in mediating both diet/taste preferences and pain sensitivity. Furthermore, access to dietary fat or sweet solutions has been shown to alter morphine analgesia. A series of experiments was performed to determine whether pain sensitivity is related to diet preferences and whether short-term ingestion of particular diets alters pain sensitivity. The tail-flick (TF) assay was used in all tests; baseline latencies generally ranged from 2.5-3.5 s. In male rats (n=52), no relationship was observed between baseline TF latencies and subsequently determined preferences for a high-fat vs. a high-carbohydrate diet. In a second experiment, rats (n=30) were food-deprived overnight and allowed to re-feed on either a high-fat or a high-carb diet; a third group was not re-fed. TF latencies were measured every 30 min for 2 hr. Food deprivation did not alter baseline TF latency. TF latencies decreased in all groups over the 2 hr test period; the largest decreases were observed in rats consuming the high-fat diet. Maximum changes occurred at 60 min in the non-feeding group (-0.20 s), at 30 min in the high-carb group (-0.29 s) and at 90 min in the high-fat group (-0.64 s). In a third experiment, morphine analgesia (morphine sulfate,10 mg/kg, i.p.) was measured in rats maintained on single diets (either high-fat or high-carb). Analgesia tended to be greater and more long-lasting in rats fed the high-fat diet. These studies support work by others indicating effects of dietary factors on pain sensitivity and/or morphine analgesia. Supported by NIDA Grant DA05471.

743.8

CTAP, NALTREXONE AND NALTRINDOLE REDUCE DEPRIVATION-INDUCED FEEDING IN PIGEONS. D.C. Jewett*, S.S. Negus and J.H. Woods. Dept. of Pharmacology; Univ. of Michigan, Ann Arbor, MI 48105.

Opioid antagonists reduce food intake in a variety of species under a number of different conditions. The effects of receptor selective opioid antagonists were studied in pigeons following short periods of food deprivation. Twelve-hr, food-deprived pigeons consume 11 gm of food in the subsequent 4-hr period of food access, whereas undeprived pigeons consume about 2 gm during a 4-hr period. CTAP, a peptidic, highly selective mu receptor antagonist delivered intraventricularly, eliminated the effects of deprivation on food intake when 100 ng was administered 15 min prior to food access. Smaller doses (10-32 ng) had intermediate effects. Naltrexone, an antagonist with highest affinity for mu receptors, also eliminated the effects of deprivation on food intake. An intramuscular dose of 0.32 mg/kg, given 15 min prior to food access, was sufficient to eliminate the 12-hr deprivation effect; smaller doses had intermediate effects. Naltrindole, a delta selective receptor antagonist, was also effective in eliminating the 12-hr deprivation effect completely. An intramuscular dose of 10 mg/kg (15 min prior to food access) was necessary; this large dose of naltrindole has antagonized mu agonist behavioral effects in pigeons. Taken together, these antagonists may be exerting these effects through the mu receptor. If the period of deprivation is increased to only 24 hr, a considerably higher dose of naltrexone (10 mg/kg) is required to eliminate the effect of deprivation.
Supported by USPHS Grants DA-00254 and DA-07268.

743.9

COMPARISON OF SYSTEMIC AND INTRACRANIAL ADMINISTRATION OF MORPHINE: EFFECTS ON HEDONIC TASTE REACTIVITY (IN RATS). S. Peciña* and K.C. Berridge, Department of Psychology and Neuroscience Program, University of Michigan, Ann Arbor, MI 48109

Opioids have been shown to increase food intake. Some have suggested that this effect is in part mediated by an increase in palatability. This hypothesis has been supported by recent findings that morphine i.p. enhances rat "hedonic" responses to a 7% sucrose solution in the Grill and Norgren taste reactivity paradigm (Doyle, Berridge and Gosnell, in press).

This experiment was designed to compare systemic and intracranial administration of morphine on hedonic and aversive reactions to sweet (7% sucrose) and bitter/sweet (7% sucrose, 0.01% quinine HCL) tastes. Animals were implanted with oral cannulae and with intracranial guide cannulae aimed at the lateral ventricles or at the hypothalamic paraventricular nucleus (PVN). On alternate days, rats were treated with morphine sulfate and with saline, either systemically (4mg/kg, i.p.) or intracranially (10, 50 and 100 nmoles for the lateral and third ventricles; 1, 10 and 50 nmoles for the PVN). Thirty minutes, 1 h, 2 h and 3 h after the injection the animals were tested with to a 1min oral infusion of a sweet or bitter/sweet solution using the taste reactivity technique. The hedonic and aversive reactions to the tastes were videotaped and quantified.

743.10

OPIOID RECEPTOR SUBTYPE ANTAGONIST EFFECTS ON DEPRIVATION AND GLUCOPRIVIC MACRONUTRIENT INTAKE IN RATS. J.E. Koch* and R.J. Bodnar. Psychology Dept., Queens Col., CUNY, Flushing, NY 11367.

Whereas mu and mu_1 opioid antagonists inhibit hyperphagia following food deprivation (FD), mu and kappa antagonists inhibit 2-deoxy-D-glucose (2DG) hyperphagia (Life Sci. 36: 829-833, 1985; Brain Res. 534: 313-316; 535: 101-109, 1990). The present study evaluated whether opioid antagonist effects selectively altered specific macronutrients. Systemic (0.1-5 mg/kg) naltrexone (NTX) inhibited all macronutrients following 2DG, and inhibited carbohydrate (CARB) and fat intake following FD. Central (1-50 ug) NTX inhibited only fat following 2DG and FD. Central beta-funaltrexamine (mu: 1-20 ug) inhibited both CARB and fat intake following 2DG and FD. Central naloxonazine (mu_1: 10-100 ug) inhibited both CARB and fat intake following only FD. Delta and kappa antagonists failed to significantly inhibit macronutrient diets. These data suggest that opioid antagonist effects upon macronutrient intake rely on the specific subtype and ingestive situation. Supported by DA04194 and Post-Doctoral DA07135.

743.11

OPIOID RECEPTOR SUBTYPE ANTAGONIST EFFECTS ON FLUID INTAKE FOLLOWING ANGIOTENSIN II AND HYPERTONIC SALINE IN RATS. H. Ruegg*, B. Hahn, J.E. Koch and R.J. Bodnar. Psychology Dept., Queens Col., CUNY, Flushing, NY 11367.

Analyses of opioid effects upon fluid intake reveal mu_2 mediation of deprivation-induced and maltose dextrin intake, kappa/mu_2 mediation of sucrose intake, and $delta_2$ mediation of saccharin intake Brain Res. 589: 291-301, 1992; in press, 1993). The present study evaluated opioid receptor subtype antagonist effects upon fluid intake following Angiotensin II (A-II, 20 ng) or hypertonic saline. Whereas systemic (0.1-2.5 mg/kg) naltrexone (NTX) inhibited both forms of intake, central (1-20 ug) NTX only inhibited A-II intake. Nor-binaltorphamine (5-20 ug, kappa) inhibited both forms of drinking. Drinking induced by A-II, but not hypertonic saline, was inhibited by mu (beta-funaltrexamine) and $delta_1$ (DALCE) antagonism. Naloxonazine (mu_1) and naltrindole ($delta_2$) were without effect. These data suggest kappa mediation of hypertonic saline intake and mu_2, $delta_1$ and kappa mediation of A-II intake. Supported by DA04194 and Post-Doctoral DA07135.

743.12

OPIOID AND SEROTONERGIC INTERACTIONS: EFFECTS UPON CARBOHYDRATE INTAKE IN RATS. A.K. Islam*, T. Dougherty, J.E. Koch and R.J. Bodnar. Dept. of Psychology, Queens Col., CUNY, Flushing, NY 11367.

Opiate antagonists significantly inhibit hyperphagia induced by food deprivation, 2-deoxy-D-glucose and insulin. Whereas the 5HT-3 antagonist ICS205930 enhanced opiate antagonism of all three forms of intake, the 5HT-2/1C antagonist ritanserin only enhanced naltrexone's inhibition of insulin hyperphagia (Pharmacol. Biochem. Behav.38: 605-610, 1991; 42: 661-669 & 671-680, 1992). Naltrexone also inhibits intake of both sucrose and maltose dextrin (MD) solutions. The present study examined whether general (methysergide: 0.5-5 mg/kg), 5HT-2/1C (ritanserin: 0.25-2.5 mg/kg) or 5HT-3 (ICS205930: 0.5-5 mg/kg) antagonists alone would alter sucrose or MD intake, and whether they would interact with naltrexone's (0.25-2.5 mg/kg) inhibition of carbohydrate intake. Whereas methysergide and ritanserin significantly increased sucrose intake, methysergide significantly decreased MD intake. Naltrexone's dose-dependent decreases in both sucrose and MD intakes were minimally affected by either methysergide or ICS-205930 pretreatment. In contrast, ritanserin blocked naltrexone's inhibition of sucrose and MD intakes. Thus, 5HT-2/1C receptors may modulate opioid control of both simple and more complex forms of carbohydrate intake. (Supported by DA04194 (RJB), Post-Doctoral Training Grant DA07135 (JEK), and H.Hughes Summer Research Program (TD).

743.13

INTERACTIVE EFFECTS OF OPIOID AND DOPAMINE$_2$ RECEPTORS UPON DEPRIVATION AND GLUCOPRIVIC INTAKE IN RATS. L.A. Schaefer*, D.J. Hobbs, J.E. Koch and R.J. Bodnar. Dept. of Psychology, Queens Col., CUNY, Flushing, NY 11367.

While dopamine (D_2) agonists and antagonists inhibit food intake, opiate antagonists typically inhibit intake. Since opioids and dopamine interact, the present study evaluated whether a D_2 agonist (quinpirole: QUIN) and D_2 antagonist (haloperidol: HAL) altered deprivation-induced and 2-deoxy-D-glucose (2DG)-induced hyperphagia alone, and naltrexone's (NTX) inhibition of each form of intake. QUIN failed to alter deprivation-induced intake. 2DG hyperphagia was stimulated by low (25 ug/kg) QUIN doses, and inhibited by high (500 ug/kg) doses. Both forms of intake were stimulated by low (50 ug/kg) HAL doses, and inhibited by high (250 ug/kg) doses. QUIN failed to alter NTX's inhibition of 2DG hyperphagia. QUIN (0.1-1 mg/kg) enhanced NTX inhibition of deprivation-induced intake. Low (5-50 ug/kg) HAL doses enhanced NTX-induced inhibition of both deprivation-induced and 2DG hyperphagia. These data indicate significant DA-opioid interactions which depend upon the type of ingestive situation. (Supported by DA04194 (RJB) and Post-Doctoral DA07135 (JEK).

743.14

NEUROPEPTIDE Y (NPY) EFFECTS ON PATTERNS OF INGESTION: COMPARISON WITH FOOD AND WATER DEPRIVATION, AND VARIATIONS IN INGESTANT PALATABILITY. W.C. Lynch*, A.M. Babcock, and P. Hart. Dept. of Psychology, Montana State Univ., Bozeman, MT 59717

Centrally injected NPY stimulates food intake, water intake (independently of food intake), and preferentially increases intake of palatable foods and fluids (e.g., Soc. Neurosci. Abstr. 18: 895, 1992). Patterns of ingestion are known to vary systematically with changes in deprivational state and with orosensory quality of ingested substances. We therefore compared the patterns of ingestion following icv NPY with those resulting from food and water deprivation and from variations in the palatability of ingested solutions. **Methods:** Adult male rats were tested repeatedly with flavored solutions and water offered in standard 2-bottle tests. Licking was monitored continuously over 1-h periods. Individual groups were tested following lateral ventricular NPY (10μg), food or water deprivation (23-h), or with various solutions types under nondeprived conditions. **Results/Discussion:** Patterns of licking were analyzed in terms of rates of ingestion as a function of time and durations of individual bouts and post-bout pauses. Preliminary results suggest that NPY stimulates intake primarily by prolonging ingestion, stimulating a distinctive pattern of intermittent licking, and reducing or delaying normal satiety. Its effects are clearly different from those resulting from food or water deprivation, and from selected variations in palatability. Supported by NSF/EPSCoR grant # RII-8921978

743.15

LESIONS OF THE AREA POSTREMA (AP)/ADJACENT NUCLEUS OF THE SOLITARY TRACT (NTS) RESULT IN ENHANCED HYPOTHALAMIC NEUROPEPTIDE Y (NPY) LEVELS.

G.L. Edwards*, B.D. White, W. Zhao, B. He, R. G. Dean and R.J. Martin. Dept. of Physiol. & Pharm., Dept. of Foods & Nutr. and Dept. of Anim. Sci., Univ. of Georgia, Athens, GA 30602.

Lesions of the area postrema and adjacent nucleus of the solitary tract (AP/mNTS-lesions) are reported to result in increased consumption of highly palatable diets (Edwards and Ritter, Brain Res. 216: 265, 1981). Recent studies suggest that neuropeptide Y may cause a preference for carbohydrate rich diets (Stanley et al., Peptides 6: 1205, 1985). Thus, it is possible that NPY may play a role in the enhanced intake of highly palatable diets by AP/mNTS-lesioned rats. In the studies reported here we have examined the effect of AP/mNTS-lesions on levels of NPY in the hypothalamic paraventricular nucleus and steady state NPY mRNA in the basomedial hypothalamus. We found that levels of NPY immunoreactivity in the PVN region were elevated in AP/mNTS-lesioned rats (APX-14.4 ± 1.1 ng/mg tissue vs SHAM-9.0 ± 0.3 ng/mg). In addition, levels of NPY mRNA were elevated in the basomedial hypothalamus of AP/mNTS-lesioned rats (APX-2.12 ± 0.37 vs SHAM-1.0 ± 0.9, arbitary units of NPY mRNA/actin mRNA). These data support the possibility that elevated hypothalamic NPY may contribute to the altered food intake in AP/mNTS-lesioned rats. (Supported by UGA Biotechnology Award)

743.16

IN VIVO AND *IN VITRO* EVIDENCE THAT NEUROPEPTIDE Y (NPY) SECRETION IN THE PARAVENTRICULAR NUCLEUS (PVN) IS REGULATED BY PERIPHERAL INSULIN.

A. Sahu*, M.G. Dube, C.P. Phelps[b], C.A. Sninsky[a], P.S.Kalra and S.P. Kalra, Depts. Ob-Gyn. and [a]Med., Univ. Fla., Gainesville, FL 32610, [b]Dept. Anat., Univ. S.Fla, Tampa, FL 33612

Recent evidence shows that feeding under normal conditions as well as in hyperphagic diabetic rats is due to increased NPY secretion in the PVN. In the present study we tested the hypothesis that increased NPY release is due to decreased levels of peripheral insulin (INS). **Expt 1:** Rats were food-deprived (FD) to reduce circulating INS levels and injected daily with either INS (Novolin, 1U/kg, sc) or saline for three days. Although FD increased NPY levels in the microdissected medial preoptic area, PVN and arcuate nucleus (ARC), this INS treatment which did not alter blood glucose level, decreased NPY levels selectively in the PVN. **Expt 2:** the effect of INS on NPY release *in vivo* from the PVN was assessed. Push-pull cannulae (PPC) were implanted in the region of the PVN and one week later, rats were FD and treated with INS as in Expt-1. Rats were perfused with artificial CSF via the PPC for 3-4 hours. Compared to FD controls, NPY levels in PVN perfusates were significantly decreased in the FD+INS rats. **Expt 3:** the effects of INS and IGF-II on NPY release from the PVN, median eminence-ARC and ventromedial nucleus of FD rats were studied *in vitro*. Both insulin (100-1000 μU/ml) and IGF-II (.07-7nM) decreased NPY release only from the PVN. These results show for the first time that peripheral INS inhibits NPY secretion from the PVN nerve terminals directly and/or via IGF-II, and that increased NPY release in the PVN of FD rats is due to decreased levels of INS. Since NPY is a natural orexigenic signal and INS is a key peripheral signal that relays changes in energy balance to the CNS, our results support the hypothesis that INS is an important regulator of NPY secretion and appetite. Supported by UF DSR KG 717 (AS) and NIH DK37273 (PSK & SPK).

743.17

GENE EXPRESSION OF NEUROPEPTIDES IN THE PARAVENTRICULAR (PVN) AND SUPRAOPTIC (SON) HYPOTHALAMIC NUCLEI OF STREPTOZOCIN (STZ)-DIABETIC RATS.

S. E. Bachus[1] and M. Jhanwar-Uniyal*[2]. [1]NIH, Bethesda, MD 20892 and [2]The Rockefeller Univ., NY, NY 10021.

Hypothalamic neuropeptides, such as corticotropin releasing factor (CRF), dynorphin (DYN), oxytocin (OT), vasopressin (VP) and galanin (GAL) are known to regulate various endocrine functions. In this study, we induced diabetes in male Sprague-Dawley rats by administering the pancreatic B-catalytic agent STZ (60 mg/kg BW, ip). Rats were sacrificed 21 days post injection when 20% loss in body weight was achieved. Levels of blood insulin (INS) were assessed by RIA, and glucose (GLU) levels were estimated by YSI glucose analyzer. *In situ* hybridization histochemistry was used to determine area and density of neuropeptide mRNAs. The results demonstrate that, as compared to control, diabetic rats show: 1) significant reduction in body weight (-20%; p<.05), increased GLU levels (p<.001) and reduced INS (p<.001) levels; 2) increased adrenal function as indicated by higher adrenal/BW ratio (p<.05); 3) reduced CRF mRNA density (p=.04) in PVN but not in SON; 4) increased DYN mRNA density in both PVN (p=.001) and SON (p=.01); but increased DYN mRNA area in PVN only (p=.02); 5) increased VP mRNA density in PVN (p=.03) and SON (p=.005), and area in PVN (p=.01) and SON (p=.02); 6) unchanged OT mRNA in both PVN and SON; and 7) increased GAL mRNA area (p=.02) but not density in PVN. Thus, these data indicate that these neuropeptides, which are involved in glucose/insulin and adrenal functions, are also affected by the pathology of diabetes.

743.18

FOOD DEPRIVATION DECREASES NEUROMEDIN B BUT NOT GASTRIN-RELEASING PEPTIDE mRNA IN MEDIAN PREOPTIC AREA.

M. W. Gunion*, M. Stone, E. Wada, J. F. Battey, and P. E. Sawchenko. Res. Service, VAMC, Sepulveda, CA 91343; NINDS, Bethesda, MD 20817; Salk Institute, La Jolla, CA 92138.

Microinjection of bombesin into the rat median preoptic area (MPO) or hypothalamic paraventricular nucleus (PVN) increases blood levels of glucose and free fatty acids, the two major metabolic fuels. Bombesin is an amphibian homolog of mammalian gastrin-releasing peptide (GRP) and neuromedin B (NMB). mRNAs for both peptides are found in the MPO, while only the GRP mRNA is found in the PVN. In this experiment, *in situ* hybridization was used to infer changes in synthesis of NMB and GRP in the MPO and PVN resulting from food deprivation, which decreases the availability of metabolic fuels. Adult male Sprague-Dawley rats (275-375 g, Hilltop) were deprived of food, but not water, for 0, 24, or 48 hr, then were deeply anesthetized (enflurane) 2-3 hr after lights on and perfused with paraformaldehyde. After 5-7 days postfixation, brains were sectioned (25 um), hybridized with 35-S labeled cRNA probes, and apposed to Chronex 4 film for 5-14 days. Data derived from video image analysis (Jandel Scientific) were tested nonparametrically. Food deprivation significantly lowered NMB mRNA in the MPO in a dose-related manner. Food deprivation had no significant effect on GRP mRNA in either the MPO or the PVN. The results suggest that NMB synthesizing neurons in the MPO may be involved in regulating metabolic fuel availability; specifically, reduction of NMB synthesis (and presumably release) in the MPO could be part of an attempt to manage energy stores during food shortage. The data do not suggest a role for GRP-synthesizing cells in either the MPO or PVN in this process. [Supported by PHS NS20660 (MWG).]

743.19

LONG-TERM TREATMENT WITH 17 β-ESTRADIOL PRODUCES CHRONIC WEIGHT LOSS AND FREQUENT SHIFTS OF FOOD PREFERENCES IN RAT.

Y.-H. Li, E. Castañeda*, C. Gustavson and J. Gustavson. Dept. of Psychology and Center for Environmental Studies, Arizona State University, Tempe, AZ 85287-1104.

Previous research has shown that administration of estrogen to neonatally androgenized rats produces taste aversion to novel foods in a manner similar to lithium chloride. The present study was conducted to evaluate further the effects of long-term exposure to estrogen on both body weight and taste preferences for novel food flavors. Thirty-six Long-Evans rats, neonatally androgenized with testosterone propionate (2 mg/0.1 ml, s.c.) and gonadectomized as juveniles, were randomly assigned to an estrogen-treated group or vehicle (peanut oil) control group. Twenty-five days after gonadectomy, rats were restricted to food access for 2 hr daily, during which they had available two flavored rat chow mashes, sweet and salty. During this period of restricted food intake, rats were administered 17 β-estradiol (0.2 mg/0.04 ml) or peanut oil injections (s.c.) daily for 7 days every other week. On the last day of each week, a third alternative flavor was made available dependent upon whether rats had received injections or not during that week. Garlic flavored mash was given at the end of injection periods and chili flavored mash was given after periods of no injection. Compared to control rats, the estrogen-treated group displayed 1) a chronic state of low body weight, and 2) a greater number of shifts in taste preference, as quantitated by the amount consumed. The present results will be discussed in terms of how they might relate to estrogen-induced food aversions that may be a basis for anorexia nervosa in humans.

743.20

THE ROLE OF SYMPATHETIC AROUSAL IN DISCRIMINATION OF INSULIN-PRODUCED HYPOGLYCEMIA

P.M. Duncan* and E.P. Hooker. Psychology Dept, Old Dominion University, Norfolk, Va. 23508.

Nine rats were trained to discriminate the normal state of euglycemia (EU) from the hypoglycemia (HG) produced by injection of 2 units /kg insulin (INS). A "drug discrimination" procedure was used with a food-motivated operant. After extensive training, rats responded on the "insulin" lever a mean of 78% after INS, compared to 16% after water injection. Sympathetic arousal accompanies HG as a mechanism to counter-regulate blood glucose. To investigate the role of this arousal in the recognition of the HG state, the rats were tested after injection of .1 mg/kg epinephrine (EPI), and .5 mg/kg propranolol (PRP) plus INS with the intent to elicit sympathetic activity during EU, and to block it during HG. These manipulations failed to simulate or to block the HG cue. Mean "insulin" response after EPI was 32%, after INS plus PRP, 91%, and after PRP-only treatment 12%. These results indicate that sympathetic arousal is not critical for recognition of hypoglycemia.

743.21

INTRACEREBROVENTRICULAR ADMINISTRATION OF INSULIN TO RHESUS MONKEYS: LACK OF CONSISTENT EFFECT ON FOOD INTAKE AND BODY WEIGHT. T. Wolden-Hanson* and J. W. Kemnitz. Neuroscience Training Program and Wisconsin Regional Primate Research Center, University of Wisconsin-Madison, Madison, WI 53715.

Centrally administered insulin has been reported to decrease food intake and body weight in baboons when continuously administered. Results from acute intracerebroventricular (ICV) injections of insulin in rodents have been less conclusive. In order to evaluate further the effects of ICV insulin in primates, young adult male rhesus monkeys (cannulated in the left lateral ventricle) were given acute injections of insulin or saline vehicle (SAL) in the morning. Food was available for 6 hrs a day and intake (FI) was measured at 1, 2, 4 and 6 hours after injection. Physical activity (as measured by ultrasound movement detectors) and body weight were also measured. **In EXP 1**, animals (n=5) were injected with 100µl of SAL, 100 or 1000mU insulin. Treatments were randomized within subjects, and each animal received the same treatment for 4 consecutive days. Daily FI was reliably suppressed by the 100mU dose in only one of the 5 animals. For 4 of the 5, however, FI was lowest at all time points with the 100mU dose. There was no effect of treatment on physical activity or body weight. The same protocol was used for **EXP 2**, which was performed 2 months later, but the doses were SAL, 50, 100 and 500mU. FI was decreased by the 100mU dose in only 1 of 4 animals, while in 2 of 4 FI was increased by the 500mU dose. There were no effects on physical activity or body weight. If acute elevations of central insulin have an effect on the pattern of eating or on total daily food intake in primates, the effect is small and inconsistent, both within and among animals. We are currently examining the effects of continuous administration of insulin on energy expenditure as well as food intake in these animals. (Supported by NIH grants RR00167 and AG07831.)

743.22

THE EFFECTS OF HPLC PURIFIED HUMAN SATIETIN (h-SAT) ON INGESTION, BODY WEIGHT, AND URINE AND FECES OUTPUT. L.L. Bellinger* and V.E. Mendel. Dept. of Biomedical Sci., Division of Physiol., Baylor College of Dentistry, Dallas, TX 75246 and Dept. Animal Physiol. and Food Intake Lab, University of California, Davis, CA 95616.

Satietin is a putative satiety agent found in the plasma of a variety of species including human, rat and bovine. Single ICV infusion of h-SAT suppresses food intake for 1-2 days and body weight for 4-14 days. In the present study, h-SAT was further purified by HPLC (Bellinger and Mendel, Brain Res Bull 25:941, 1990) and either h-SAT (100 µg/rat, 10 µl volume, n=7) or a-CSF (n=9) was infused ICV into male Sprague Dawley rats. The rats were housed in Nalgene Metabolic Cages (no. 650-0350). Following infusion, both food intake (Purina powdered chow) (10.5±1.2 vs 18.2±1.4 g, $P<0.01$) and water intake (15.2±2.0 vs 27.4±2.8 mls, $P<0.01$) of the h-SAT treated group were suppressed for only the first day post-infusion. Over the next five days, both group's food intake and water intake were very similar and there was no overconsumption of either food or water. Body weight, expressed as body weight change, was significantly ($P<0.01$) attenuated in the experimental group for three days (12.6, 8.9, 9.6 g difference) following infusion. Urine and feces output of both groups were similarly attenuated the first day post-infusion and did not differ significantly over the next five days. Previous studies have shown plasma Na^+, K^+, and osmolality are normal in h-SAT treated rats. The present data suggests that the lowered body weight of the h-SAT treated group is not due to excessive urine or feces output. Supported by NIH-DK 42635.

743.23

MEAL PATTERN ANALYSIS IN RATS DURING CHRONIC COELIAC ARTERY INFUSION OF A BOMBESIN RECEPTOR ANTAGONIST. T.C. Kirkham*, N. Geary, G.P. Smith and J. Gibbs. Bourne Behavioral Research Laboratory, The New York Hospital - Cornell Medical Center, White Plains, NY 10605.

Bombesin-like peptides in both brain and periphery may be involved in the control of food intake. Blockade of central bombesin receptors can induce a significant elevation of food intake, providing important support for a central role of these peptides in satiety.The potent and selective bombesin receptor antagonist, BW2258U89, abolishes the satiety action of peripherally administered bombesin. In this study we examined whether chronic, peripheral administration of this antagonist would also produce significant alterations in spontaneous feeding behavior. Adult male albino rats (n=6) were implanted with chronic coeliac artery catheters. After 4 days, rats were lightly anesthetized and provided with 200 µL osmotic minipumps, connected subcutaneously to the coeliac catheters. Each pump contained BW2258U89 and delivered the antagonist at 0.95 µL hr^{-1} at a dose of approximately 100 µg $kg^{-1}hr^{-1}$. These rats and a control group (n=6, equivalently anesthetized but unoperated) were housed (on a 12:12 hr light-dark cycle) in feeding chambers which permitted the continuous, automated monitoring of powdered food consumption. Meal patterns were recorded for 10 days following pump insertion.

In contrast to the effects of acute, centrally administered bombesin antagonists, this chronic peripheral treatment failed to exert significant effects upon any meal parameter (meal size, duration, intermeal interval).

Supported by DK 33248 (TK, JG), DK 32448 (NG) and MH00149 (GPS)

743.24

TIMECOURSE CHANGES IN CENTRAL BOMBESIN-LIKE PEPTIDE RECEPTOR BINDING DURING A MEAL. C. C. Kateb*[1] and Z. Merali[1,2]. [1]School of Psychology and [2]Department of Pharmacology, University of Ottawa, Ottawa, Ont., Canada, K1N 6N5

The objective of these expeiments was to quantify the density of bombesin (BN)-like peptide receptor binding sites in specific brain regions at different timepoints of a meal. Four groups of rats were used; 1) an *ad libitum* fed control group, and three experimental groups of animals that were deprived of food, but not water, for a 12 hr period and then 2) left unfed (preprandial), 3) given food for 10 min, or 4) given food for 35 min (postprandial). The order of sacrifice was randomized for each of the 8 experimental days, and the sections taken from each group were all processed for receptor binding and applied to a single autoradiography film on each day of the study. Triplicate sections were taken of areas containing the nucleus accumbens (Acb), fundus striatum (Fstr), bed nucleus of stria terminalis, medial preoptic area, paraventricular hypothalamic area (PVN), hippocampus, and nucleus tractus solitarius. When compared to the *ad libitum* condition, receptor binding in the Acb was significantly elevated in preprandial animals. In the Acb, Fstr, and PVN receptor binding in postprandial animals was significantly lower than that observed in preprandial rats. All analyses were performed using two-way ANOVA, with Tukey post-hoc comparisons. Significant differences were observed at $p<0.01$. Based on our results we suggest that, during food intake, BN-like peptide receptors may be internalized in response to BN-like peptide release in those nuclei. This suggestion is presently only speculative and is deserving of further investigation. It is clear that these receptor changes are rapid, locus-specific, and respond to feeding status.

743.25

MICROSTRUCTURAL ANALYSIS OF LICKING BEHAVIOR FOLLOWING PERIPHERAL ADMINISTRATION OF BOMBESIN. T.R. Stratford*, J. Gibbs and G.P. Smith. E.W. Bourne Behavioral Research Laboratory, New York Hospital - Cornell Medical Center, White Plains, NY 10605.

While it has been demonstrated that bombesin dose-dependently decreases intake of both solid and liquid foods in rats, little is known about its effect on the microstructure of feeding. In the present study, ten male Sprague-Dawley rats were trained to ingest a nutritionally complete, high carbohydrate liquid diet during a 30 min presentation in test cages equipped with lickometers. On test days, the animals received intraperitoneal injections of either bombesin (2, 4 or 8 µg/kg) or the isotonic, bacteriostatic saline vehicle and were immediately placed in the test cages where the time of each lick was recorded to the nearest 10 msec. Twenty micro-structural variables were derived from the data and were analyzed using the Quick Lick software program (Davis, 1993).

Dose BN (µg/kg)	0	2	4	8
Volume (mls)	12.0 ± 0.9	8.6 ± 1.2	7.0 ± 0.6	3.5 ± 0.9
Total Licks	1514 ± 128	1064 ± 135	792 ± 61	536 ± 138
Duration (min)	15.7 ± 2.5	15.6 ± 3.1	12.6 ± 3.1	7.3 ± 2.6

Bombesin dose-dependently decreased the volume of liquid diet ingested by significantly reducing the total number of licks taken and the duration of the meal. There were no significant changes in any of the microstructural variables that could not be accounted for by the decrease in meal duration. Our results confirm and extend those of Hsiao and Spencer (1983) and suggest that bombesin reduces the amount of time spent feeding, but that while the animal is feeding, it does so in a manner not significantly different from that of control animals.
Supported by NIH DK08836 (TRS), DK33248 (JG), and NIMH MK00149 (GPS).

743.26

BOMBESIN INJECTIONS SUPPRESS NaCl INTAKE IN SODIUM DEFICIENT RATS. F.W. FLYNN.* Dept. of Psychology and Neuroscience Program, Univ. of Wyoming, Laramie, WY 82071

Peripherally administered bombesin (BN) reduces food intake, but has a much smaller, if any effect on water intake. The following experiments pursued the issue of the behavioral specificity of BN by measuring the effects of BN on NaCl intake in sodium deficient and sodium replete rats. In two experiments, rats (n=14) were placed on a low sodium diet and sodium appetite was induced by treating the rats with DOCA and furosemide. The following day, rats were administered (ip) either saline, 4 µg/kg BN, or 8 µg/kg BN and then given access to .5 M NaCl for 1 hr. Injections of 4 µg/kg BN had no effect on sodium appetite, whereas 8 µg/kg BN reliably suppressed NaCl intake compared to saline injections, $p<.002$. The effects of BN on NaCl intake by sodium replete rats was tested. A preferred concentration of NaCl was selected (.15 M) that was likely to be consumed. Rats were familiarized with the test procedure: food and water were removed for 1 hr and then a single bottle of .15 M NaCl was attached to each cage for 1 hr. During testing, rats were administered either saline or 8 µg/kg BN immediately prior to having access to NaCl. BN did not reduce intake of .15 NaCl by sodium replete rats during the 1 hr intake test. (Supported by NIH NS24879)

743.27

MODULATION OF THE SATIETY EFFECT OF CCK BY CENTRAL IMPLANTS OF DILUTE ESTRADIOL

P. Butera*, M. Xiong and R. Davis. Department of Psychology, Niagara University, Niagara, NY 14109.

Although peripheral treatment with estradiol (E2) potentiates the effects of exogenous CCK on food intake, the site at which such a synergistic interaction occurs remains to be specified. Twenty-six ovariectomized rats received unilateral guide cannula stereotaxically placed in either the paraventricular nucleus (PVN) or ventromedial nucleus (VMN) of the hypothalamus. Three weeks after surgery, animals received central implants of dilute E2 (10%) or a control. Two days after central steroid treatment, subjects were food deprived for 24 h. and were given ip injections of CCK (5.0 ug/kg) or .9% saline the following day. Food intake was measured 60 minutes after CCK treatment. E2 implants in the PVN, but not in the VMN or ventricles, suppressed food intake and body weight during the 2-day period of central steroid treatment. In addition, the satiety effect of CCK during the feeding tests was augmented by E2 implants in the PVN but not by implants in other brain areas. Food intake and body weight were not differentially suppressed in animals with cornified vaginal smears, suggesting that peripheral changes produced by leakage from the central implants were not responsible for the observed behavioral changes. These findings indicate that there is a synergistic interaction between peripheral CCK and central E2, and suggest that the effects of E2 on feeding behavior may be mediated by the potentiation of an afferent signal produced by the stimulation of CCK receptors in the periphery.

(Supported by NIH Grant DK45499)

743.28

RECEPTOR MEDIATION OF THE STIMULUS PROPERTIES OF CCK WITHIN THE CONDITIONED TASTE AVERSION BASELINE OF DRUG DISCRIMINATION LEARNING.

P.M. Melton* and A.L. Riley. Psychopharmacology Laboratory, The American University, Washington, D.C. 20016.

Recently, Melton, Kopman and Riley (Pharm. Biochem. & Behav. 44: 249-252, 1993) reported the rapid acquisition of drug discrimination learning using a relatively low dose of the sulfated form of cholecystokinin (CCK) within the conditioned taste aversion baseline of drug discrimination learning. The present study was designed to further explore the receptor mediation of the stimulus properties of CCK within this procedure. Every fourth day, experimental subjects were given CCK-saccharin-LiCl pairings, and on the intervening recovery days, saccharin alone. Once discriminative control was established, doses of the CCK receptor antagonists devazepide (CCK-A receptor subtype) and L-365,260 (CCK-B receptor subtype) were administered in combination with the training dose of CCK. Unlike L-365,260 (1 - 1000 ug/kg), devazepide (1.0 ug/kg) blocked the CCK stimulus, suggesting that within this design CCK's stimulus properties are mediated by the CCK-A receptor subtype.

743.29

CHOLECYSTOKININ ALTERS INGESTIVE, BUT NOT AVERSIVE, TASTE REACTIVITY RESPONSES IN RATS.

L.A. Eckel* and K.-P. Ossenkopp. Neuroscience Program, University of Western Ontario, London, Ontario, Canada, N6A 5C2.

Cholecystokinin (CCK) reduces food intake in many species. This experiment examined the effects of CCK on taste reactivity responses to sucrose. Following implantation of intraoral cannulae, rats were injected with either CCK (4, 8, or 16 μg/kg, i.p.) or saline. Ingestive and aversive taste reactivity responses were videotaped during 30 sec intraoral infusions of a 0.30 M sucrose solution. Infusions began 2 min post-injection and were repeated at 2 min intervals for 10 min. In response to intraoral sucrose infusions, control rats produced a high frequency of ingestive responses, consisting primarily of tongue protrusions. In contrast, rats exposed to CCK produced significantly fewer ingestive responses ($ps < .001$), consisting primarily of mouth movements. A trend was apparent for the frequency of ingestive responses to decrease as the dose of CCK increased. The decline in ingestive responses observed in CCK treated rats was not accompanied by a significant increase in aversive responses. Therefore, CCK was found to alter both the frequency and pattern of ingestive responses, but had little effect on the production of aversive responses. The present results are consistent with a satiety effect of CCK. (Supported by an NSERC to KPO).

743.30

CCK MEDIATES SATIETY CUES INDUCED BY PHYSIOLOGICAL LEVELS OF INTESTINAL STIMULATION.

P.B. Tracey* and R.C. Ritter. Dept. of VCAPP, Washington State Univ., Pullman, WA 99164.

Reductions of sham feeding produced by intestinal infusions of some nutrients are attenuated by CCK_A receptor antagonists, suggesting that intestinal stimulation contributes to satiation via endogenous CCK. To determine whether CCK-dependent intestinal signals alter intake under physiological conditions we measured 1) the rate of emptying of a spontaneously ingested 15% sucrose meal 2) the sucrose concentration, osmolality and pH of the meal emptied and 3) sham ingestion, with and without CCK_A receptor antagonist (MK329) administration, during intestinal sucrose infusion under conditions measured for stomach emptying. During real feeding rats consumed 16.9±2.0ml of sucrose over a 30min period. 12.6±1.3ml of this intake were during the first ten minutes of the meal. The gastric emptying rate during this period was 0.73±0.04ml/min. The average pH of the stomach contents during the same period was 3.06±0.17,and the osmolality was 437±5 mOsm. Sucrose concentration in the stomach 10 minutes into the meal was 340±10 mM. When sucrose (340mM, pH 3.06, adjusted to 437mOsm) was infused into the intestine of sham feeding rats at 0.73ml/min., complete termination of intake did not occur. However, 30min sham intake was reduced by 35.2±4.6%. The sucrose-induced reduction of intake was abolished by MK329. These results support a role for postgastric nutrient receptors in physiological satiation. Also, the results corroborate previous studies, suggesting that endogenous CCK is necessary for control of intake by some intestinal stimuli. Since sucrose does not elevate plasma CCK in the rat, the source of CCK involved is likely to be neuronal or paracrine. Supported by NS20561.

743.31

NEURONAL cFOS EXPRESSION IN NEONATAL RAT BRAIN IN RESPONSE TO TREATMENTS THAT ARE ANOREXIGENIC IN ADULT RATS.

L. Rinaman*, G.E. Hoffman, E.M. Stricker and J.G. Verbalis. Departments of Behavioral Neuroscience, Neurobiology, and Medicine, University of Pittsburgh, Pittsburgh, PA 15260.

Previous work in our laboratories using adult rats showed that peripheral injections of CCK or hypertonic NaCl inhibit gastric emptying and feeding, stimulate pituitary hormone secretion, and produce very similar patterns of cFos activation in the nucleus of the solitary tract (NST), area postrema (AP), paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus, and several other brain regions. Others have shown that CCK also inhibits gastric emptying and feeding in neonatal rats, whereas hypertonic NaCl stimulates feeding in early neonates. To study possible relationships between the postnatal development of gastric and ingestive controls and the postnatal development of central neural circuits, we examined neuronal cFos expression in 2-day-old rat pups following ip injection of 200 μl of CCK octapeptide (10 μg/kg), hypertonic NaCl (1.0 M), or isotonic saline vehicle. Rat pups were anesthetized and perfused with acrolein-paraformaldehyde fixative 75 min after treatment, and their brains processed for immunocytochemical localization of cFos (antiserum from Oncogene Science). CCK activated cFos expression in the NST and AP but not in the PVN or SON, whereas hypertonic NaCl activated cFos expression in the PVN and SON but not in the NST or AP. These results indicate that the inhibitory effects of CCK on feeding and gastric emptying in neonates may be mediated by activation of medullary vagal sensory circuits without hypothalamic activation, whereas the stimulatory effects of dehydration on neonatal ingestion may be mediated by hypothalamic activation without vagal sensory activation. These pronounced treatment-specific differences in medullary and hypothalamic neuronal activation between neonatal and adult rats likely reflect postnatal maturation of central pathways connecting the hypothalamus and brainstem that coordinate visceral control and ingestive behavior. *Supported by NIH Grants NS28477 and MH25140 (MERIT award).*

743.32

CCK_A RECEPTOR ANTAGONIST DEVAZEPIDE INCREASED FOOD INTAKE IN MALE, BUT NOT FEMALE, OBESE ZUCKER RATS.

A. Strohmayer* and D. Greenberg. Department of Neurology, North Shore University Hospital-Cornell University Medical College, Manhasset, NY 11030 & E.W. Bourne Behavioral Research Laboratory, Department of Psychiatry, NY Hospital-Cornell Medical Center, White Plains, NY 10605.

The genetically obese Zucker rat (fa/fa) is hyperphagic compared to lean controls (Fa/?). This hyperphagia is accomplished by eating larger meals. In the present study we tested the role of endogenous CCK in controlling food intake at test meals by blocking CCK_A receptors with the specific antagonist devazepide. We further explored the response of male and female Zucker rats to CCK blockade. Male obese (n=6) and lean (n=6) and female obese (n=4) and lean (n=6) were adapted to a 60 min test meal of Ensure Plus liquid diet during mid light phase (1400 hr). *Ad lib* chow and water were available until one hour before the test meal. Injections (IP) of antagonist or carboxymethycellulose vehicle alone, were made 30 min before the test meal. All rats were tested at 0.375 and 0.75 mg/kg of devazepide. Food intake was measured every 15 min. Male obese and lean rats significantly increased food intake following devazepide. The maximum mean increase for obese male rats was 4.0 ml (± 1.18) and 2.2 ml (± 0.83) for lean male rats compared to vehicle. Neither obese nor lean female rats significantly increased food intake following devazepide. These results suggests a gender difference in CCK-mediated satiety in an animal model of human obesity.

Support: The International Life Sciences Institute and NIH DK-38757(DG).

744.1

PREOPTIC AND ZONA INCERTA CONNECTIONS WITH THE CAUDAL BRAINSTEM HELP REGULATE THE SEXUAL BEHAVIOR OF MALE RATS. D. A. Edwards* & C.-A. Maillard-Gutekunst. Department of Psychology, Emory University, Atlanta, GA 30322.

Bilateral axon-sparing lesions of both the medial preoptic anterior hypothalamus (MPAH) and the caudal zona incerta (ZI) virtually eliminate copulation in male rats -- neurons intrinsic to each of these regions are involved in the control of sexual behavior. To date, the pathways through which the MPAH and the ZI regulate sexual behavior are not known, although preoptic axons passing caudally through the medial forebrain bundle are likely to be involved. In agreement with earlier published work (Paxinos, 1972), we find that large coronal knife cuts through the pontine tegmentum decrease copulation. The MPAH and the ZI each send projections ipsilaterally through the midbrain to the pontine and medullary brainstem. If the projections connecting the MPAH and/or ZI with the caudal brainstem are essential for male sexual behavior, bilateral interruption of these projections should eliminate copulation. It should not matter whether the destruction of these projections in one hemisphere is produced by a MPAH or ZI lesion and the destruction of the connections in the other hemisphere is accomplished by knife-cut transection -- bilateral interruption of the pathway(s) linking the MPAH and ZI with brain structures caudal to the cut should eliminate copulation. We combined a unilateral excitotoxin (.12M NMDA) lesion of either the MPAH or ZI with a coronal transection of the contralateral pontine tegmentum. In both cases, asymmetric brain damage substantially decreased mating suggesting that connections linking the caudal brainstem with the MPAH and ZI participate in the regulation of male sexual behavior.

744.2

MUSCULO-SKELETAL AND NEURAL SEXUAL DIMORPHISM IN SPINAL SEGMENTS OF A TELEOST. E. Rosa-Molinar, B. Fritzsch, S. E. Hendricks, and J. F. Rodriguez-Sierra*. Depts. of Psychiatry, Cell Biol. & Anat., Univ. Nebraska Medical Center, and Dept. Biomed. Sci., Creighton Univ., Omaha, NE 68198-5575.

Sexual dimorphism of the neuromuscular system controlling spinal reflexes related to copulation has been well documented in some mammals (Breedlove, J. Neurosci. 12 [1992] 4133-4142). We present here the first account of muscular and neural sexual dimorphism as it relates to the function of an intromittent organ (the gonopodium) in a teleost, the Western mosquitofish. Musculo-skeletal differences between the sexes are striking and involve dimorphic organization of at least four spinal segments forming the suspensorium used by males for the circumduction that produces the rostral movement of the gonopodium necessary for copulation. The male possesses a hypertrophied set of *m. inclinator* muscles, almost absent in the female, which facilitates this movement. Lesions of the nerves supplying these *m. inclinator* muscles impair circumduction and prevent thrusting, but have no effect on abduction of the anal fin. The motoneurons supplying the *m. inclinator* muscles in females are among the smallest in the spinal cord and are situated adjacent to the central canal as are other motoneurons supplying intercostal musculature. In males, however, these motoneurons are at least twice the diameter observed in females and are situated more laterally.

744.3

ULTRASTRUCTURAL EFFECTS OF LORDOSIS-INHIBITING DOSES OF 3α-ANDROSTANEDIOL ON ESTROGEN-SENSITIVE VENTROMEDIAL HYPOTHALAMIC NEURONS. M.S. Erskine* and S. Miller. Department of Biology, Boston University, Boston, MA 02215.

Although 3α-androstanediol (5α-androstane-3α,17β-diol, 3α-Adiol) inhibits estradiol (E_2)-induced lordosis, the mechanisms by which this 5α-reduced androgen act are unknown. This study examined whether 3α-Adiol inhibits lordosis by interfering with the actions of E_2 on cells within the ventrolateral portion of the ventromedial nucleus of the hypothalamus (VL-VMN). Rats (3-4/group) were treated 6-8 days after ovariectomy with 1) E_2 in subcutaneous capsules for two 2-hr pulses (hrs 0-2 & 7-9; E_2); 2) E_2 and s.c. injections of 3α-Adiol (6 mg/kg) 3 hr prior to each capsule implantation (E_2/3α-Adiol); 3) 3α-Adiol injections only (3α-Adiol); and 4) empty capsules/vehicle injections at the same times as in the combined treatment group (Control). Animals were anesthetized and perfused intracardially with 3% glutaraldehyde/2% paraformaldehyde 24 hr after the first treatment. The VL-VMN was extirpated from vibratome-cut sections and processed for EM analysis using standard procedures. As previously reported (Jones, et al., J. Comp. Neurol. 239:255-266, 1985), stacking of RER, absence of heterochromatin and increased somal and nuclear size were seen in the E_2 group. The RER and chromatin distribution effects were prevented by co-treatment with 3α-Adiol, while the effects on somal and nuclear size occurred in all 3 steroid-treated groups. Thus, 3α-Adiol may interrupt protein synthesis induced by E_2 in VL-VMN cells which may account for the lordosis-inhibiting actions of this steroid. Supported by HD21802 to M.S.E..

744.4

PROJECTIONS TO THE PROGESTERONE-SENSITIVE SITE OF THE VTA IN HAMSTERS: A FLUOROGOLD STUDY. D.S. Cross and J.F. DeBold*. Department of Psychology, Tufts Univ., Medford, MA 02155.

The ventral tegmental area (VTA), along with the ventromedial nucleus of the hypothalamus (VMH), are both important sites for progesterone's effects on sexual receptivity in female hamsters. In rats the VTA is much less important than the VMH for receptivity and consequently studies on the neural circuitry mediating receptivity have focused on the connections of the VMH. The minimal neural circuitry necessary for the induction of receptivity in hamsters has not been worked out but must include the VTA. This study investigates how the progesterone responsive site within the VTA may be connected with other rostral areas of the brain.

Fluorogold (0.3 µl, 4 % in dH_2O) was micro-injected into the VTA using the same stereotaxic coordinates as those which affect receptivity. Following a 5-10 day survival period the hamsters were sacrificed and perfused with PBS and 4 % paraformaldehyde. Frozen coronal sections of 40 µm were examined for neuronal epifluorescence.

Preliminary analysis have localized labeled cells in several sites in the diencephalon and mesencephalon. Confirming our earlier work with the retrograde tracer HRP, labelled cells have been seen nearby in the superior colliculi and the red nucleus. Filled cells were also seen in several diencephalic sites. For example, dense labeling was seen in the ipsilateral lateral habenula and, too a lesser extent, the medial habenula. Much of the lateral hypothalamus and lateral preoptic area also contained fluorescent cells. In addition, occasional but consistent labeling was found in the ipsilateral bed nucleus of the stria terminalis. These observations suggest possible routes by which progesterone-sensitive sites for sexual receptivity may communicate with other areas in hamster brain.

744.5

Changes in the Morphology of the Sexually Dimorphic Preoptic Nucleus in Japanese Quail Associated with Changes in Adult Breeding Condition. Richmond Thompson* and Elizabeth Adkins-Regan. Dept. of Psychology, Cornell University, Ithaca, NY 14853.

The nucleus preopticus medianus (POMn) is a sexually dimorphic nucleus in the preoptic area of Japanese quail that has been directly implicated in the control of male sexual behavior. POMn morphology can be influenced by photoperiodic manipulations in this seasonal breeder: males housed under long-day conditions (LD) between 4 and 6 weeks of age (the period immediately preceeding sexual maturity) have larger POMn volumes and larger neuronal areas within a dorsolateral region of the nucleus than do males housed under short-day conditions (SD), an effect mediated by the differences in circulating testosterone between LD and SD males (Panzica. et al, 1991). However, it has not yet been demonstrated that POMn morphology changes in fully adult birds in association with the seasonal transitions into and out of breeding condition that accompany changes in photoperiod.

Therefore 18 adult male quail were housed under LD conditions (16L-8D) until 17 weeks of age. Six of these males were then perfused and prepared for histology. The other 12 birds were changed to SD conditions (8L-16D) for 4 weeks, and 6 more were then perfused. The remaining 6 birds were then changed back to LD conditions for 4 more weeks before perfusion. Brains were cut in 40 µm sections and stained with cresyl violet. POMn volume was approximately 20% greater in both LD conditions than in the SD condition; that is, POMn volume decreased under SD conditions and then increased again when birds were returned to LD conditions. The neuronal subpopulation located dorsolaterally within POMn in LD males had significantly larger somal areas than neurons located dorsolaterally within or immediately outside of POMn boundaries in SD males. Thus, POMn volume and the somal areas of a distinct neuronal subpopulation do change in association with changes in adult breeding condition, effects which may reflect behaviorally relevant neuroanatomical changes in the brain of this species.

Supported by NSF BNS 8809441

744.6

THE EFFECTS OF MATERNAL STIMULATION ON MOTOR NEURON NUMBER IN THE LUMBAR SPINAL CORD ARE SPECIFIC TO THE SNB. C.L.Moore*, H.Dou and J.M.Juraska. Depts. of Psychology, Univ. Massachusetts, Boston, MA 02125 and Univ. Illinois, Champaign, IL 61820.

We previously reported that perineal stimulation directed to rat pups by their dams contributes to the number of motor neurons in the spinal nucleus of the bulbocavernosus (SNB). As in the previous study, we used intranasal zinc sulfate to render some dams anosmic and reduce the amount of perineal licking that they performed. The spinal cords of their adult offspring were celloidin embedded, sectioned at 50 microns, and stained with methylene blue. Motor neurons having visible nucleoli were counted in the dorsolateral (DLN) and retrodorsolateral (RDLN) nuclei. Unlike the SNB, differential afferent input had no effect on cell number in either nucleus. All three nuclei are located in the same sections at L6, but the medially located SNB extends more rostrally. The SNB may be particularly affected by neonatal stimulation because of this or because its cells have recently undergone a secondary migration from a lateral location.

The sexually dimorphic SNB and DLN function during intromission and ejaculation. Differences in either or both of these nuclei may underlie the effects of maternal stimulation on the copulatory behavior and reproductive success of males. Supported by NSF RII 89-05498.

744.7

PRENATAL STRESS ALTERS THE SIZE OF THE ANTERIOR COMMISSURE (AC) IN THE RAT BRAIN. H.E. Jones, R. Rowe, B. Billack, C. Hancock, M. Ruscio, C. Gonzalez, K.G. Lambert[1] & C.H. Kinsley* Depts. Psychol., Univ. Richmond, VA 23173 & [1]Randolph-Macon Col. Ashland, VA 23005.

Allen & Gorski (1992) reported that the AC was larger in homosexual relative to heterosexual men. In rats, prenatal stress (PS) alters sexual differentiation and brain morphology. Since the AC is a sexually dimorphic region, and PS modifies sexual behavior and neuroanatomy, we examined the influence of PS on the development of the AC. Female rats were stressed via thrice daily light/heat/restraint during the last week of pregnancy; controls remained undisturbed. Between 90-100 days of age the brains were extracted, blocked and serially sectioned (40 um) in the coronal plane. The area of the AC was traced and measured using a Bioquant image analysis system and Summagraphics digitizing pad. Control males had a larger AC relative to control females, whereas PS increased the size of the AC in both males and females, compared to controls. PS, therefore, may be a factor influencing the sexual development of the AC.

744.8

CHARACTERIZATION OF MALE BRAIN AND SPINAL CORD MORPHOLOGY IN RATS (*RATTUS NORVEGICUS*) EXPOSED VERY EARLY IN DEVELOPMENT TO AN AROMATASE INHIBITOR. G.M. Lange , R.A. Pax*, and L.G. Clemens. Department of Zoology, Michigan State University, East Lansing, MI 48824.

Sexual differentiation is a sequential process initiated in mammals by genes on the Y-chromosome (Sinclair et al., 1990. *Nature* 346:240). Through these genes, gonadal differentiation into either the testis or ovary occurs. In turn, hormones secreted by the differentiated gonad lead to dimorphic development of the peripheral and central nervous system tissues. Recently, the aromatase enzyme has been implicated as a major factor in gonadal differentiation (Elbrecht and Smith, 1992. *Science*. 255:467-470). In the rat, very early exposure to the aromatase inhibitor 1,4,6-androstatrien-3,17-dione (ATD) has been shown to virilize males, alter phenotypic sex ratios, and alter male copulatory behavior. In this study, we describe the behaviors and neuroanatomical features of rats exposed to an aromatase inhibitor prenatally.

MONOAMINES AND BEHAVIOR: NUCLEUS ACCUMBENS

745.1

CHRONIC FOOD DEPRIVATION DAMPENS BASAL AND CHALLENGED DOPAMINE OUTPUT IN THE NUCLEUS ACCUMBENS. E. Pothos[1]*, E. Rodriguez[2], I. Creese[2] L. Hernandez[3]& B. G. Hoebel[1]. [1]Dept. of Psych., Princeton Univ., Princeton, NJ 08544. [2]Ctr. Molec. & Beh. Neurosc., Rutgers Univ., Newark, NJ. [3]Univ. de los Andes, Merida, Venezuela.

It has been shown that weight loss dramatically increases voluntary drug intake in animals, and significantly decreases extracellular dopamine (DA) levels in the nucleus accumbens (NAC) of freely moving rats (Pothos et al, *Neurosci. Abstrs 1989*, 227.10). In the present study, animals at 80% of free-feeding weight (FFW) were challenged with morphine (20 mg/kg, i.p.), *d*-amphetamine (1.5 mg/kg, i.p.) or food (5-7g pellets) while NAC DA levels were monitored by *in vivo* microdialysis. Underweight rats had significantly lower basal DA levels than controls ($p<.05$). Both drugs and food failed to raise DA output to control levels ($p<.05$). In separate groups, no difference was observed in 1nM [^{3}H]SCH23390 or [^{3}H]spiperone binding in the NAC or the striatum. The above results suggest that chronic food deprivation and weight loss (a) attenuate DA release in the NAC with no apparent postsynaptic compensation in D1 or D2 receptor density, and (b) weaken the DA-releasing ability of natural and drug reinforcers. These findings may explain the increased voluntary drug intake observed in underweight animals as a compensation for low DA release in the NAC. Supported by USPHS grant NS 30697.

745.2

COCAINE-INDUCED CHANGES IN EXTRACELLULAR (EC) DOPAMINE (DA) LEVELS IN THE NUCLEUS ACCUMBENS (NAS) OF FISCHER AND LEWIS RATS. R. E. Strecker*, W. F. Eberle, and C. R. Ashby†. Dept. of Psychiatry, SUNY, Stony Brook, NY 11794 and †Medical Dept., Brookhaven National Lab., Upton, NY 11973.

Variations in the susceptibility of individuals to self-administering drugs of abuse may have a biological basis. Comparisons of Fischer F344 and Lewis inbred rat strains can serve as an animal model of this variation since Lewis rats readily self-administer drugs of abuse, whereas Fischer rats do not. Lewis rats also exhibit a greater behavioral response to cocaine. Evidence suggests that the mesocorticolimbic DA projections to the NAS are a critical part of the central reward system involved in drug abuse. Hence, we examined basal and cocaine-induced EC DA levels in the NAS of Lewis and Fischer male rats to determine if neurochemical differences exist that could account for the behavioral differences. Microdialysis sample collection coupled to HPLC-EC revealed that basal EC DA levels were slightly lower in Lewis rats than in Fischer rats (6.7±1.0 pg/20min sample vs. 8.4±1.7 pg/sample), but this difference was not significant. The two rat strains also did not differ greatly in EC DA levels after low doses of cocaine (3 & 10mg/kg, ip). However, following a high dose of cocaine (30mg/kg, ip) the increase in EC DA measured in Fischer rats was significantly greater than in Lewis rats ($P<0.05$). A second injection of cocaine 3hr later (30mg/kg) produced similar increases in EC DA in both strains of rats. Thus, the Lewis rats exhibited an enhanced DA response to repeated cocaine injections, which may be a neurochemical index of sensitization. These data support the conclusion that individual variability in NAS DA function may underlie vulnerability to drug abuse. (Supported by PHS award DA07456)

745.3

PHARMACOLOGICAL AND ANATOMICAL CHARACTERIZATION OF ORAL BEHAVIOUR IN THE NUCLEUS ACCUMBENS OF RATS. E.P.M. Prinssen and A.R. Cools*. Dept. of Psycho- and Neuropharmacol., Univ. of Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

In cats oro-facial dyskinesia, viz. unwanted side-effects of chronic administration of dopaminergic agents in man, is produced by stimulation of so-called DAi receptors (Spooren et al., Brain Res **539**:85, 1991). In order to investigate whether such phenomena are also present in rats, we examined the effect of intra accumbens administration of the DAi receptor agonist DPI and its antagonist ergometrine on oro-facial behaviour in freely moving rats. DPI (5.0-10.0 μg) administered in the central n. accumbens, increased dose-dependently oral behaviours (chew, tremor and sniff) and induced abnormal behaviour (large amplitude-chew). Ergometrine (100 ng) attenuated the effects of DPI. It is concluded that the DPI-induced effects are DAi receptor-specific.

Next, we analyzed the anatomical substrate in more detail. For, different subterritories of the n. accumbens have been defined on the basis of anatomical connections, viz. the rostral pole, core and shell (Zahm, Neurosci **50**:751, 1992). We administered DPI in two of these areas, viz. the rostral pole and the shell. DPI (5.0 μg) administered into the shell increased chewing, tongue protrusion, sniffing and grooming and induced large amplitude chewing. In contrast, DPI (5.0 μg) administered into the rostral pole did not affect any (peri-)oral behaviour, except sniffing. Finally we analyzed the effects of the "inactive enantiomer" of sulpiride ((+)-sulpiride) since, like DPI, (+)-sulpiride showed high affinity to a (non-D_1/D_2) binding site in the n. accumbens (Csernansky et al., Experientia **41**:1419, 1985; and personal communication). (+)-sulpiride (10-50 ng) dose-dependently antagonized the effects of DPI, suggesting that (+)-sulpiride is a potent DAi receptor antagonist. It is suggested that the DPI-induced changes in oral behaviour of rats and cats is a useful animal model for analyzing mechanisms underlying drug-induced oro-facial dyskinesia in man.

745.4

SELECTIVE IMPAIRMENTS IN FORAGING BEHAVIOR FOLLOWING TRANSIENT LIDOCAINE-INDUCED LESIONS OF THE NUCLEUS ACCUMBENS. J.K. Seamans, S.B. Floresco, A.G. Phillips*. Dept. of Psychology, Univ. British Columbia, Vancouver B.C. Canada, V6T 1Z4.

The Nucleus Accumbens (N.Acc.) appears to play an important role in foraging behavior in the rat (Kelley & Stinus 1985). The present study examined the relative contributions of extra-maze spatial cues, spatially-mediated working memory and task complexity, to deficits in foraging behavior produced by reversible lesions of the N.Acc. Microinjections of lidocaine (2%, 1 μl infused over 2min.) were used to produce a reversible lesion of the N.Acc. during training and test phases of a Spatial Win-Shift radial arm maze task. In well trained subjects, lidocaine injections had no effect on efficient retrieval of food from 4 open and baited arms during the training phase or from the 4 novel arms with all 8 arms open during the test phase 30 min. later, when the anesthetic effects of the drug had dissipated. In contrast, lidocaine infusions made 3 min. prior to the test phase severely impaired test phase performance. Vehicle-treated animals retrieved 4 pellets in $x=5.1$ choices whereas the lidocaine group required $x=9.7$ choices. Data from a separate study utilizing a spatially cued Morris Water Maze, indicated that similar lidocaine infusions into the N.Acc. had no effect on learning to navigate to a hidden platform using spatial extra-maze cues. Collectively, these data suggest that the N.Acc. is not involved in the acquisition or utilization of spatial information in a water maze, or when foraging in a simple 4-arm maze environment, but is essential for executing efficient search strategies based on information about previous arm choices in a more complex 8-arm maze.

745.5

DOPAMINE AND INSTRUMENTAL BEHAVIOR: INVOLVEMENT IN RESPONSE SELECTION. M.S. Cousins*, J.D. Sokolowski, J.D. Salamone. Dept. of Psychology, Univ. of Connecticut, Storrs, CT 06269-1020.

Rats were tested in an operant chamber in which there was a choice between lever pressing to receive a preferred food (Bioserve pellets) or feeding upon a less-preferred food (lab chow). In experiment 1, ventrolateral striatal (VLS) dopamine (DA) depletions produced by local injections of 6-hydroxydopamine decreased both lever pressing and chow consumption, indicating that VLS DA depletions produce motor deficits that interfere with both behaviors. Nucleus accumbens (ACC) DA depletions decreased lever pressing but increased consumption of lab chow. In experiment 2, rats were tested with the same procedure described above on Mondays, Wednesdays, and Fridays of each week, but on Tuesdays and Thursdays chow was not concurrently available in the chamber. ACC DA depletions decreased lever pressing and increased chow intake on days when lab chow was available in the test chamber, but had much less effect on lever pressing when lab chow was not available. Although rats with ACC DA depletions remained directed towards food aquisition and consumption, these rats had deficits in lever pressing that were most evident when another food source was available.

745.6

DOPAMINE AND INSTRUMENTAL BEHAVIOR: INVOLVEMENT IN RESPONSE INITIATION. L.D. McCullough*, P. Kurth, M.S. Cousins, J.D. Sokolowski, J.D. Salamone. Dept. of Psychology, Univ. of Connecticut, Storrs, CT 06269-1020.

Rats were trained to press a lever on a fixed ratio 5 schedule, and a computer program recorded the interresponse time (IRT) for each response. The IRT is the time between each lever pressing response, which is equal to the reciprocal of the local response rate. Local injections of 6-hydroxydopamine were used to deplete dopamine (DA) in the nucleus accumbens, medial striatum or ventrolateral striatum (VLS). DA depletion in all regions significantly reduced lever pressing. Rats with DA depletions showed reductions in the proportion of IRTs with low time values (high local response rate), and increases in the relative number of IRTs with high time values (low local response rate). The greatest reductions in responding and the most pronounced alterations of the IRT distribution were shown by rats with VLS DA depletions. DA levels in the VLS were correlated with the total number of responses ($r=0.71$, $p<.05$). These results demonstrate that DA depletion produces a slowing of local response rate, and that DA in the VLS is particularly necessary for maintaining very high rates of instrumental responding.

745.7

DOPAMINE AND INSTRUMENTAL BEHAVIOR: MICRODIALYSIS STUDIES OF INSTRUMENTAL AND CONSUMMATORY BEHAVIOR. J.D. Salamone*, M.S. Cousins, L.D. McCullough, R.J. Berkowitz and D.L. Carriero, Dept. of Psychology, Univ. of Connecticut, Storrs, CT 06269-1020.

Microdialysis methods were used to study dopamine (DA) release and metabolism in the nucleus accumbens. Four behavioral conditions were used: performance on a fixed ratio 5 (FR 5) schedule of food reinforcement, consumption of Bioserve food pellets, consumption of laboratory chow, and food deprivation control. The rats that pressed a lever on a FR 5 schedule showed significant increases in extracellular DA and DA metabolites. Within the group that responded on the FR5 schedule, there was a significant curvilinear (hyperbolic) correlation between the number of responses and the increases in DA release. Rats that received food pellets or lab chow consumed large quantities of food, but showed no significant increases in DA release. This experiment demonstrated that lever pressing behavior is accompanied by an increase in accumbens DA release and metabolism, and that accumbens DA release is more closely related to the performance of highly active instrumental responses than it is to the performance of consummatory behavior.

745.8

ACTIVATION OF D_1 DOPAMINE RECEPTORS IN NUCLEUS ACCUMBENS POTENTIATES ACOUSTIC STARTLE

M.H. Lewis[1,*] L.L. Cook[1], S. Whatley[1], D.E. Nichols[2], R.B. Mailman[3,4]. [1]Department of Psychiatry, University of Florida, Gainesville, FL, 32610, [2]School of Pharmacy, Purdue University, West Lafayette, IN, 47907, [3]Brain Develop. Res. Ctr. and [4]Department of Psychiatry, University of North Carolina, Chapel Hill, NC, 27599.

We have recently observed a pronounced reactivity to mild social stimulation in mice following systemic administration of the full efficacy, selective D_1 agonist dihydrexidine. Dihydrexidine-induced increases in escape, reflexive kicking, and vocalizations were reversed by a D_1 but not a D_2 antagonist. We have extended these findings by examining non-social reactivity in male Sprague-Dawley rats following intrastriatal or intra-accumbens administration of dihydrexidine (1, 3, and 10 μg) or vehicle. In the present experiments, reactivity was measured by quantifying the amplitude of the startle response to an acoustic stimulus. When injected into the caudate nucleus, no effect of drug on startle was observed at any of the three doses tested. Conversely, when administered into the nucleus accumbens, dihydrexidine at the 3.0 μg dose significantly potentiated the startle response. Intra-accumbens administration of the higher dose (10 μg) resulted in no increase in startle over that observed following vehicle. Systemic administration of dihydrexidine to rats did not induced hyperreactivity to non-social stimuli. The availability of a full efficacy agonist has provided new information concerning the functional roles of D_1 dopamine receptors. The emotional response of rodents to both social and non-social stimuli appear to be modulated by D_1 accumbens receptors. While species comparisons require great caution, it may be that D_1 dopamine receptors also play a role in emotional responding in humans (Supported, in part, by PHS Grants MH45371, MH40537, and MH42705).

745.9

COLCHICINE LESIONS OF THE DORSAL HIPPOCAMPAL FORMATION ALTER SPATIAL MEMORY, ACTIVITY, AND DOPAMINE LEVELS IN THE NUCLEUS ACCUMBENS. J.P. Ryan*, T. Bliven, M. Lorenzo, C. Moon, and A. Neveu. Department of Psychology, State University of New York, Plattsburgh, New York 12901.

The purpose of this study was to investigate the psychomotor contribution to spatial memory deficits in the water maze. Forty-eight Long-Evans hooded rats were divided into one of four treatment groups: two control groups (Nonlesioned and Cerebrospinal Fluid) and two colchicine groups (Low Dose-15μg/μL and High Dose-25μg/μL). Cerebrospinal fluid and colchicine treatments were administered bilaterally into the dorsal hippocampal formation. Animals were tested for sensorimotor abilities, activity in the Digiscan Activity Chamber and spatial memory in the water maze. Microdialysis probes were bilaterally implanted into the nucleus accumbens in anesthetized animals following seven days of behavioral testing. The high dose colchicine group exhibited intact sensorimotor skills, spatial memory impairments, increased speed, and altered dopamine levels in comparison to control animals. The study implicates a psychomotor component to the behavioral deficits in the water maze.

745.10

THE EFFECTS OF VENTRAL TEGMENTAL (VTA) INJECTIONS OF D-ALA,N-ME-PHE-GLY-OL-ENKEPHALIN (DAGO) ON DOPAMINE LEVELS IN NUCLEUS ACCUMBENS AND PREFRONTAL CORTEX: AN IN VIVO ELECTROCHEMICAL STUDY. M. B. Noel* and A. Gratton. Douglas Hosp. Res. Ctr., McGill University, Montreal.

Injection of opiates into the VTA have been found to enhance the effects of naturally occurring rewards such as food and sexual activity. Opiates have also been found to be rewarding in their right; animals will self-administer opiates directly into the VTA. It has been suggested that opiates produce their rewarding effect by activating the mesolimbic dopamine system. The objective of the present study was to monitor the effects of VTA injections of the selective mu opiate, DAGO, on the extracellular concentration of dopamine (DA) in nucleus accumbens (NAcc) and prefrontal cortex (PFC) of freely behaving rats using high speed chronoamperometry. Intra-VTA DAGO (0.01, 0.1 and 1.0 nmole) produced reliable, dose-dependent increases in both NAcc and PFC extracellular DA concentration; the highest dose of DAGO increased NAcc and PFC DA levels by about 500 nM. This increase lasted approximately 90 minutes in NAcc and 130 minutes in PFC. The lowest dose of DAGO caused an average increase of approximately 300 nM, that lasted approximately 30 and 60 minutes in NAcc and PFC respectively. Pretreating animals with naloxone (2 mg/kg) significantly attenuated the increase in NAcc and PFC DA levels produced by the 0.1 nmole dose of DAGO. Pretreament with a low dose of the dopamine receptor agonist apomorphine (50 μg/kg), attenuated the DAGO-induced increase in DA levels in NAcc but not in PFC. These results provide evidence that an enkephalinergic input to the VTA modulates the activity of mesolimbic as well as mesocortical DA neurons. (Supported by NSERC and FRSQ).

745.11

IN VIVO ELECTROCHEMICAL MONITORING OF CONDITIONED STRESS RESPONSES IN NUCLEUS ACCUMBENS AND PREFRONTAL CORTEX OF RAT. Z. Elbaz*, J. Rochford and A. Gratton. Douglas Hosp. Res. Ctr, McGill Univ. & Ctr Studies Behav. Neurobiol., Concordia Univ., Montréal, Canada.

A brief exposure to an environmental stress is well known to elicit an increase in the extracellular concentration of dopamine (DA) in prefrontal cortex (PFC) and nucleus accumbens (NAcc). In the present study, we used high-speed chronoamperometry to monitor changes in DA-dependent electrochemical signals recorded within NAcc and PFC of rats presented with a conditioned stimulus (CS) paired with a stress. Male Long-Evans rats with electrochemical probes implanted in NAcc or PFC were presented, on three consecutive days, with a 30 sec tone immediately before each of three 5 min exposures to tail-pinch stress and on the forth day with the tone alone. As we have previously shown, tail- pinch stress elicited increases in the electrochemical signals recorded in NAcc and PFC. In addition to producing a very noticeable "freezing" response in all animals tested, presentation of the tone alone elicited reliable increases in signals recorded from PFC; the signals increased abruptly during the first 20 secs of the tone and peaked approximately 10 sec after tone offset before slowly returning to baseline 4-5 mins later. However, either no change, slight decreases or negligeable increases in signal were recorded in NAcc during tone presentation. In additional tests, some of the animals were repeatedly presented with a distinct 30 sec CS (light) that was followed by a food reward. In contrast to the effects of the stress-CS, presentation of the food-CS alone elicited reliable increases in electrochemical signals in PFC and NAcc that were associated with intense exploration of the food dispenser. The present results indicate that an otherwise neutral stimulus previously paired with an environmental stress can, alone, stimulate DA release in PFC but not in NAcc. The results also suggest that conditioned increases in NAcc DA levels are more readily elicited by a stimulus that predicts the availability of a positive reinforcer. *Supported by the Medical Research Council of Canada.*

745.12

PERINATAL ASPHYXIA INCREASES SENSITIZATION OF THE MESOLIMBIC DOPAMINE RESPONSE TO REPEATED STRESS. W.G. Brake*, M.B. Noel, P. Boksa and A. Gratton. McGill University, Depts of Psychiat. and of Neurol. & Neurosurgery, Douglas Hospital Research Center, Montréal, Canada.

Complications during birth, such as brief asphyxia, are increasingly thought to contribute to a number of disorders including schizophrenia. In the present study, we examined the effects of repeated exposure to stress on the mesolimbic dopamine (DA) projection to nucleus accumbens (NAcc) in a rat model of perinatal asphyxia (Bjelke et al., Brain Res., 1991, 543,1). On the day of parturition, the uterus was removed by caesarian section and submerged in a warm saline bath for 5 or 15 min; vaginally born pups served as controls. Four-five months later, animals from the three groups were each implanted with an electrochemical probe in NAcc. High-speed chronoamperometry was used to monitor DA-dependent electrochemical signals elicited by each of 5 consecutive, once daily exposures to 15 min of tail-pinch stress. The results show that while the 1st tail-pinch produced similar increases in signal in all animals, the signals elicited by each subsequent exposure to stress became progressively longer in animals that had been subjected to perinatal asphyxia but not in the vaginally born animals. The responses to the 4th and 5th exposures to stress were significantly longer in both groups of asphyxiated animals compared to controls whereas the peak amplitude of the response did not differ between groups or between test days. During additional recording sessions, pretreatment with apomorphine (100 µg/kg sc) was found to attenuate tail pinch-induced increases in signal, indicating that DA was the primary electroactive species contributing to the electrochemical signal. Taken together, these findings indicate that a brief period of asphyxia during birth leads to an increased response of mesolimbic DA neurons to the sensitizing effects of repeated stress. They also suggest that this and other birth complications may contribute to the pathophysiology of disorders involving central DA neurons such as schizophrenia and Parkinson's disease. *Supported by the American Scottish Rite Foundation and the Medical Research Council of Canada.*

745.13

CONVERGENCE OF SEROTONIN AND DOPAMINE IN VENTROLATERAL NUCLEUS ACCUMBENS: ANATOMICAL AND *IN VIVO* ELECTROCHEMICAL ANALYSIS. C.F. Phelix*[1], L. Tschoepe[1], and P.A. Broderick[2]. Div. Life Sciences, Univ. Texas, San Antonio, TX 78249[1]; Dept. Pharmacol., CUNY Med. Sch., NY 10031[2].

The purpose of the present study was to assess the anatomical localization concomitantly with *in vivo* electrochemical detection of serotonin (5HT) and dopamine (DA) in an A10 terminal field, the ventrolateral nucleus accumbens (vlNAcc). The significance of the selection of this subdivision of NAcc is its possible involvement in a negative feedback circuit with the ventral tegmental area, due to reciprocal connectivity. Light microscopic immunocytochemistry, using a silver intensification procedure, was used to detect 5HT and tyrosine hydroxylase (TH) in coronal sections of formaldehyde-fixed rat brain. Within the caudal 1/3 of the NAcc, corresponding to the level from the first appearance of the posterior horn of the anterior commissure to the rostral-most bed nucleus of the stria terminalis, both TH-immunoreactive (IR) and 5HT-IR axons were distributed in a mosaic pattern. In the vlNAcc, the core contained a dense terminal field of TH-IR axons that had an extensive overlap with 5HT-IR axons in the periphery within the core. *In vivo* electrochemical detection of DA and 5HT was assessed concomitantly, on line and within seconds in the ventral most aspect of this overlap zone. Thus a functional interaction of 5HT-DA axon terminals in vlNAcc is indicated.

745.14

CEREBRAL METABOLIC EFFECTS OF 6-0HDA LESIONS TO THE ROSTRAL POLE OF THE RAT NUCLEUS ACCUMBENS D. Huston-Lyons*, E. Schicatano, L. Williams-Hemby, J.E. Smith & L.J. Porrino, Dept. Physiology & Pharmacology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, N.C. 27157.

Local cerebral metabolic rates ($LCMR_{glu}$) were assessed in Sprague Dawley rats one week after unilateral micro-injection of 6-OHDA into the rostral most region of the nucleus accumbens (rNACC) to deplete dopamine (saline injected into opposite hemisphere) seeking evidence of changes in metabolic activity corresponding to recently described rNACC anatomical connections. $LCMR_{glu}$ was quantitatively assessed in 58 structures throughout the brain including projection areas of the rNACC. Comparisons between lesioned animals and untreated controls showed bilateral increases in metabolism within selective portions of the projection fields of the rNACC: the hypothalamic lateral preoptic area (LPO), substantia nigra pars reticulata and ventral tegmental area. In particular, the LPO showed a robust change that may also explain the increased metabolism seen in the habenula which receives afferent projections from the LPO but not the rNACC. Caudal portions of the ventral striatum were affected with apparently greater changes in the accumbens shell and olfactory tubercle than the accumbens core. Lesions also lead to increased $LCMR_{glu}$ in the hippocampus, a region with strong projections to the nucleus accumbens. These data indicate that a small lesion within the rNACC produced alterations in brain activity in a selective subset of regions along the projection pathway of the rNACC, as well as other central sites. (Supported by NIDA grants DA07246 & P50 DA06634)

745.15

EVIDENCE AGAINST 5-HT_3 RECEPTOR MODULATION OF DOPAMINE-MEDIATED HYPERACTIVITY IN RATS. K. Szczepanski, E. H .F. Wong, R. M. Eglen, K.R. Bley* and D. J. Fontana. Department of Neurosciences, Institute of Pharmacology, Syntex Discovery Research, Palo Alto, CA 94304, U.S.A.

As serotonin may modulate mesolimbic/nigrostriatal dopamine neurotransmission, we evaluated the effects of several 5-HT_3 receptor antagonists on locomotion in rats in three models of dopamine-mediated hyperactivity. In the first model, Di-Me-C7 (1, 3, 5, and 10 µg in 2 µl), a substance P analog, microinjected into the ventral tegmental area (A10), resulted in a dose-related increase in locomotor activity. Haloperidol (300 µg/kg, i.p.) and eticlopride (400 µg/kg, i.p.), dopamine receptor antagonists, blocked the Di-Me-C7-induced hyperactivity. In contrast, ondansetron (3-1000 µg/kg, i.p.) and (R/S)-zacopride (100-1000 µg/kg, i.p.), 5-HT_3 receptor antagonists, had no effect. In the second model, cocaine (20 mg/kg, i.p.) produced hyperactivity. Although haloperidol (50 and 100 µg/kg, i.p.) decreased the hyperactivity, ondansetron (0.1-100 µg/kg, i.p.), MDL 7222 (1-1000 µg/kg, i.p.), and ICS 205-930 (0.1-100 µg/kg, i.p.), 5-HT_3 receptor antagonists, had no effect. In the third model, hyperactivity produced by microinfusion of d-amphetamine (10 µg in 2 µl) into the nucleus accumbens was completely blocked by haloperidol (100 µg/kg, i.p.) but not affected by ondansetron (10-1000 µg/kg, i.p.) or (R/S)-zacopride (10-1000 µg/kg, i.p.). Therefore, our results suggest that the 5-HT_3 receptor may not be involved directly in the modulation of mesolimbic/nigrostriatal dopamine activity.

745.16

THE RESPONSE OF MESOLIMBIC DOPAMINERGIC NEURONS TO THE AFFECTIVE VALUE OF STIMULUS IS REGIONALIZED AND LATERALIZED. A. Louilot*, C. Besson and M. Le Moal. INSERM U. 259 - Université de Bordeaux II - Domaine de Carreire - 33077 Bordeaux Cedex - France.

We demonstrated previously that the responses of mesolimbic dopaminergic (DAergic) neurons to an appetitive or to an aversive stimulus are opposite in the left *core* of the nucleus accumbens (ACC). In the present study, we tested the hypothesis that these DA responses were different in the *core* and the *shell* parts of the ACC on one hand and in the left and the right hemisphere on the other hand.

The DAergic reactivity was followed using the voltammetric measurements of DA and its main presynaptic metabolite, DOPAC, in the ACC of freely moving male rats. The experimental paradigm was as following : animals were placed during one hour in the experimental cage; they were thus exposed for one hour to an appetitive olfactory stimulus (banana) and received consecutively either an injection of saline (NaCl 0.9%) (control group) or an injection of LiCl (0.15 M) (experimental group) and stayed then one more hour in the experimental cage; 72 h later animals were again exposed for one hour to the conditional olfactory stimulus (CS).

The main results were as follows : During the 2nd presentation of the CS, 1) in the left *core*, a transient decrease in the DA signal of about 30% was observed for the experimental group and a DA increase of about 100% was obtained for the control group, 2) in the right *core*, the decrease in the DA signal was modest for the experimental group whereas the DA increase was of about 150% for the control group, 3) in the left *shell*, moderate increases in the DA signal were observed for both groups, the DA response being more elevated for the experimental group, 4) in the right *shell* similar results, although less pronounced were obtained. No significant variation in the DOPAC signal was noticed.

The results of the present study showing that the DA response to an aversive stimulus is more related to the left *core* and the DA response to an appetitive stimulus to the right *core* strongly suggest that the response of mesolimbic DAergic neurons to the affective value of a stimulus is regionalized and lateralized.

746.1

EFFECTS OF TEMPORAL POLE LESIONS ON AMYGDALOID AND HYPOTHALAMIC NEUROTRANSMITTERS BY IN-VIVO MICRODIALYSIS IN MONKEY. A.S.KLING*, K.TACHIKI, R.LLOYD. Psychiatry Service, Veterans Health Administration Medical Center, and Department of Psychiatry, U.C.L.A. School of Medicine, Sepulveda, CA 91343.

The Kluver-Bucy syndrome is a well known consequence of lesions of the temporal lobe, but the neural mechanisms remain obscure. To elucidate the neurochemical changes in this syndrome, we utilized in-vivo microdialysis of amygdala and hypothalamus in two Cebus monkeys (C. apella) before and after bilateral lesions of the temporal pole (TP). Both subjects were housed and observed in a social group when not being dialyzed. Behavioral changes consequent to the TP lesion included early postoperative anorexia, adipsia, hunched posture, tameness, and lethargy. Subsequently, loss of fear, hyperorality, loss of social rank, and social withdrawal were observed. Neurochemical changes in amygdala included fall in DA metabolites, increase in NE, and fall in 5-HIAA. The amino acids glutamate and aspartate were both lower postoperatively but more so in the subject with the greatest behavioral change. Similar changes were noted in hypothalamus except for DA metabolites which remained unchanged. The Kluver-Bucy syndrome appears related to a partial deafferentation of excitatory projections (or ablation) to amygdala, lowering of DA and 5-HIAA and increase in NE.

746.2

RELEASE OF DOPAMINE WITHIN THE MEDIAL PREFRONTAL CORTEX ELICITED BY PRIMARY INCENTIVE STIMULI. J.B. Mitchell*, Dept. of Psychology, Boston College, Chestnut Hill, MA, USA 02167.

Sex-related olfactory cues elicit dopamine (DA) release within the nucleus accumbens, a terminal field of the mesolimbic DA system (Mitchell & Gratton, Brain Res., 1991, 551:20). Furthermore, depletion of mesocortical DA enhances mesolimbic DA release elicited by exposure to sex-related olfactory cues, and especially to DA release elicited by presentation of a highly palatable food, suggesting that the mesolimbic DA system is under inhibitory cortical (medial prefrontal) control (Mitchell & Gratton, J. Neurosci., 1992, 12:3609). The involvement of DA release within the medial prefrontal cortex in mediating the response to primary incentive stimuli was further explored by directly measuring DA efflux within the medial prefrontal cortex during exposure to a highly palatable food and to sex-related olfactory cues (bedding from cages that housed estrus female rats). During presentation of these stimuli, extracellular DA concentrations were measured using high speed chronoamperometry. The electrochemical signal was obtained by applying a +0.55 V pulse, relative to a Ag/AgCl reference electrode, to a Nafion-coated carbon fiber electrode at a rate of 5 Hz. The electrochemical signal recorded within the medial prefrontal cortex increased when animals approached and ate a highly palatable food. Investigation of sex-related olfactory cues, however, had only a small and variable effect on the electrochemical signal: the electrochemical signal showed small increases, decreases, or no change across different animals and within the same animal across different tests. That is, although both a highly palatable food and sex-related olfactory cues activate the mesolimbic dopamine system, only the highly palatable food increased activity within the mesocortical dopamine system.

746.3

A COMPARISON OF MESOLIMBIC AND NIGROSTRIATAL DOPAMINERGIC ACTIVITY DURING FOOD CONSUMPTION AND CONDITIONED APPETITIVE BEHAVIOR, AS DETERMINED BY *IN VIVO* ELECTROCHEMICAL DETECTION. T.J. Brozoski*, G.A. Gardner, and M.E. Cox, Dept. of Psychology, Grinnell College, Grinnell, IA 50112.

It has been hypothesized that the mesolimbic (ML) and nigrostriatal (NS) dopamine (DA) systems of the mammalian brain carry out different, and perhaps complementary functions related to reinforcement. To test this general hypothesis, DA activity, as measured by *in vivo* electrochemical detection of dopamine metabolites, was quantified during feeding and conditioned appetitive behavior (without food), in the ML and NS systems of food-deprived rats. The response of each system was found to be unique to different reinforcement conditions: Under conditions of moderate motivation (24-hr deprivation) and food reinforcement, DA activity increased during feeding periods in a major terminal field of the NS system (dorso-anterior caudate-putamen) but showed no increase in a major terminal field of the ML system (nucleus accumbens). Under the same motivational conditions (24-hr deprivation) and conditioned reinforcement only (auditory signal previously paired with food, but **no food** delivery), the opposite was true: DA activity increased during feeding periods in the ML terminal field but not in the NS terminal field. Under conditions of high motivation (48-hr deprivation) and food reinforcement, both systems responded with increased DA activity in their terminal fields during feeding periods. But while the increase was appreciable in the ML system (nucleus accumbens), it was much smaller in the NS system (dorso-anterior caudate-putamen). These results support the hypothesis that the ML and NS DA systems serve different aspects of reinforcement. They further suggest that the NS system is more directly involved in primary reinforcement, such as that associated with food consumption under moderate deprivation conditions. In contrast the ML system may be more directly involved in other parameters of reinforcement, such as those associated with conditioned stimuli or extreme deprivation.

746.4

ESTIMATING EXTRACELLULAR CONCENTRATIONS OF DOPAMINE IN NUCLEUS ACCUMBENS AND STRIATUM USING MICRODIALYSIS: RELATIONSHIPS BETWEEN *IN VITRO* AND *IN VIVO* RECOVERIES. S.D. Glick, N. Dong, R.W. Keller, Jr., J.N. Carlson and B. Zimmerberg[1], Dept. of Pharmacology and Toxicology, Albany Medical College, Albany, NY 12208 and [1]Dept. of Psychology, Williams College, Williamstown, MA 01267

In microdialysis studies probes are frequently "calibrated" in artificial CSF and *in vitro* recoveries determined for substances of interest. Dialysate concentrations are then "corrected" for *in vitro* recoveries in order to provide "estimates" of extracellular concentrations. However, at least for dopamine (DA), *in vitro* and *in vivo* recoveries are significantly different (Parsons & Justice, 1992) and, therefore, an estimate of extacellular DA based on correction for *in vitro* recovery is likely to be erroneous. Generally, it is the relative relationship of such estimates among animals that is of interest rather than the "actual" absolute values. Such relationships would be valid to the extent that estimated values are correlated with or predictive of actual values. Using the "no net flux" procedure, the present study sought to determine if *in vitro* and *in vivo* recoveries of DA would correlate with each other as well as if respective "estimated" and "actual" values of DA would. Probes (3 mm; BAS/CMed MF-5393), calibrated *in vitro*, were lowered into the nucleus accumbens and striatum of freely moving rats the day before sample collection was begun. *In vitro* and *in vivo* recoveries of DA were not significantly correlated (r= 0.1-0.3), although there were significant correlations (r= 0.7-0.8) between estimated and actual values of DA. Surprisingly, absolute dialysate levels with no *in vitro* corrections were even better correlated (r=0.9-0.95) with actual values of DA. These results indicate that, at least for the commercial probes used in this study, *in vitro* calibrations provide little or no useful information, adding only "noise" to estimates of extracellular DA that are better indicated by absolute dialysate concentrations (supported by DA03817 and AA08599).

746.5

STRESS-INDUCED SENSITIZATION OF NOREPINEPHRINE EFFLUX IN PREFRONTAL CORTEX: FURTHER CHARACTERIZATION. J.M. Finlay*, A.D. Rabinovic, P.J. Gresch, A.F. Sved and M.J. Zigmond. *Department of Behavioral Neuroscience, University of Pittsburgh, Pgh., PA.*

Exposure to chronic cold (5°C) for 2-3 weeks results in enhanced levels of extracellular norepinephrine (NE) in prefrontal cortex (PFC) in response to an acute novel stressor presented 1 day after rats are removed from the cold environment (Finlay & Abercrombie, *Soc Neurosci Abs*, 1991). The present experiment assessed whether stress-induced sensitization of extracellular NE in PFC occurs when rats are exposed to chronic cold for 1 week and subsequently exposed to acute tail shock either 1 or 14 days after being removed from the cold environment. Using *in vivo* microdialysis, we observed that basal extracellular NE in PFC is not different in control rats and rats exposed to chronic cold for 1 week and subsequently tested either 1 day or 14 days after being removed from the cold (4.0 ± 0.4, 4.1 ± 0.2 and 3.6 ± 0.3 pg/20 ul, respectively; n = 4-6/group). Rats exposed to acute tail shock 1 day after being removed from the cold exhibited a greater increase in extracellular NE in response to the stressor than naive rats (265 ± 13% and 206 ± 15% of baseline, respectively). In addition, NE levels remained elevated longer in chronically stressed rats such that, at 30-45 min after cessation of the tail shock, extracellular NE remained elevated in chronically stressed rats, whereas it had returned to basal values in naive controls (181 ± 11% and 107 ± 14% of baseline, respectively). In rats exposed to tail shock 14 days after being removed from the cold, the stress-induced increase in extracellular NE was no longer sensitized (166 ± 9% of baseline). These data indicate that following exposure to 1 week of chronic cold, presentation of an acute novel stressor elicits sensitized NE efflux in the PFC 1 day after removal from the cold. Furthermore, 14 days after removal from the cold the sensitized response has dissipated. *[Supported by an MRC of Canada Postdoctoral Fellowship (JMF), and USPHS Grants MH45156 and MH43947.]*

746.6

LOCAL APPLICATION OF DESIPRAMINE INCREASES BASAL AND STRESS-INDUCED DOPAMINE EFFLUX IN MEDIAL PREFRONTAL CORTEX. P.J. Gresch*, A.F. Sved, M.J. Zigmond and J.M. Finlay. Dept. of Behavioral Neuroscience, University of Pittsburgh, Pittsburgh, PA 15260

We have previously observed that prior exposure to chronic cold results in enhanced levels of extracellular dopamine (DA) and norepinephrine (NE) in medial prefrontal cortex (mPFC) in response to acute tail shock, as measured by *in vivo* microdialysis. However, stress-induced sensitization of DA efflux did not occur in either the nucleus accumbens or neostriatum (Gresch et al., *Soc Neurosci Abs*, 1992). Unlike the nucleus accumbens and neostriatum, the mPFC receives an extensive innervation by NE-containing neurons which overlaps with the DA innervation. We have proposed that stress-induced DA efflux in mPFC may, in part, result from an influence of NE neurons on extracellular DA. We have now examined the influence of the NE uptake inhibitor, desipramine (DMI), on basal and acute stress-induced DA and NE efflux in the mPFC (results expressed as pg/20µl ± SEM; n=5). DMI ($10^{-6}M$), infused via a microdialysis probe in mPFC, increased basal NE (from 4.6 ± 0.7 to 12.4 ± 1.2 pg ; $p<0.05$) and DA efflux in the mPFC (from 1.2 ± 0.3 to 2.7 ± 0.4 pg; $p<0.05$). In contrast, DMI ($10^{-6}M$) delivered to neostriatum did not affect basal striatal DA efflux, suggesting that DMI is not directly affecting DA terminals. Relative to control rats, DMI potentiated the stress-induced increase in extracellular DA (1.2 ± 0.1 vs. 6.6 ± 1.7 pg above basal efflux, respectively; $p<0.05$) and NE (1.4 ± 0.2 vs. 19.9 ± 2.9 pg above basal efflux, respectively; $p<0.05$). This suggests that (a) NE influences DA release, or (b) DA can be taken up by a DMI-sensitive transporter, possibly that found on NE nerve terminals. [*Supported by the Scottish Rite Schizophrenia Research Program and an MRC fellowship (JMF), and USPHS grants MH29670 and MH45156.*]

746.7

CHRONIC COLD STRESS ALTERS THE BASAL AND EVOKED ELECTROPHYSIOLOGICAL ACTIVITY OF NORADRENERGIC NEURONS IN THE LOCUS COERULEUS. M.J. Mana* and A.A. Grace. *Depts. of Behavioral Neuroscience & Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA 15260*

Chronic cold stress increases several indices of neurochemical activity in the norepinephrine (NE)-containing neurons originating in the locus coeruleus (LC) of the rat, including the induction of tyrosine hydroxylase synthesis and activity and the evoked release of NE. However, the effect of chronic cold stress on the electrophysiological activity of LC cells is unknown. In the present experiments *in vivo* extracellular single-unit recording techniques were used to examine the effects of 21 days of chronic cold stress (5°C) on the basal and evoked electrophysiological activity of LC neurons in chloral hydrate anesthetized rats. Twenty-four hours after termination of cold-stress, NE neurons from cold-stressed rats displayed a significant elevation in basal firing rate (mean = 1.8 ± 0.2 Hz for cold-stress v. 1.2 ± 0.1 Hz for controls), accompanied by an increase in the incidence of spontaneous burst-firing activity (observed in cells in 3/17 control rats v. 4/5 cold-stressed rats). Sciatic nerve stimulation (5 mA, 0.5 ms, 0.2 Hz) evoked bursts of spikes in LC cells in every rat in both the control and cold-stress groups; however, evoked bursts were less likely in cold-stressed rats (cold-stress mean = 24 bursts/50 stimulations; control mean = 44 bursts/50 stimulations). In addition, LC cells in cold-stressed rats displayed increased sensitivity to the autoreceptor-mediated inhibitory effects of the α-2 adrenoreceptor agonist clonidine (0.5 - 8.0 μg/kg iv). These stress-induced alterations in the basal and evoked electrophysiological activity of neurons in the LC contrast with their enhanced neurochemical activity, suggesting that the net effect of chronic stress may represent an alteration in the balance between neurochemical capacity and electrophysiological responsivity within the LC. *Supported by USPHS MH 43947 and an MRC of Canada Postdoctoral Fellowship (MJM).*

746.8

TYROSINE HYDROXYLASE mRNA IN LOCUS COERULEUS AND ADRENAL MEDULLA INCREASES IN RESPONSE TO ACUTE COLD AND REMAINS ELEVATED DURING A 24 HOUR POST-STRESS PERIOD. M.K. Hahn* and T.G. Sherman. Department of Behavioral Neuroscience, University of Pittsburgh, Pittsburgh, PA, 15260-7700.

Exposure to cold results in an enhanced capacity for catecholamine (CA) synthesis in locus coeruleus (LC) and adrenal medulla (AM) through an increase in tyrosine hydroxylase (TH) enzyme that is preceded by an increase in TH mRNA. It is unclear how TH expression is regulated following release from a stressor. The present study examined the regulation of TH mRNA in LC and AM in response to acute cold exposure and following a 24 hr post-stress period at room temperature. Rats were shaved and exposed to 3 hr of cold (5°C). Following cold exposure, some rats were maintained at room temperature for 24 hr prior to sacrifice. Twelve μm sections were cut through the AM and LC for *in situ* hybridization. Slides were hybridized for 16-22 hr at 56°C with an ^{35}S-labelled antisense cRNA probe containing 475 nucleotides of rat TH cDNA sequence. Image analysis was performed by measuring percent area covered by silver grains in AM and number of grains per cell in LC. Three hr of cold exposure resulted in increases in TH mRNA that were 400±87% of control in AM and 139±4% of control in LC ($p<.05$). TH mRNA levels in rats exposed to a 24 hr post-stress period remained elevated at 327±40 and 123±7% of control in AM and LC, respectively ($p<.05$). These data indicate that AM and LC respond similarly to 3 hr of cold exposure followed by a 24 hr post-stress period. We are currently investigating the regulation of TH mRNA in LC and AM in response to chronic cold followed by a post-stress period to determine (1) if LC and AM are regulated in parallel under these conditions and (2) if the rate of return of stress-induced TH mRNA to basal levels is dependent on the length of cold exposure. Research supported by NIMH Grant MH29670.

746.9

EFFECT OF ACUTE STRESS ON DOPAMINE SYNTHESIS IN STRIATUM AND NUCLEUS ACCUMBENS. S.L.Castro*, A.F.Sved and M.J.Zigmond. Department of Behavioral Neuroscience, University of Pittsburgh, Pittsburgh, PA 15260.

Acute stress increases dopamine (DA) release in neostriatum and nucleus accumbens as evidenced by an increase in both extracellular DA and DA turnover in tissue. To further delineate the factors involved in the stress-induced increase in DA release, we examined the effect of intermittent tail-shock stress on DA synthesis in these structures using two measures of *in vivo* DA synthesis. DOPA levels in neostriatum and nucleus accumbens were measured in adult male rats treated systemically with the aromatic amino acid decarboxylase inhibitor NSD-1015 (100 mg/kg, i.p.) just prior to the onset of tail-shock and sacrificed immediately following 30 min of the stress. In additional rats, the effect of 30 min of tail shock on DOPA levels in extracellular fluid was measured using microdialysis during the local administration of NSD-1015 (100 μM) through the dialysis probe. No change in tissue DOPA accumulation was detected in neostriatum; however, an increase (+27%) was observed in nucleus accumbens. Similarly, using extracellular DOPA levels as an index of DA synthesis, tail shock did not appear to increase DA synthesis in neostriatum, while in nucleus accumbens it was significantly enhanced (+95%). These results suggest that the stress-evoked increase in DA release observed in nucleus accumbens is accompanied by a rapid increase in DA synthesis, whereas that observed in neostriatum is not. (Supported in part by USPHS grants MH45156, MH43947, MH00058, and MH09972.)

746.10

DOPAMINE EFFLUX IN STRIATUM IS NOT ALTERED BY LESIONS OF DOPAMINE TERMINALS IN MEDIAL PREFRONTAL CORTEX. D. King*, M.J. Zigmond, and J.M. Finlay. Department of Behavioral Neuroscience, University of Pittsburgh, Pittsburgh, PA 15260.

Lesions of dopamine (DA) terminals in the medial prefrontal cortex (mPFC) are reported to increase basal or evoked DA turnover in subcortical sites as determined by tissue levels of DA and its metabolites. We used *in vivo* microdialysis to examine the impact of such lesions on basal and evoked DA efflux in neostriatum. First, we determined the effect of locally administered 6-hydroxydopamine (6-OHDA) on the DA and norepinephrine (NE) content in mPFC of rats pretreated with desmethylimipramine (DMI, 25 mg/kg, ip). Whereas higher doses of 6-OHDA (4-8 μg/side) depleted both catecholamines in mPFC, 1 μg of 6-OHDA produced a large depletion of DA without significantly decreasing norepinephrine content (21% DA and 86% NE remaining). The latter method was then used to lesion the DA terminals in mPFC and two weeks later a microdialysis probe was implanted in neostriatum of these rats. Approximately 18 hours after implantation of the dialysis probe, lesioned and control rats were exposed to tail pressure (30 min) and d-amphetamine (1.5 mg/kg, ip) in a counterbalanced order. Extracellular DA and dihydroxyphenylacetic acid (DOPAC) concentrations were determined at 15 min intervals (all data are expressed per 20 μl of dialysate). Basal levels of extracellular DA and DOPAC in rats with 6-OHDA lesions of mPFC were not different from those found in control rats (DA: 12.9 ± 1.3 vs. 13.5 ± 0.9 pg, respectively; DOPAC: 4.3 ± 0.6 vs. 4.7 ± 0.4 ng, respectively; n = 9 and 11, respectively). Moreover, whereas tail pressure increased extracellular DA, there was no significant difference in the responsiveness of the lesioned and control rats (122 ± 5% and 122 ± 4% of baseline, respectively). Amphetamine, which caused a much greater increase in extracellular DA than did tail pressure, also had the same effect in lesioned and control rats (677 ± 59% and 615 ± 64% of baseline, respectively). These data suggest that DA efflux in the neostriatum is not regulated by mesocortical DA, either under basal conditions or during stress or amphetamine challenges. [*Supported by an MRC of Canada Postdoctoral Fellowship (JMF), Tourette Syndrome Association and Scottish Rite Schizophrenia Research Program.*]

MONOAMINES AND BEHAVIOR: DOPAMINE AND MOVEMENT

747.1

NORADRENERGIC ALPHA-1 AND ALPHA-2 ANTAGONISTS BLOCK L-DOPA-INDUCED AIR-STEPPING IN DECEREBRATE NEONATAL RATS. L.L. Taylor, A.E. Sickles, D.J. Stehouwer* and C. Van Hartesveldt. Psychology Dept., Univ. of Florida, Gainesville, FL 32611.

Five-day-old rats suspended above a surface and administered L-DOPA engage in a locomotor behavior termed air-stepping, which can be blocked either by the noradrenergic alpha-1 antagonist prazosin or the alpha-2 antagonist idazoxan. L-DOPA-induced air-stepping has been demonstrated in decerebrate rat pups. The purpose of this experiment was to determine if noradrenergic receptor antagonists would block L-DOPA-induced air-stepping in decerebrate neonatal rats.

Precollicular/postmamillary decerebrations were performed on 5-day-old rats, which were pretreated with 0.5 mg/kg prazosin, 0.5 mg/kg idazoxan, or saline s.c., suspended, administered 100 mg/kg L-DOPA s.c., and videotaped for 1 hr. L-DOPA-induced air-stepping was blocked by each antagonist. Thus, the forebrain is not involved in noradrenergic modulation of L-DOPA-induced air-stepping.

747.2

BEHAVIORAL AND PHARMACOLOGICAL DETERMINANTS OF D_1 DOPAMINE AGONIST SUBSTITUTION FOR THE DISCRIMINATIVE STIMULUS INDUCED BY DIHYDREXIDINE. Q.D. Walker*[1], D.M. Black[2], D.A. Eckerman[3], D.E. Nichols[5] and R.B. Mailman[1,4,5]. Curric. in Toxcol.[1], Depts. Biology[2], Psychol.[3], Psychiatry[4], & Pharmacol[5]. Univ. of N. Carolina, Chapel Hill, NC 27599, and Dept. Med. Chem., Purdue University[6], West Lafayette, IN 47907.

Dihydrexidine (DHX) induces robust discriminative stimulus (DS) effects in rats that are mediated by D_1 receptor stimulation. Although DHX also has significant D_2 affinity (albeit 10-fold less than D_1), D_2 receptor stimulation does not comprise part of the DS properties of DHX (i.e., the D_2 antagonist remoxipride does not block DHX and D_2 agonists do not substitute). SKF38393 substituted for DHX but less potently when a DHX (rather than a vehicle) conditioning session, preceded the substitution test. For example, 8 mg/kg SKF38393 induced >90% drug lever responding when tested after a vehicle conditioning session, but only 40%, after a drug session. Several lines of evidence suggest that the decreased potency after a drug session is not attributable to a short term neurochemical desensitization induced by DHX: 1) no day-before effect was observed for lower doses of DHX; 2) administration of the training dose of DHX in the home cage immediately following a vehicle training session did not have the same potency decreasing effect on SKF38393 substitution as a drug training session; 3) increasing the interval between a drug training session and an SKF38393 test session increased its substitution; 4) the effect of a drug training session within the past 24 hours was negated by an intervening vehicle session. This day-before effect also was observed for SKF82958, A68930 and 2-methyl-DHX. A significant correlation ($r=0.91$, $p<.03$) was found between D_1/D_2 selectivity and the change in potency following vehicle and drug sessions. Increased D_1 selectivity resulted in greater decreases in substitution potency following a drug session. This relationship was supported by the demonstration that coadministration of the D_3/D_2 agonist quinpirole potentiated substitution of either SKF38393 or A68930. These data indicate that the training session prior to a test session greatly influences agonist substitution. Moreover, we conclude that the D_2 agonist properties of DHX are important for determining D_1 agonist substitution even though the DHX cue was found to be mediated primarily by D_1 receptors.

747.3

DOI-INDUCED HEADSHAKES ARE ATTENUATED BY DOPAMINE D_1-LIKE RECEPTOR ACTIVATION AND FACILITATED BY D_2-LIKE RECEPTOR ACTIVATION. W.Fischer, L.A. Pohorecky, E.I. Saiff*[1], and D. Benjamin. Center of Alcohol Studies, Rutgers University, Piscataway, NJ 08855, [1]Deptartment of Theoretical and Applied Sciences, Ramapo College of New Jersey, Mahwah, NJ 07430.

Considerable evidence indicates a functional interaction of the 5-HT and dopaminergic (DA) neuronal systems while behavioral studies indicate a decrease in D_2 activity results from the activation of the 5-$HT_{2/1C}$ system, however, less is known of the influence of DA on 5-HT systems. This study assessed the possible reciprocal relationship between postsynaptic DA and 5-HT function. In rats, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a 5-$HT_{2/1C}$ agonist, causes stereotypical behaviors such as headshakes. DOI (1.0 mg/kg IP) was administered alone, and with either the $D_{1/2}$ agonist apomorphine (0.0625-0.5 mg/kg IP), the selective D_1 agonist SKF 38393 (1.0-6.0 mg/kg IP), or the $D_{2/3}$ agonist quinpirole (2.0-4.0 mg/kg IP). The number of headshakes exhibited served as a measure of 5-HT_2 receptor responsiveness. Apomorphine ($F_{(4,29)}=5.037;p=.01$) and SKF 38393 ($F_{(3,18)}=9.056;p=.001$) reliably inhibited DOI-induced headshakes dose-dependently. Quinpirole increased headshaking at the highest dose compared to controls. SKF 38393 showed a more robust inhibition of DOI induced headshaking than the $D_{1/2}$ agonist apomorphine. The ability of quinpirole to increase headshaking was significant but showed greater variability. We conclude that a D_1 mechanism appears to be the primary mechanism of interaction, and activation of the DA D_1 receptor mediates inhibition of the 5-$HT_{2/1C}$ mechanisms. (Supported by Smithers Prevention and NIAAA grant AA08499).

747.4

RESERPINE-INDUCED ORAL DYSKINESIA IS ATTENUATED BY 6-HYDROXYDOPAMINE LESIONS IN RATS. J. L. Neisewander*, H. J. Elson, E. Castañeda, and D. A. Davis. Department of Psychology, Arizona State University, Tempe, AZ 85287-1104.

Rats develop spontaneous oral dyskinesia following repeated administration of reserpine. This response is dose-dependently blocked by the dopamine (DA) D2 antagonist spiroperidol. Repeated administration of reserpine also produces a compensatory increase in monoamine turnover in the striatum and an increase in behavioral sensitivity to DA agonists. It was, therefore, hypothesized that reserpine-induced oral dyskinesia may be mediated by residual endogenous dopamine stimulating supersensitive DA receptors in the striatum. To test this hypothesis, nigrostriatal DA neurons were lesioned with 6-hydroxydopamine (6-OHDA) to further deplete residual dopamine. Animals were infused bilaterally with either vehicle or 6-OHDA (5 µg/4µl/side) into the substantia nigra. Two weeks later, half of each group was injected with vehicle and half was injected with reserpine (1 mg/kg, SC) every other day for 6 days. Animals were observed for oral dyskinesia by recording the incidence of tongue protrusions (TPs) for 30 minutes 24 hr after their last injection. 6-OHDA lesions alone did not alter TPs, however, the lesions did attenuate reserpine-induced TPs. DA turnover was measured in the striatum as a ratio of DOPAC/DA levels. 6-OHDA lesions alone produced a slight increase in DA turnover. Reserpine treatment alone produced a 10-fold increase in DA turnover that was significantly reduced by the 6-OHDA lesions. The results are consistent with the hypothesis that reserpine-induced oral dyskinesia is mediated, in part, by residual endogenous dopamine in the striatum. These findings may have important implications for understanding L-DOPA-induced dyskinesia and tardive dyskinesia.

747.5

ONTOGENIC EFFECTS OF INTRASTRIATAL QUINPIROLE ON LOCOMOTION IN THE RAT. C. Van Hartesveldt* and T. J. Potter. Psychology Dept., Univ. Florida, Gainesville, FL 32611.

We have previously shown that in the adult rat, quinpirole, a dopamine D2/D3 receptor agonist, suppresses locomotor activity at low doses, while at higher doses it first suppresses and then activates locomotion whether the drug is injected peripherally or intrastriatally. We have also shown that quinpirole given peripherally only activates locomotion until 20-30 days of age, when the biphasic effect appears. The present study was designed to determine at what age the biphasic effect can be elicited from the striatum.

Male and female S. D. rats at 10, 20, or 30 days of age were tested in an automated activity monitor after intrastriatal injection of 0 (vehicle), 1, 5, 10, or 40 µg quinpirole in 0.25 µl solution for 2 hr collecting data every 5 min. At 10 days of age only activation was seen; at both 20 and 30 days of age a biphasic effect was observed depending on the dose. Thus both effects can be elicited from the striatum during development. These results are discussed with respect to the controversy regarding the role of the dopamine autoreceptor in the suppression of behavior.

747.6

VACUOUS CHEWING INDUCED BY N-n-PROPYL DIHYDREXIDINE: A D_2-LIKE (D_3) SELECTIVE DOPAMINE AGONIST. H.P. Smith[1]*, C.P. Lawler[1], A.M. Eaton[1], D.E. Nichols[2], and R.B. Mailman.[1] University of North Carolina[1], Chapel Hill, NC, 27599, Purdue University[2], West Lafayette, IN, 47907.

The induction of oral dyskinesias and vacuous chewing in rats has traditionally been associated with activation of D_1 receptors, although it does not appear to be linked to the regulation of adenylate cyclase activity (Downes & Waddington, *EJP.* 234:135,1993). Because acute D_2 antagonism enhances the observed frequency of this behavior, D_2-like receptors have been reported to have a modulatory role in the induction of vacuous chewing. N-n-propyl dihydrexidine (PrDHX) is a member of the novel class of hexahydrobenzo[a]phenanthridine dopaminergic ligands. PrDHX binds with ten-fold selectivity to D_2-like vs. D_1-like receptors, and has D_2-like agonist functional activity both *in vivo* and *in vitro*, although this seems to be confined to post-synaptic functions (Mottola et al. *SON Abstr.* 17: 818, 1991). In addition, we have recently shown that PrDHX has > 30-fold selectivity for D_3 receptors over D_2 receptors in molecular expression systems (Mayleben et. al., SON 1993). We now report for the first time that this D_2-like agonist can induce vacuous chewing in a dose-dependent fashion. Male Sprague-Dawley rats were injected s.c. with PrDHX, and their behavior quantified by computer-supported observational methods for one hour following dosing. The frequency of vacuous chewing increased dose-dependently at doses of 0.5-4.0 mg/kg, but was not induced at doses of 0.062-0.25 mg/kg. While PrDHX has some D_1-affinity, it is only a partial efficacy D_1-agonist unlike its parent compound dihydrexidine (DHX), which is of higher potency and full efficacy at D_1-like receptors. Yet DHX does not induce vacuous chewing behaviors in a dose range of 0.3 to 30 mg/kg s.c. Together, these data suggest that vacuous chewing is not primarily a D_1-mediated behavior, and raise the possibility that stimulation of a subset of D_2-like receptors may play a crucial role in eliciting oral dyskinesias such as those observed clinically during neuroleptic therapy.

747.7

POST-WEANLING EFFECTS OF DOPAMINE RECEPTOR AGONISTS IN RATS WITH NEONATAL 6-HYDROXYDOPAMINE LESIONS. B.S. Neal-Beliveau* and J.N. Joyce. Depts. of Psychiatry and Pharmacology, Univ. of Penn. Sch. of Med., Phila., PA 19104.

Previous studies suggest that a plasticity exists in rats with neonatal dopamine (DA) lesions that is qualitatively different from that of adult lesions. Adult 6-hydroxydopamine (6-OHDA) lesions induce a D2 receptor supersensitivity, and an increase in striatal D2 receptor density. In contrast, rats with lesions made on day of birth or postnatal day 1 (P0/P1) are supersensitive to D1 receptor agonists in adulthood (P90), and have a small, but significant loss of striatal D1 receptors (Synapse **11**: 35-46, 1992). The aim of this study was to further explore how DA receptor expression is altered after early neonatal lesions (ENL). Rats received intrastriatal injections of 6-OHDA (4 µg per side) or vehicle on P0/P1. ENL rats exhibited increased locomotor responses to various DA receptor agonists on P30-P37: Apomorphine (APO; D1/D2), SKF38393 and SKF82958 (D1), quinpirole (QUIN; D2) and QUIN+ SKF38393 or SKF82958. An increased incidence of oral dyskinesias was observed with SKF38393 (32 mg/kg), but not with 10 mg/kg, as is seen when ENL rats are tested at P90. APO (≤1.0 mg/kg) induced D1 receptor-mediated behaviors (oral dyskinesias and grooming), although a much higher dose (10 mg/kg) induced robust gnawing, as did high doses of QUIN+SKF38393. Facial grooming was also observed in ENL rats with QUIN + a D1 agonist. QUIN alone induced D1-associated behaviors in post-weanling rats. These data suggest that the normal interactions between D1 and D2 receptors are not fully developed in young rats, although ENL rats are capable of exhibiting a D1 receptor supersensitivity by P30-P37. (Supported by USPHS grant MH43852).

747.8

D1 - D2 MEDIATION OF SENSORIMOTOR BEHAVIOR DIFFERS BETWEEN ANIMALS DEPLETED OF DOPAMINE ON POSTNATAL DAY 1 vs DAY 3. M. Sandstrom*, E. McCone, B. Johnson, and J.P. Bruno. Dept. of Psychology and Neuroscience Program, The Ohio State University, Columbus, OH 43210

The D1-D2 mediation of sensorimotor behavior in rats changes after forebrain DA depletions on postnatal Day 3. Intact adults require co-activation of D1 and D2 receptors, while rats depleted of DA on Day 3 demonstrate independent D1/D2 mediation of sensorimotor behavior. In these depleted animals, both receptor subtypes must be blocked in order to produce deficits. Since important changes in DA receptor ontogeny occur during the first postnatal week, we compared the effects of DA depletions on Day 1 vs on Day 3. Rats received either 6-OHDA (100 µg) + DMI or its vehicle on Day 1 or on Day 3. Rats were tested for the ability of several DA antagonists to induce sensorimotor deficits. Adults depleted of DA (> 95%) at the 2 ages exhibited similarities and differences. Individual D1 or D2 antagonists had no effect on sensorimotor behavior in rats depleted at either age, yet produced marked deficits in controls. Simultaneous blockade of D1 and D2 receptors produced deficits in controls and in rats depleted on Day 3, but not in animals depleted on Day 1. Inhibition of DA synthesis impaired all animals. These results suggest that DA receptor activation is necessary for behavior in both groups of depleted animals yet the role of DA receptor subtypes may differ.

747.9

DEVELOPMENTAL PLASTICITY IN THE D1 AND D2 MEDIATION OF SENSORIMOTOR BEHAVIOR FOLLOWING NEONATAL DOPAMINE DEPLETIONS. E. McCONE*, Y.M. UGHRIN, AND J.P. BRUNO Dept. of Psychology and Neuroscience Program, Ohio State Univ. Columbus OH 43210

We have reported that the normal ability of either D1 or D2 antagonists to induce sensorimotor deficits is lost in adults depleted of DA as neonates. The present study determined the emergence of these altered receptor interactions as a function of time after the DA depletion. Rats received either 6-OHDA (100 ug) or its vehicle on postnatal Day 3 and were tested on Postnatal Day 10, Day 20, or Day 28. The D1 antagonist SCH 23390 and the D2 antagonist clebopride increased the duration of both the dorsal immobility response (DIR) and catalepsy in vehicle-treated animals at all ages. In contrast, while both SCH 23390 and clebopride resulted in an increased DIR and catalepsy in 6-OHDA-treated animals tested on postnatal Day 10, the effect of these individual antagonists on DIR and catalepsy in 6-OHDA-treated animals tested on postnatal Day 20 and Day 28 was markedly reduced. These results suggest that the profile of D1 and D2 receptor mediation of sensorimotor behavior observed in 6-OHDA-treated neonates tested as adults develops over time with the most significant alterations occuring between postnatal Day 10 and Day 20. Such protracted changes in receptor interactions may facilitate the discovery of neuronal mechanisms underlying these events.

747.10

STRIATAL DOPAMINE-ACETYLCHOLINE INTERACTIONS DO NOT MEDIATE SPARING FROM SENSORIMOTOR DEFICITS IN RATS DEPLETED OF DOPAMINE AS NEONATES. B.J. Johnson* and J.P. Bruno. Dept. of Psychology, Ohio State University, Columbus, OH 43210.

D1 and D2 receptors become independently capable of mediating sensorimotor behavior in adult rats depleted of DA as neonates, but not in intact animals or in animals depleted of DA as adults. Given the importance of striatal DA and ACh interactions for sensorimotor behavior in normal animals and in rats depleted of DA as adults, we utilized in vivo microdialysis to compare the effects of D1 and D2 receptor ligands on striatal ACh release in awake adults treated (ivt) with 6-OHDA or its vehicle on Day 3. Systemic administration of D1 agonists or D2 antagonists stimulated ACh efflux whereas D2 agonists or D1 antagonists inhibited ACh efflux. Although the pattern of results was very similar in both groups of rats, DA depleted animals were supersensitive to the effects of low doses of DA ligands. Local administration of DA antagonists via the dialysis probe revealed that clebopride (10 μM) stimulated ACh efflux whereas local SCH 23390 (10 μM) had no effect. The effectiveness of clebopride to stimulate ACh efflux was unaffected by repeated dialysis sessions. These data suggest that the alterations in D1-D2 mediation of sensorimotor behavior in rats depleted as neonates do not involve plasticity at the level of striatal DA-ACh interactions.

747.11

STRIATAL LESIONS MODIFY CATALEPTOGENIC PROPERTIES OF HALOPERIDOL BUT NOT OF CLOZAPINE **G. E. Jaskiw*, G. Hussain, S. Stephans, B. K. Yamamoto, H. Y. Meltzer. Psychobiol. Lab. Case Western Reserve Univ. Cleveland, OH/ Brecksville VAMC, Brecksville, OH.**

Although clozapine (CLOZ) does not normally induce catalepsy, it has been reported, that CLOZ-induced catalepsy is elicited in animals with either nonspecific or dopamine (DA) depleting striatal lesion. To test this, groups of rats received either vehicle (AP +0.2, ML ±3.0, VD -5.9 from bregma), 6OHDA (20µg/4µl) or ibotenic acid (IA) (12µg/1.2µl) bilateral stereotaxic infusions. After 14d, the catalepsy response to vehicle, HAL (0.75 mg/kg) or CLOZ (20 mg/kg) was determined. The 6OHDA lesion depleted 90% of striatal DA and augmented HAL catalepsy. In IA lesioned animals, neuronal loss was evident through most of the caudate-putamen and HAL catalepsy was reduced. CLOZ-induced catalepsy was not evident after either lesion. The relative inability of CLOZ to induce catalepsy does not depend either on the integrity of nigrostriatal DA terminals nor on striatal efferents. Supported by NARSAD.

747.12

ALTERATIONS IN EXTRACELLULAR STRIATAL DOPAMINE DURING CATALEPTIC BEHAVIORAL SENSITIZATION TO FLUPHENAZINE W.M. Meil*and R. E. See. Department of Psychology, Washington State University, Pullman, WA, 99164-4820.

Behavioral sensitization is a ubiquitous phenomenon, resulting from a variety of pharmacological or environmental challenges and manifesting in a wide spectrum of behaviors; however its neural basis remains poorly understood. In the present study intracranial microdialysis was used to assess alterations in extracellular striatal dopamine (DA) concentrations following sensitization of the cataleptic response to a single neuroleptic pretreatment. Female, Sprague-Dawley rats received pretreatment (ip) with fluphenazine (FLU) (0.3, 1 mg/kg) or saline and the duration of catalepsy measured, using the horizontal bar test, for 5 hrs at 30 min intervals. Simultaneously, dialysates were collected every 20 min and analyzed for extracellular DA using high performance liquid chromatography (HPLC) with electrochemical detection. Fifteen or thirty days after pretreatment, a second FLU (0.3, 1 mg/kg) or saline challenge injection was given and catalepsy and DA were measured using the same procedures. Significant time and dose related increases in catalepsy to FLU administration were found, while no sensitization occurred in animals pretreated with saline. Dose dependent elevation of striatal DA concentration was maintained for 5 hrs following FLU administration. Behavioral sensitization was accompanied by decreases in the FLU induced striatal DA overflow at both doses and time points. These findings support previous research demonstrating that acute exposure to a neuroleptic can result in long-term behavioral and neurochemical changes. Supported by National Institues of Health Grant DE09678.

747.13

MID-COLLICULAR/POST-NIGRAL TRANSECTION DOES NOT PREVENT L-DOPA-INDUCED AIR-STEPPING IN NEONATAL RATS. A.E. Sickles,* D.J. Stehouwer, C. Van Hartesveldt. Psychology Dept., Univ. of Florida, Gainesville, FL 32611

L-DOPA administered to pre-weanling rats that have been suspended in air induces a highly stereotypic locomotor response called air-stepping. In subjects that have received pre-collicular/post-mammillary transections, L-DOPA induces air-stepping that is similar to that of intact subjects. Air-stepping can be blocked in both intact pups and pups with pre-collicular/post-mammillary transections by pre-treatment with dopaminergic antagonists. These findings implicate midbrain dopaminergic systems in the production of air-stepping. The substantia nigra (SN) is a dopaminergic midbrain structure involved in locomotion.

This experiment examined the role of the SN in L-DOPA-induced air-stepping in neonatal rats. Five day-old rat pups were given mid-collicular/post-nigral transections, injected with L-DOPA s.c., and suspended in slings. Removal of the SN by this transection did not prevent the expression of L-DOPA-induced air-stepping. Thus the SN is not necessary for the production of L-DOPA-induced air-stepping in neonatal rats.

747.14

VACUOUS JAW MOVEMENTS INDUCED BY ACUTE RESERPINE: INTERACTIONS WITH PRE- AND POST-SYNAPTIC DOSES OF APOMORPHINE. P. Baskin* and J.D. Salamone, Dept. of Psych., Univ. of Connecticut, Storrs, CT 06269-1020

Two experiments were conducted in order to study the vacuous jaw movements (VJMs) induced in rats by acute administration of the monoamine-depleting agent reserpine (RES). In the first experiment, three doses of RES (1.25, 2.5 and 5.0 mg/kg, IP) were assessed for their ability to induce VJMs. Acute administration of RES induced a dose-related increase in VJMs, with the two highest doses being significantly different from the vehicle control. In the second experiment, interactions between 5.0 mg/kg RES and the dopamine agonist apomorphine (APO) were investigated. Co-administration of RES with the lowest dose of APO (0.1 mg/kg IP) significantly increased VJMs in RES-treated rats. The two higher doses of APO (0.5 and 1.0 mg/kg IP) significantly decreased VJMs in RES-treated rats. These results demonstrate that VJMs are induced by acute administration of RES in a dose-related manner. In addition, the interactions with APO suggest that VJMs are stimulated by decreases in dopamine release produced by pre-synaptic doses of APO, but that these movements are decreased by higher doses of APO that are known to act post-synaptically.

747.15

DIFFERENCES IN SPONTANEOUS AND D1 AGONIST INDUCED REPETITIVE JAW MOVEMENTS (RJM) IN TWO POPULATIONS OF INBRED RATS. H.Rosengarten, J.W.Schweitzer and A.J.Friedhoff. Dept. of Psychiatry, N.Y.U. School of Medicine, New York, N.Y.10016

RJM have been shown previously to be enhanced by stimulation of D1 receptors or D2 blockade and inhibited by D2 stimulation or by D1 blockade. In the present study we have investigated the effect of chronic fluphenazine (FLU) treatment on high and low RJM responders (RJMH and RJML) inbred through 8 generations. During washout we examined spontaneous and D1 agonist (SKF 82958 and A-68930) stimulated RJM, NPA inducible stereotypy (NPAS) and D1 and D2 receptor binding. FLU augmented significantly spontaneous and agonist stimulated RJM in both RJMH and RJML groups and the RJMH group remained significantly higher. NPAS were not different in vehicle RJMH and RJML groups but were equally supressed after chronic FLU. D2, but not D1, Bmax was increased in FLU animals. There were no changes in Kd values for D2 or D1 receptors in any of the groups. The persistently elevated RJM scores in the RJMH group, with or without neuroleptic may be relevant to neuroleptic induced tardive dyskinesia dyskinesia.

747.16

CHOLINERGIC STIMULATION OF RAT SUBSTANTIA NIGRA AND VENTRAL TEGMENTAL AREA: RESPONDING FOR CONDITIONED REINFORCEMENT AND FORMATION OF PLACE PREFERENCES. H.M. Brace, F. Calder, P. Cooke, W.L. Inglis, G.C. Parker A. Robertson and P. Winn (SPON: Brain Research Association) Dept. Psychol., Univ. St Andrews, Fife, Scotland KY16 9JU.

DA stimulation of nucleus accumbens (NAS) but not caudate-putamen (CP) increases responding for conditioned reinforcement (CR) and promotes conditioned place preferences (CPP). DA-containing neurons in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) are excited by cholinergic stimulation. Can this also increase responding for CR and CPP formation? Rats with bilateral guide cannulae aimed at VTA or SNc (each n=18) were trained to associate food in a standard operant chamber with a compound visual/auditory stimulus. In test trials one lever produced CR, while the other did not (NCR). In test sessions rats were microinjected (individually randomized order; 0.5µl/min) with 0.5µl saline; 0.1µg carbachol (CARB)+0.055µg nicotine (NIC); 0.1µg CARB+0.1µg NIC; 0.1µg CARB+0.25µg NIC. No differences were found between VTA and SNc injections but all rats showed rate-dependent increases in food hopper panel pressing. For further analysis rats were divided into high and low baseline groups. NCR lever pressing was unaffected but cholinergic stimulation increased CR lever pressing in the low baseline rats. To examine CPP rats were microinjected with 0.4 or 0.8mM NIC on either one or other side of a standard CPP apparatus (2-3 trials). 0.8mM (but not 0.4mM) NIC in VTA but not SNc produced a mild CPP. These data show that microinjections of cholinergic drugs into VTA and SNc mediate different behavioral processes, but unlike DA stimulation of NAS and CP, cholinergic stimulation of VTA and SNc have the same effect on responding for CR.

MONOAMINES AND BEHAVIOR: ELECTROPHYSIOLOGY

748.1

WITHDRAWN

748.2

MODULATION OF FOREBRAIN EEG BY MEDIAL SEPTAL NORADRENERGIC β-RECEPTORS C.W. Berridge*, S. Bolen, S.L. Foote. Dept. Psychiatry, Univ. Calif., San Diego, CA 92093.

In the halothane-anesthetized rat, the locus coeruleus (LC) is a potent modulator of forebrain EEG state (Berridge & Foote, 1991). Such influences are mediated, at least partly, through noradrenergic β-receptors. It is not known whether LC affects EEG state via monosynaptic projections into neocortex and hippocampus or through LC projections to intermediate sites. The medial septum/diagonal band (MS) and the substantia innominata/nucleus basalis (SI) areas receive a dense LC innervation and are known to exert modulatory actions on hippocampal and neocortical EEG, respectively. The present studies examined whether β-receptors within MS or SI modulate forebrain EEG state in the halothane-anesthetized rat. Unilateral infusions (150 nl) of either vehicle or the β-receptor agonist, isoproterenol (25 µg/µl), were made into MS, SI, lateral septum, striatum, or lateral nucleus accumbens. Vehicle infusions into these sites had no EEG effects. MS ISO infusions produced forebrain EEG activation, i.e. decreased slow-wave activity in neocortex and increased theta activity in hippocampus. ISO had no EEG effects when infused into sites other than MS, including SI (150-450 nl). MS, but not SI, infusions of amphetamine (12.5-25 µg/µl), which acts to increase synaptic concentrations of endogenous NE, were extremely potent in inducing EEG activation. These results indicate that, under these experimental conditions, stimulation of β-receptors unilaterally within MS, but not SI, is sufficient to induce bilateral activation of forebrain EEG. Additional studies indicated that EEG activation, including that observed following MS ISO and amphetamine, is not atropine-sensitive in the halothane-anesthetized rat (see accompanying poster). Thus, this experimental preparation provides a useful paradigm for the study of cholinergic-independent forebrain EEG activation. Future studies will need to address which MS efferent system(s) is involved in the noradrenergic-dependent modulation of EEG state.

748.3

SINGLE-UNIT ACTIVITY OF VENTRAL TEGMENTAL DOPAMINE NEURONS IN RESPONSE TO SENSORY STIMULI J.C. Horvitz*, C. Fornal, and B.L. Jacobs. Prog. Neurosci., Dept. of Psychol., Princeton Univ., Princeton, NJ 08544

Mesolimbic dopamine (DA) neurons are thought to play a role in behavioral responses to reinforcing stimuli and stimuli that signal reward. However, little is known regarding the response of these neurons to unconditioned sensory stimuli. In the present study, single-unit activity of VTA DA neurons was recorded in freely moving cats. DA neurons were identified on line by their slow firing rates (3-8 HZ), occasional burst firing, long duration action potentials (>2 msec), and apomorphine-induced rate suppression. Auditory and visual stimuli of 1 msec duration (101 dB clicks and 1.9 x 10^9 lumens light flashes, respectively) were presented once every 5 sec. DA cells responded to the stimuli with either a consistent excitation or inhibition occurring approximately 90 msec after stimulus presentation and lasting for approximately 140 msec. With repeated stimulus presentation, neuronal responses were attenuated; this neuronal habituation coincided with decreased behavioral response as measured by EMG, EOG and EEG activity. Supported by grants from the AFOSR (90-0294) and the NIMH (MH23433).

748.4

SHARPENING FREQUENCY RECEPTIVE FIELDS (FRF) OF AUDITORY CORTEX NEURONS BY IDAZOXAN-INDUCED RELEASE OF NOREPINEPHRINE. J-M Edeline* and S.J. Sara; NAM, Univ. Paris-Sud Orsay and IDN, Univ. Paris VI, France

Idazoxan (IDA) is an alpha2 antagonist of adrenoreceptors which (1) increases spontaneous activity of locus coeruleus neurons and (2) increases release of norephinephrine (NE) from noradrenergic terminals. We examine here the effect of such an increased amount of extracellular NE on FRF of neurons in the auditory cortex. Single units (n=26) were recorded in urethane anesthetized rats and the FRF was determined by presenting at 70 dB a set of 11 ascending frequencies to the contralateral ear via a calibrated earphone. IDA was administrated either by systemic (i.p. 2-4mg/kg) injections or by local applications directly on the exposed cortex . In both cases saline injections were used as control. Relative to saline, IDA produces a significant and clear decrease in both spontaneous and evoked activity, by 33% and 26% respectively. The range of frequencies to which the neurons responded (quantified by the square root transform $\sqrt{f2}$-$\sqrt{f1}$) was significantly decreased from 1.30 to 0.86. Moreover, the strength of the evoked response at the best frequency relative to the responses at all the other frequencies in the neuron FRF was significantly increased from 40% to 54%. Thus, enhanced NE release in the auditory cortex promotes a sharpening of the neuron's FRF. Supported by a MRT grant # 91CO956.

748.5

THE RELATIONSHIP OF SLOW CEREBRAL POTENTIALS TO PLASMA NOREPINEPHRINE DURING A WARNED REACTION-TIME MOTOR TASK. Jennifer West, University of Wisconsin-Oshkosh.
Previous research has demonstrated norepinephrine (NE) as crucial to cellular bases of attention and learning. NE has also been associated with the potentiation of slow-cortical waves commonly observed in event-related brain potentials (Skinner, 1991). Slow cerebral potentials are commonly accepted measures of both attention and motor preparation. This is demonstrated through a contingent negative variation (CNV) in amplitude which has been attributed both to response preparation and to expectancy to receive external information. Our study investigated the relationship between plasma NE and CNVs recorded from the scalp during a warned reaction time (RT) task. Twenty adults between 22-32 years-of-age [mean = 25.6] served as subjects (Ss). The warned reaction time (RT) task involved squeezing a hand dynamometer set at 40% of each subject's maximum squeeze strength [range = 12-23 kg]. The S1-S2 interval was one second. Fifty trials were collected from each subject. Brain potentials were recorded with Grass (Model 7P1) amplifiers (TC=2 s) via miniature electrode placement. To facilitate measures of plasma NE, a 21-gauge catheter was inserted into a superficial vein in the left arm 30 minutes prior to the reaction-time task. Blood sampling occurred immediately after the 50 RT trials. Results included a group mean plasma NE of 375 pg/ml. Averaged RT was 309 ms. Peak CNV amplitudes [across all subjects] were -6.4 uV at Fz and -7.3 uV at Cz. A Pearson correlation between CNV amplitudes and plasma NE depicted $r = -.567$ ($p=.043$) at Fz and $r = -.509$ ($p=.065$) at Cz. The results of this study suggest a relationship between plasma NE and cortical indices of attention [i.e., CNVs] during a warned RT task. Rapidly developing knowledge of cellular-level bases of attention should provide continued interpretation of the plasma NE correlations in this study.

DRUGS OF ABUSE: ETHANOL—DEVELOPMENT

749.1

BEHAVIORAL EVIDENCE OF HIPPOCAMPAL DYSFUNCTION IN CHILDREN WITH ALCOHOL RELATED BIRTH DEFECTS. L. Nadel* and A. Uecker, Department of Psychology, University of Arizona, Tucson, AZ 85721.
Rodent models of alcohol related birth defects (ARBD) have provided both behavioral and neuroanatomical evidence of hippocampal dysfunction. Parallel evidence in human beings, however, has not been forthcoming. Hippocampal lesions lead to spatial memory deficits in both animals (Morris et al., 1982) and humans (Smith & Milner, 1981). Fifteen Native American (NA) children with ARBD (mean age=9.85, SD=2.32) and 15 NA control children (mean age=9.67, SD=2.40) performed Smith and Milner's object and spatial memory task. There was no significant difference between the groups on the object recall task, and no effect due to time of recall, immediate or delay. A significant interaction ($F[1,28]=7.12$, $p<.01$), however, indicated a differential pattern of remembering: the control group remembered more objects in delayed recall then in immediate recall, and the children with ARBD remembered less. On the spatial recall task, the children with ARBD performed worse than the control group ($F[1,28]= 4.93$, $p<.05$) and there was a significant effect due to time of recall ($F [1,28]=25.81$ $p<.001$). There was no interaction.
Hippocampal dysfunction in the individuals with ARBD is suggested both by differential remembering in object recall and by the spatial memory impairment. Because previous research has demonstrated that extensive damage to the right hippocampus results in a similar pattern of impairment (Smith & Milner, 1981), it appears that left neocortical structures may be intact.

749.2

EFFECTS OF PRENATAL ETHANOL EXPOSURE ON RAT HIPPOCAMPAL NEUROCHEMISTRY AT 90 DAYS OF POSTNATAL AGE. A.C. Black, Jr.* and L.W. Goolsby. Div. Basic Sciences and Dept. of Obstetrics and Gynecology, Mercer Univ. School of Medicine, and Medical Center of Macon Georgia, Macon, GA 31207.
Ethanol was administered in a liquid diet (Bio-Serv) to pregnant Sprague-Dawley rats on days 1-21 of gestation. For liquid diet control rats, ethanol was replaced with an isocaloric amount of maltose. After birth progeny were cross-fostered and allowed to reach 90 days of postnatal age. They were then sacrificed by decapitation and their hippocampi removed and pre-incubated in Eagle's Medium containing 5 mM theophylline and 2.2 mM $CaCl_2$ for 30 min at 37 C, then incubated for 2.5 min in the same solution containing 500 micromolar bethanechol. Hippocampi were then frozen in liquid nitrogen and analyzed for cyclic GMP by radioimmunoassay and for protein by the method of Lowry et al. Prenatal exposure to ethanol produced a statistically significant increase in the amount of cyclic GMP produced by maximal stimulation with bethanechol compared to liquid diet controls.

Supported by AA9092 and AA9213 and the Medical Center of Central Georgia.

749.3

CONCURRENT EXPOSURE OF COCAINE AND ETHANOL DURING THE BRAIN GROWTH SPURT: STUDIES OF SOMATIC GROWTH AND BRAIN DEVELOPMENT. W.J. Chen, K.H. Andersen and J.R. West*. Dept. of Human Anatomy and Medical Neurobiology, Texas A&M University, College Station, TX 77843
The prevalence of concomitant use of cocaine and ethanol among drug abusers has raised public concern and has provided the impetus for many studies. The aim of the present study was to assess the interactive effects of cocaine and ethanol on somatic and brain development using an animal model system. Six groups of artificially-reared Sprague-Dawley rat pups were given either 0 or 40 mg/kg cocaine in combination with either 0, 3.3 or 4.5 g/kg ethanol daily during the brain growth spurt period (postnatal days 4 through 9). An additional suckled control group raised by its natural dam was included to control for artificial rearing. The results are summarized as follows: (1) Drug-induced lethality was significantly higher in cocaine-treated animals as compared with controls, but not in the ethanol-treated animals. (2) Somatic growth, in terms of body weight, was not affected by cocaine, ethanol or the combination of both drugs using the artificial-rearing technique. (3) Ethanol exposure during this brain growth spurt period significantly reduced the whole brain weight, as well as the forebrain, cerebellum and brainstem weights. (4) In contrast to ethanol, cocaine failed to exert a detrimental effect on brain development during this early postnatal period. (5) No antagonistic or synergistic toxicity by concurrent administration of cocaine and ethanol was observed among the dependent measures investigated in this study. Supported by NIH grants DA07364 and AA05523.

749.4

REACTIVE ASTROGLIOSIS FOLLOWING SHORT TERM ALCOHOL EXPOSURE DURING THE BRAIN GROWTH SPURT. J.T. Leo, A. Ricketts, J.C.Mahoney, C.R.Goodlett*, and J.R. West. Dept. of Human Anatomy and Medical Neurobiology, Texas A&M University, College Station, TX 77843
We have previously documented a prominent reactive astrogliosis in the cerebral cortex of ten day old rats following alcohol exposure from postnatal days (PD) 4 through 9. In the cortex, glial fibrillary acidic protein (GFAP) was increased 300% compared to controls. Immunohistochemistry revealed that much of this increase was due to an abundance of hypertrophied astrocytes in cortical layer V. A limitation of this study was that alcohol exposure from PD 4-9 encompassed a relatively large portion of the brain growth spurt.
The goal of the present study was to determine the minimum exposure period which produces a reactive astrogliosis in cortical layer V of ten day old rat pups. All pups were gastrostomized on PD 4 and given 4.5 g/kg of alcohol per day [delivered in 2 of 12 daily feedings as a 10.2% (v/v) solution in milk formula] or a calorically matched diet free of alcohol. There were three alcohol exposed groups which varied in the time span of alcohol exposure: 1) PD 4-5, 2) PD 4-6, and 3) PD 4-7. Pups were perfused on PD 10 and 40 µm thick frozen coronal sections were processed for GFAP immunoreactivity using peroxidase anti-peroxidase immunocytochemistry. Matched sections from somatosensory cortex of control and alcohol treated pups were evaluated microscopically for the presence of reactive astrocytes in cortical layer V.
Alcohol exposure from PD 4-7 and PD 4-6 resulted in increased GFAP immunoreactivity in layer V compared to controls. Increases in GFAP following alcohol exposure on PDs 4-5 were less reliable. These results suggest that the developing cortex is susceptible to a binge-like alcohol exposure paradigm. Supported by NIH grants AA 07313 and AA 05523.

749.5

ULTRASTRUCTURAL ALTERATIONS IN THE CEREBELLAR CORTEX OF MICE FETUSES EXPOSED TO DIAZEPAM. M.C. Márquez-Orozco,* A. Márquez-Orozco, M.V. Gazca-Ramírez and R. Andrade-Martínez. Dept. of Embryology, School of Medicine, University of México. México 04510 D.F.

Our purpose was to investigate whether diazepam (DZ) causes ultrastructural alterations in the cerebellar cortex of mice fetuses. Three groups, of gestating mice of the CD-1 strain were injected sc between the 6th to 17th day of gestation, either with single daily DZ doses (2.7 mg/kg/bw) or same dose of 0.9% saline solution (S) and the other group was non treated (NT). On the 18th day all were killed with CO_2 atmospher to remove the fetuses. The cerebellum was fixed with 2.5% glutaraldehide, post-fixed in OsO_4 and embedded in epoxic resin. Fine sections were contrasted with uranyl acetate and lead citrate and then observed under a transmission microscope Zeiss EM-10. In both the external and internal granular layer of the DZ fetuses, the nuclear density per area was greater than in the S and NT fetuses ($p < 0.05$). Chromatin was atypically distribute in the nuclei and in the Golgi complex. The rough endoplasmic reticulum showed distended cisternae. The cytoplasmic branches and mitochondriae were disorganized. These ultrastructural alterations were not observed in S and NT fetuses. Such alterations could be attributed to DZ inhibiting mitosis, actin and myosin synthesis and to the modification of the metabolic pathways mediated by central and peripheral types of benzodiazepines receptors.

749.6

FETAL ALCOHOL EFFECTS ON SACCHARIN CONSUMPTION AND REWARD. **L. Middaugh,* D. Gentry, and R. Banik. Medical University of South Carolina, Charleston, S.C. 29425.**

We previously reported that adult male and female fetal alcohol exposed (FAE) mice responded less than controls for food rewards delivered on either fixed ratio or progressive ratio (PR) schedules of reinforcement. The generality of the reduced efficacy of rewards exhibited by FAE mice was assessed in the present study by comparing adult female FAE and control mice on their consumption of saccharin and their responding for saccharin rewards delivered on a PR5 schedule of reinforcement. Dams of FAE mice (E) were maintained on liquid diets containing 25% ethanol derived calories throughout gestation. Controls were offspring of dams pair-fed 25% sucrose diets (S) or fed lab chow (C). FAE elevated neonatal mortality and reduced weight gains during the preadolescent growth spurt. On two-bottle preference tests, saccharin (1,3,9,30,60 mM) consumption increased with increasing concentration up to 9 mM. FAE mice consumed more saccharin than controls at concentrations of 3, 9, and 30 mM. When saccharin was delivered on a PR5 schedule, mice responded more for 4.5 than for either 2.5 or 9.0 mM solutions. Responding by FAE mice did not differ from controls at any saccharin concentration; however, FAE mice exhibited greater changes in responding when concentration was changed from 9.0 to either 4.5 mM or 2.25 mM solutions. (NIAAA Grant 06611)

749.7

SOCIAL RECOGNITION IN RATS: EFFECTS OF ALCOHOL EXPOSURE DURING DEVELOPMENT. S.E.Thomas, J.L.Grant and S.J.Kelly*. Dept. of Psychology, Univ. of South Carolina, Columbia, SC 29208

An animal model of fetal alcohol syndrome was used to test hypothesized deficits in social behavior. Long-Evans rats were exposed to alcohol during the brain growth spurt, postnatal day (PD) 4-10, via an artificial rearing technique. Rats in the alcohol group were given 5 g/kg/day of ethanol condensed into 4 of 12 daily feedings. Control groups consisted of pups artificially reared but not exposed to alcohol, and pups reared normally by dams. All pups were reared by dams from PD 12-21, at which time they were weaned and group housed. At PD 109 the rats were tested in a social recognition task.

Experimental animals were presented with a nonexperimental juvenile rat for two 10-minute sessions daily. The interval between the end of the first session and the start of the second session was 5, 15, 30, 60, 90, or 120 minutes. Each subject was tested for each interval on separate days in a counter-balanced manner. Time spent actively investigating the juvenile was measured.

Male rats spent substantially more time than female rats investigating the juveniles. With short intervals (5 and 15 min), alcohol-exposed male rats investigated the juveniles in the second session more than control rats. There was no difference among male rats in the first session. (Supported by NIAAA Grant AA08080 to S.J.K.)

749.8

SEXUAL BEHAVIOR OF FEMALE MICE PRENATALLY TREATED WITH DIAZEPAM. L.A.I.Hernández-Alvarez*, M.C.Márquez-Orozco, y A.Márquez-Orozco. Dept. of Embryology, School of Medicine, BUAP and Dept. of Embryology School of Medicine, UNAM. México 04510 D.F. MEXICO.

Foregoing research works have shown alterations in cell structure and in behavior of prenatally diazepam (DZ) treated mice. We evaluated the effect of such alterations upon the sexual behavior of female CD-1 strain mice prenatally exposed to DZ. One group of female mice was sc treated with DZ (2.7 mg/kg/d) from the the 6th to the 17th days of gestation and a control group (S) received saline 0.9% solution. On the 6th month, the spontaneous female sexual activity from DZ and S groups to S males of the same age was tested in one session during the dark stage of the photoperiod (4-6 AM) and videorecorded under infrared light. Precopulating behavior tended to be shorter in treated animals. In copulating phase, their lordotic indexes, proportion of lordotic females by test and intensity of lordosis were greater ($p < 0.05$). These results indicate easier mating patterns which could be due to modification of neurotransmission caused by the drug during development.

749.9

EFFECTS OF PRENATAL ETHANOL EXPOSURE ON N-METHYL-D-ASPARTATE-MEDIATED CALCIUM ENTRY. Y-H. Lee*, P.K. Randall and S.W. Leslie. Div. of Pharmacology and Toxicology, Col. of Pharmacy, The Univ. of Texas, Austin TX, 78712.

The effects of prenatal ethanol exposure on N-methyl-D-aspartate(NMDA)-activated calcium entry into dissociated neurons were studied. Three groups of pregnant Sprague-Dawley rats were individually fed throughout gestation. The first group received a liquid diet containing ethanol providing 36% of total calories. The second, pair-fed group was fed a liquid diet with a dextrin-maltose mixture substituted for ethanol isocalorically. The third group received rat lab chow and water ad libitum. Dissociated brain cells were isolated from less than 1 day old pups in each group and loaded with fura-2. Prenatal ethanol exposure significantly decreased the NMDA receptor-stimulated calcium entry compared to both pair-fed and ad libitum groups. To determine the mechanisms of the prenatal ethanol exposure on the NMDA-mediated ion channel decrements, modulatory sites of the NMDA receptor complex were studied. Glycine(0.1, 1, 10 and 100μM) did not reverse the decreased calcium entry by the prenatal ethanol exposure. Low concentrations of MK801(25 and 50nM) did not further inhibit calcium entry beyond that observed with the prenatal ethanol exposure, but significantly inhibited control group responses. Also, magnesium(100μM) showed a similar result as MK801, but this response was less prominent. Thus, these results suggest that prenatal ethanol exposure inhibits the function of NMDA receptor-mediated ion channels by possibly altering the structural properties of the ion channel itself, and not the glycine site. (supported by NIAAA grant R37 AA05809)

749.10

Electrophysiological Characterizations of Neurons in the Cerebellum of Postnatally Ethanol-Exposed Rats. **Cristina Bäckman*, James R. West and Michael R. Palmer. Dept. of Pharmacology, Univ. of Colorado Health Sci. Ctr., Denver, CO 80262, and Dept. Anatomy, Univ. of Iowa, Iowa City, IA 52242.**

Bonthius and West, Teratology, 44:147-163, 1991 previously found that ethanol exposure of rat pups between postnatal days 4-10, which corresponds to third trimester ethanol exposure in humans, results in Purkinje neuron loss in lobules IX and X of the cerebellar vermis. We have now investigated the electrophysiology of Purkinje neurons and interneurons in these affected areas to determine if the remaining neurons appear to function normally. Alcohol (4.5 g/kg/day condensed into two hours apart) or control diets were delivered intragastrically to rat pups via an artificial rearing procedure during postnatal days 4-10. After maturation, extracellular recordings were made from lobules IX and X cerebellar vermis, and in some cases the parallel fiber inputs were activated by surface stimulation. Firing rates and firing patterns of Purkinje neurons were no different between the control and ethanol-exposed animals except that very few cells expressed complex spikes in the animals postnatally exposed to ethanol. In other respects, the Purkinje cells recorded in this study resembled those routinely recorded from lobules VI and VII in untreated animals. Interneurons were no different in firing rate or firing pattern between the control and ethanol-fed animals, however the firing patterns of these cells were much less regular than those observed in lobules VI and VII. These data suggest that although postnatal ethanol exposure causes cell loss in the cerebellar vermis, the remaining cells appear to function normally. However, climbing fiber afferents from the inferior olive may have been selectively affected by the ethanol exposure since the climbing fiber-induced complex spikes were lacking in firing patterns of the Purkinje neurons of ethanol-exposed rats. (Supported by USPHS grants AA05915, AA05523 and AA00102. MP is supported by an ADAMHA Research Scientist Development Award.)

749.11

SPONTANEOUS ALTERNATION AND ACTIVITY IN AGING MICE AFTER AN ACUTE EMBRYONIC EXPOSURE TO ALCOHOL. A. Rabe*, R. Dumas, A.Aiyer, M.Devinoff, C.Ostrow. NYS Institute for Basic Research in Developmental Disabilities, Staten Island, N.Y. 10314.

Long-term memory for place is drastically impaired in middle-aged and old C57Bl/6J mice that have been exposed to a teratogenic dose of alcohol on gestation day 9 (5.8 g of alcohol per kg of maternal body weight, 25% v/v) . We have now examined whether this treatment also impairs short-term memory, as measured by spontaneous alternation in a symmetrical Y-maze. In a 5-min-session, a continuous procedure was used to record the normal tendency of rodents to visit the least recently experienced place (i.e., arm). The subjects were 4-5-mo-old alcohol- and dextrose-exposed mice (n=26,29), 12-14-mo-old alcohol- and dextrose-exposed mice (n=32,36), and 22-24-mo-old alcohol- and dextrose-exposed mice (n=27,26). There was an Age effect in the number of place alternations and arm entries (both $p < 0.0001$): the older the group, the lower the score. The % of alternations also showed a significant Age effect ($p < 0.05$), but only when the activity level was kept constant through a covariance analysis. The dextrose- but not alcohol-exposed mice showed modest position preferences (Treatment, $p < 0.05$). To the extent that spontaneous place alternation involves short-term memory, embryonic exposure to alcohol had no deleterious effect at any age.

DRUGS OF ABUSE: ETHANOL—MONOAMINES

750.1

ETHANOL AFFECTS THE FUNCTION OF NEURONAL NICOTINIC CHOLINERGIC RECEPTORS EXPRESSED IN *XENOPUS* OOCYTES. C.M. de Fiebre*, J. Singer, N.B. Bloss and E.M. Meyer. Dept. of Pharmacology & Therapeutics, Univ. of Florida College of Medicine, Gainesville, FL 32610-0267.

While the correlation between smoking and drinking is very large, little is known about the biological factors which regulate the co-use of nicotine (NIC) and ethanol (EtOH). Previous evidence has suggested that sensitivity to these agents is genetically correlated because EtOH modulates nicotinic acetylcholine receptor (nAChR) function by stabilizing nAChRs in the nonfunctional, desensitized form; however, direct measurements of receptor function have not been made. Here we report that ethanol affects neuronal nAChRs in a subtype-selective fashion. Neuronal nAChRs subtypes were expressed in *Xenopus* oocytes from cRNA and studied under two-electrode voltage clamp for responsiveness to bath-applied ACh (10 μM), NIC (10 μM) and EtOH (50 mM). By itself, EtOH produced minimal responses. In oocytes expressing $\alpha2\beta2$ receptors, co-application of EtOH and NIC produced responses which were weaker than responses to NIC by itself and produced attenuated responses to ACh applied 5 min following NIC. In contrast, co-applied EtOH increased response at $\alpha2\beta4$ receptors to NIC without affecting subsequent ACh response. At $\alpha4\beta2$ receptors, effects of EtOH have not yet been seen. Dose-response and time-course analyses are currently being conducted at these as well as at other nAChR subtypes. These results suggest that EtOH may display distinct pharmacological properties at different neuronal nAChR subtypes.

Supported in part by training grant AG-00196. The cDNA clones were kindly provided by Dr. Jim Boulter of the Salk Institute.

750.2

EFFECTS OF ETHANOL ON SPONTANEOUS AND EVOKED SINGLE-UNIT ACTIVITY OF NUCLEUS ACCUMBENS NEURONS J.R. Criado*, G. Berg, and S.J. Henriksen, Scripps Research Institute, La Jolla, CA 92037.

The nucleus accumbens (NAcc) has been shown to be involved in the reinforcing properties of ethanol. Studies from our group proposed that the NAcc consists of several physiologically different types of cells (Hakan and Henriksen, Neurosci. Lett. 83:307, 1987). Further characterization of NAcc cell types and comparison to the type and extent of ethanol-related responses in each cell are required in order to understand ethanol-NAcc pharmacology. This approach may help elucidate the possible role of the NAcc in alcohol self-administration. To characterize the neuronal population within the NAcc sensitive to ethanol we examined both spontaneous and synaptically driven cells. The effects of systemic (BALs>100 mg%) and local administration of ethanol were studied in halothane-anesthetized Sprague-Dawley rats. Spontaneous single-unit activity of NAcc cells (3.74 Hz ± 1.12, n=14) showed variable responses to intraperitoneal administration of ethanol. The majority of NAcc cells encountered were not affected by ethanol (9/14; 64.3%). Less frequently, ethanol excited (2/14; 14.3%) or inhibited (3/14; 21.4%) single-unit activity. Microelectrophoretic application of ethanol (0.3M) was tested on a limited number of spontaneously active cells (1.57 Hz ± 0.44, n=4). Similar to the effects of systemic administration, ethanol had no significant effect (2/4; 50%) or inhibited (2/4; 50%) spontaneously active NAcc cells. Stimulation of the ipsilateral fimbria evoked two types of NAcc cells with characteristic latencies (early, 6 msec ± 0.68, n=6; late, 16.5 ± 1.06, n=6). Most of the synaptically driven cells in the NAcc were not affected by ethanol (7/12, 58.3%). However, ethanol also excited (3/12, 25%) or inhibited (2/12, 16.7%) evoked single-unit activity. These findings suggest a heterogeneous sensitivity of NAcc cells to ethanol. Microelectrophoretic studies are currently in progress to characterize the pharmacological profile of NAcc cells according to their susceptibility to ethanol. (Supported by ARC AA06420 to SJH).

750.3

Characterization of the *In vivo* action of (*R*)-salsolinol, an endogenous metabolite of alcohol, on serotonin and dopamine metabolism : A microdialysis study. Daiichiro Nakahara[1], WakakoMaruyama[2], Hiroyuki Hashiguti[3] and Makoto Naoi[4]. [1]Dept. of Psychology, Nagoya Univ. Coll. of Med. Technol., [2]Dept. of Neurology, Nagoya Univ. Sch. of Med., [3]Dept. of Psychiatry, Miyazaki Med. Coll. and [4]Dept. of Biosciences, Nagoya Inst. of Technol., Nagoya 461, Japan.

Using a microdialysis-HPLC technique in conscious rats, we examined the action of (*R*)-1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline,(*R*)-salsolinol (R-Sal), a possible endogenous metabolite of alcohol, on serotonin (5-HT) and dopamine (DA) metabolism in four regions of the brain: the striatum, the substantia nigra, the hippocampus and the hypothalamus. Following 1 mM R-Sal perfusion, extracellular 5-HT in the striatum tremendously increased from non-detectable levels to 4127.6±572.0 nM, while DA increased from 3.4±0.9 nM to 190.1±60.4 nM . This increase was one order of magnitude larger in 5-HT than in DA. Conversely, the output of 5-hydroxyindoleacetic acid (5-HIAA) decreased markedly to non-detectable levels, while DOPAC(3,4-dihydroxyphenylaceticacid) and homovanillic acid (HVA) outputs decreased below 40% of basal levels. These effects were dose-related to R-Sal (1 μM to 1.0 mM) and were confirmed also in 3 other brain regions. The R-Sal-induced responses in the striatum were observed even after pretreatment of 2 μM tetrodotoxin, a blocker of nerve-firing activity, via the dialysis membrane. The potencies of 1 mM R-Sal to increase the release of 5-HT and DA were approximately 750.5-fold and 1.8-fold stronger, respectively, than those of the same dose of methamphetamine. These results suggest that R-Sal acts as a powerful releaser of monoamines, especially 5-HT, with inhibition of monoamine oxidase and catechol-O-methyltranseferase activities. This R-Sal-induced monoamine release may depend on exchange diffusion at the storage vessicles in the nerve terminals.

750.4

DOPAMINE D1 RECEPTORS IN SUBSTANTIA NIGRA AND STRIATUM OF CHRONIC ALCOHOLIC FISCHER 344 RATS. J.M. Woods* and M. Druse-Manteuffel. Department of Molecular and Cellular Biochemistry, Loyola U. Med. School, Maywood, IL. 60153.

This laboratory has previously demonstrated a deficiency of dopamine D1 receptors in the nucleus accumbens and frontal cortex of 3-month-old male Fischer 344 rats, which consumed ethanol on a chronic basis (Pellegrino and Druse, 1992). In the present study we examined the effects of chronic ethanol consumption on dopamine D1 receptors in Fischer 344 rats, aged 5, 14, and 24 months at the time of sacrifice. D1 receptors were assessed using quantitative autoradiography. [^{3}H]-SCH23390 was used to radiolabel the D1 receptors. Spiperone (100 nM) was included to block 5-HT$_2$ receptors. Nonspecific binding was determined in the presence of 2 μM (±)butaclamol.

These studies demonstrated that there were no significant differences in the specific binding of [^{3}H]-SCH23390 to D1 receptors in the striata of ethanol-fed rats at 5, 14, and 24 months of age. In addition, there were no ethanol-associated differences in D1 binding in the substantia nigra at any of the ages examined.

This research was supported by a grant from the USPHS-AA08451.

750.5

QUANTITATIVE AUTORADIOGRAPHIC STUDY OF DOPAMINE D2 RECEPTORS IN ALCOHOL-FED FISCHER 344 RATS. M. Druse-Manteuffel* and N. F. Tajuddin. Department of Molecular and Cellular Biochemistry, Loyola U. Med. School, Maywood, IL. 60153.

Previous studies in this laboratory demonstrated abnormalities in the mesolimbic and nigrostriatal dopamine system of 3-month-old male Fischer 344 rats, which consumed ethanol on a chronic basis (Pellegrino and Druse, 1992). As an extension of these studies we investigated the effects of chronic ethanol consumption on dopamine D2 receptors in Fischer 344 rats, aged 5, 14 and 24 months at the time of sacrifice. D2 receptors were examined using quantitative autoradiography. [^{3}H]-Spiperone was used to radiolabel the receptors. Ketanserin (100 nM) was used to block 5-HT$_2$ receptors. Nonspecific binding was determined in the presence of 2 μM (±)butaclamol.

The results of these studies demonstrated a decrease in the specific binding of [^{3}H]-spiperone to D2 receptors in the striata of 5-month-old rats. In contrast no apparent differences in D2 binding sites were found in the frontal cortex at any of the ages examined.

This research was supported by a grant from the USPHS-AA08451.

750.6

EXTRACELLULAR CONCENTRATIONS OF ETHANOL AND MONOAMINES IN THE NUCLEUS ACCUMBENS OF THE ALCOHOL PREFERRING AA AND ALCOHOL AVOIDING ANA RATS. K. Kiianmaa*, M. Nurmi[1] and J.D. Sinclair. Biomedical Research Center, Alko Ltd, and [1]Department of Zoology, University of Helsinki, Helsinki, Finland.

The importance of central monoamines and the distribution of ethanol in the brain in the control of voluntary ethanol consumption was examined by studying the extracellular levels of ethanol and monoamines in the nucleus accumbens of the alcohol preferring AA (Alko Alcohol) and alcohol avoiding ANA (Alko Nonalcohol) rats with *in vivo* microdialysis. Samples for the assay of ethanol with headspace GC were collected from freely moving animals at 1-5 min intervals after administration of ethanol (0.5, 1, or 2 g/kg, IP). The results show that there is a steep rise in brain ethanol concentration within minutes after the injection, but there does not seem to be a difference in the distribution of ethanol into the brain of the two lines of rats. The concentrations of the monoamines and their metabolites were determined with smallpore HPLC; the dialysate samples were collected every 15 minutes. Ethanol significantly increased the extracellular levels of dopamine, DOPAC, HVA, and 5-HIAA in a dose dependent manner suggesting stimulation of dopamine release by ethanol. No difference in the extent or time course of stimulation of dopamine release between the AA and ANA rats was found. The results could so far give no indication that the differential ethanol consumption by AA and ANA rats could be explained in terms of differences in the distribution of ethanol to the nucleus accumbens or in ethanol-induced stimulation there of dopamine release.

750.7

ACTIVATION OF ALCOHOL-PREFERRING (P) RATS BY ALCOHOL SELF-ADMINISTRATION: BLOCKADE BY DOPAMINE (DA) AND 5-HT$_3$ RECEPTOR ANTAGONISTS. Michael J. Lewis*, Tracey Smith, Kevin Domangue, John Bryant, and Harry L. June. Neurobehav Lab, Dept of Psych, Temple Univ., Phila., PA 19122/Howard University, Washington, D.C. 20059

P rats orally self-administer alcohol (A) at high concentrations (>10%). P rats also increase locomotor activity after IP A. The present study examined the effects of orally self-administered A on open field activity in these animals. P rats were given a two bottle choice between 10% A and water for periods 10 and 60 min. Animals then were injected with the DA antagonist pimozide (0.1 - 0.5 mg/kg, ip), the 5-HT$_3$ antagonist MDL72222 (.5 - 2.0 mg/kg ip), or saline after each period of A self-administration. They were then placed in an open field (Digiscan) for 10 min. P rats showed increases after both self-administration periods with saline injection. Both pimozide and MDL72222 blocked the increase in activity at low doses. At higher doses, both antagonists suppressed behavior below saline or baseline levels. These data suggest that dopamine and 5-HT$_3$ receptor mechanisms play a role in alcohol-induced activation. (Supported in part by AA06263 and RR08016).

750.8

AMPHETAMINE-INDUCED HYPERACTIVITY: DIFFERENCES BETWEEN RATS WITH HIGH OR LOW PREFERENCE FOR ALCOHOL. C. Fahlke*, S. Hansen, J. A. Engel and E. Hård. Dept. of Psychology, University of Göteborg, P.O. Box 14158, S-400 20 Göteborg, Sweden.

This study determined the relationship (if any) between ethanol intake, and spontaneous and amphetamine-induced locomotor activity. Locomotion was studied in high- (HP; >70 % of total fluid intake consumed as alcohol) and low-preferring (LP; <20 % of total fluid intake consumed as alcohol) male and female Wistar rats, with free access to water and a 6 % (v/v) ethanol solution for 3 weeks. Following an alcohol-free 3 week-period, the animals were tested for spontaneous motor activity for 1 hr. One week later, locomotion was recorded in the same activity boxes following a SC injection with d-amphetamine sulfate (1 mg/kg). There was no difference between HP and LP rats with regard to spontaneous locomotor activity. Amphetamine stimulated locomotion in both sexes, females being more responsive than males. However, among males, the activating effect of amphetamine was found to be related to ethanol preference determined several weeks earlier: HP rats were significantly more active when given amphetamine than were the LP males. This relationship was not found among HP and LP female rats. These data indicate that, in male rats of strain, the same neural substrate (e.g. the mesolimbic dopamine system) may mediate important aspects of both ethanol drinking and amphetamine responsiveness. Individual differences in the properties of this substrate may account for the finding that ethanol drinking and amphetamine responsiveness co-vary. Alternatively, it may be that consumption of high levels of ethanol sensitizes the neural substrate responsible amphetamine hyperactivity. - Supported by the Bank of Sweden Tercentenary Foundation, the Swedish MRC and the HSFR.

750.9

HARMAN (I-ME-ß-CARBOLINE) INDUCES MAINTENANCE OF DEPENDENT BEHAVIOUR IN SOME ALCOHOLICS BY ITS MAO-A INHIBITING PROPERTIES. **H.Rommelspacher*, L.G.Schmidt. Dept. of Neuropsychopharmacology, Free University, Ulmenallee 30, Berlin 19, Germany**

Evidence will be presented that the naturally occuring ß-carboline harman is one of several causes for relapses of alcoholics with concomitant depressive syndrome. 1. Chronic ethanol ingestion induces an increase of glucose turnover. 2. Glucose is the precursor of pyruvate. 3. Pyruvate is the precursor of harman and salsolinol. 4. Harman is an natural inhibitor of monoamine oxidase-type A. 5. Inhibitors of MAO-A are effective antidepressants. 6. Harman levels are elevated in the blood plasma of alcoholics at the day of admission in a hospital. 7. The levels of some patients remained elevated up to 6 months. 8. Calculation of the correlations revealed that only patients with relapses had elevated levels of harman. 9. Those patients with relatively low levels (but still elevated) of harman at the first day of admission in a hospital relapsed relatively earlier. 10. The concentration of harman three months after admission correlated positively with the depression score (SDS-scale). These findings suggest that alcoholics with depressive syndromes utilize ethanol for self treatment.

***Supported by Deutsche Forschungsgemeinschaft (HE-916/7-1)**

750.10

ACTION OF TETRAHYDROBIOPTERIN (6R-BH4) IN MICE WITH DIFFERENT ALCOHOL PREFERENCES. K.Yoshimoto and S.Komura. Dept.of Legal Medicine, Kyoto Prefectural University of Medicine, Kyoto 602, Japan.

This study was conducted to determine the function of 6R-BH4 in the inbred strains of mice, C57BL/6J, C3H/HeJ and DBA/2J, which have genetically different alcohol preferences. The level of 6R-BH4 was measured in two regional brain areas of the mouse. The striatal 6R-BH4 level in the DBA/2J mice was higher than that in the two other strains of mice. The 6R-BH4 level in the midbrain didn't show any significant difference among the three strains of mice. I.P. administration of ethanol (EtOH) (0,1,2 and 4g/kg) significantly and dose-dependently reduced the levels of striatal and midbrain 6R-BH4 in the DBA/2J. In C57BL/6J and C3H/HeJ (high or middle alcohol preference), even EtOH (4g/kg,i.p.) didn't any change the 6R-BH4 level. Four hr after the i.v. administration of 6R-BH4 or saline, C57BL/6J and DBA/2J were injected EtOH (4g/kg,i.p.) to compare the EtOH-induced sleep time. 6R-BH4 pretreatment reduced the EtOH-induced sleep time in DBA/2J ($p<0.05$). These findings indicate that the brain 6R-BH4 was distributed in the dopaminergic nervous system, and that the EtOH sensitivity in the low alcohol preference mice was related to the 6R-BH4 level.

750.11

ETHANOL AND NICOTINE SELF ADMINISTRATION IN TRANSGENIC MICE OVEREXPRESSING BOVINE GROWTH HORMONE AND C57BL/6 MICE. C.J. Meliska*, A. Bartke, G.M. McGlacken, and R.A. Jensen. Departments of Psychology and Physiology, Southern Illinois University at Carbondale, Carbondale, IL 62901-6502.

Male transgenic (T) mice overexpressing bovine growth hormone (bGH) genes display elevated hypothalamic dopamine turnover rates relative to T females and non-T littermate controls. We recently reported (Meliska, C.J. et al., 1992, *Neurosci. Abs.*, 227.15) that, in a two-bottle choice situation, adult male bGH Ts display greater preference for 10% ethanol solutions than male non-T controls and female Ts. We now report that male Ts also show a greater preference for drinking 25 μg/ml nicotine solutions than male controls and T females. In parallel experiments, male and female C57BL/6 mice, which are known to self-administer ethanol, opiates, and some stimulant drugs more readily than other mouse strains, preferred to drink 10% ethanol solutions to approximately the same degree as male Ts. However, male Ts preferred to drink 25 μg/ml nicotine solutions more than male or female C57s. The results with T mice support hypotheses implicating forebrain dopamine function in the modulation of ethanol and nicotine self-administration. Furthermore, T mice overexpressing bGH genes may provide a useful model for studies of the biological determinants of self-administration of alcohol and other drugs.

750.12

MEDIAN RAPHE INJECTIONS OF 8-OH-DPAT AND MUSCIMOL INCREASE ETHANOL INTAKE IN A LIMITED ACCESS PARADIGM. D.M. Tomkins[1], P.J. Fletcher[2] and E.M. Sellers*[1]. [1]Pre-Clinical Pharmacology, Addiction Research Foundation, and [2]Clarke Institute of Psychiatry, Toronto, Ontario, Canada M5S 2S1.

We have recently shown that low doses of the 5-HT_{1A} agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) increase ethanol consumption (Tomkins et al, 1993). Since reducing brain 5-HT function increases ethanol consumption it is likely that the effects of 8-OH-DPAT involve a suppression of brain 5-HT activity, possibly at the level of raphe somatodendritic autoreceptors. In order to test this hypothesis the effects of median raphe injections of 8-OH-DPAT on ethanol intake were examined. The effects of muscimol injections were investigated for comparative purposes. Following a standard ethanol acquisition procedure, adult male rats were equipped with a guide cannula aimed at the MR, and given access to 12% ethanol and water in daily 40 min sessions. Once stable baseline intakes had been attained the effects of MR injected 8-OH-DPAT (0, 0.1, 1 & 5 μg) on ethanol and water intake were assessed. At the highest dose, 8-OH-DPAT increased ethanol intake by approximately 40% above control levels. Water intake was not significantly altered. MR injections of muscimol (0, 2, 10 & 50 ng) produced a greater increase in ethanol consumption at the highest dose (approx. 120%). However, water intake was also increased. These results are in agreement with our previous findings that 8-OH-DPAT selectively increases ethanol intake and that this effect is mediated, at least in part, by suppressing the activity of 5-HT MR efferents. The effects of muscimol, which interacts with both 5-HT and non-5-HT systems, are probably a consequence of the general behavioural activation induced by this compound.

750.13

THE EFFECT OF SEROTONIN TO INCREASE THE POTENCY OF ETHANOL-INDUCED EXCITATION OF VTA NEURONS DIFFERS IN FISCHER 344 AND LEWIS RATS, M.S. Brodie* and R.D. Trifunović, Dept. Physiology and Biophysics, University of Illinois at Chicago, Chicago, IL 60612.

Excitation of dopamine neurons of the ventral tegmental area (VTA) may be a critical factor for the rewarding effect of ethanol; individual differences in the potency of ethanol to excite VTA neurons may underlie the etiology of alcoholism. Ethanol (EtOH) increases the firing rate of VTA neurons *in vivo* (Gessa, et al., 1985) and *in vitro* (Brodie, et al., 1990), and the potency of EtOH to excite VTA neurons of Sprague-Dawley rats is increased by serotonin (5-HT; Brodie and Shefner, 1992). Responses to EtOH and to 5-HT (alone and in combination) were tested in VTA neurons from two different rat strains which have been demonstrated to differ in their voluntary intake, Fischer 344 (F344) rats, which exhibit low voluntary EtOH intake, and Lewis rats, which show higher voluntary EtOH intake. Coronal brain slices containing the VTA were prepared from young adult F344 (n=14) and Lewis rats (n=17). Concentrations of EtOH (40 - 160 mM) were tested in the absence and presence of 5-HT (10 μM). All neurons studied had electrophysiological characteristics typical of dopamine-containing neurons, and were excited by EtOH. The percentage of cells excited, inhibited and unchanged by administration of 5-HT alone were 21%, 21% and 58% for F344 rats, and 47%, 12% and 41% for Lewis rats. 5-HT increased the potency of EtOH by 125% in F344 VTA neurons, but Lewis neurons exhibited only a 43% increase in ethanol potency after administration of 5-HT. 5-HT may be an important factor in controlling the response of VTA neurons to ethanol, and differences in serotonergic input may underlie individual differences in voluntary ethanol intake. Grant Support: PHS AA-09125 and the Alcoholic Beverage Medical Research Foundation.

750.14

ISOPROTERENOL POTENTIATES ETHANOL-INDUCED DEPRESSIONS OF CEREBELLAR PURKINJE NEURONS IN RAT BRAIN. **Anya M-Y. Lin, Ronald K. Freund and Michael R. Palmer*. Dept. of Pharmacology, Univ. of Colorado Health Sci. Ctr., Denver, CO 80262.**

We previously found that ethanol-induced depressions of cerebellar Purkinje neurons were blocked by bicuculline, a $GABA_A$ antagonist, but that ethanol alone did not reliably potentiate GABA responses on these cells. Even so, we found that ethanol consistently potentiated GABA effects on these neurons if the GABA responses were simultaneously facilitated by isoproterenol, a β-adrenergic agonist. If ethanol-induced depressions of the firing of Purkinje neurons are mediated by a $GABA_A$ mechanism in the cerebellum as is suggested by their sensitivity to bicuculline, then this effect should also be facilitated by β-adrenergic receptor stimulation. In the present study we investigated the influence of isoproterenol on ethanol-induced depressions of neuronal activity in the cerebellar cortex. We recorded single cerebellar Purkinje neurons from one barrel of a multibarrel micropipette while locally applying drugs from other barrels of the same pipette in urethane-anesthetized rats. Ethanol was applied by electro-osmosis, while isoproterenol and timolol were applied by microiontophoresis. We found that the isoproterenol augmented the depressant effects of locally applied ethanol on cerebellar Purkinje neurons, and timolol, a β-adrenergic antagonist blocked this isoproterenol-induced potentiation. These data suggest that similar to the previously reported ethanol potentiations of $GABA_A$ mechanisms in cerebellum, the ethanol-induced depressions of cerebellar neuronal activity observed in this study are facilitated by β-adrenergic receptor activation and lend support to the hypothesis that these two ethanol effects may be regulated by the β-adrenergic modulation of the $GABA_A$ mechanism.

(Supported by USPHS grants AA05915 and AA00102. MP is supported by an ADAMHA Research Scientist Development Award.)

750.15

PENTOBARBITAL INHIBITS NMDA, KAINATE AND K^+-INDUCED [^{3}H]-NOREPINEPHRINE EFFLUX IN RAT BRAIN CORTEX AND HIPPOCAMPUS. L.M. Brown*, Dept. of Pharmacology, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio 44272.

The effect of Pentobarbital on three types of chemical methods which induce [^{3}H]-Norepinephrine ([^{3}H]NE) efflux from rat brain cortical and hippocampal slices was examined. Pentobarbital has been demonstrated to cause differential inhibition of N-methyl-D-aspartate (NMDA) and non-NMDA mediated cellular events (Morgan, Eur J. Pcol, 204:335-8, 1991; Teichberg, Brain Res, 291:285-292, 1984).

Brain slices (350 µm) from the cortex and hippocampus of male and female Sprague-Dawley rats were used. The slices were washed and incubated in oxygenated Krebs-Ringers bicarbonate buffer and allowed to accumulate [^{3}H]NE. After uptake of the label, the slices were washed again and aliquots placed into baskets which were transferred through a series of vials containing varying concentrations of NMDA or Kainate (10, 30, 100, 300 and 1000 µM) or K^+ (50 mM) in the presence or absence of pentobarbital (300 µM).

In the cortex and hippocampus, NMDA and kainate resulted in a concentration-dependent increase in [^{3}H]NE overflow. K^+ caused a significant increase in efflux. Pentobarbital caused a significant inhibition of efflux in all cases. Pentobarbital caused percent inhibitions of 20 ± 5, 60 ± 10 and 29 ± 2 in NMDA, Kainate and K^+ stimulated efflux in cortex and caused percent inhibitions of 31 ± 6, 47 ± 5, and 34 ± 7 in the hippocampus respectively. These results indicate that in the brain slice preparation, pentobarbital in the µM concentration range has a wide range of depressant actions.

751.1

BEHAVIORAL CORRELATES OF NEURAL ACTIVITY IN THE RAT VENTRAL TEGMENTAL AREA AND PREFRONTAL CORTEX. A.E.Kosobud*, G.C.Harris and J.K.Chapin. Hahnemann University, Philadelphia, PA, 19102, USA.

Multiple bundles containing 4-6 microwire electrodes were chronically implanted in the ventral tegmental area (VTA) or prefrontal cortex (PFC) of male rats, 450-500g. Following recovery from surgery, multi-single unit recordings were obtained during lever pressing for a sucrose solution on a fixed-ratio schedule of reinforcement. All sessions were videotaped for behavioral analysis. Changes in neural activity related to reward consumption, bar pressing, and a tone signaling reward availability were evaluated. In both the VTA and PFC, almost all of the units displayed activity changes associated with behavioral events. Four principle patterns of activity change were seen: 1) Punctate changes, including short bursts proximate to individual lever presses (7/19 neurons), transient excitation at the beginning and inhibition at the end of reward consumption (2/19 neurons) and excitation at the end of reward consumption (4/19 neurons). 2) Decreased activity throughout the interval of reward consumption (7/19 neurons). 3) Interval decreases characterized by a gradual decrease relative to reward availability and consumption, but an abrupt increase at termination of reward consumption (5/19 neurons). 4) One neuron showed a unique pattern of activity, increasing its activity around the time the animal began licking and turning off abruptly exactly at tone offset, although this typically occurred in the middle of reward consumption. Neuronal firing rates could be roughly grouped as high (>30 Hz), medium (3-12 Hz) or low (<2 Hz). Low firing rates have been shown to be characteristic of dopaminergic VTA neurons, while non-dopaminergic neurons in the VTA generally show higher firing rates. The type of behavioral correlation displayed by a given neuron appeared to be independent of basal firing rate. Furthermore, administration of drugs which modify dopaminergic systems did not have a consistent effect on VTA neurons. It is possible that in the awake animal, circuit interactions strongly modulate neural activity, rendering the action of pharmacological agents on any given neuron relatively unpredictable. Supported by grants NS26722, AA06965, K02-AA00089 and AFOSR 90-0266.

751.2

PSYCHOSTIMULANT INFLUENCES ON CONDITIONED PLACE PREFERENCE BEHAVIOR OF RHESUS MONKEYS. J. Wertz, B. Hepner, R. Lepovich and S. M. Pomerantz*. Depts. of Cell Biology and Physiology and Psychology, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA 15261.

Previous research in our lab has indicated that cocaine (0.05 - 0.80 mg/kg) can produce a conditioned place preference (CPP) in rhesus monkeys (Pomerantz et al., Abst. Soc. Neurosci. 18:1572, 1992). The present study was designed to further characterize CPP with cocaine, as well as to evaluate the effects of other psychostimulants on CPP behavior. When conditioned with either 0.10 or 0.40 mg/kg cocaine in an eight-day (four drug and four saline injections) conditioning paradigm, eight adult male rhesus monkeys exhibited a CPP for the cocaine environment that was maintained for five weeks ($p<.0001$). In a four-day (two drug and two saline injections) conditioning paradigm, monkeys receiving 0.40 mg/kg cocaine exhibited a place preference ($n=8$, $p<.01$) for the cocaine environment, while monkeys receiving 0.10 mg/kg cocaine did not. In order to examine whether other psychostimulants can produce CPP, additional studies were conducted using the eight-day conditioning paradigm. The mixed dopamine (DA) and norepinephrine (NE) reuptake inhibitor, nomifensine, produced a CPP for the drug environment at 0.10 mg/kg ($n=8$, $p<.0001$) and 0.40 mg/kg ($n=8$, $p<.002$). By contrast, apomorphine, a mixed D1/D2 DA receptor agonist, did not produce a CPP at any of the doses tested (0.10, 0.20 and 0.40 mg/kg). In conclusion, these data indicate that monoamine reuptake inhibitors which stimulate DA and NE activity are sufficient to support CPP in rhesus monkeys. Although the DA receptor agonist, apomorphine, did not produce a CPP, further studies are needed with other selective DA receptor agonists and DA reuptake inhibitors to determine whether DA stimulation alone is capable of producing CPP.

751.3

CEREBRAL METABOLISM AND BEHAVIOR WITH COCAINE IN THE RAT A. Dhuna*, J.B. Arnold, S.C. Strother, D.A. Rottenberg. VA Medical Center, Minneapolis, MN 55417

We identified three distinct cocaine-induced behaviors in male Sprague-Dawley rats: (1) hyperactivity without significant stereotypy, observed after 14 days of 5 mg/kg ip cocaine; (2) hyperactivity with significant stereotypy, observed after 14 days of 10 mg/kg or a single dose of 50 mg/kg; and (3) stereotypy with no locomotor activity, observed after 10 days of 50 mg/kg.

Using 2-[C14]deoxyglucose quantitative autoradiography the lateral habenular nucleus (Lhb) was *hypo*metabolic in 10 mg/kg acute ($p<0.05$) and in 5 and 10 mg/kg chronic cocaine animals ($p<0.005$) compared to saline controls. Additionally, the acute 10 mg/kg cocaine group demonstrated *hyper*metabolism in the substantia nigra pars reticulata (SNr), lateral septum (LS) and olfactory tubercle (OT). The chronic 10 mg/kg group were *hyper*metabolic in the SNr and the cerebellar vermis (CV), but *hypo*metabolic in the LS and OT compared to the acute 10 mg/kg group. SSM analysis of autoradiographic data from the combined cocaine and saline control groups (Moeller and Strother, *J Cerebral Blood Flow Metabol*, 1991) extracted two patterns of regional metabolic covariation. The first pattern, characterized by relative Lhb hypometabolism, separated saline controls from all cocaine animals. The second "combined" pattern, which consisted of the Lhb, anterior cingulate cortex, ventrolateral thalamic nucleus and basolateral amygdala, distinguished saline, 5 mg/kg, and 10 mg/kg cocaine animals. Our results suggest that Lhb may play a role in cocaine addiction and that chronic 10 mg/kg rats develop metabolic tolerance in mesocorticolimbic pathways. The "combined" pattern of metabolic covariation may provide a dose-dependent measure of cocaine effects on regional cerebral metabolism.

751.4

ANIMAL MODELS OF COCAINE-SEEKING BEHAVIOR. R. Weissenborn*, M. Yackey, G.F. Koob and F. Weiss Department of Neuropharmacology, The Scripps Research Institute, La Jolla, California 92037

The present series of experiments aimed to develop valid behavioral tests modeling different aspects of cocaine-seeking behavior ("craving" and "propensity to relapse") for the evaluation of potential treatment drugs using intravenous self-administration in rats. In Exp.1, a priming-induced shift in preference for food vs. cocaine associated CS was examined. Wistar rats implanted with intravenous catheters were trained on a Multiple Schedule, where food or cocaine reward were paired with discrete conditioned stimuli (CS). At the beginning of the schedule, both CS were concurrently available for 10 min. Priming with food or drug reward prior to the onset of the CS component resulted in a significant shift of responding in the direction of the primed stimulus. This response may be indicative of "craving". In Exp.2, priming-induced recovery of responding following extinction was examined. Wistar rats were implanted with intravenous catheters and trained on the Multiple Schedule described above. The CS component, as well as presentation of cocaine and the associated CS were then eliminated from the schedule until extinction of responding for the drug was obtained. Following extinction, the initial 10 min component and CS presentation during the drug components of the schedule were reinstated. Subsequently, rats additionally received cocaine priming infusions at the beginning of each drug component. Extinction criteria were met within 6 days and rats did not relapse in response to presentation of the drug CS alone under the present conditions. However, a significant increase in responding on the cocaine lever was observed with cocaine priming injections prior to each drug component. This response may be indicative of the "propensity to relapse". The results indicate that these paradigms may represent a reliable model of cocaine-induced "craving" and the "propensity to relapse" after limited access to cocaine. The model may therefore provide a useful tool for assessing the therapeutic efficacy of potential treatment drugs of cocaine abuse.

751.5

EFFECTS OF CHRONIC COCAINE ADMINISTRATION ON FIXED-CONSECUTIVE NUMBER RESPONDING IN RATS: COMPARISON OF PRE- AND POST-SESSION ADMINISTRATION. G.F. Guerin*, C.C. Schuster and N.E. Goeders. Depts. of Pharmacology and Psychiatry, LSU Med. Center, Shreveport, LA 71130-3932.

The effects of chronic cocaine administration were examined in rats responding under a fixed-consecutive-number (FCN) 8 schedule of food reinforcement. Under this schedule, adult male Wistar rats were trained to respond 8 or more times on one lever, then respond once on a second lever. In one component of the schedule, an external discriminative stimulus was presented following the completion of the response requirement on the first lever, while no stimulus change was programmed during the other component. When stable baselines under both components of the schedule were observed, acute cocaine dose response curves (1 to 30 mg/kg, ip) were generated. The rats were then divided into four groups: saline-before, saline-after, cocaine-before and cocaine-after. The rats in the before groups received chronic cocaine (10 or 17 mg/kg, ip) or saline immediately prior to the start of the behavioral session, while those in the after groups received their chronic injections after each session. The animals receiving chronic injections of cocaine before each behavioral session showed a marked tolerance to the effects of cocaine (10 and 17 mg/kg, ip), while rats injected after each session were significantly more sensitive to cocaine (3 to 30 mg/kg, ip) during both components of the schedule. These data suggest that either tolerance or sensitization to cocaine can be demonstrated using FCN schedules of reinforcement, depending on when the animals are injected.

This research was supported by USPHS grant DA04293.

751.6

INVERSE RELATIONSHIP BETWEEN EXPLORATORY, AGORAPHOBIC BEHAVIOR AND ACUTE COCAINE-ANTAGONISM OF AGORAPHOBIC BEHAVIOR: RELATIONSHIP TO ANXIETY. F. Eng*[1], A. Charles[2], and P.A. Broderick[1,2]. Dept. Pharmacol., CUNY Med. Sch.[1], Dept. Biol., *H. Hughes Post-Bacc. Prog.*, CUNY Grad. Sch.[2], Convent Ave. and W. 138th St., Rm. J910, N.Y. 10031.

Agoraphobic behavior is defined as a natural tendency of the Norway laboratory rat to prefer exploration in the periphery vis-à-vis the center of the behavioral chamber. The ability to overcome this natural tendency toward the agoraphobic (fear-related) response and move into the center of the behavioral chamber is closely related to an anxiolytic (anxiety-reducing) response (Geyer, M.A. In: *Testing and Evaluation of Drugs of Abuse*. (M.W. Adler and A. Cowan, eds), A.R. Liss, NY,1990, 81-99). We studied agoraphobic behavior in male, virus free, Sprague-Dawley rats (348g-394g) by monitoring central ambulations before and after administration of cocaine (20 mg/kg (SC)) with computerized infrared photocell beam detection (San Diego Instr., CA). The results showed that, when the tendency to exhibit fear-related agoraphobic responses during exploration was significantly small ($p<0.0496$), the tendency toward cocaine-effects on agoraphobia were significantly large ($p<0.0001$). Conversely, when anxiolytic (fear reduction) behavioral responses were significantly high ($p<0.0496$) during the exploratory period, the response to cocaine administration was a suppression of the usual cocaine effects ($p<0.0001$). These data suggest that cocaine's effects might be influenced by pre-existing behavior or temperament. SUPP:R01 DA04755; PSC/CUNY Awards RF 669201, 661188 & 663202; DHHS PHS 2-S07-RR07132-20.

751.7

THE EFFECTS OF CROWDING STRESS ON COCAINE-INDUCED REVERSE TOLERANCE IN MICE. M. A. Blackshear* and B. Quarles Dept. of Biological Sciences, Tennessee State University, Nashville, TN 37209-1561.

This study investigated crowding stress on the chronic effects of cocaine administration in mice. The effects of cocaine on "reverse tolerance" were assessed using locomotor activity as a behavioral paradigm. Reverse tolerance is a behavioral phenomenon characterized by increased behaviors following repeated drug treatments. Male mice (25-30g) were divided into four groups: saline/saline; saline/cocaine; cocaine/ saline; cocaine/cocaine (according to the drugs received on day 1/day 17, respectively). The mice in each group received 14 daily injections of 20 mg/kg of cocaine hydrochloride or physiological saline. The animals were housed 10 mice per cage (5.6 cm^2 floor space per mouse or singly housed (562 cm^2 floor space per mouse). Locomotor activity was monitored automatically on day 17 (72 hr. after the last dose) in an animal activity meter following a challenge dose of 5 mg/kg of cocaine or 0.01 ml/gm of physiological saline. Although crowding did decrease isolation-induced aggressiveness, it did not alter the development of reverse tolerance in crowded mice. It is possible that the effects of crowding are subject to the development of tolerance after repeated cocaine administration.

(Supported by NIH-RCMI Crant G12RR03033)

751.8

CHRONIC COCAINE SENSITIZES THE EXPRESSION OF FEARFUL BEHAVIOR. T.B. Borowski and L. Kokkinidis*. Dept. Psych. Univ. of Saskatchewan, Saskatoon, Canada S7N 0W0.

Cocaine use is associated with an increased risk of a) anxiety, b) panic attack, and c) the emergence of psychosis with paranoid symptomatology. In animals the evolution of behavioral sensitization has been used to model the long-term consequences of stimulant drugs, and it is known that chronic exposure to cocaine sensitizes its acute psychomotor properties. The purpose of this research was to determine the effects of chronic cocaine treatment on emotional behavior by assessing the relationship between repeated cocaine exposure and the expression of fearful responses in rats.

Subjects were conditioned to associate a light (CS) with footshock and were subsequently tested for fear-potentiated startle. In this paradigm, the acoustic startle response elicited by a brief burst of white noise is potentiated by the CS presented immediately prior to the acoustic stimulus. After conditioning, subjects were administered an intraperitoneal injection of either cocaine (40 mg/kg) or saline once daily for 7 consecutive days either in their home cage environment, or were placed in the shock apparatus with or without the presentation of the light for 60 min after drug treatment. Animals were not exposed to shock during the chronic drug treatment phase of the experiment.

The results showed that cocaine administered in the context of the CS induced a marked enhancement in the magnitude of the fear potentiated startle response. The demonstration that cocaine sensitizes the expression of fearful behavior in animals, provides a new approach for exploring the involvement of limbic and related areas in the clinical pathology associated with cocaine use.

751.9

ENHANCEMENT OF COCAINE- AND METHAMPHETAMINE-INDUCED HYPERACTIVITY BY PHENOBARBITAL OR DIAZEPAM IN MICE. N. Ono* and K. Sakamoto. Dept. of Pharmacol., Fac. of Pharmaceut. Sci., Fukuoka Univ., Fukuoka, 814-01, Japan.

Central mechanisms of psychostimulants were studied by measurements of behavioral parameters and brain biogenic amines. Both cocaine (COC) and metamphetamine (MAP) were present dose-dependent hyperactivity in open field apparatus in doses of 1-5 mg/kg and 5-10 mg/kg, respectively. The hyperactivity of COC (10 mg/kg) and MAP (2 mg/kg) were augmented dose-dependently by the pretreatment with phenobarbital (25-50 mg/kg) and diazepam (1-5 mg/kg). The hyperactivities of both psychostimulants and reinforcing effects by phenobarbital or diazepam were inhibited by picrotoxin, Cl^- channel blocker (0.5-1 mg/kg). But the hyperactivity of COC and MAP were not potentiated by baclofen, a $GABA_B$ agonist. In the experiment of measurement of brain biogenic amines, norepinephrine, dopamine and DOPAC levels were measured 30 min after COC or MAP by HPLC-ECD. COC and MAP reduced DOPAC levels in frontal cortex, but not in striatum. The reduction of DOPAC was inhibited dose-dependently by diazepam. Our data suggest that behavioral effects of both psychostimulants may participate a modification of central Cl^- channel via $GABA_A$ system and dopaminergic system.

751.10

FURTHER ANALYSIS OF THE ROLE OF MESOLIMBIC AND NIGROSTRIATAL DOPAMINE IN THE CONDITIONED EFFECTS OF COCAINE. A. Pert*, R.M. Post and D.N. Thomas. Biological Psychiatry Branch, NIMH, Blg. 10, Rm 3N212, Bethesda, MD 20892

Stimuli associated with cocaine acquire, through classical conditioning, the ability to elicit motoric effects that are similar to those produced by the drug itself. We previously reported that such conditioned stimuli are capable of increasing extracellular levels of dopamine (DA) in the nucleus accumbens (Nac), suggesting a role for mesolimbic DA in the expression of cocaine conditioned behaviors. These studies extend this finding and further test its anatomical specificity. In the first study, one group of rats was injected daily for 7 days with 40mg/kg cocaine before exposure to a locomotor activity chamber (PAIRED), whilst the other group received saline (UNPAIRED). Both groups received the opposite drug treatment following return to the home cage. On the eigth day,one half of the rats in each group were lesioned in the Nac with 6-OHDA, the other half received sham lesions. When the animals were tested for conditioning one week later, only the sham lesioned rats demonstrated conditioned increases in locomotor activity. These findings confirm the importance of meso-accumbens DA in the expression of cocaine conditioned locomotor activity. The second series of studies evaluated DA function during the expression of cocaine conditioned increase in locomotor activity with in vivo microdialysis. PAIRED v's UNPAIRED rats were trained for one day as described above. On day 2 microdialysis probes were introduced into the striatum or amygdala through chronically implanted guides. Exposure to the apparatus under a low dose of cocaine (10mg/kg) revealed conditioned increases in locomotor activity in the PAIRED groups, but no concomitant increases in extracellular DA overflow, suggesting that DA is not involved in mediating the conditioned effects of cocaine in either brain region.

751.11

SEPARABLE EFFECTS OF MOTIVATION AND MOTOR READINESS ON REACTION TIME DISTRIBUTIONS OF RHESUS MONKEYS. E.M. Bowman*, T.G. Aigner and B.J. Richmond. NIMH, Bethesda, MD 20892.

To distinguish the reaction time effects of motivation from those of sensory and motor processes, we used a task in which 3 rhesus monkeys released their grip on a bar when a visual target changed colors. There were two variables that were manipulated across trials. First, the length of a forewarning period before the color change was randomly varied. Second, the number of correct trials required to earn a reward was randomly varied from 1-3. The brightness of a cue presented above the target before each trial signaled the monkeys what their progress would be toward earning a reward if they responded correctly. The length of the forewarning period was used to assess motor readiness, whereas the brightness of the cue was used to assess motivation.

Performance improved as the length of the forewarning period increased and as the brightness of the cue approached the level signaling that reward was directly available. Both the brightness of the cue and the length of the forewarning period affected reaction times, but only the former affected the probability of making responses we counted as anticipatory or late. Increasing the length of the forewarning period shifted the peaks of the reaction time distributions along the latency axis. As the cue's brightness approached the level that signaled reward, the peaks of the reaction time distributions increased in height relative to their tails, but the locations of the peaks did not shift.

We infer that the length of the forewarning period changed the processing time needed to initiate the response, since it shifted the positions of the peaks of the reaction time distributions. By contrast, the cue's brightness appeared to act as a gate for the signals culminating in responses, since it altered the heights of the peaks without shifting them.

751.12

NEURONS IN RHESUS MONKEY VENTRAL STRIATUM CARRY DIFFERENT SIGNALS REGARDING JUICE AND COCAINE REINFORCEMENT. T.G. Aigner*, E.M. Bowman and B.J. Richmond. NIMH, Bethesda, MD 20892.

The ventral striatum is considered to be an important component of a neural system subserving motivation and reward. We focused on two questions: First, do ventral striatal neurons carry signals related to the motivation to perform an operant task? Second, does their activity change when the reward is intravenous cocaine instead of juice? We recorded from single neurons while monkeys performed the reaction time task described in the accompanying abstract, using juice and then intravenous cocaine as the reinforcer. This task allowed us to separate the reaction time effects of motivation from the potentially confounding psychomotor effects due to cocaine administration.

We recorded from neurons in the ventral striatum of two monkeys. Two response types were noted. First, many neurons appeared to be tonically activated during some portion of the task. Second, some neurons responded to the activation of the reward apparatus. During testing with juice reward, the activity of most task-related neurons was qualitatively different when a cue signaled that reward was directly available. However, the activity other neurons changed gradually as the monkeys progressed toward earning a reward. In effect, these latter neurons carried a signal related to the proportion of the multitrial task that had been successfully completed. The property of being task-related while the monkeys worked for juice was statistically independent from the property of being task-related while the monkeys worked for cocaine, even though the sensory parameters in both conditions were identical. Moreover, during the cocaine condition the activity of many task-related neurons ceased to vary as a function of the proximity of reward.

Our results show that the reward-related activity in the ventral striatum is not the same for juice and cocaine.

751.13

ISOLATION-REARING ENHANCES THE LOCOMOTOR RESPONSE BOTH TO A NOVEL ENVIRONMENT AND COCAINE, BUT IMPAIRS BOTH THE INTRAVENOUS SELF-ADMINISTRATION OF COCAINE AND THE BILATERAL INTRA-ACCUMBENS SELF-ADMINISTRATION OF *d*-AMPHETAMINE. G.D. Phillips, R.B. Whitelaw, S.R. Howes, T.W. Robbins[1], B.J. Everitt. (SPON: Brain Research Association). Depts of Anatomy & [1]Experimental Psychology, University of Cambridge, Cambridge CB2 3DY, UK.

Rats were raised from weaning either alone (isolation-reared) or in groups of five (socially housed controls). In experiment 1, isolation-reared animals were shown to be more active in a novel environment, and more responsive to the locomotor-stimulant action of cocaine. Experiment 2 examined the effects of isolation-rearing upon the acquisition of the intravenous self-administration of cocaine, or the bilateral intra-accumbens self-administration of *d*-amphetamine. Two levers were present in the operant chambers. Depression of one lever resulted in drug delivery, responses upon a control lever were recorded but had no programmed consequences. Socially housed animals acquired a selective response upon the drug lever more rapidly than isolation-reared animals. Experiment 3 found that isolation-rearing shifted the intravenous cocaine, or intra-accumbens *d*-amphetamine, dose-response functions to the right. In experiment 4, intra-accumbens infusions of SCH-23390 or sulpiride enhanced the rate of the intravenous self-administration of cocaine, or intra-accumbens self-administration of *d*-amphetamine in socially housed controls. Isolation-rearing impaired this response. Experiment 5 examined the effect of isolation-rearing upon the response to a conditioned reinforcer associated previously with cocaine. The contingent availability of the conditioned reinforcer alone enhanced selectively the rate of response by socially housed controls. Isolation-reared animals were unresponsive. Thus, isolation-rearing leads to dysfunctioning of the mesoaccumbens dopamine system.

751.14

OPPOSING EFFECTS OF ACUTE VS CHRONIC HALOPERIDOL TREATMENT ON COCAINE CONDITIONED PLACE PREFERENCE. TA Kosten *, S Chi, & EJ Nestler. Dept of Psychiatry, Yale University School of Medicine, New Haven, CT 06519.

Cocaine's (COC) behavioral effects are mediated, in part, through dopamine (DA). Accordingly, DA antagonists, such as haloperidol (HAL), have been proposed as "blocking" agents for COC abuse. While acute HAL blocks some behavioral effects of COC, chronic HAL treatment may lead to behavioral supersensitivity and enhance COC's effects. We assessed the effects of acute vs chronic HAL treatments on COC conditioned place preference (CPP). For the acute study, rats were given vehicle (VEH) or active HAL in their drinking water (approx. dose: 1.2 mg/kg/day) on training days during which they received 1 of 4 COC doses (0, 7.5, 15, 30 mg/kg). Baseline CPP measures were obtained on Day 1. On Days 2-9, rats were maintained on VEH or HAL and on alternate days, received pairings of COC with 1 side of the CPP apparatus and vehicle with the other side. On Day 10, CPP was assessed as the time shift to the COC-paired side compared to baseline. Acute HAL rats showed significantly less COC CPP than VEH rats, $F(1,49)=5.7$; $p<0.05$. Using similar procedures, chronic (30 days) HAL pretreated rats showed significantly greater COC CPP compared to VEH rats, $F(1,26)= 8.1$; $p<0.01$, particularly at lower COC doses. The latter results suggest that chronic DA receptor blockade leads to behavioral supersensitivity for some of COC's effects which may contraindicate the use DA antagonists as blocking agents for COC abuse. [NIDA grant, P50-04060].

751.15

CONDITIONED TASTE AVERSION (CTA) IS A POTENT EXPERIMENTAL CONFOUND IN STUDIES OF PHARMACOLOGICAL AGENTS THAT ATTENUATE THE REINFORCING PROPERTIES OF DRUGS OF ABUSE. W. J. PIZZI* and D. F. COOK, Northeastern Illinois Univ. Chicago, IL. 60625

Psychopharmacologists are seeking drugs which will modify the reinforcing properties of cocaine and other drugs of abuse. The effects of agents on the reduction of drug self-administration and sweet solution intake are two common animal models employed in this research. When these agents are effective in reducing the reinforcing properties of a drug the cause is usually attributed to a neuronal mechanism such as modification of neurotransmitter action. An alternative interpretation is that these agents produce a CTA leading the animal to avoid further intake of the reinforcing drugs. We will demonstrate that CARBAMAZEPINE and ISRADIPINE, drugs which have been reported to reduce the reinforcing properties of cocaine and sweet solutions, produce a CTA at the doses employed by other investigators. Future research will need to dissociate the therapeutic effects of these agents from their toxic effects.

751.16

COCAINE DISCRIMINATION IN MALE AND FEMALE WISTAR RATS. K. G. Anderson and F. van Haaren*. Dept. of Psychology, Univ. of Florida, Gainesville, FL 32611.

The effects of the presence or absence of gonadal hormones on cocaine discrimination were studied. Twelve male and twelve female Wistar rats (half in each group were gonadectomized) served as subjects and were trained to discriminate 10.0 mg/kg cocaine (IP) from vehicle (saline) in a two-lever operant chamber under a tandem RI 30-s FR 10 schedule of food reinforcement. After subjects reached the discrimination criterion of at least 80% correct responses, probe doses of cocaine (1.0, 1.7, 3.0, 4.2, 5.6, and 17.0 mg/kg) were tested during extinction. Two generalization tests were conducted. The first test began ten minutes post-injection and the second test began thirty minutes post-injection. The extinction tests lasted until subjects completed the response requirement (tandem RI 30-s FR 10) on one of the levers, or 5 min, whichever came first. In general, male rats reached the discrimination criterion faster than any of the rats in the other groups. Four of the six ovariectomized female rats failed to reach the discrimination criterion under the behavioral contingencies of this experiment. Intact male rats tolerated larger doses of cocaine and response rates were less affected by cocaine administration. Also, cocaine's ED_{50} was higher for intact male rats than for castrated male and intact female rats. For all subjects, the discriminative stimulus properties of cocaine decreased as a function of time since injection, as the dose-effect curves established 30 min post-injection were shifted to the right of the curve established 10 min post-injection.

Supported by NIDA DA-06463.

751.17

EFFECT OF INTRA-AMYGDALOID SCH 23390 ON THE DISCRIMINITIVE STIMULUS PROPERTIES OF COCAINE. A. McGregor and D.C.S. Roberts*. Life Sciences Research Centre, Carleton University, Ottawa, K1S 5B6, Canada.

The role of the amygdala in cocaine-induced CNS effects is very unclear. Recently we have shown that the amygdala does have a significant role to play in cocaine reinforcement mechanisms. Blockade of the D1 receptor subtype with SCH 23390 produced very large increases in rate of cocaine self-administration under a FR schedule but little effect on breaking point under a PR schedule. These results suggested a possible role for this region in monitoring the internal cue or stimulus properties of the cocaine. To test this hypothesis, rats (N = 8) were trained in a two lever operant paradigm to discriminate 10.0 mg/kg (ip) cocaine from saline. Preoperatively, a dose-response curve was generated using 0, 2.5, 5.0 and 10.0 mg/kg ip cocaine. Bilateral intracerebral cannulae were then implanted above the amygdala and injections of 1.0μg/0.5μl SCH 23390 or vehicle were administered immediately prior to injection of cocaine (0, 2.5, 5.0 and 10.0 mg/kg ip). SCH 23390 injections into the amygdala blocked cocaine-appropriate responding in a dose-dependent manner. Moreover, SCH 23390 does not produce a non-specific disruption of lever-appropriate responding as shown by saline-appropriate responding following intra-amygdaloid SCH 23390 injection. These data further implicate the amygdala in cocaine CNS action and more specifically in some aspect of the interoceptive stimulus properties of the drug.

751.18

NORADRENERGIC INFLUENCES IN THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE. R.D. Spealman*, Harvard Medical School, New England Regional Primate Research Center, Southborough, MA 01772-9102.

The role of noradrenergic (NE) mechanisms in the discriminative-stimulus (DS) effects of cocaine was investigated in squirrel monkeys trained to discriminate cocaine from vehicle. When tested alone, cocaine engendered dose-related increases in cocaine-appropriate responding. Pretreatment with the α_1 antagonist prazosin (0.3 mg/kg) produced small but consistent rightward shifts in the cocaine dose-response function indicative of surmountable antagonism, whereas the α_2 antagonist efaroxan (up to 1.0 mg/kg) and the β antagonist propranolol (up to 3.0 mg/kg) were ineffective. In substitution experiments, the α_1 agonist ST 587 (up to 10 mg/kg), the α_2 agonist clonidine (up to 1.0 mg/kg), the β agonist clenbuterol (up to 1.8 mg/kg) and the NE uptake inhibitor talsupram (up to 18 mg/kg) engendered little or no cocaine-appropriate responding. Another NE uptake inhibitor, tomoxetine, substituted partially for cocaine after doses ≥ 10 mg/kg in about half the subjects. The partial cocaine-like effects of tomoxetine in these subjects were blocked by prazosin (0.3 mg/kg), but not by efaroxan (1.0 mg/kg). The dopamine (DA) uptake inhibitor GBR 12909 substituted completely for cocaine after doses ≥ 10 mg/kg. Pretreatment with talsupram (10 mg/kg) did not markedly alter the DS effects of cocaine, but did potentiate the cocaine-like DS effects of GBR 12909. Although stimulation of NE receptors alone is insufficient to reproduce the DS effects of cocaine, NE mechanisms (possibly α_1) appear to facilitate DA mediation of these effects. (Supported by DA00499, DA03774, MH07658 and RR00168).

751.19

REWARDING ELECTRICAL BRAIN STIMULATION MAY SUBSTITUTE FOR COCAINE IN A DRUG DISCRIMINATION SITUATION. J. Buggy*, R.B. Saunders, Z. Ying, and J.B. Appel. Depts. of Physiology and Psychology, University of South Carolina, Columbia, SC 29208.

Self-administration studies demonstrate that both cocaine and electrical stimulation of the mesocorticolimbic dopaminergic system (MCL) are rewarding. While both the rewarding and discriminative stimulus effects of cocaine are antagonized by dopaminergic blockade, the extent to which the MCL is involved in the discriminative stimulus effects of cocaine is not clear. We therefore assessed the ability of rewarding brain stimulation of the ventral tegmental area (VTA) to substitute for cocaine in a two lever, drug discrimination paradigm by training rats to discriminate cocaine (10 mg/kg ip) from saline. The animals were then given different current intensities of VTA stimulation (1.5 Hz trains of 100 msec with 100 Hz pulses of 0.5 msec, 10 minutes prior to and during periods of access to the two levers) on separate test sessions interspersed with training sessions. VTA stimulation produced responding on the cocaine lever with a current-dependent relationship similar to that seen with intracranial self-stimulation (ICSS): at low current intensities (which did not support ICSS), rats selected the saline lever; at intensities supporting self-stimulation, rats responded 78.6% on the cocaine lever at the most effective intensity for substitution. Thus, VTA stimulation was at least partially similar to cocaine.

DRUGS OF ABUSE: COCAINE—CELL MEMBRANE

752.1

ROLE OF D1 AND D2 DOPAMINE RECEPTORS IN THE ABILITY FOR AMPHETAMINE PREEXPOSURE TO SENSITIZE RATS TO COCAINE'S REINFORCING EFFECTS. A. Broadus* and S. Schenk, Psychology Dept., Texas A&M Univ., College Station, TX, 77843.

This study was designed to assess the role of D1 and D2 receptor subtypes in the development of sensitization to cocaine's reinforcing effects produced by pretreatment with amphetamine. Male Sprague Dawley rats were pretreated on two consecutive days with either the D1 antagonist, SCH 23390 (0.1 mg/kg, IP), the D2 antagonist, sulpiride (15.0 mg/kg, IP) or physiological saline. These treatments were followed 30 min later by injections of amphetamine (4.0 mg/kg, IP) or an equal volume of physiological saline. Latency to acquire intravenous cocaine self-administration (0.25 mg/kg/infusion) was then assessed in 8 daily 2 hr sessions. Depression of an active lever resulted in an infusion of cocaine whereas depression of an inactive lever was without consequence. Amphetamine preexposure resulted in a reduced latency to develop of a preference for the cocaine associated lever when compared to vehicle injected control rats. This effect was blocked by both the D1 and D2 antagonist. These data suggest that both D1 and D2 receptors contribute to the development of sensitization to cocaine's reinforcing effects produced by amphetamine.

752.2

COCAINE STIMULATES ENTOPEDUNCULAR METABOLIC RATE BY ACTIVATING D_1 RECEPTORS IN DORSAL AND VENTRAL STRIATUM. W.L. Thomas, Jr., E.S. Cooke, and R.P. Hammer, Jr.*, Laboratory of Cellular & Molecular Neuropharmacology, University of Hawaii School of Medicine, Honolulu, HI 96822.

Acute cocaine administration increases regional cerebral metabolic rate for glucose ($rCMR_{glc}$) in the entopeduncular nucleus (EP) and a few other regions. Cocaine-induced increase of striatal dopamine level is probably involved, but the pharmacologic mechanism is unknown. Therefore, we examined whether dopamine D_1 receptor blockade disrupts this effect. Adult male Sprague-Dawley rats were injected i.p. with either cocaine HCl (30 mg/kg) or saline vehicle following pretreatment with SCH 23390 (0, 50 or 500 µg/kg), and prepared for the quantitative [^{14}C]2-deoxyglucose procedure. Autoradiographic analyses of 54 discrete regions showed that D_1 receptor blockade decreased $rCMR_{glc}$ in a dose-dependent manner in caudate-putamen (CP), globus pallidus, EP, subthalamus, substantia nigra, ventral tegmental area, and several other areas, but not in nucleus accumbens (NAc). Selective activation of striatal circuits by cocaine was further examined by iontophoretic injection of 4% fluorogold into the ventromedial EP, and subsequent hybridization of striatal sections with an ^{35}S-labeled, 48 bp oligonucleotide probe complementary to rat c-*fos* mRNA. Isotopic labeling was visualized using NTB-2 liquid emulsion. Retrograde-labeled neurons were observed exclusively in the ventromedial CP and NAc core; double-labeled cells were observed equally in both regions. Since SCH 23390 pre-treatment blocks induction of striatal c-*fos* mRNA, we propose that activation of D_1 receptors on both CP and NAc core neurons contributes to psychomotor stimulation of EP by cocaine.

752.3

THE ABILITY OF A D1/D2 ANTAGONIST COMBINATION TO ANTAGONIZE THE DISCRIMINATIVE STIMULUS PROPERTIES OF COCAINE. B. Geter* and A. L. Riley. Psychopharmacology Laboratory, The American University, Washington, DC 20016.

Whereas dopamine reuptake inhibitors have been shown to substitute for the discriminative stimulus properties of cocaine (Kleven, Anthony & Woolverton J. Pharm. Exper. Ther. 254: 312-317, 1990), selective D1 and D2 agonists fail to substitute consistently for the cocaine cue (Colpaert, Niemegeers & Janssen Pharm. Biochem. & Behav. 10: 535-546, 1979). Further, selective D1 and D2 antagonists fail to block it consistently (Barrett & Appel Psychopharm. 99: 13-16, 1989). These findings suggest that the concurrent activity of dopamine at both receptor subtypes may be required to mediate these properties. To test this hypothesis, rats were trained to discriminate cocaine from distilled water in either the conditioned taste aversion (Experiment 1) or traditional operant (Experiment 2) baselines of drug discrimination learning. Following training, the D1 antagonist, Schering 23390 (SCH), and the D2 antagonist, haloperidol (HAL), were given alone and in combination prior to cocaine. In both studies, most animals displayed partial antagonism of the cocaine cue with at least one dose of each antagonist. However, when SCH/HAL combinations were given prior to cocaine, complete antagonism did not occur, suggesting that simultaneous blockade of both D1 and D2 receptors may not be sufficient to block completely the cocaine cue.

752.4

EFFECT OF CHRONIC INJECTION OR MINIPUMP COCAINE ON STRIATAL D_{1A} AND D_2 RECEPTOR mRNA AND BINDING SITE DENSITY. C.P. Silvia, Z. Xue, U. Schambra,* M.G. Caron and E.H. Ellinwood, HHMI and Depts. of Cell Biology and Psychiatry, Duke Univ. Medical Center, Durham, NC 27710.

After daily injections of cocaine, a behavioral sensitization phenomenon is observed which persists for a long period of time following cessation of treatment. This sensitization does not occur in animals treated for the same duration using a constant infusion of cocaine via osmotic minipump; these animals are desensitized to challenge doses of cocaine. To test if changes in D_{1A} or D_2 receptor densities in striatum were altered after seven days of withdrawal from cocaine treatment using these two regimens we performed binding analysis of striatal membranes from control, injected, and pump-treated groups. We also measured D_{1A} and D_2 mRNA levels by reverse-transcription/polymerase chain reaction (RT/PCR) using actin as an internal standard. RT/PCR conditions were controlled to give a linear product curve, and probed with a [^{32}P] end-labeled oligodeoxynucleotide specific for the amplified receptor cDNA segment.

No differences were found among the treatment groups in the receptor density of either D_{1A} or D_2 receptors. D_{1A} mRNA levels were decreased in both cocaine treatment groups, and administration of a challenge dose of cocaine prior to sacrifice additionally decreased levels slightly in all groups. D_2 mRNA levels were decreased only in animals receiving cocaine by daily injection; pump-treated animals had mRNA levels similar to saline controls. It appears that mRNA levels do not correlate with receptor number at withdrawal day seven, possibly indicating a homeostatic mechanism for maintaining receptor number that involves changes in receptor turnover and mRNA synthesis/catabolism. It also appears that the mechanisms underlying the differences in behavioral sensitization between injection and pump treaments are not related to changes in D_{1A} or D_2 receptor number.

752.5

BEHAVIORAL SENSITIZATION, BUT NOT TOLERANCE, TO COCAINE IS ASSOCIATED WITH INCREASED OCCUPATION OF DOPAMINE D1- AND D2-LIKE RECEPTORS BY DOPAMINE IN STRIATUM AND ACCUMBENS. L.Y. Burger* and M.T. Martin-Iverson. Neurochemical Research Unit, University of Alberta, Edmonton, Alta. Canada T6G 2B7.

Male Sprague-Dawley rats (N=8 per group) were given daily injections of cocaine (10 mg/kg IP) or continuous infusions of an equivalent dosage of cocaine with osmotic minipumps (10 mg/kg/day, SC). In addition, rats were pretreated with vehicle or nimodipine (10 mg/kg, IP), an L-type calcium channel antagonist. Locomotor activity was assessed daily for 1 h periods daily for 14 days. On the last day of treatment, rats were injected with N-ethoxycarbonyl-3-ethoxy-1,2-dihydroquinoline (EEDQ, 5 mg/kg, IP), 30 min after cocaine injections and the rats were killed by guillotine decapitation 24 h later. Protection from EEDQ irreversible denaturation of dopamine receptors enables the assessment of the density of receptors occupied by dopamine after cocaine treatments. The brains were removed and the striatum and nucleus accumbens were dissected out. Receptor binding assays for D1 and D2 receptors were performed as previously described (Burger & Martin-Iverson, Synapse 13, 20, 1993). Daily injections with cocaine produced a gradual augmentation of cocaine's locomotor stimulant effects and increased the occupation of both D1-like and D2-like receptors in both striatum and accumbens by about 100%. Tolerance to the locomotor stimulant effects occurred with continuous cocaine infusions, and no increase in occupation of dopamine receptors was observed. Nimodipine blocked both the behavioral sensitization and the increased protection from EEDQ-denaturation induced by daily cocaine injections. It is concluded that behavioral sensitization to cocaine is associated with increased dopamine activity at both D1 and D2 receptors in both striatum and accumbens, and that this effect depends on L-type calcium channels.

752.6

DOPAMINE D_1 RECEPTOR AGONISTS EXHIBIT DIFFERENTIAL EFFICACIES FOR STIMULATING ADENYLYL CYCLASE ACTIVITY IN SQUIRREL MONKEY AND RAT CAUDATE. S. Izenwasser* and J.L. Katz. Psychobiology Section, NIDA Addiction Research Center, Baltimore, MD.

Some dopamine D_1 receptor agonists produce different behavioral effects in rats and in primates. The dopamine D_1 receptor is linked to adenylyl cyclase such that D_1 agonists stimulate adenylyl cyclase activity. This activity appears to distinguish many of the dopamine D_1 receptor agonists with regard to their intrinsic efficacy. In the present study, the effects of several dopamine D_1 receptor agonists were examined on adenylyl cyclase activity in both rat caudate-putamen and monkey caudate. Basal adenylyl cyclase activity did not significantly differ in the two species. Dopamine stimulated adenylyl cyclase activity, in a concentration-dependent manner, to approximately 200% over basal activity in both squirrel monkey caudate and rat caudate-putamen. Although the maximal effects observed with 100 μM dopamine were similar, the rat caudate-putamen was significantly more sensitive than the monkey to stimulation by dopamine. The selective dopamine D_1 receptor agonists SKF 82958, A68930, dihydrexidine, CY 208-243, and SKF 75670 each produced similar maximal stimulation across the two species, with SKF 82958, A68930 and dihydrexidine exhibiting the highest efficacies. Differences in efficacy between the two species were observed for several of the benzazepine compounds (SKF 38393, SKF 81297, and 6-Br-APB), each of which exhibited a significantly greater maximal effect in rat than in monkey. None of the compounds tested produced a greater stimulation of adenylyl cyclase activity in the monkey than in the rat. These results suggest that there may be differences in dopamine D_1 receptors in these two species. (Supported in part by a National Research Council - (NIDA) Research Associateship to SI).

752.7

DISCRIMINATIVE STIMULUS EFFECTS OF D_1 DOPAMINE RECEPTOR AGONISTS IN SQUIRREL MONKEYS AND RATS TRAINED TO DISCRIMINATE COCAINE FROM SALINE. J.L. Katz*, S. Izenwasser, P. Terry and J.M. Witkin. Psychobiology Section, NIDA Addiction Research Center, Baltimore, MD 21224, U.S.A.

The role of D_1 dopamine receptor actions in the discriminative stimulus effects of cocaine was examined. Squirrel monkeys (*Saimiri sciureus*) and rats were trained to discriminate injections of cocaine (0.3 i.m. or 10.0 i.p. mg/kg, respectively) from saline. Food was presented after each 30 (monkeys) or 20 (rats) consecutive responses on one lever after administration of cocaine and the other lever after administration of saline. Once stable performances were obtained, effects of various doses of cocaine, pentobarbital, and several D_1 agonists were assessed during test sessions in which 20 or 30 consecutive responses on either lever were reinforced. Cocaine produced a dose-related increase in the percentage of responses on the cocaine-appropriate lever, reaching 100% at the training dose. Pentobarbital was not active up to doses that decreased response rates. The greatest substitution for cocaine in monkeys was produced by administration of the D_1 agonists, SKF 82958 and SKF 81297. Each of these drugs produced a partial substitution for cocaine, reaching maximums of 60% and 40%, respectively. Maximum substitution obtained with the other D_1 agonists did not exceed 20%. The greatest substitution for cocaine in rats was produced by administration of the D_1 agonists, SKF 75670 and SKF 82958. Each of these drugs produced a partial substitution for cocaine, reaching maximums of 79% and 66%, respectively. Among the D_1 agonists that were tested for both cocaine discrimination and stimulation of adenylyl cyclase, there was no correlation in either species of maximal substitution for cocaine and maximal efficacy for stimulation of adenylyl cyclase in caudate. [SI was supported by a National Research Council - (NIDA) Research Associateship.]

752.8

NOVEL 3α-DIPHENYLMETHOXY-TROPANE ANALOGS THAT ARE UNSUBSTITUTED AT THE 2-POSITION ARE POTENT DOPAMINE UPTAKE INHIBITORS. A.H. Newman*, A.C. Allen, S. Izenwasser, J.L. Katz, Drug Development Group, Psychobiology Section, NIDA-ARC, Baltimore, MD 21224.

Psychomotor stimulant and reinforcing effects of cocaine and related analogs correlate with binding to cocaine recognition sites on the dopamine transporter and consequent inhibition of dopamine uptake. Structure-activity relationships and proposals for hypothetical binding domains for numerous tropane-analogs at the cocaine recognition site have previously been deduced. Benztropine (BZT, 3α-diphenylmethoxy)-1αH,5αH-tropane) is a dopamine uptake inhibitor, equipotent to cocaine, that exhibits CNS stimulant activity in animal models. BZT shares the common tropane ring moiety of cocaine and the diphenylmethoxy substituent of the GBR series of selective dopamine uptake inhibitors. Thus, a series of *para*-substituted diphenylmethoxy-tropane analogs was prepared generally by reacting tropine with the appropriate *para*-substituted benzhydrylchloride at 160°C and isolation as the HCl salts. All of these compounds monophasically displaced [^{3}H]WIN 35, 428 binding in rat caudate-putamen with IC_{50} values ranging from approximately 0.01 to 3 μM. The rank order of potency for both binding and inhibition of [^{3}H]dopamine uptake was 4,4'-diF>4,4'diCl>4-Cl>BZT=4-OMe>3β-4-Cl>4,4'-diOMe. Interestingly, when the diphenylmethoxy substituent was in the 3β-position, as is the 3β-benzoyl group of cocaine, potencies for binding and inhibition of [^{3}H]dopamine uptake were decreased by approximately 100-fold. The lack of a 2-position substituent, which is necessary for cocaine analogs, and the sensitivity to phenyl ring substitution in this series suggests an additional binding domain that could be exploited for the identification of potential cocaine antagonists.

752.9

EFFECTS OF CHRONIC COCAINE ADMINISTRATION ON DOPAMINE TRANSPORTER DENSITY IN THE RAT STRIATUM. S.R. Letchworth, L.J. Vogt*, K. Migliarese, L.J. Porrino. Dept. of Physiology & Pharmacology, Bowman Gray School of Medicine, Winston-Salem, NC 27157 USA.

Chronic administration of cocaine produces sensitization as seen in increased locomotor behavior. The neuorbiological basis of this sensitization is not fully understood. Our purpose was to examine the potential changes in the dopamine system of rats following repeated exposure to cocaine. Quantitative *in vitro* autoradiography with [^{3}H]mazindol according to the procedures of Javitch et al (1985) was used to determine the distribution of dopamine transporter sites in the striatum of male Sprague-Dawley rats treated with cocaine (10 mg/kg) or saline IP for 8 days and sacrificed 1 hr after the final dose. Cocaine-treated rats displayed increased locomotor activity as compared to saline or acutely treated controls. The distribution of mazindol binding sites was heterogeneous, with a marked dorsoventral gradient in the striatum, as well as a greater density in the shell than core of the nucleus accumbens. An increased density of sites was observed in the anterior nucleus accumbens and olfactory tubercle and accumbens shell in cocaine-treated rats. No changes, however, were observed in the caudate. These data indicate that repeated administration of low doses of cocaine can selectively alter dopamine systems in the ventral striatum and further underscore the importance of this region in mediating the long-term effects of cocaine.

Supported by NIDA Grants DA07522 and P50 DA06634.

752.10

RELATIONSHIP BETWEEN COCAINE-INDUCED CHANGES IN DOPAMINE CLEARANCE MEASURED WITH *IN VIVO* ELECTROCHEMISTRY AND ELECTRODE LOCALIZATION TO PATCH/MATRIX IN RAT STRIATUM E.J. Cline*, C.E. Adams, G.A. Gerhardt, and N.R. Zahniser Depts. Pharmacology, Neurology, and Psychiatry, Univ. Colorado Hlth. Sci. Ctr., Denver, CO, 80262.

Acute systemic cocaine administration produces dose-dependent changes in dopamine (DA) clearance in striatum in the anesthetized rat. DA clearance, an index of activity of the DA transporter, was measured by pressure ejecting finite amounts of DA at 5-min intervals from a micropipette positioned 300 ± 20μm from an electrochemical electrode. Heterogeneity of the DA signal has been observed in rat striatum. To address the hypothesis that this heterogeneity may be related to previously described differences in DA transporter distribution in striatal patch vs. matrix, we examined the relationship between DA clearance and recording site after cocaine. Animals received saline or 15 mg/kg cocaine IP, and DA clearance was measured. Maximum increases in signal amplitude occurred at 5-15 minutes with an average increase over saline of 79 ± 20%. Electrode localizations (n=4) were confined to 1.2 - 1.6 mm anterior to bregma and 3.8 - 4.5 mm ventral to brain surface. In vitro autoradiography was performed on brain sections from these rats using [^{3}H] diprenorphine or [^{3}H]naloxone to differentiate patch from matrix. The most ventral electrode placements were all localized to matrix by superimposing images of stained sections with autoradiographic images. These preliminary results suggest changes in DA clearance after cocaine are variable even within the DA transporter rich matrix in rat striatum (Supported by DA 04216 and DA 00174).

752.11

CHRONIC COCAINE INCREASES WIN 35428 BINDING IN RABBIT CAUDATE. Vincent J. Aloyo, John A. Harvey* and Alexander L. Kirifides. Dept. of Pharmacology, Medical College of Pennsylvania, Philadelphia, PA, 19129

The cocaine analog WIN 35428 (WIN) is widely employed to investigate the properties of cocaine binding sites on the dopamine transporter. WIN binding was investigated under conditions of single-site kinetics (Kirifides et al. Life Sci., 1992). Binding assays were performed using a crude membrane fraction prepared from fresh rabbit caudate at 0°C in 20 mM phosphate pH 7.4 (at 0°C) containing 0.32 M sucrose. Nonspecific binding was defined as the binding remaining in the presence of 30 μM cocaine. Rabbits were administered cocaine at a dose of 4 mg/Kg iv twice daily for 22 days. Animals sacrificed 24 to 48 hr after the last cocaine administration exhibited a significant increase in WIN binding as compared to saline treated rabbits. Scatchard analysis revealed chronic cocaine increased the B_{max} without altering the K_d. However, by 96 hr following the last cocaine injection there was no significant difference between cocaine and saline treated rabbits. These results suggest that chronic cocaine results in a transient up regulation of the dopamine transporter. (Supported by NIDA Grant DA06871-01).

752.12

OXADIAZOLE ANALOGS OF COCAINE: SELECTIVE AND ESTERASE RESISTANT LIGANDS FOR THE DOPAMINE TRANSPORTER. T. Kopajtic*, J.W. Boja, F.I. Carroll, J.L. Grey, M.A. Kuzemko, A.H. Lewin, P. Abraham, and M.J. Kuhar. Molecular Pharmacology Section, NIH-NIDA Addiction Res Center, P.O. Box 5180, Baltimore, MD 21224.

Previously this group has reported on the synthesis of several cocaine analogs that are more selective for the dopamine transporter (DAT) than cocaine itself. Several analogs of cocaine were prepared that contain the esterase resistant oxidiazole ring structure in the C-2 position, these compounds were then tested for their affinities at the DA, NE and 5-HT transporters. The most potent oxadiazole analogs possessed a Cl atom at the para position of the C-3 phenyl ring and either a phenyl or methoxyphenyl group at the C-3' position of the oxadiazole ring. The phenyl group at the C-3' position also afforded selectivity for the DAT compared to the NE and 5-HT transporters as previously demonstrated. However, the greatest selectivity was demostrated when a methoxy phenyl group was present at the C-3' position. While the affinity for the DAT was identical to that of the compound with the phenyl group only at the C-3' position, the binding affinities at both the NE and 5-HT transporters were approximately 3 times less. It can be speculated that there is a site for hydrogen bonding in the DAT that is lacking in both the NE and 5-HT transporters. These compounds, as well as additional componds based upon esterase resistant chemistry that exhibit with low nanomolar potency, may be very useful as potential substitution medications for the treatment of cocaine addiction .

752.13

[^{3}H]WIN 35,428 BINDING TO THE DOPAMINE TRANSPORTER IN COCAINE OVERDOSE DEATHS. I. Staley,* D.D. Flynn, F. Stitt, C.V. Wetli, and D.C. Mash. Depts. Neurology, Pharmacology, Epidemiology and Pathology, Univ. of Miami School of Medicine and the Metro-Dade County Medical Examiner Dept., Miami, FL. 33101

The dopamine transporter is a primary recognition site for cocaine that is related to drug abuse. Alterations in the affinity, density or regulation of the cocaine recognition site on the dopamine transporter may contribute to the behavioral and toxic effects of cocaine. We have used the cocaine congener [^{3}H]WIN 35,428 ([^{3}H]CFT) to label the dopamine transporter in the human striatum from cocaine overdose deaths. We have determined that [^{3}H]WIN 35,428 recognizes multiple sites in human putamen membranes with KD values of 3.5 nM (BMAX = 13.5 pmol/g tissue) and 80 nM (BMAX = 197.2 pmols/g tissue). The number of [^{3}H]WIN 35,428 binding sites in putamen membranes from cocaine overdose deaths were significantly elevated with the highest densities seen in subjects with known histories of chronic cocaine abuse. In contrast to these findings, we observed no significant elevation in the densities of [^{3}H]WIN 35,428 binding sites in the excited delirium subgroup of cocaine overdose deaths. These observations agree with our previous estimates of striatal cocaine recognition sites in autoradiographic studies with the potent cocaine analog [^{125}I]RTI-55. The altered densities of the cocaine recognition site detected by [^{3}H]WIN 35,428 in the human putamen were correlated with the numbers of [^{125}I]RTI-55 binding sites determined in parallel binding assays. Taken together, these observations suggest that chronic cocaine exposure may regulate dopamine transporter densities in the human brain (Supported by DA06227).

DRUGS OF ABUSE: COCAINE—GLUTAMATE

753.1

DIFFERENTIAL EFFECTS OF A NITRIC OXIDE (NO) SYNTHASE INHIBITOR ON COCAINE-INDUCED TOXICITIES AND ON THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE. M.A. Napolitano*, K.M. Kantak and Y. Itzhak, Dept. Psychol., Boston Univ., Boston, MA 02215 and Dept. Biochem. and Molec. Biol., Univ. of Miami Sch. Med., Miami, FL 33101.

Activation of the N-methyl-D-aspartate (NMDA) receptor increases the synthesis of NO, and blockade of the enzyme NO synthase provides protection against NMDA-mediated glutamate neurotoxicities. Since this neuroprotective effect is similar to that produced by the noncompetitive NMDA antagonist MK-801, which also protects against cocaine-induced toxicities, the effects of the NO synthase inhibitor N$^{\omega}$-nitro-L-arginine methyl ester (L-NAME) on cocaine-induced toxicities in mice and on the discriminative stimulus (DS) effects of cocaine in rats were examined. Repeated administration of cocaine (45 mg/kg/day, i.p., 7 days) in Swiss Webster mice induced a progressive increase in the convulsive response to the drug, and augmentation in lethality rate. The increase in convulsive response and lethality were completely blocked by 1 hr pretreatment with L-NAME (100 mg/kg/day, i.p.). Cocaine (0.1-17.8 mg/kg, i.p.) engendered dose-related increases in cocaine-appropriate responding in rats trained to discriminate 10 mg/kg cocaine from saline. In substitution tests, L-NAME alone (3-100 mg/kg, i.p.), administered either 15 min or 1 hr prior to the session, engendered primarily saline-appropriate responding. In contrast, following pretreatment with L-NAME (100 mg/kg) 1 hr prior to cocaine, full substitution (>90%) for the 10 mg/kg training dose was observed with doses as low as 1 mg/kg cocaine. These data demonstrate a marked potentiation of the DS effects of low to intermediate doses of cocaine by an acute injection of L-NAME and a marked blockade of the toxic effects of a high dose of cocaine by repeated injections of L-NAME. Supported partially by DA07589 to Y.I.

753.2

L-NAME AND MK-801 BLOCK SENSITIZATION TO THE LOCOMOTOR-STIMULATING EFFECT OF COCAINE. C.M. Pudiak* & M.A. Bozarth. *Department of Psychology, University at Buffalo, Buffalo, NY 14260-4110.*

Molecular mechanisms that may be involved in the development of cocaine sensitization were examined using an animal model of behavioral sensitization. Several laboratories have reported that the noncompetitive NMDA antagonist MK-801 can block the behavioral sensitization to apomorphine and d-amphetamine after repeated administration. NMDA receptor activation increases the conversion of L-arginine to nitric oxide via nitric oxide synthase. The nitric oxide synthase inhibitor Nω-nitro-L-arginine (L-NAME) was used to determine if nitric oxide is also involved in sensitization to the locomotor-stimulating effect of cocaine.

Male, Long-Evans rats were tested in locomotor activity chambers daily for 90-min sessions. Each animal received two daily injections and was tested for 21 consecutive days. All animals received a 30-min pretreatment of either physiological saline (1 mg/kg, i.p.), MK-801 (0.2 mg/kg, i.p.), or L-NAME (30 mg/kg, i.p.). A second injection of either saline or cocaine hydrochloride (10 mg/kg, i.p.) was administered immediately prior to testing. Forty-eight hours after the last injections, all animals were injected with cocaine (10 mg/kg, i.p.) and tested for behavioral sensitization.

Animals pretreated with MK-801 showed greater behavioral activation during the first 6 days than those injected with cocaine alone. Subjects pretreated with L-NAME showed less locomotor stimulation than those receiving cocaine throughout the 21-day period. Animals pretreated with MK-801 or L-NAME failed to show sensitization to cocaine, while the saline-pretreated group showed sensitization to the cocaine injection administered 48 hrs after termination of the 21-day period. Despite the fact that MK-801 and L-NAME had opposite effects on locomotor activation following acute cocaine, they both blocked behavioral sensitization resulting from chronic cocaine administration. These data suggest that both NMDA receptor activation and increased release of nitric oxide may be involved in the development of sensitization to cocaine.

(Supported by DA2285 from the National Institute on Drug Abuse.)

753.3

DIFFERENTIAL EFFECT OF CHRONIC COCAINE TREATMENT ON APOMORPHINE AND MK-801 INDUCED BEHAVIORS: FUNCTION OF TIME AFTER WITHDRAWAL. A. Hitri, M. Stambuk and S.I. Deutsch NIDA Research and Psychiatry Serv. DVAMC, Washington DC 20422

The cocaine abstinence phenomenon is a complex process which has only recently been associated with symptoms that emerge at specific times after withdrawal. In this study we investigated the delayed behavioral effects of cocaine treatment, by monitoring the apomorphine (APO) and MK-801 induced behaviors as a function of time following withdrawal. Mice were treated with either cocaine (10mg/kg/2xday) or saline for 7 days. At weeks 1,2,3,4,5,6 following the last injection, the cocaine and saline treated mice were divided into four groups (each n=8) and challenged with one of the following: nothing, APO (1mg/kg), MK-801(1mg/kg) and saline; locomotor behaviors were monitored in a Digiscan activity monitor. While exerting no effect on unstimulated or saline stimulated behaviors, cocaine exhibited a continuous enhancement (50% week 1 through 6) in APO induced locomotion. In contrast, the cocaine treated mice, challenged with MK-801showed a significant time delay in the onset of cocaine's effect [$F(1,6)=2.9, p<0.01$); the reduction of 41% ($p<0.05$) not present prior to week 4 persisted to the sixth week of withdrawal. Cocaine affected differentially only the stereotypic components of MK-801 and APO induced locomotor behaviors.

753.4

MK-801 COADMINISTRATION PREVENTS SENSITIZATION BUT DOES NOT ALTER THE ACUTE EFFECTS OF AMPHETAMINE OR COCAINE ON LOCOMOTOR ACTIVITY OR DOPAMINE RELEASE IN THE NUCLEUS ACCUMBENS. M.E. Wolf* and C.J. Xue. Dept. of Neuroscience, University of Health Sciences/The Chicago Medical School, North Chicago, IL 60064.

Behavioral sensitization refers to the progressive enhancement of the locomotor stimulatory properties of drugs such as amphetamine (AMP), cocaine (COC), or morphine (MOR) during their repeated administration. Considerable evidence indicates that sensitization is related to changes in the function of mesolimbic dopamine (DA) neurons. However, recent work has shown that the development of sensitization to AMP, COC or MOR is prevented by coadministration of N-methyl-D-aspartate (NMDA) antagonists such as MK-801, suggesting that NMDA receptor stimulation is required for the long-term neuronal changes responsible for the development and persistance of sensitization. Other recent studies have suggested that NMDA antagonists also attenuate the acute locomotor stimulatory effects of AMP or COC, raising the possibility that this effect is responsible for the prevention of sensitization during the repeated administration of these stimulants. To examine this issue further, *in vivo* microdialysis in behaving rats was used to evaluate the effects of acute AMP (2.5 mg/kg) or COC (15 mg/kg) on locomotor activity and DA release in the nucleus accumbens. Pretreatment with MK-801 (0.1 mg/kg; 30 min before AMP or COC) did not alter behavioral or neurochemical responses to either stimulant. In contrast, pretreatment with this dose of MK-801 did prevent the development of behavioral sensitization during the repeated administration of AMP or COC. We conclude that MK-801 prevents behavioral sensitization by interfering with an NMDA receptor-dependent step subsequent to, and independent of, the acute effects of psychomotor stimulants on locomotor activity or DA release in the nucleus accumbens. Supported by USPHS Grant DA 07735.

753.5

REPEATED ADMINISTRATION OF d-AMPHETAMINE OR COCAINE *ATTENUATES THE EXCITATORY EFFECTS* OF GLUTAMATE ON RAT NUCLEUS ACCUMBENS NEURONS. X.-T. Hu*, M.E. Wolf and F.J. White. Dept. of Neuroscience, UHS/The Chicago Med. Sch., North Chicago, IL 60064.

Repeated administration of amphetamine (AMPH) and cocaine (COC) to rats causes sensitization to their locomotor stimulating effects, a phenomenon which involves alterations in the responsiveness of the mesoaccumbens dopamine system. However, recent studies have demonstrated that the development of behavioral sensitization is prevented by NMDA receptor antagonists, suggesting an essential role for excitatory amino acids (EAA) in this process. Yet, little is known regarding alterations in EAA systems following repeated administration of psychomotor stimulants. In the present study, extracellular single cell recording and microiontophoresis were used to investigate the possibility that repeated administration (5 daily i.p. injections) of AMPH (5 mg/kg) or COC (15 mg/kg) might alter the excitatory effects of glutamate (GLU) on neurons within the rat nucleus accumbens (NAc) following a 3 day withdrawal period. During 30 sec ejection pulses, GLU (1-128 nA) caused a current-dependent increase in the firing of NAc neurons. Continuous high current (128-256 nA) ejection of GLU drove NAc cells into a state of apparent depolarization block (DB), in which activity gradually ceased, concurrently with decreases in action potential amplitude. All cells were brought out of apparent DB by a sufficient pause (5-20 min) in GLU application. In rats pretreated with either AMPH or COC, GLU-induced excitation was significantly reduced (rightward shift in the current-response curve) as compared to cells recorded in control rats. Moreover, the duration of ejection required to induce apparent DB was significantly increased in AMPH-treated rats. This effect was not as apparent in COC-treated rats. These results suggest that behavioral sensitization following AMPH or COC may be related to decreased sensitivity of NAc neurons to GLU. Supported by USPHS Grants DA 04093 (FJW) and DA 07735 (MEW).

753.6

EXOGENOUS GANGLIOSIDE GM1 PROTECTS AGAINST THE CYTOTOXIC EFFECTS OF THE MAJOR METABOLITE OF COCAINE, BENZOYLECGONINE. Y. Lin and K. C. Leskawa*. Dept. of Anatomical Sciences and Neurobiology, University of Louisville, Louisville, KY 40292.

Upon exposure to cocaine during gestation the major metabolite, benzoylecgonine, accumulates in brains of developing fetuses to an extent far greater than that measured in the brains of the maternal dams. We have recently explored the effects of benzoylecgonine using NG108-15 and C6 cells as in vitro models of neurons and glia, and previously reported that benzoylecgonine is cytotoxic to both cell types at low concentrations (below 20 μM). Early morphological responses were characterized by a retraction of cellular processes within 15 minutes (Lin and Leskawa, Soc. Neurosci., 1992).

Exogenous gangliosides have been shown to promote neuritogenesis of cells in culture and to protect against damage in vivo. For these reasons, the interactions between exogenous gangliosides and benzoylecgonine were examined. NG108-15 and C6 cells were cultured in media containing ganglioside GM1 for 24 hr. Benzoylecgonine was added (20 μM) and the cultures examined 24 hr later. Prior exposure to exogenous GM1 significantly protected against the cytotoxicity of benzoylecgonine in both cell types, as determined by the activity of mitochondrial dehydrogenases. In addition, pretreatment with exogenous ganglioside GM1 prevented the withdrawal of processes by both cell types. In summary, the major metabolite of cocaine, benzoylecgonine, is cytotoxic to both neuronal and glial cells in culture and pretreatment with GM1 reduces this cytotoxicity.

753.7

DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE: INFLUENCE OF TRAINING DOSE ON SUBSTITUTION BY DOPAMINE AGONISTS AND N-METHYL-D-ASPARTATE (NMDA) ANTAGONISTS. K.M. Kantak*, M.A. Napolitano and R.D. Spealman, Boston Univ., Boston MA 02215 and New England Regional Primate Research Center., Southborough, MA 01772.

The effects of the D_1 agonist SKF 77434, the D_2 agonist (+)-PHNO, the D_1/D_2 agonist apomorphine, the indirect dopamine agonists GBR 12909 and (+)-amphetamine, the NMDA receptor blocker NPC 17742, and the NMDA-associated ion channel blockers dizocilpine, phencyclidine and $MgCl_2$ were studied in rats trained to discriminate cocaine from saline. Discriminative control was maintained by either a high (10 mg/kg) or a low (2 mg/kg) training dose. The cocaine dose-response functions determined under the low training dose conditions were shifted in parallel to the left compared to those determined under the high training dose conditions. In substitution tests under the high training dose conditions, SKF 77434, (+)-PHNO, GBR 12909 and (+)-amphetamine engendered full (>90%) substitution for cocaine, whereas apomorphine, NPC 17742, dizocilpine, phencyclidine and $MgCl_2$ engendered primarily saline-appropriate responding. Under the low training dose conditions, full substitution for cocaine and nonparallel leftward shifts in the dose-response functions were observed with SKF 77434, GBR 12909 and (+)-amphetamine. In contrast, partial (65%) substitution was observed with (+)-PHNO. Full or partial (75-96%) substitution also was observed with apomorphine, dizocilpine, phencyclidine and $MgCl_2$, but not with NPC 17742. The results support the view that training dose can be an important determinant of drug substitution profiles in cocaine-discrimination studies. In particular, they show that NMDA-associated ion channel blockers reproduce the discriminative stimulus effects of cocaine only when discriminative control is maintained by a low dose of cocaine. In contrast, the cocaine-like stimulus effects of a D_2 agonist were amplified when discriminative control was maintained by a higher dose of cocaine.

753.8

INVOLVEMENT OF EXCITATORY AMINO ACIDS IN THE VTA IN BEHAVIORAL SENSITIZATION TO COCAINE. Peter W. Kalivas*, Patricia Duffy, Joy Alesdatter. Department of Veterinary and Comparative Anatomy, Pharmacology and Physiology, College of Medicine, Washington State University, Pullman, WA 99164-6520.

An action by psychostimulants in the ventral tegmental area (VTA) has been implicated in the initiation of behavioral sensitization. Behavioral sensitization is associated with enhanced mesoaccumbens dopamine transmission and a potent excitatory influence on dopamine cells in the VTA is provided by the excitatory amino acid (EAA) projection from the prefrontal cortex. In the present study, the microinjection of antagonists to the NMDA receptor subtype, MK-801 or CPP, into the VTA prevented the development of behavioral sensitization to systemic cocaine administration. The blockade was dose-dependent (0.01 to 1.0 nmol) and was not produced by MK-801 microinjection into the nucleus accumbens. Previous studies have shown that the microinjection of D_1 receptor antagonists into the VTA also prevent the development of behavioral sensitization to systemic psychostimulants. The fact that D_1 receptors are located on afferent terminals in the VTA poses the possibility that D_1 receptors may regulate the release of EAA's in the VTA. To evaluate this, ascending concentrations of the D_1 agonist, SKF-82958, were administered through a dialysis probe in the VTA. In a portion of the rats, D_1 receptor stimulation produced a marked increase in extracellular glutamate in the VTA. Taken together, these data support a role for EAA transmission in the VTA in behavioral sensitization to cocaine.

753.9

EFFECTS OF NON NMDA GLUTAMATE ANTAGONISTS ON COCAINE-INCREASED DOPAMINE LEVELS IN THE RAT NUCLEUS ACCUMBENS DURING IN VIVO MICRODIALYSIS S.Tacconi, L.Romanelli, P.Beardsley, F.Crespi, A.Reggiani* and D.G.Trist. Glaxo Research Lab. Via Fleming 4, 37100 Verona, ITALY.

Stimulant drugs are thought to exert their action via dopamine (DA)-mediated transmission localized especially in limbic system structures such as the Nucleus Accumbens (NAcc). Evidence has been collected suggesting that DA-ergic transmission in the rat NAcc is modulated by glutamate (Glu) receptors (e.g., antagonists to AMPA/kainate receptors inhibit locomotor stimulation induced by amphetamine when injected into the NAcc). The aim of the present work is to investigate the action of CNQX (AMPA/kainate antagonist) on basal and cocaine increased DA levels in rat NAcc in vivo.

Male Sprague-Dawley rats were implanted in left NAcc with a 2 mm concentric design microdialysis probe; outflow was connected to an on-line, HPLC/electrochemical detector for quantitative determination of DA, DOPAC, HVA and 5HIAA. Cocaine perfused through the probe (10-6M, 10-5M, 10-4M) dose dependently increased DA levels with no significative effects on DOPAC, HVA, or 5HIAA levels. CNQX 10-5 M administered via the probe before and during the cocaine challenge did not modify either basal DA release or cocaine stimulated DA levels. These results suggest that DA basal tone in rat NAcc is not under tonical AMPA/kainate receptor control and that AMPA/kainate receptor antagonism does not modify DA levels elevated by a DA-transporter blocker such as cocaine. From these results the efficacy of AMPA/kainate receptor antagonists in inhibiting central stimulant behavioural effects cannot be explained simply by an inactivation of AMPA/kainate receptors on DA-releasing terminals in Rat NAcc.

753.10

MODULATION OF LOCOMOTOR ACTIVITY BY NMDA RECEPTORS IN THE NUCLEUS ACCUMBENS CORE AND SHELL. L. Pulvirenti*, M. Kreifeldt, R. Berrier and G.F. Koob Dept. of Neuropharmacol., Scripps Res. Inst., La Jolla, Ca 92037 and *Un. of Rome "Tor Vergata", Rome, Italy

Two substructures have been recently identified within the rat nucleus accumbens (NAC) on the basis of immunocytochemical differences, namely the "core" and the "shell". The pattern of their neural connections and functional studies suggest that the core may be related to motor behavior, while the shell might be involved in limbic functions. A major contingent of neural afferents to the NAC appears to consist of glutamatergic fibers of putative allocortical origin and NAC NMDA receptors have been shown to modulate drug-induced psychomotor activation, possibly through a preferential interaction with dopamine function. We therefore tested whether NMDA neurotransmission in the core and shell regions differentially modulated spontaneous and cocaine-induced locomotion. Microinfusion of the competitive NMDA receptor antagonist aminophosphonovaleric acid (AP-5) (0.75-3.0 μg/side) within the NAC core but not shell region reduced cocaine-induced locomotion in a dose-dependent manner. In contrast, microinfusion of the same doses of AP-5 within the shell of naive rats caused a dose-dependent *increase* of spontaneous locomotion, while microinfusion within the core was ineffective. It is therefore possible that the locomotor behavior of naive or drug-activated animals is modulated by different subsets of glutamatergic afferents to discrete regions of the NAC.

753.11

IMPACT OF THE AMPA-SUBTYPE EXCITATORY AMINO ACID ANTAGONIST CNQX ON THE COCAINE-INDUCED INCREASE IN EXTRACELLULAR NUCLEUS ACCUMBENS DOPAMINE Angela Pap*, and C.W. Bradberry Yale Univ. Sch. Med., Dept. of Psychiatry and the West Haven VA Medical Center, West Haven, CT 06516.

Increasing attention is being given to the role of excitatory amino acids in regulating dopamine (DA) release. This includes studies of possible involvement in the acute and chronic actions of drugs of abuse. Because it has been shown that non-NMDA receptor subtype antagonists block the ability of DA uptake inhibitors to increase DA when coinfused through striatal microdialysis probes, we have examined the impact of local infusion of the AMPA receptor subtype antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) on the increases in extracellular DA in nucleus accumbens induced by systemic cocaine hydrochloride (15 mg/kg, i.p.). Pretreatment with 50 uM CNQX in the dialysis probe 10 min prior to, and continuing throughout systemic cocaine did not alter DA levels. However, 20 min pretreatment with 100 uM CNQX, continuing throughout, inhibited the cocaine-induced increase in extracellular DA in the nucleus accumbens. We are currently examining the impact of longer pretreatment times with lower concentrations of CNQX to more closely mimic what might occur if an antagonist permeable to the blood brain barrier were to be used clinically. Such a class of compounds could have potential applications in drug abuse therapy. This work was supported by DA 08073, the Yale-VA Center on Alcoholism, and a NARSAD Young Investigator Award to C.W.B.

753.12

EFFECT OF COCAINE ON BRAIN REGIONAL GLUTAMATE AND GABA. P.M. Kunko*, J.R. Pascua, K.P. McDowell, D.L. Tracey, and S.E. Robinson. Dept. of Pharmacology & Toxicology, Medical College of Virginia, VCU, Richmond, VA 23298-0613.

Excitatory amino acids have been implicated in certain behavioral effects of stimulants. The effect of cocaine HCl was studied on the turnover rate of glutamate (TR_{glu}), as well as that of the inhibitory amino acid GABA (TR_{GABA}), in the nucleus accumbens (N. Acc.), striatum (S), and parietal (PC) cortex of male Sprague-Dawley rats. Rats were infused via the tail vein for 6 min with uniformly labeled ^{13}C-D-glucose (75 μmol/kg/min) following intraperitoneal injection of either cocaine, CFT, or physiological saline and euthanized by focussed microwave irradiation (1.3 sec, 10 kW) immediately at the end of the infusion. Brains were rapidly dissected on ice and stored at -70°C until analysis. TR_{glu} and TR_{GABA} were calculated using a gas chromatographic/mass fragmentographic technique (Wood et al, Neuropharmacology 27: 669, 1988). Neither glutamate nor GABA content were affected by cocaine in any brain region studied. TR_{glu} was significantly increased 30 min after injection of 15 and 30, but not 5, mg/kg of cocaine HCl. TR_{glu} was not affected in the striatum. On the other hand, all 3 doses of cocaine reduced TR_{glu} in the PC. There was also a strong trend for a reduction in TR_{GABA} in the PC 30 min after cocaine. No changes in TR_{GABA} were observed in any other brain region studied. Because there is no consistent cocaine effect on TR_{glu} or TR_{GABA} across brain regions, these changes likely do not represent a direct effect of cocaine on glutamatergic or GABAergic neurons. (Supported by DA04746, DA05274, and DA07027).

DRUGS OF ABUSE: COCAINE—LOCOMOTOR

754.1

INTERACTIONS BETWEEN CAFFEINE AND COCAINE IN TESTS OF MOTOR ACTIVITY: ROLE OF ADENOSINE A2 RECEPTORS. Steven Snow* and Susan Schenk, Texas A&M Univ., Psychol. Dept., College Station, TX, 77843.

Horizontal activity was measured in rats that were treated with an acute injection of caffeine (0.0, 10.0, 20.0 or 40.0 mg/kg), cocaine (0.0, 5.0, 10.0 or 20.0 mg/kg) or their combination. Both drugs increase horizontal activity in a dose/dependent fashion. The combination of drugs produced an additive effect, with combinations of low doses of each drug producing greater effects. An increase in motor activity could also be produced by administration of the specific adenosine A2 antagonist, DMPX and the caffeine-induced increase in activity was antagonized by the adenosine A2 agonist DMPA.In contrast, the ability for cocaine to increase motor activity was unaffected by administration of the A2 agonist although a wealth of data from other laboratories have indicated that antagonism of mesolimbic dopamine decreases the ability for cocaine to induce this behavioral effect Therefore, it appears that although caffeine and cocaine both produce horizontal activity, this activity is mediated via the activation of distinct neurochemical systems. The additive effects of the two drugs implies that these parallel systems converge at some point so that the final behavioral output of the two drugs is mediated via a common pathway.

754.2

ELECTRICAL KINDLING OF THE MEDIAL PREFRONTAL CORTEX SENSITIZES RATS TO COCAINE'S MOTOR ACTIVATING EFFECTS. Susan Schenk* and Steven Snow, Texas A&M Univer., Dept. Psychol., College Station, TX, 77843.

Rats were implanted with stimulating electrodes in either the medial prefrontal cortex (PFC) or hippocampus. After 35 daily stimulation sessions, stage 5 seizures were elicited by stimulation of either site. A 14 day waiting period followed to allow the immediate effects of the stimulation to subside. The motor activating effects of cocaine (0.0, 5.0 or 10.0 mg/kg, IP) were then assessed for PFC kindled, hippocampus kindled and respective sham control rats. Rats from all conditions showed dose/dependent increases in horizontal activity. PFC and Hippocampus shams were not significantly different from each other on this measure. Hippocampus shams and kindled rats were also not different. However, the PFC kindled rats were more sensitive to cocaine than either the hippocampus kindled rats or the sham controls. For these rats, the dose/response curve for cocaine's motor activating effects was shifted to the left. Thus, kindling of the PFC but not the hippocampus is sufficient to sensitize rats to cocaine's behavioral effects.

754.3

DIFFERENTIAL EFFECTS OF INTRAVENOUS AND INTRAPERITONEAL ROUTES OF ADMINISTRATION ON THE REWARDING AND STIMULANT PROPERTIES OF COCAINE. L.E. O'Dell*, T. Khroyan, E. Martinez and J.L. Neisewander. Department of Psychology, Arizona State University, Tempe, AZ 85287-1104.

Dose-dependent differences in the rewarding and stimulant properties of cocaine administered IV (0, 0.3, 1, and 3 mg/kg) and IP (0, 10, 20, and 40 mg/kg) were compared. The rewarding properties were assessed using conditioned place preference (CPP). Rats received six 40-min exposures to a conditioning compartment immediately following injections, and six exposures to a distinctly different compartment without injection on alternating days. They were then allowed free access to both compartments simultaneously for 15 min to assess CPP. Both routes of administration produced CPP at the two highest doses. To assess the stimulant properties of cocaine, locomotor activity was measured each day during conditioning. Stereotypy was also measured on the first and last days. Acute administration of cocaine IV did not produce an increase in locomotor activity or stereotypy at any dose, nor were there any changes in these behaviors following repeated administrations. In contrast, acute IP administration of cocaine produced a slight increase in locomotor activity in animals injected with 10 mg/kg. Following repeated IP administrations of cocaine, there was no sensitization to locomotor activity, however, sensitization to stereotyped headbobbing was evident at the two highest doses. This sensitization response was also evident in animals challenged with cocaine in the noninjection compartment, indicating that it involves context-independent mechanisms. Furthermore, the results suggest that at doses that produce CPP, sensitization occurs in animals receiving IP injections, but not in animals receiving IV injections. (Supported by USPHS grant DA07730 and an ASU FGIA).

754.4

SUPPRESSION OF COCAINE-INDUCED LOCOMOTION BY IMMUNIZATION WITH A NOVEL COCAINE CONJUGATE. R. Carrera*[1], J.A. Ashley[2], P.M. Wirsching[2], K.D. Janda[2], and G.F. Koob[1]. [1]Dept. of Neuropharmacology, [2]Dept. of Molecular Biology and Chemistry, The Scripps Research Institute, La Jolla, CA 92037.

The existing psychopharmacological medications have been largely unsuccessful in treating cocaine abuse. New immunotherapeutic techniques offer an attractive strategy for treating this addictive disorder. The effect of immunization with a cocaine conjugate on acute cocaine-induced locomotor activity was tested. Male Wistar rats were tested in photocell cages after i.p. administration of cocaine-HCl (15mg/kg) to determine pre-immunization drug response (baseline). Experimental animals were immunized i.p. 3 days later with a cocaine analogue covalently linked to a carrier protein keyhole limpet hemocyanin (KLH) in an emulsion with an adjuvant (RIBI). Control animals were vaccinated with a similar emulsion containing KLH solution only. This treatment was followed by boosts at 21 and 35 days. Serum antibodies to the cocaine analogue were assayed by ELISA 10 days after each boost. When sufficient titers were achieved, the rats were challenged with systemic cocaine and their locomotor responses were again measured. Compared to baseline, experimental rats as a group showed a 42% decrease in photocell beam breaks whereas controls showed an increase of 19%. In the ambulatory measure (crossovers), there was a 42% decrease in the experimental group and a 30% increase in the control group compared to their respective baseline values. A progressive decrease in both measures was seen in vaccinated animals upon 3 subsequent challenges. The maximum decrease was observed at the time of the last challenge, 51% decrease in beam breaks and 63% in crossovers compared to baseline. Differences in locomotion between groups were significant across challenges ($p<0.02$). Although the exact physiology of the observed suppression remains to be elucidated, these results suggest that immunopharmacotherapy may be a promising treatment for cocaine abuse.

754.5

COCAINE LOCOMOTOR SENSITIZATION MECHANISMS: A NEW PARADIGM TO ASSESS RESPONSE CHANGES TO DRUG AND NON DRUG CONTEXTUAL CUES. Ernest N. Damianopoulos* and Robert J. Carey. Research and Development Service -151, VA Medical Center, Syracuse, NY 13210

Repeated cocaine administration can often lead to an enhancement of cocaine induced behavioral effects. The contribution to this phenomenon of cocaine conditioned and non-associative, non-specific prior treatment effects remains problematic. The present study was designed to assess and differentiate between associative and non-associative contributing factors to cocaine motoric sensitization. A unique test paradigm was employed in which two distinct test environments were used. In one test environment, the rats always received a non-drug test. In the second environment, the animals (Sprague-Dawley male rats) received either cocaine (10 or 20 mg/kg ip) or vehicle, depending on group assignment. Every other day, separate groups of rats received the non-drug tests followed by 10 or 20 cocaine or vehicle treatments. Across all drug treatment days and conditioning tests there were no statistical differences between cocaine and vehicle groups in the non-drug test environment. Thus, non-specific, non-asssociative response sensitization effects were not observed. Cocaine, however, had a marked dose related stimulatory effect on locomotor behavior in the drug test environment. This behavioral differentiation between test environments permitted an evaluation of the selectivity of treatment effects which modulate cocaine conditioned and unconditioned responses. With this methodolgy several classes of variables were studied including: (a) withdrawal interval; (b) stress hormones; (c) activation level; and (d) dopaminergic activity. Critically, withdrawal had selective effects on locomotor behavior which were manifested as a suppression of locomotion in the non drug test environment. This result points to aversive effects with cocaine withdrawal that are selective to context stimuli associated with non drug injection. Present findings have substantial implications for CPP paradigms as well as for cocaine abuse treatment issues.

754.6

EFFECT OF 5,7-DIHYDROXYTRYPTAMINE LESIONS ON COCAINE-INDUCED BEHAVIORAL ACTIVITY IN RATS. S.K. Sahni, D. Wirtshafter, J.M. Davis and J.I. Javaid*. Illinois State Psychiatric Institute, University of Illinois at Chicago, Chicago, IL 60612.

In order to examine the role of serotonergic function in cocaine-induced behavioral effects, rats were injected bilaterally into the lateral ventricles with 5,7-dihydroxytryptamine (5,7-DHT) or physiological saline (sham) following desmethylimipramine treatment. Animals were allowed to recover from surgery (7 to 10 days). Cocaine (10 mg/kg, i.p,) was administered to both groups once daily for 5 days; after two days of withdrawal, animals were injected with a 6th cocaine injection as a "challenge." Locomotor activity (horizontal activity) and hole pokes (verticle activity) were measured for one hour before and 2 hours after each injection in activity cages equipped with photocells. Although there were large interindividual variabilities in both behavioral responses, the animals with 5,7-DHT lesions consistently showed lower total horizontal activity and higher numbers of hole pokes than sham animals. Both groups showed a progressive enhancement ("behavioral sensitization") in these behaviors with repeated cocaine injections. The 5,7-DHT lesions consistently produced over 90 percent depletion of 5-HT whereas dopamine and norepinephrine levels were not altered in various areas of the brain examined. These results suggest that 5-HT containing neurons play an important role in cocaine-induced behavioral effects, although non-serotonergic mechanisms may be more important in behavioral sensitization with repeated cocaine administration.

754.7

DIFFERENTIAL EFFECTS OF COCAINE AND GBR-12935 ON LOCOMOTOR ACTIVITY AND STEREOTYPY IN TWO INBRED MOUSE STRAINS. B.K. Tolliver and J.M. Carney*. Department of Pharmacology, University of Kentucky College of Medicine, Lexington KY 40536.

Cocaine is known to interact with a number of macromolecular sites in the brain, including the transporters responsible for the neuronal reuptake of dopamine, norepinephrine, and serotonin. Mesocorticolimbic and nigrostriatal dopamine systems have been implicated in the locomotor stimulation and stereotypy produced by cocaine. GBR-12935 is a selective dopamine uptake inhibitor structurally unrelated to cocaine. The current study compares the acute and long-term effects of GBR-12935 and cocaine on locomotor activity and stereotypy in two genetically distinct strains of mice. Cocaine stimulated locomotor activity maximally in both the DBA/2J and C57BL/6J strains at 32 mg/kg, whereas GBR-induced locomotor stimulation peaked at 10 mg/kg in both strains. Interstrain differences were found in locomotor responsiveness to both acute and repeated cocaine but not to GBR-12935. A single injection of cocaine stimulated locomotion to a greater degree in DBA/2J mice (2470 +/- 216 photocell counts/hr) than in C57BL/6J mice (1481 +/- 92 counts/hr). In contrast, GBR-12935 elevated locomotion to a similar extent in DBA/2J (1594 +/- 94 counts/hr) and C57BL/6J mice (1867 +/- 68 counts/hr). The stimulant effects of cocaine diminished to near control levels in DBA/2J mice upon repeated injections, whereas cocaine continued to stimulate C57BL/6J mice consistently throughout the 7-day test period. Locomotor stimulation by GBR-12935 remained consistent in both strains with repeated injections. Cocaine and GBR-12935 also differed in their abilities to induce stereotypy upon repeated exposures. Cocaine induced stereotypy in DBA/2J mice after 4 days (11.33 +/- 4.40 stereotypies observed/hr) and 7 days (19.83 +/- 4.39) of repeated injections. Cocaine induced no stereotypies in C57BL/6J mice on any test day. No stereotypies were induced by GBR-12935 in either strain on any test day. Moreover, although sensitization developed to cocaine-induced stereotypy in DBA/2J with repeated injections, no cross-sensitization between cocaine and GBR-12935 was observed. These results demonstrate substantial differences in the behavioral effects of two dopamine uptake inhibitors. Furthermore, these results suggest that the behavioral effects of cocaine are not wholly attributable to dopamine uptake inhibition, and that other factors influencing cocaine-induced locomotion and stereotypy are under genetic control. (Supported by NIDA grants DA-07219 and DA-05312)

754.8

PREEXPOSURE TO THE NEUROTENSIN ANTAGONIST SR 48692 RETARDS THE DEVELOPMENT OF SENSITIZATION TO THE LOCOMOTOR ACTIVATING EFFECTS OF COCAINE. B.A. Horger*, J.D. Elsworth, J.R. Taylor, R.H. Roth. Departments of Pharmacology and Psychiatry, Yale University School of Medicine, New Haven, CT 06510.

The locomotor activating effects of neurotensin (NT) administered directly into the ventral tegmental area (VTA) have been shown to increase upon repeated exposures (Kalivas and Taylor, 1985; Elliot and Nemeroff, 1986; Kalivas and Duffy, 1990). Recently, we have obtained evidence that acute cocaine exposure in anesthetized rats increases extracellular levels of NT in the VTA (unpublished data). The present experiment assessed the role of NT in the development of sensitization to repeated exposures of cocaine using the new selective non-peptide bioavailable NT antagonist SR 48692 (Gully et al., 1993). Male rats received 5 daily injections of SR 48692 (80 µg/kg, IP) or vehicle in the home cage. Seven days after the last preexposure injection subjects received the first of 5 cocaine (15 mg/kg, IP) injections. Cocaine-induced locomotor activity was then assessed using automated activity monitors. No difference in activity counts was observed between SR 48692- and vehicle-preexposed subjects following the initial cocaine exposure. On cocaine challenge days 2 through 5, activity counts in the vehicle-preexposed subjects were significantly augmented relative to day 1 activity levels. Activity counts in the SR 48692-preexposed subjects were not significantly elevated above that observed on day 1 until the fourth cocaine exposure. It was not until the fifth cocaine challenge that activity counts in the SR 48692-preexposed subjects approached levels comparable to that of the vehicle-preexposed controls. Delaying cocaine testing by one week reduced the ability of SR 48692-preexposure to retard the development of sensitization suggesting that this effect is relatively long lasting but not permanent. These data suggest a role for NT in the development of cocaine sensitization. This project was funded in part by a USPHS grant-MH 14092. SR 48692 was generously donated by Sanofi Recherche.

754.9

PREDICTIVE VALIDITY OF LOCOMOTOR ACTIVITY ANALYSIS FOR ACTION OF DOPAMINE RECEPTOR ANTAGONISTS ON THE COCAINE DISCRIMINATIVE STIMULUS. M.J. Forster*, M. L. Beckley, D. A. Lytle and M.W. Emmett-Oglesby. Dept. Pharmacology, Texas College of Osteopathic Medicine, Fort Worth, TX 76107.

The D_1/D_2 receptor antagonist flupentixol, the D_1 antagonist, SCH 23390, and the D_2 antagonist, sulpiride were tested for their ability to antagonize spontaneous and cocaine-induced locomotion of mice using a Digiscan apparatus. A ratio of the potency for reduction of cocaine-induced locomotor stimulation (AD_{50}) versus potency for reduction of spontaneous activity (ID_{50}) was calculated for each drug. These ratios were compared with the ability of each compound to produce a shift in the cumulative dose-effect for substitution of cocaine in a group of rats trained for cocaine discrimination. Flupentixol and SCH 23390 had ID_{50}/AD_{50} ratios of 16.3, and 2.3, respectively, whereas sulpiride had a ratio approaching unity. In discrimination studies, sulpiride had only a marginal influence upon the cocaine stimulus, whereas flupentixol and SCH 23390 produced a 2-3-fold shift to the right in the cocaine dose-effect curve. These findings suggest that low ID_{50}/AD_{50} ratios may identify compounds with low efficacy for modification of the discriminative stimulus produced by cocaine. [Supported by U.S.D.H.H.S.-P.H.S. grant RO1-DA-4137 and contract NO1-DA-2-9305.]

754.10

SCH 39166, A D1 RECEPTOR ANTAGONIST, SELECTIVELY BLOCKED A COCAINE-INDUCED INCREASE IN SPONTANEOUS LOCOMOTOR ACTIVITY IN MICE DANIEL T. MCHUGH AND VICKI L. COFFIN* *Schering-Plough Res. Inst., Kenilworth, NJ 07033*

The effects of a selective D1 receptor antagonist SCH 39166, and a selective D2 receptor antagonist raclopride, were studied on cocaine-induced locomotor stimulation in mice. Male CF-1 mice were orally pretreated with a dose of SCH 39166, raclopride or vehicle, followed 20 min later with a subcutaneous dose of cocaine or vehicle. Spontaneous locomotor activity (SLMA) was measured 10 min later for an 8 min period.

SCH 39166 or raclopride, when given alone, produced a dose-dependent decrease in the SLMA. The minimum effective dose (MED) for both drugs was 0.3 mg/kg. Cocaine, when given alone, produced a dose-dependent increase in SLMA with an MED of 1.0 mg/kg.

SCH 39166 selectively blocked the cocaine-induced increase in SLMA at all doses of cocaine tested. The MED of SCH 39166 inhibition of cocaine-induced increase in SLMA was between 0.03 mg/kg to 0.1 mg/kg, depending on the dose of cocaine used (3-30 mg/kg). These doses were 3 to 10 fold lower than the MED of SCH 39166 (0.3 mg/kg) required to decrease SLMA when given alone.

In contrast, raclopride did not affect cocaine-induced increases in SLMA until 1 to 10 mg/kg, depending on the dose of cocaine used. These doses were 3 to 30 fold higher than the MED of raclopride (0.3 mg/kg) required to decrease SLMA when given alone.

In summary, SCH 39166, a D1 receptor antagonist, but not raclopride, a D2 receptor antagonist, selectively blocked the psychomotor stimulant effect of cocaine. These studies suggest that the increase in SLMA induced by cocaine is predominately mediated by the D1 receptor system.

754.11

LOCOMOTOR RESPONSE TO NOVELTY DOES NOT PREDICT COCAINE PLACE-PREFERENCE CONDITIONING IN RATS. W. Gong*, D. B. Neill, and J. B. Justice, Jr. Depts. of Psychology and Chemistry, Emory University, Atlanta, GA 30322.

Previous work has indicated that rats with a high spontaneous locomotor response to a novel environment (High Responders) more readily acquire intravenous self-administration of amphetamine and show a greater locomotor response to amphetamine and cocaine. We examined whether High Responders would more readily develop place preference conditioning with cocaine. Rats were screened for their locomotor response to novelty by placing them in a Digiscan photocell activity device for 30 min. Rats with ambulation n the upper 1/3 of the distribution were selected as High Responders and rats with ambulation in the lower 1/3 of the distribution were selected as Low Responders. All rats were subsequently conditioned in place-preference chambers. Using a balanced design, I.P. injections of 2.5 or 5.0 mg/kg cocaine HCL or saline were paired twice each with one of two chambers. Both High Responder and Low Responder groups developed significant conditioning at 5.0 but not 2.5 mg/kg. No group difference was observed. These results show that, as measured by the place-preference method, these two groups of rats do not differ in their responses to the rewarding effect of cocaine.

DRUGS OF ABUSE: COCAINE—MICRODIALYSIS

755.1

CHARACTERIZATION OF DOPAMINE RELEASE USING QUANTITATIVE MICRODIALYSIS. R.J. Olson-Cosford* and J.B. Justice, Jr., Dept. of Chemistry, Emory University, Atlanta, GA 30322.

Quantitative microdialysis may be performed under transient conditions using a method based on the point of no net flux method for steady state (Olson and Justice, Anal. Chem., 65, 1017-1022, 1993).Extracellular analyte concentration and in vivo probe recovery are determined simultaneously throughout the experiment. Previous work demonstrated that inhibition of uptake results in a decrease of in vivo probe recovery which is independent of changes in extracellular dopamine (DA_{ext}) levels.In this study, we examined the effect of blocking and increasing DA release on in vivo probe recovery.

Three groups of rats (n=3 per group) were perfused at 0.6 µl/min through 2mm probes implanted in the n.acc. with either 0, 5 or 10 nM dopamine (DA_{in}).Dialysate DA was measured at regular intervals. Following baseline, 1 µM tetrodotoxin (TTX) was included in the perfusate for a period of 30 minutes, following which, perfusion with the original solutions continued for 1 hour. Data obtained from the three groups were combined at each time point and used with linear regression to determine the DA_{ext} and in vivo probe recovery for each sampled interval.TTX administration resulted in a decrease of DA_{ext} from 4.5 ± 0.3 nM to 0.1 ± 0.3 nM. Recoveries obtained during baseline and TTX were not significantly different (37 ± 6 % and 40 ± 4% respectively).Thus, while inhibition of uptake resulted in decreased recovery, inhibition of release had no effect on recovery.

The experiment was also conducted under conditions of increased release (60 mM K^+ for 60 min) with four groups of rats receiving 0, 5, 10 and 20 nM DA_{in} (n=5 per group). During K^+, DA_{ext} increased from 4.9 ± 0.5 nM to 25.8 ± 0.3 nM. Recovery during baseline did not change during the period of physiological release (43 ± 3% versus 41± 1% at t=10, n.s.).However,following this period a decrease in recovery was observed which may be due to the onset of other physiological effects of prolonged K^+ stimulation. These results are consistent with previous work which demonstrated no change in recovery following DA release by haloperidol as well as theory which predicts that changes in zero order processes, such as release resulting from behavior or drug administration, will not affect recovery (Morrison et al., 57, 103-119, 1991).

755.2

DO THE FIBERS IN FASCICULUS RETROFLEXUS WHICH DEGENERATE FOLLOWING CONTINUOUS COCAINE CARRY NEGATIVE FEEDBACK FROM STRIATUM ONTO SUBSTANTIA NIGRA CELLS? A MICRIDIALYSIS STUDY. A. S. KEYS* AND G. D. ELLISON. Department of Psychology, UCLA, 405 Hilgard Ave., Los Angeles, CA 90024

In a study using silver-staining procedures, we recently reported that rats administered chronic amphetamine or cocaine showed a strong pattern of degenerating axons confined to lateral habenula and fasciculus retroflexus. Lesions of these same structures have been reported to markedly attenuate the suppression of SN cell firing induced by systemic methamphetamine, suggesting they mediate at least part of the negative feedback circuitry from post-synaptic dopamine receptors onto dopamine cell bodies.

In order to test for the possibility that cocaine-induced degeneration attenuates negative feedback onto these dopamine nuclei, rats were implanted with either slow-release cocaine or control pellets, given a recovery period of at least 14 days, and then dialysates from caudate were collected prior to and during local perfusion with the D1 agonist SKF38393. Dopamine levels in caudate were markedly reduced in the controls but not in the cocaine animals during SKF38393 perfusion, whereas changes in GABA did not differ between the two groups. This result indirectly suggests an alteration in the neural circuitry mediating negative feedback following continuous cocaine.

755.3

EFFECTS OF REPEATED COCAINE ON SUBSEQUENT COCAINE- AND AMPHETAMINE-INDUCED CHANGES IN EXTRACELLULAR DOPAMINE LEVELS IN THE MEDIAL PREFRONTAL CORTEX

Barbara A. Sorg* and Peter W. Kalivas. Department of Veterinary and Comparative Anatomy, Pharmacology and Physiology, Washington State University, Pullman, WA 99164-6520.

We have previously shown in cross-sensitization experiments that exposure to five daily footshock sessions or cocaine injections produces an apparent tolerance of medial prefrontal cortex (mPFC) extracellular dopamine levels to subsequent footshock stress or cocaine challenge administered one week later. The present study used a similar daily treatment schedule to determine the effects of daily cocaine on cocaine-or amphetamine-induced changes in mPFC extracellular dopamine concentrations by use of the *in vivo* dialysis technique. Rats were administered cocaine (15 mg/kg, i.p.) or saline (1 ml/kg, i.p.) once daily for five days, and one week later, either acute cocaine (15 mg/kg) or saline followed by amphetamine (1.75 mg/kg, i.p.) was given. Control rats pretreated with saline showed a maximum increase of 343% of baseline extracellular dopamine levels in the mPFC following the cocaine challenge. However, cocaine pretreated animals showed a significantly reduced response to cocaine (214% of baseline), indicating a tolerance of mPFC dopamine neurons to subsequent cocaine. Following acute amphetamine challenge, preliminary data demonstrated no significant differences between the increase in extracellular dopamine levels between saline or cocaine pretreated animals (saline = 225%; cocaine = 330% of baseline). Thus, exposure to daily cocaine produced an apparent tolerance of the mPFC dopamine response to a subsequent cocaine challenge, similar to previous findings from the cross-sensitization experiments. However, the lack of a difference between treatment groups following amphetamine challenge suggests that the tolerance effect to subsequent stimuli may depend on impulse flow of mesocortical dopamine neurons.

755.4

THE EFFECT OF NALOXONE ON COCAINE AND AMPHETAMINE-INDUCED INCREASE IN EXTRACELLULAR DOPAMINE AND LOCOMOTOR ACTIVITY

C.A. Schad*, J.B. Justice, Jr.[1], and S.G. Holtzman, Departments of Pharmacology and Chemistry[1], Emory University, Atlanta, Georgia, 30322.

Using *in vivo* microdialysis, this study looked at the effect of the opioid receptor antagonist naloxone on the increase in extracellular dopamine in the striatum (STR) and nucleus accumbens (NACC) along with locomotor activity induced by two psychomotor stimulants, cocaine and amphetamine. Microdialysis was performed on adult male rats (300-350g) that were pretreated with a subcutaneous injection of 5 mg/kg naloxone or saline followed by cumulative doses of IP cocaine (0,3,10,30,56 mg/kg) or SC d-amphetamine (0.0,0.1,0.4,1.6,6.4 mg/kg) at 30 minute intervals. The microdialysis samples were collected at ten minute intervals at a flow rate of 0.6 µl/min. The effect on extracellular DA levels was observed in the STR or NACC at the same time locomotor activity counts were being monitored. Preliminary microdialysis studies indicate that, naloxone significantly reduces the amphetamine-induced increase in DA release and locomotor activity (naloxone: n=4 in STR; n=4 in NACC; saline: n=3 in STR; n=4 in NACC), as previously reported (Hooks, et.al., Pharmacol. Biochem. and Behav., 42, 765-770, 1992). However, naloxone showed no significant effect on the cocaine-elicited DA or locomotor activity increase (naloxone: n=4 in STR; n=4 in NACC; saline: n=3 in STR; n=2 in NACC). These findings indicate that though both cocaine and amphetamine cause an increase in extracellular dopamine, their actions are differentially mediated through opioid receptors.

755.5

COMPARISON OF DOPAMINE MICRODIALYSIS THEORY AND EXPERIMENT,

P.M. Bungay[1], A.D. Smith, R. J. Olson-Cosford, P. Newton, J.B. Justice,Jr.*, Biomed. Eng. & Instrum. Prog., N.I.H[1]., Dept. of Chemistry, Emory Univ., Atlanta, GA 30322.

Microdialysis of neurotransmitters has produced experimental results which are markedly different from results obtained on metabolites and relatively inert solutes. The microdialysis modeling approach of Bungay et al. (Life Sci, 46, 105-119, 1990) was extended to incorporate the dopaminergic nerve terminal model of Justice et al. (J Neurosci Meth, 22, 239-252, 1988). The model predicts that uptake and metabolism, as well as diffusion, are important in determining the *in vivo* differences in microdialysis behavior. Illustrative simulations for basal conditions suggest DA is sampled from within 20 µm of the probe surface, while DOPAC and HVA are sampled from substantially further (500µm).

In comparisons with experimental microdialysis measurements, the model qualitatively reproduces the major features of responses to inhibition of DA uptake by cocaine administered i.p. or in probe perfusate, and inhibition of the enzymes COMT and MAO by perfusate tropolone and pargyline, respectively.

Inhibition of uptake by cocaine (20 mg.kg, i.p.) elevated extracellular DA levels while reducing *in vivo* probe recovery by up to 40%. This effect was reproduced by the mathematical model, as was an experimentally observed overshoot in the increase in extracellular DA in response to a step change in perfusate cocaine.

Inhibition of COMT by tropolone (100 µM) produced no detectable change in the measured extracellular DA level or probe recovery for DA in agreement with model predictions. The model further predicted a 25% decrease in recovery for DOPAC associated with blocking DOPAC conversion to HVA. The model also predicted that blocking MAO conversion of 3-MT to HVA would result in a 75% reduction in recovery for 3-MT.

Inhibition of MAO by pargyline (100 µM) increased the measured extracellular DA level without significantly altering probe recovery for DA. Similarly, the model predicted MAO inhibition would produce an increase in the extracellular DA and only a 10% decrease in probe recovery for DA. The results suggest ways in which the model and quantitative experimental techniques can be utilized together to improve the interpretation of microdialysis measurements in dopaminergic tissue.

755.6

THE EFFECT OF INHIBITION OF METABOLISM AND UPTAKE ON THE IN VIVO RECOVERY OF DOPAMINE USING QUANTITATIVE MICRODIALYSIS.

A.D. Smith* and J.B. Justice, Jr., Department of Chemistry, Emory University, Atlanta, Georgia, 30322.

The effects of clearance mechanisms on the in vivo probe recovery of dopamine (DA) in the nucleus accumbens were examined using the point of no net flux method. Clearance of DA from the extracellular space occurs via uptake and metabolism. To examine the effect of metabolism on recovery, the metabolism of DA to DOPAC and 3-MT was inhibited by the addition of pargyline or tropolone to the perfusate. The effect of uptake on DA recovery was examined by the addition of cocaine to the perfusate. Anesthetized rats were implanted with 20 gauge guide cannula in the nucleus accumbens. The night prior to the experiment a 2 mm probe was inserted and perfused with artificial cerebrospinal fluid (CSF) at 0.6 µl/min. On test day, the perfusate was changed to an aCSF solution containing either 100 µM tropolone (n=5), 100 µM pargyline (n=5), 1 µM cocaine (n=5), 20 µM cocaine (n=8) or normal aCSF (control; n=5) with 0, 25, 50 or 100 nM DA. Dialysate samples were collected for 1 hour at 15 minute intervals and frozen on dry ice. The perfusate was then randomly switched to one of the remaining DA concentrations. Dialysate samples were assayed by injecting 0.5 µl onto a smallbore HPLC. The extracellular conc. and the in vivo probe recovery were obtained by linear regression of the data. The conc. of DA increased with the addition of pargyline (27 nM vs 8 nM) and cocaine (19.6 nM DA for 1 µM COC, 59.6 nM DA for 20 µM COC vs 8 nM DA) to the perfusate but showed no change with tropolone (7 nM vs 8nM). Furthermore, inhibiting metabolism had no effect on the in vivo recovery of DA, whereas inhibiting uptake with 20 µM cocaine decreased the in vivo probe recovery (28% vs 44%) . From these results we can conclude that given the two extracellular clearance mechanisms, uptake has a pronounced effect on recovery while the effect of metabolism is negligible.

755.7

MICRODIALYSIS WITH ONE MINUTE SAMPLING INTERVALS: FOLLOWING RAPID CHANGES OF EXTRACELLULAR DOPAMINE,

A.P. Newton* and J.B. Justice, Jr., Department of Chemistry, Emory University, Atlanta, Georgia, 30322.

A microdialysis method using one minute sampling intervals has been developed to follow rapid changes in the extracellular concentration of dopamine (DA) in the rat brain. Samples were analyzed for DA on a smallbore HPLC system with electrochemical detection.

Anesthetized rats were implanted with four mm dialysis probes in the striatum (AP +2.5, LR -2.5 from bregma and DV -4.7 from dura). Baseline samples were collected at 1.6 µl/min every minute for 15 minutes. The perfusate was then alternated between 20 µM cocaine and CSF resulting in two 15 minute perfusions with each. Samples were collected every minute and stored on dry ice. A volume of 0.5 µl was injected onto a 0.5 mm x 10 cm column.

For n=3, average baseline dialysate DA concentrations were approximately 2.5 nM. During the cocaine perfusions, DA levels in the dialysate reached a maximum of approximately 25 nM between 2 to 4 minutes and then gradually declined. The second cocaine perfusion showed a lower maximum DA conc. than the first. During the CSF perfusions (zero cocaine), DA rapidly fell and returned to its baseline level within 5 minutes.

The observation of the early increase in DA during the cocaine perfusion indicates that the in vivo probe response is fast enough to follow fluctuations in the extracellular conc. of DA during behaviors such as cocaine self-administration. The observed decline of DA during the CSF perfusion was slower than the rise during the cocaine perfusion. In vitro probe response under similar conditions responded to a change in DA conc. within 2 min., suggesting that the slower decline of DA following the CSF perfusion with cocaine may have been due to residual cocaine in the tissue.

755.8

A FURTHER EVALUATION OF PHARMACOKINETIC PARAMETERS FOR COCAINE IN THE RAT, AS STUDIED BY IN VIVO MICRODIALYSIS.

S.M. Welch* and J.B. Justice, Jr. Dept. of Chemistry, Emory University, Atlanta GA 30322.

A two-compartment open model was used to examine the pharmacokinetics of cocaine in the blood and the nucleus accumbens (N.Acc.) of the rat. Data used in the modeling were concentrations of cocaine in the blood and N. Acc. resulting from administration of cocaine by various routes and measured by microdialysis and HPLC with UV detection. The doses examined were an intraperitoneal (i.p.) dose of 30 mg/kg, an intravenous (i.v.) dose of 7.5 mg/kg and a constant i.v. infusion of 0.3 mg/kg/min. Original parameter estimates (Pan et al., *J.Neurochem.* 1991, 56, 1299) were based on in vitro estimates of probe recovery. Recovery of cocaine in the N. Acc. has since been determined to be 17.8% (Menacherry et al., *Anal. Chem.* 1992, 64, 577) for the flow rate and probe length used. Parameter estimates were revised based on these data.

Sensitivity of estimates of pharmacokinetic parameters for cocaine to uncertainty in estimates of microdialysis recovery in the blood was examined. Assumption of a blood recovery ranging from three times greater than recovery in vitro to that 1/3 the in vitro recovery did not significantly affect estimates of the i.p. absorption constant k_a, the elimination constant k_{el} or the rate constants for blood-brain and brain-blood transfer (k_{12} and k_{21}, respectively). Significant effects were observed only on the estimates of F, the fraction of the i.p. dose absorbed and on V_1, the apparent volume of the blood compartment. Preliminary data indicate that the difference method used to determine probe recovery in the brain is also applicable for determination of in vivo recovery in the blood.

755.9

EVIDENCE THAT COCAINE-INDUCED ACTIVATION OF MESOLIMBIC DOPAMINE NEURONS IS ANTAGONIZED BY GBR-12909 PRETREATMENT. M.H. Baumann*, G.U. Char, B.R. de Costa, K.C. Rice and R.B. Rothman. Clinical Psychopharmacology Section, NIDA, ARC, Baltimore, MD 21224 and Laboratory of Medicinal Chemistry, NIDDK, NIH, Bethesda, MD 20892.

It has been proposed that dopamine (DA) reuptake inhibitors could be helpful for treating cocaine withdrawal symptoms in human addicts. Since cocaine itself is a DA reuptake blocker, many questions remain regarding such therapy. In the present study, we used the technique of intracranial microdialysis to assess the effects of 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine(GBR-12909)on cocaine-induced stimulation of DA overflow in the nucleus accumbens of conscious rats. Cocaine (0.3-3.0 mg/kg, iv) or GBR-12909 (0.3-3.0 mg/kg, iv) alone caused dose-related increases in dialysate DA levels. GBR-12909, however, was associated with a slow onset of action and a persistent elevation of extracellular DA (>2 hrs). In drug combination studies, GBR-12909 was injected 1 hr before cocaine challenge. A subeffective dose of GBR-12909 (0.3 mg/kg, iv) reduced the magnitude of the DA increase after a modest dose of cocaine (1.0 mg/kg, iv) whereas a higher dose of GBR-12909 (1.0 mg/kg, iv) suppressed cocaine's effects on extracellular DA in a dose-related manner. GBR-12909 also attenuated the DA-releasing action of amphetamine (1.0 mg/kg, iv). Our results suggest that GBR-12909 interferes with the interaction of cocaine, and amphetamine, at DA transporter sites. We are exploring this hypothesis using in vivo and ex vivo binding methods. Finally, our data provide a rationale for testing high-affinity DA reuptake inhibitors, such as GBR-12909, as cocaine antagonists or substitutes in human subjects.

755.10

DOPAMINERGIC RECOVERY AND SUBSEQUENT RESPONSE TO "RELAPSE" FOLLOWING CHRONIC COCAINE "BINGE" ADMINISTRATION. I.M. Maisonneuve* and M.J. Kreek, The Rockefeller University, New York, NY 10021.

The aims of this study were to determine how the dopamine (DA) systems adjust following the discontinuation of chronic cocaine "binge" administration (hourly x 3 ip) and respond to a subsequent "binge" pattern readministration of cocaine. Male Fisher rats were treated for 13 days with cocaine (C) (3 x 15 mg/kg) or saline (S) (3 x 1 ml/kg). On day 14, microdialysis was performed on the S and half of the C groups; all animals received cocaine (3 x 15 mg/kg). The remaining C animals were kept abstinent for the next 8 days and on day 21 they were challenged with cocaine (3 x 15 mg/kg) during microdialysis. In all cases dialysate samples were collected from the nucleus accumbens (NAC) and striatum (STR). One day after 13 days of cocaine DA basal levels were lowered in NAC (3.50 $\pm$ 0.37 nM vs 5.66 $\pm$ 0.58 nM, $p<0.01$, n=6,7) and in STR (6.88 $\pm$ 0.22 nM vs 10.00 $\pm$ 1.04 nM, $p<0.03$, n=5,7). In C animals the cocaine "binge" on day 14 resulted in extracellular DA levels lower than their corresponding values in S animals (pretreatment effect, $p<0.04$ in the NAC; $p<0.05$ in the STR) while the percent increases were of similar amplitude. After 8 days of cocaine abstinence DA basal levels were back to control levels in NAC (5.47 $\pm$ 0.21 nM, n=6), but still significantly lower than control in STR (6.82 $\pm$ 0.85 nM, n=6, $p<0.04$). Readministration of cocaine binge resulted in similar absolute DA levels whether performed one day (day 14) or 8 days (day 21) after cessation of chronic administration. However, in the NAC after 8 days of abstinence, the DA changes from baseline were each successively of smaller amplitude than the changes seen after one day of abstinence (time x pretreatment, $p<0.003$) or when contrasted to changes observed in the S group (time x pretreatment, $p<0.04$). These results suggest that chronic cocaine binge administration leaves its imprint for more than a week in both brain regions, that reexposure or relapse to cocaine evokes a different response, and that the responsivity of the mesolimbic and nigrostriatal DA systems to cocaine differs. (Supported by NIDA-05130 and the Aaron Diamond Foundation).

DRUGS OF ABUSE: COCAINE—MONOAMINES

756.1

INHIBITION OF LOCUS COERULEUS (LC) NEURONS BY SYSTEMICALLY ADMINISTERED COCAINE (COC) IS NOT SOLELY MEDIATED BY α_2 ADRENERGIC RECEPTOR ACTIVATION. A.L. Curtis* and R.J. Valentino. Div. Behav. Neurobiol., Dept. Mental Health Sci., Hahnemann University, Philadelphia, PA 19102, U.S.A.

The present study pharmacologically characterized the mechanism of inhibition of LC activity by systemically administered COC in halothane-anesthetized rats. COC (1 mg/kg, i.v.) inhibited LC spontaneous discharge rate by 57 $\pm$ 6 % (n=21). This effect was not antagonized by pretreatment with the α_2 antagonist, idazoxan (0.3-3.0 mg/kg, i.v.). In contrast, clonidine (7 µg/kg, i.v.), which inhibits LC discharge by activation of α_2 adrenergic receptors, was antagonized by idazoxan in a dose-dependent manner (IC 50=0.05 mg/kg). Although idazoxan was ineffective as a cocaine antagonist when administered by itself, pretreatment of rats with a combination of idazoxan (1 mg/kg, i.v.) and the nonselective serotonergic antagonist, methiothepin (0.1 mg/kg, i.v.), completely prevented inhibition by COC. Methiothepin alone was ineffective as a COC antagonist. Likewise, pretreatment with a combination of idazoxan (1 mg/kg, i.v.) and the α_1 adrenergic antagonist, prazosin (1 mg/kg, i.v.) completely antagonized COC, although prazosin was ineffective by itself. In contrast, pretreatment with either the serotonergic antagonist, methysergide (3 mg/kg, i.v.), the $5HT_{1a,b}$ and beta antagonist, pindolol (3 mg/kg, i.v.), and the dopaminergic antagonist, haloperidol (0.3 mg/kg, i.v.) were ineffective COC antagonists when administered alone, or in combination with idazoxan . LC discharge evoked by repeated sciatic nerve stimulation was also inhibited by COC and clonidine and this inhibition was sensitive to the same antagonists as was inhibition of LC spontaneous discharge by the respective agonists. These results indicate that the inhibitory effects of systemically administered COC on LC discharge are more complex than activation of somatic α_2 receptors. Supported by PHS Grants MH42796, MH00840, MH40008.

756.2

PHARMACOGENETIC ANALYSIS OF THE EFFECT OF COCAINE ON DOPAMINE AND SEROTONIN IN MOUSE BRAIN. M.N. Cook, X. Hou, V. G. Erwin, W. B. Severs* and B.C. Jones. Program in Biobehavioral Health, The Pennsylvania State University, University Park, PA 16802-6508.

Male and female C57BL/6 and DBA/2 mice were treated with a single injection of either saline or cocaine (15mg/kg i.p.) and killed by cervical dislocation 5, 10, 15, or 30 min post-injection. Brains were removed and dissected into medial prefrontal cortex (MPFC), nucleus accumbens (NA), caudate-putamen (CP), and ventral midbrain (VMB). Brain dopamine (DA), serotonin (5HT), dihidroxyphenylacetic acid (DOPAC), 5-hydroxyindoleacetic acid (5HIAA), and homovanillic acid (HVA) were determined by HPLC. Utilization of DA and 5HT were evaluated by HVA/DA and 5HIAA/5HT. Cocaine increased DA utilization in the MPFC of C57 males and DBAs; C57 females showed increased utilization at 5-10 min and decreased utilization at 15-30 min. Cocaine decreased DA utilization in the NA of C57 males and increased utilization in DBAs. C57 females showed decreased utilization at 5 min. In CP, cocaine decreased DA utilization in C57 males and increased utilization in DBA females. C57 females showed increased utilization at 10-15 min, but decreased utilization 5 and 30 min. This same pattern was seen in DBA males. Cocaine increased DA utilization in the VMB of C57 males 5 and 10 min, but decreased utilization at all other times. Cocaine decreased utilization in C57 females and DBAs at 5 min, but increased utilization at all other times. Cocaine decreased 5HT utilization in the MPFC of C57 males and DBA females but increased utilization in C57 females. DBA males showed increased 5HT utilization at 10-15 min, but decreased utilization at 5 and 30 min. 5HT utilization was also increased in the VMB of C57 females and DBA males. Supported by USPHS Grants # DA 07171, AA 08454, AA 08125 and MH 01882 to MNC.

756.3

STRUCTURE-ACTIVITY RELATIONSHIPS OF COCAINE CONGENERS IN INHIBITING [^{3}H]DOPAMINE UPTAKE INTO BRAIN SYNAPTIC VESICLES. M.E.A. Reith, L.L. Coffey, and P.C. Jobe*, Dept. of Basic Sciences, University of Illinois College of Medicine, Peoria, IL 61656.

Our previous work (Res. Comm. Subst. Abuse 10(1989)205) showed a moderate potency of cocaine (COC) (IC_{50} of 97 uM) in inhibiting uptake of [^{3}H]dopamine (DA) into brain synaptic vesicles. With this potency, administration of high doses of COC could transiently produce drug concentrations interfering with monoamine storage, possibly relevant to the DA depletion theory. In the present study, the structure-activity relationships were determined for COC congeners in inhibiting ATP-Mg^{2+}-dependent, reserpine-sensitive [^{3}H]DA uptake into synaptic vesicles prepared from brain minus cerebellum of Sprague-Dawley rats. Selection of a dopaminergic brain region was not attempted because of the low recovery of synaptic vesicles and the lack of monoamine selectivity of the vesicular transporter. N-Demethylation (norCOC), removal of the esteratic linkage between the tropane and phenyl rings (WIN 35428, WIN 35065-3), or removal of the carbomethoxygroup on C_2 (benzoyltropine, benzoylpseudotropine) had little or no effect on vesicular [^{3}H]DA uptake, whereas moving the latter group from an axial to an equatorial position (pseudoCOC, WIN 35140, WIN 35004) increased the potency. In COC, the potency was substantially reduced by hydrolysis of the C_2 carbomethoxy or C_3 benzoyl group (ecgonine methylester, benzoyl(nor)ecgonine, ecgonine) or by making C_3 axial (allococaine). These structure-activity relationships differ from those for the interaction between COC congeners and the DA transporter in the plasma membrane and the voltage-dependent sodium channel. The present differences between close congeners also argue against the weak base model involving disruption by COC of the intravesicular acidic milieu by proton trapping. Supported by NIDA 03025.

756.4

LACK OF LONG-TERM CHANGES IN COCAINE AND MONOAMINE CONCENTRATIONS IN RAT CNS FOLLOWING CHRONIC ADMINISTRATION OF COCAINE. M.E. Alburges* [1,2,3], D.J. Crouch[1], J.K. Wamsley[2] and D.M. Andrenyak[1]. [1]Cent. Human Toxicol., Pharma-Toxicol. Dept., University of Utah, Salt Lake City, UT 84108. [2]Pharm-Toxicol. Dept. University of Zulia, Venezuela. [3]Pharm. Sci. Dept. North Dakota State University, Fargo, ND 58105.

In previous studies, we reported time-dependent and dose-dependent changes in the rat dopaminergic receptor system following chronic administration of cocaine. The aim of the present investigation was to monitor the concentration of monoamines (using HPLC-ECD) and cocaine (using GC/MS) in the rat CNS following a dose schedule (5, 10, 15, 20 and 25 mg/kg, i.p., b.i.d.) for 21 days period. Twelve hours after the last cocaine injection, cortical and striatal concentrations of the monoamines and their metabolites were not significantly different in saline vs. cocaine treated animals. In addition, cocaine concentration in the brain regions did not change with the different doses used. These findings indicate that changes in the dopaminergic receptor system following chronic cocaine administration are not due to changes in neurotransmitter concentration or brain cocaine accumulation. (Supported in part by USPHS Research Grant DA 05167).

756.5

COCAINE INHIBITS DORSAL RAPHE 5-HT ACTIVITY THROUGH 5-HT1A-DEPENDENT AND -INDEPENDENT MECHANISMS. R.T. Windh* and K.A. Cunningham, Dept. Pharmacol., Univ. Texas Med. Branch, Galveston, TX 77550.

Systemic and microiontophoretic cocaine application inhibits the spontaneous activity of dorsal raphe (DR) serotonin (5-HT) neurons, presumably by increasing somatodendritic 5-HT1A autoreceptor activation consequent to inhibition of 5-HT reuptake. To test this hypothesis, we compared the ability of two putative 5-HT1A antagonists (*l*-propranolol and WAY 100135) to block the suppressive effects of cocaine and the 5-HT1A agonist 8-OHDPAT. Single barrel extracellular recording was used to measure the spontaneous cell firing of 5-HT DR neurons in chloral hydrate-anesthetized male Sprague-Dawley rats (175-325g). Intravenous cocaine (1 mg/kg, n=2) or 8-OHDPAT (5 ug/kg, n=2) alone completely inhibited 5-HT neuron firing in less than 1 min. Thus the first 3 min of neural activity following administration of either drug were used to assess the effects of 5-HT1A antagonists. WAY 100135 (200 ug/kg i.v., 2 min pretreatment) reduced 8-OHDPAT-induced inhibition of cell firing during the first 3 min to 80, 76 and 87% of baseline (n=3), respectively, indicating that this dose of WAY 100135 produces an effective 5-HT1A antagonism. The same dose of WAY 100135 was less effective in antagonizing the cocaine-induced suppression of cell firing: the firing rates during the first 3 min. after cocaine in the presence of WAY 100135 were 71, 54 and 41% of baseline (n=6). Similarly, *l*-propranolol (1 mg/kg i.v., 3 min pretreatment) only partially antagonized the cocaine-induced inhibition of cell firing to 59, 43 and 37% of baseline (n=8). Neither WAY 100135 (97% of baseline, n=9) nor *l*-propranolol (105% of baseline, n=9) alone affected cell firing at the doses used. These results suggest that cocaine inhibition of 5-HT DR neuronal firing is partially mediated through 5-HT1A receptors, but other mechanisms, possibly including other 5-HT or catecholamine receptors, also appear to be involved. More complete dose-response analysis with WAY 100135 and *l*-propranolol as well as other monoamine antagonists is currently underway. Supported by NIDA DA05708 and DA06511.

756.6

EFFECTS OF THE 5-HT$_3$ ANTAGONIST ZACOPRIDE ON DEVELOPMENT AND EXPRESSION OF COCAINE SENSITIZATION. *R. De La Garza II and K.A. Cunningham*. Dept Pharmacol, Univ Texas Med Sch, Galveston TX 77550.

Cocaine (COC) is known to interact with serotonin (5-HT) systems in the brain which may contribute to its behavioral effects. Antagonists for the 5-HT$_3$ receptor have recently been shown to block several unconditioned behavioral effects of cocaine, including locomotor hyperactivity. In the present study, we examined the effects of the 5-HT$_3$ antagonist zacopride (ZAC) on the development and expression of behavioral sensitization to cocaine. Male Sprague-Dawley rats (n=6/grp) were treated in automated test enclosures with saline (SAL) or ZAC (0.1 mg/kg, ip) followed 30 min later by SAL or COC (15 mg/kg, ip) twice daily for 7 days (Days 1-7). On Day 1, rats in both SAL+COC and ZAC+COC groups exhibited modest increases in locomotor activity not seen in either SAL+SAL or ZAC+SAL rats while ZAC+SAL rats did not exhibit any overt behavioral disruption. Comparison of the activity between Day 1 and Day 7 indicated that rats treated with SAL+COC, but not ZAC+COC, developed behavioral sensitization. On Days 8-11, the locomotor activity of rats was monitored after challenge with SAL, COC, SAL+COC and ZAC+COC to assess the effects of ZAC on the expression of sensitization. Following ZAC (0.1 mg/kg) plus COC (15 mg/kg), ZAC was unable to block the expression of sensitization in SAL-COC rats. Thus, while ZAC suppresses the *development* of cocaine sensitization, this 5-HT$_3$ antagonist may not block the *expression* of sensitization. Experiments with additional doses of ZAC as well as other 5-HT$_3$ antagonists are currently underway to assess the reproducibility and generality of this finding. *Supported by DA 05708, DA 06511.*

756.7

5,7-DHT REDUCES THE EFFICACY OF 5-HT$_3$ RECEPTOR ANTAGONISTS TO BLOCK COCAINE-INDUCED HYPERACTIVITY. A.L. Svingos* & R.J. Hitzemann, Departments of Psychiatry & Psychology, SUNY Stony Brook, Stony Brook, NY 11794-8101 & VAMC Northport, Northport, NY 11768.

We have previously reported that *p*-chlorophenylalanine (*p*-CPA) administration attenuates the ability of 5-HT$_3$ antagonists to inhibit cocaine-induced hyperactivity (Svingos & Hitzemann, 1992a). We have also shown that this effect persists for a fourteen day period after *p*-CPA treatment (Svingos & Hitzemann, 1992b). It has been documented that *p*-CPA is a relatively short lasting and non-uniform depleter of 5-HT (Jequier et al., 1967, Aghajanian et al., 1973). Therefore in the present study we expanded our investigation using 5,7-dihydroxytryptamine (5,7-DHT) treated animals. Previous studies demonstrate that depletion of 5-HT with 5,7-DHT is an effective way of elucidating 5-HT associated behaviors (Azmitia et al., 1978, Frankfurt et al., 1985). Animals received intraventricular injections of 5,7-DHT and were either behaviorally tested or processed for immunochemistry 14 or 28 days later. The results from the 5,7-DHT treated animals show that on recovery days 14 and 28 zacopride was unable to block cocaine-induced hyperactivity, thereby supporting the finding that endogenous 5-HT is necessary for 5-HT$_3$ antagonists to block cocaine-induced hyperactivity. We also looked at possible anatomical sites of action for the 5-HT$_3$ antagonist-cocaine interaction. Our laboratory and others have implicated both the caudate-putamen and nucleus accumbens as possible sites of 5-HT$_3$ action (Blandina et al., 1988, Chen et al., 1990, Svingos & Hitzemann, 1992b). Local 5,7-DHT lesions of the nucleus accumbens confirm this proposition.

756.8

TIME COURSE OF COCAINE-INDUCED CHANGES IN THE BIOSYNTHETIC ENZYMES FOR DOPAMINE AND SEROTONIN S.L. Vrana, K.E. Vrana, T.R. Koves, J.E. Smith and S.I. Dworkin*, Center for the Neurobiological Investigation of Drug Abuse, The Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC 27157-1083

Cocaine is a local anesthetic with psychomotor stimulant properties that is abused by humans and acts as a potent reinforcer in laboratory animals. Cocaine blocks the reuptake of dopamine (DA), norepinephrine, and serotonin (5-HT) into presynaptic neurons by inhibiting the respective amine transporters. The effect of cocaine treatment on the activity of the rate-limiting enzymes in DA and 5-HT biosynthesis (tyrosine hydroxylase [TH] and tryptophan hydroxylase [TPH], respectively) were examined. Cocaine HCl (0.33 mg/infusion, every 8 min for 6 hr) was administered to male Fischer 344 rats implanted with indwelling i.v. jugular catheters for 3, 7, 14, 21 or 28 days, while saline was infused for 7 or 28 days. TH activity was examined in dopaminergic cell body regions (ventral tegmental area, VTA; substantia nigra, SN) and terminal field regions (corpus striatum, CS; nucleus accumbens, NAc) using a radioenzymatic assay. TPH activity was assessed in the raphe nuclei using a similar procedure which we recently developed. Following 3 days of cocaine treatment (45 mg/kg/day), there was no effect in any of the brain regions on the activity of TH or TPH. However, by 7 days, there was an increase in the activity of TH and TPH in all of the brain regions tested, which remained elevated in the remaining extended time periods. These results indicate that cocaine treatment increases TH and TPH activity at some point following 3 days of treatment. *Supported by DA-07246 (S.L.V.), GM-38931 (K.E.V.), and DA-03628, P50-DA06634 (J.E.S., S.I.D.).*

756.9

WITHDRAWAL FROM CONTINUOUS OR INTERMITTENT COCAINE: 5-HT$_3$ RECEPTOR REGULATION OF BEHAVIOR. G.R. King, C.J. Joyner, and E.H. Ellinwood, JR*. Behavioral Neuropharmacology Section, DUMC, Durham, NC 27710

The present experiments examined alterations in the abilities of 5-HT$_3$ receptors to regulate behavior during withdrawal from continuous or intermittent cocaine. The rats were withdrawn from a 14 day pretreatment regimen for 7 days. In Experiment 1 rats received IP injections of ondansetron. In Experiment 2, the rats received IP ondansetron in combination with a 15 mg/kg IP cocaine injection. In Experiment 3, the subjects received IP injections of ondansetron in combination with a 7.5 mg/kg IP cocaine injection. Following these injections the subjects' behavior was rated. In Experiment 1 ondansetron had no differential effect on the behavior of the subjects. In Experiment 2 ondansetron had no effect on cocaine-induced locomotion in the saline control rats, but did have a slight suppressive effect in the injection rats. In contrast, ondansetron had a robust facilitative effect on cocaine-induced locomotion in the continuous infusion rats. In Experiment 3 ondansetron had no effect on cocaine-induced locomotion in the saline control or the cocaine injections pretreatment subjects. In the continuous infusion subjects, ondansetron did have a slight facilitative effect on cocaine-induced locomotion. The present results indicate that the continuous infusion of cocaine for 14 days alters the ability of 5-HT$_3$ receptors to regulate cocaine-related behaviors.

756.10

SEROTONERGIC PROPERTIES OF COCAINE: EFFECTS ON A 5-HT$_2$-MEDIATED BEHAVIOR AND ON EXTRACELLULAR CONCENTRATIONS OF SEROTONIN AND DOPAMINE. **W.D. Essman*, A. Singh and I. Lucki. Departments of Psychiatry and Pharmacology, University of Pennsylvania, Philadelphia, PA 19104.**

The present study examined the ability of cocaine to enhance serotonin (5-HT) neurotransmission. Initially, the effects of cocaine were examined on the head shake response, a behavior mediated by the activation of 5-HT$_2$ receptors. Pretreatment with the selective 5-HT uptake inhibitor fluoxetine (10 mg/kg) potentiated the head shake response to the 5-HT precursor, 5-hydroxytryptophan (5-HTP; 75 mg/kg) in male Sprague-Dawley rats. Similarly, pretreatment with cocaine (10 mg/kg) increased the number of head shakes following 5-HTP administration. In contrast, pretreatment with the selective norepinephrine uptake inhibitor desipramine (10 mg/kg) and the selective dopamine (DA) uptake inhibitor GBR 12909 (10 mg/kg) failed to potentiate the head shake response when injected prior to administration of 5-HTP.

The effects of cocaine on extracellular concentrations of DA and 5-HT in the nucleus accumbens were examined using *in vivo* microdialysis in a separate group of rats. Cocaine (10 mg/kg) increased the extracellular concentrations of both DA and 5-HT by 300-350% over baseline levels. Cocaine's ability to increase the head shaking response and to increase extracellular concentrations of 5-HT may be due to its ability to block 5-HT uptake. These results provide direct evidence for behavioral and neuropharmacological effects of cocaine on 5-HT systems that may be important to understanding its abuse potential. Supported by USPHS Grants DA 05186, GM 34781, MH 36262 and MH 48125.

756.11

DOPAMINE AND SEROTONIN RELEASE-REGULATING AUTORECEPTOR SENSITIVITY IN A_9/A_{10} CELL BODY AND TERMINAL AREAS FOLLOWING WITHDRAWAL OF RATS FROM CONTINUOUS INFUSION OF COCAINE. N-H.Chen and M.E.A. Reith*. Dept. of Basic Sciences, Uni. of Illinois Coll. of Medicine at Peoria, Peoria, IL 61656.

The effects of dopamine (DA) and serotonin (5-HT) autoreceptor agents on electrically-induced [^{3}H]DA and [^{3}H]5HT release from superfused slices of striatum (STR), nucleus accumbens (NACC), and ventral mesencephalon (VM) containing A_9 and A_{10} neurons were investigated in rats made tolerant to the stimulatory effect of cocaine on locomotor and stereotyped behavior by a 14-day continuous infusion of cocaine (30 mg/kg/day) by s.c. implanted osmotic minipumps followed by a 7-day drug-free period. In VM, electrically-induced [^{3}H]DA was increased, the ability of pergolide to inhibit this release was abolished, but the ability of sulpiride to facilitate the release was potentiated, implicating a higher concentration of synaptic DA modifying the responsiveness of somatodendritic D_2 autoreceptors to D_2 agents. Both electrically-induced [^{3}H]5HT release from VM and the stimulatory effect of in vitro cocaine on this release were enhanced while the effects of both 5-methoxytryptamine and methiothepin were attenuated, indicating subsensitivity of 5HT autoreceptors in DA cell body regions. In STR and NACC, no significant changes were observed in [^{3}H]DA and [^{3}H]5HT release, except for a modest reduction in the effects of both pergolide and sulpiride on electrically-induced [^{3}H]DA release from STR. These results emphasize the importance of pretreatment-induced changes in DA cell body regions, rather than terminal areas, under the present conditions. The observed subsensitivity of 5-HT release-regulating autoreceptors and increase in synaptic DA concentration in the VM, along with known 5-HT/DA interactions, provide an explanation for behavioral tolerance upon cocaine challenge following continuous cocaine. Supported by NIDA 03025.

756.12

REPEATED COCAINE EXPOSURE INHIBITS THE NEUROENDOCRINE RESPONSES TO THE 5-HT RELEASERS P-CHLOROAMPHETAMINE AND D-FENFLURAMINE. **A.D. Levy*, P.A. Rittenhouse, Q. Li, & L.D. Van de Kar Dept. Pharmacol., Stritch Sch. Med., Loyola Univ. Chicago, Maywood IL 60153.**

Previous studies determined that chronic cocaine inhibits the ACTH, prolactin and renin responses to a single high dose of the serotonin (5-HT) releaser p-chloroamphetamine (PCA) (Neuropharm. 31:169,1992; Brain Res. 580:6, 1992). To confirm whether these changes represent deficits in presynaptic 5-HT neurons, we compared the influence of cocaine exposure on the neuroendocrine responses to 5-HT releasers PCA and d-fenfluramine. Adult male rats (N=8/group) received saline or cocaine (15 mg/kg i.p., b.i.d.) for 7 days. After a 42 hr withdrawal period, the dose-response effects of PCA (0, 2, 5 or 8 mg/kg i.p.) or d-fenfluramine (0, 0.2, 0.6, 2 or 5 mg/kg i.p.) were examined. Trunk blood was collected for radioimmunoassays of plasma ACTH, prolactin and renin concentrations. Initial studies confirmed that PCA (8 mg/kg) and d-fenfluramine (5 mg/kg) induced stimulations of ACTH, prolactin and renin secretions are prevented by the 5-HT uptake inhibitor fluoxetine ($p<.01$ ANOVA and Newman-Keuls' tests), indicating 5-HT mechanisms. Cocaine exposure inhibited the ACTH responses to PCA and d-fenfluramine ($p<.05$). The prolactin and renin responses to PCA ($p<.05$) but not d-fenfluramine were inhibited in cocaine pretreated rats. The cocaine-induced reduction of the ACTH response to 5-HT releasers may reflect subsensitive postsynaptic 5-HT_{1A} receptors. We have recently observed that cocaine also inhibits the ACTH response to the 5-HT_{1A} agonist, 8-OH-DPAT (Col.Prob.Drug Depend. 1993 abstr.). However, presynaptic deficits cannot be excluded. Differential effects of cocaine on the prolactin and renin responses to PCA and d-fenfluramine suggest that these two 5-HT releasers exert slightly different influences on secretions of these hormones.

(Supported by DA04865, MH45812, & Loyola Univ. Neurosci. & Aging Inst.)

DRUGS OF ABUSE: COCAINE—NEONATAL

757.1

BODY COMPOSITION IN FETAL RATS AFTER PRENATAL COCAINE OR ALCOHOL EXPOSURE. M.W. Church*, C.A. Morbach and L.L. Woodard. Fetal Alcohol Res Ctr, Dept Ob/Gyn, Wayne State Univ Sch Med, Detroit, MI 48201.

Cocaine has a number of adverse effects on pregnant animals such as reduced food consumption and weight gain. Cocaine also has adverse effects on the offspring such as low birth weight, malformations, hemorrhaging, and behavioral anomalies. We investigated the influence of prenatal cocaine and alcohol exposures on fetal body composition.

Sprague-Dawley rats were prenatally exposed to cocaine by administering 20, 30, 40 or 50 mg/kg cocaine (s.c.) twice daily to pregnant dams from gestation days 7-20. Pair-fed and untreated control groups were also used. Another group received 3.0 g/kg alcohol (p.o.) twice daily and served as a positive control group (n=12-16/group). Pregnant females were sacrificed on gestation day 21. One female and one male fetus from each litter were removed, weighed, minced, desiccated, weighed once again, defatted, then weighed again. This allowed us to determine total body water (TBW), dry weight (DW), fat-free mass (FFM), and total body fat (TBF).

Fetuses in the alcohol and the 50 mg/kg cocaine groups had significantly lower body weights, TBF, DW, TWB, and FFM than the other groups. When correcting for differences in body weight, group differences in % TBW, % DW, % FFM were marginal. However, the alcohol and 50 mg/kg cocaine groups still had significantly lower percentages of fat (% TBF). For example, male and female offspring in the alcohol and 50 mg/kg cocaine groups had mean % TBF between 0.34 - 0.37% while cohorts in the pair-fed and untreated control groups had values between 0.40 - 0.46% ($p<.001$).

This suggests that prenatal cocaine or alcohol exposure can affect body composition and thereby the physical well-being of the offspring. (Supported by NIDA grant #DA05536-05 and NIAAA grant #AA07606).

757.2

AUTORADIOGRAPHIC ASSESSMENT OF THE EFFECTS OF PRENATAL COCAINE EXPOSURE ON THE ONTOGENY OF THE DOPAMINE UPTAKE COMPLEX (DAUC). L.M. Collins* and J.S. Meyer. Dept. of Psychology, Neuroscience and Behavior Program, Univ. of Massachusetts, Amherst, MA 01003.

Cocaine readily crosses the placental and blood-brain barrier. It has been found to block the reuptake of [^{3}H]dopamine in fetal rat brain as early as embryonic day 15 (Meyer et al., Psychopharmacology, in press). Chronic prenatal cocaine was previously reported to reduce [^{3}H]WIN 35,428 binding in 6-week-old mouse striatum (Pritchard et al., Soc. Neurosci. Abs. 18: 1456, 1992). To further assess the effects of *in utero* cocaine exposure on the DAUC, pregnant Sprague-Dawley rats were subjected either to daily s.c. injections of cocaine HCl (40 mg/kg/day from gestational day (GD) 8 through 21) or to s.c. implantation of 2 capsules each containing 60 mg of cocaine base from GD19 through 21. Density of postnatal DAUC in striatum, nucleus accumbens, substantia nigra, and ventral tegmental area was determined by quantitative receptor autoradiography (QAR) utilizing the dopamine reuptake blocker [^{3}H]GBR 12935. QAR analysis at postnatal days 30 and 60 showed no significant effect of maternal cocaine injections on the density of the DAUC in any of the brain areas analyzed. Thus, the ability of prenatal cocaine exposure to alter DAUC expression may depend on a number of factors, including species, treatment regimen, and ligand used to label the transporter. Supported by DA-06495.

757.3

PRENATAL COCAINE TREATMENT REDUCES HALOPERIDOL-INDUCED CATALEPSY AT POSTNATAL DAY 10. J. Meyer,* P. Robinson, and M. Todtenkopf. Dept. of Psychology, Neuroscience and Behavior Program, Univ. of Massachusetts, Amherst, MA 01003.

We previously showed that prenatal cocaine treament reduced sensitivity to cocaine-stimulated wall climbing on postnatal day (PD) 11 (Meyer et al., Neurotoxicol. Teratol. 14: 183, 1992). The present study examined the influence of prenatal cocaine treatment on subsequent haloperidol-induced catalepsy. Rats were given daily injections of 40 mg/kg cocaine HCl s.c. from gestational day 8 to 20. Pair-fed/saline-injected and untreated control groups were also run. On PD 1, litters were culled to 8 (sex-balanced if possible) and fostered to surrogate mothers. On PD10 and PD15, 1 male and 1 female from each litter were injected s.c. with 1 mg/kg of the dopamine receptor antagonist haloperidol. Another pair of subjects was injected with vehicle. Each pup was tested for catalepsy 1 h later by placing its forepaws on an elevated, horizontally-oriented dowel rod and measuring the latency to remove at least one paw from the dowel. All subjects, regardless of prenatal treatment, exhibited short response latencies when given vehicle on the test day. However, significantly fewer cocaine-exposed subjects showed a cataleptic response to haloperidol when tested on PD10. These results suggest that prenatal cocaine may alter either the dopamine system or any of several other neurotransmitters known to influence neuroleptic-induced catalepsy. Supported by DA-06495.

757.4

NEONATAL COCAINE EXPOSURE ALTERS SENSITIVITY TO THE REWARD-POTENTIATING PROPERTIES OF COCAINE IN ADULT RATS.

D.Y. Lin , J.S. Schwartzbaum, and C.K. Kellogg*. Dept. of Psychology, Univ. of Rochester, Rochester, NY 14627.

Early cocaine exposure has been shown to alter performance on a wide range of behaviors in young adolescent rats, some of which may be due to altered dopaminergic function. Since dopamine has been strongly implicated in normal reward processes, persistent changes in dopaminergic function due to early cocaine exposure may affect reward processes in the adult. Rate-frequency functions provide a quantitative measure of the efficacy of rewarding electrical stimulation that is independent of motor/performance effects. The present study investigated the impact of early postnatal cocaine exposure on responsiveness to cocaine in adulthood. Adult offspring from litters injected s.c. once daily from postnatal day 1-7 with 20 mg/kg cocaine or saline were implanted bilaterally in the medial forebrain bundle with monopolar stimulating electrodes. After baseline rate-frequency functions were established, animals were injected i.p. with 2.5, 5, or 10 mg/kg cocaine just prior to testing. Cocaine produced orderly dose-related shifts of the function toward lower frequencies in all groups indicating a reward enhancing and threshold lowering effect of the drug on brain stimulation reward. No systematic changes in motor/performance capacity were observed in any group. Neonatal exposure to cocaine enhanced the potentiation of electrical brain stimulation reward following acute cocaine administration and this effect was greater in females than in males.

757.5

CONCENTRATIONS OF COCAINE IN HEARTS AND BRAINS OF CHICKEN EMBRYOS AFTER INJECTION INTO EGGS ON DAY 18 OF EMBRYOGENESIS: RELATIONSHIP TO SUPPRESSION OF MOTILITY. S.B.Sparber*, M.A. Kubak and A. Wasserman, Dept. of Pharmacology, Univ. of Minn., Mpls., MN 55455.

^{3}H-cocaine HCl was injected into eggs on E18 at doses which suppress embryonic motility 20 min later and reduce hatchability dose-relatedly (Sparber et al.,Neurosci. Soc. Abs. 18:546,1992). Twenty min and 2.5 hr after their hearts and brains were removed, weighed, and homogenized in NaF solution. Aliquots were dissolved in base and analyzed by liquid scintillation spectrometry for total radiolabel. Other aliqouts were subjected to organic extraction and unmetabolized cocaine determined. Parallel experiments were carried out to determine the relationship between cocaine concentrations in these organs and the degree of suppression of motility at 20 min and 2.5 hr. Twenty min after injecting either 22.5 or 67.5 mg/kg egg (1.125 or 3.375 mg/50 g egg) about 75% of label (DPM/mg) was extracted from either organ as cocaine, even though the concentration of radiolabel or cocaine was greater after the higher dose. While about 30% of the ^{3}H was extracted as unchanged cocaine from hearts 2.5 hr after injection, about 50% of it was in brains at this time. Regression analyses of the concentrations of cocaine 20 min and 2.5 hr after injection indicated that about twice as much cocaine was in brains, relative to hearts at these times. Significant correlations between individual brains and hearts at 20 min and 2.5 hr (R^2=0.97; 0.74) supported the reliability of the results. Various measures of motility at these times showed dose-related depression, the effects of the low dose absent at the later time. The pattern and duration of the behavioral effects, coupled with the concentration data suggest the possible development of acute tolerance to some of cocaine's action in these older embryos. Supported in part by USPHS grant DA04979.

757.6

THE EFFECT OF PRENATAL COCAINE EXPOSURE ON THE LOCOMOTOR RESPONSE TO ACUTE SKF-38393 IN WEANLING RATS. H. E. Hughes*, E. A. Grose and D. L. Dow-Edwards. Laboratory of Cerebral Metabolism, Department of Pharmacology, SUNY Health Science Center, Brooklyn, N. Y., 11203.

Our lab has previously demonstrated that locomotor activity in weanling and adult rats is sensitive to the effects of perinatal cocaine exposure. Statistically significant effects of perinatal drug treatment, acute drug challenge and gender have been observed in various experiments using this behavioral assay. The present study investigated the effects of prenatal cocaine exposure on locomotor activity following acute administration of a dopamine (D-1) receptor agonist in 21-22 day old rats. Pregnant Sprague-Dawley rats were gastrically intubated with 30 or 60 mg/kg/day cocaine HCl or vehicle during gestational days 8-22. Vehicle-treated rats were pair-fed/watered to rats receiving 60 mg/kg cocaine. At parturition, litters were culled to five males and five females and were surrogate fostered. At 21-22 days of age, subjects received a single sc injection of 1.0, 10.0 or 30.0 mg/kg SKF-38393 or vehicle only and were placed in Digiscan Activity Monitors interfaced with a computer and Omnitech software. The activity chambers contained 36 infrared sensors (24 horizontal and 12 vertical). Activity counts were collected in one minute intervals over a 60 min. period of activity monitoring. Preliminary data indicate that prenatal cocaine exposure predicts the changes in activity due to acute administration of SKF-38393. A complete statistical analysis is forthcoming. Supported by ADAMHA grant #DA04118.

757.7

PRENATAL COCAINE ALTERS MESOLIMBIC DOPAMINE IN DEVELOPING RATS AS MONITORED BY IN VIVO MICRODIALYSIS. R.W. Keller, Jr.*, K.S. Johnson, A.M. Snyder-Keller#, J.N. Carlson, S.D. Glick. Dept. of Pharmacol. & Toxicol., Albany Medical Col., Albany, NY 12208 and #Wadsworth Ctr., NYS Dept. Health, Albany, NY 12201

Pregnant rats were given injections of saline or cocaine (COC, 10 mg/kg twice daily, SC) between gestational days 7-21. Awake offspring were examined by microdialysis to study the effects of prenatal COC on the mesolimbic dopamine (DA) system. In young rats (12-30 d) N. accumbens (NA) was monitored while in adults (>60 d) NA and frontal cortex (FC) were monitored. 20-min samples were assayed for DA, DOPAC, HVA and 5-HIAA. After collecting baseline samples, each rat was exposed to 20 min of intermittent tail pinch and monitored for 4 samples; an acute injection of COC (20 mg/kg, IP) followed and 6 samples were collected. Basal dialysate levels of DA in NA were quite similar in young and adult rats; however, DA metabolites were markedly reduced in young rats as compared with adults. Prenatal COC exposure led to an approximate doubling of basal DA but little change in metabolites in young rats. In adult rats no prenatal COC effects were observed in the NA, although an elevated level of HVA was observed in FC. The response to tail pinch was significant only in the FC and was enhanced in adult rats prenatally exposed to COC. In absolute magnitude, the increase in dialysate DA induced by acute COC was greater in prenatal-COC rats; however, expressed as percent of baseline the groups did not differ. [Supported by DA-06199]

757.8

PRENATAL COCAINE EXPOSURE ALTERS SENSITIVITY TO COCAINE-KINDLED SEIZURES. A.M. Snyder-Keller* and R.W. Keller, Jr., Wadsworth Center for Labs and Research, New York State Dept. Health, Albany, NY 12201 and Dept. of Pharmacology & Toxicology, Albany Medical College, Albany, NY 12208.

The offspring of Sprague-Dawley rats given daily injections of 40 mg/kg cocaine (s.c.) between gestational days 10 and 20 were tested for their sensitivity to cocaine-induced seizures later in life. Beginning at one month of age, they were given daily injections of cocaine: 40 mg/kg (i.p.) for 6 days, followed by 45 mg/kg for 6 days, and then 50 mg/kg for 6 days. Prenatally cocaine-treated females were more likely to seize within the first 6 days (33%) than prenatally saline-treated or untreated females (8%). Males kindled more slowly, but also showed a greater susceptibility to cocaine-kindled seizures as a result of prenatal cocaine treatment (27% seizing by 10 days, vs. 0%). This enhanced sensitivity was not seen upon first exposure to cocaine (acute tests), even at higher doses (up to 60 mg/kg). We are investigating whether individual differences in the rate of cocaine kindling are related to the degree of striatal serotonergic hyperinnervation found to occur in these animals (Snyder-Keller and Keller, Dev. Brain Res. 1993). Both acute and cocaine-kindled seizures induced c-fos in limbic regions (hippocampus, amygdala, cortex) with no obvious differences as a result of prenatal cocaine treatment. Fos-immunoreactive cells were numerous in striatum and nucleus accumbens after acute cocaine, but the response was down-regulated with chronic treatment, even when cocaine-kindled seizures occurred. (Supported in part by DA-06199).

757.9

ALTERATIONS IN CEREBRAL BLOOD FLOW FOLLOWING ACUTE COCAINE ADMINISTRATION IN 11 DAY OLD RATS. D.L. Dow-Edwards*, E.A. Grose, H.E. Hughes and L.A. Freed-Malen Lab. of Cerebral Metabolism, Dept. of Pharmacology, SUNY-Brooklyn, NY.

Previous studies from this lab have shown that exposure to cocaine during postnatal days 1-10 produces alterations in brain glucose metabolism in adulthood (e.g. Dev. Brain Research 42:137, 1988). Postnatal exposure resulted in increased glucose metabolism in many brain regions in adult females and no alterations in males. In an effort to determine why such large gender differences in response to cocaine would occur, we examined the acute effects of cocaine on cerebral function during the early postnatal period in the present study. Here cerebral blood flow was used as an indication of function. Rat pups were anesthetized at 10 days of age and femoral arterial and venous catheters were inserted. The catheters were looped under the skin and the pups were returned to the dam in the home cage. On the following day, the catheters were freed, the pups were placed in an incubator maintained at 35°C until they were injected with either cocaine HCl at 25mg/kg or vehicle. At 6 min. post-injection, an infusion of 20μCi/cc [^{14}C] iodoantipyrine (NEN) was begun and 10 μl arterial samples were collected continuously until the pup was decapitated at 1.5 min. The brains were removed and frozen immediately and later processed for autoradiography. Computerized image analysis using the M1 Imaging System (Imaging Research) showed that the effects of cocaine on cerebral blood flow at 11 days of age are quite different from those published by others examining adult rats (see Stein, E. et al JPET 262:327, 1992).

Supported by NIDA grant DA04118.

757.10

EFFECTS OF COCAINE ON STRIATAL TYROSINE HYDROXYLASE IMMUNOREACTIVITY IN PREGNANT RATS. D. Jackson*, M.S. Manley, L.D. Manley, S.J. Young, and P.M. Groves, Dept. of Psychiatry, Univ. of California at San Diego, La Jolla, CA, 92093-0603.

We have observed that *in utero* cocaine exposure (15 mg/kg, b.i.d, ED15-21) produces a persistent reduction in non-islandic striatal tyrosine hydroxylase (TH) immunoreactivity and the appearance of swollen TH-positive fibers in female offspring (Jackson et al., 1992). The basis for this gender-related neurotoxic effect of cocaine has yet to be elucidated although it may be related to an increased rate of dopamine (DA) turnover. There are some indications that DA turnover rates are greater in female rats. Findings that the reproductive hormones, progesterone and estrogen, have profound effects on the activity of nigrostriatal DA neurons suggest that exposure to high levels of these hormones could contribute to increased sensitivity to cocaine in females. In the present study, we have examined the effects of cocaine exposure during pregnancy, a condition in which levels of reproductive hormones are increased, on striatal TH immunoreactivity. Gravid Long Evans rats (275-400 g) were injected with saline or cocaine hydrochloride (15 mg/kg b.i.d. or 40 mg/kg qd., s.c. in saline) during embryonic days 15-21. Non-pregnant females were injected under the same dose regimens for a period of seven days. Twenty seven days after the last injection, animals were perfused and post-fixed with 4% paraformaldehyde in phosphate buffer. Brains were removed, cryoprotected, then cut with a freezing microtome. Tissue was processed for peroxidase localization of TH immunoreactivity with a sheep anti-TH polyclonal followed by standard avidin-biotin staining methods. Bright-field images and density measurements were obtained from striatum using an image analysis system. TH immunoreactivity in non-pregnant rats was not altered by either dose of cocaine. In contrast, striatal TH immunoreactivity in the dams was significantly reduced with either dose of cocaine. These findings suggest that females are particularly vulnerable to neurotoxic effects of cocaine during pregnancy possibly due to alterations in levels of reproductive hormones. Supported by grants NIDA DA 02854 and NSF BNS 9006155

757.11

PRENATAL EXPOSURE TO COCAINE PRODUCES SUSTAINED SUBCELLULAR REDISTRIBUTION OF PROTEIN KINASE C (PKC). H.-Y. Wang*, E. Yadin and E. Friedman. Department of Psychiatry, Medical College of Pennsylvania/EPPI, Philadelphia, PA 19129.

Redistribution of hippocampal PKC from cytosol to membranes has been associated with memory and learning processes. Prenatal exposure to cocaine appears to hamper learning ability. In an attempt to investigate the possible molecular mechanism(s) for these effects of cocaine, the impact of prenatal exposure to cocaine on hippocampal PKC was examined in offsprings of cocaine-injected female rabbits. The subcellular distribution of PKC activity and immunoreactivity were determined in hippocampi from 10-, 50- and 100-day-old rabbits which were exposed to cocaine prenatally. PKC activity in cytosolic and particulate fractions were assessed with or without stimulation with the phorbal ester, PMA. The results show that prenatal exposure to cocaine markedly redistributes PKC activity from the cytosol to membranes. This effect appears to last for at least up to 100 days postnatally. The extensive increase in membrane-associated PKC activity renders ineffective PMA-induced enzyme redistribution in these animals. Immunoblot analyses reveal that the increase in membrane PKC activity is due to increases in the three PKC isozymes - α, ß and γ - in cocaine-exposed animals. The results suggest that prenatal exposure to cocaine promotes an increase in membrane PKC membranes which last into adulthood and may be associated with functional alterations in these animals.

Supported by USPHS grant # 5P01DA06871

757.12

MATERNAL/FETAL DRUG ABUSE: A CHRONIC INTRAVENOUS MODEL FOR THE PREGNANT AND/OR GROUP-HOUSED RAT. C.F. Mactutus*, A.S. Herman and R.M. Booze. College of Pharmacy, Tobacco & Health Res. Inst. & College of Medicine, University of Kentucky, Lexington, KY 40546-0236.

Animal models for studying the developmental effects of maternal drug abuse are often based on chronic exposure of the pregnant rat. The suitability of animal models, however, has been constrained by the availability of an appropriate route of administration. The commonly employed s.c. and p.o. routes of administration fail to mimic the pharmacokinetics observed in humans with licit (e.g. nicotine) and illicit (e.g., cocaine, methamphetamine) drugs abused via inhalation or i.v. injection. The present study provides a method for the routine use of an i.v. model in pregnant and/or group-housed rats. Prior to mating, young adult female Sprague-Dawley rats were anesthetized (Ketamine/Rompun) for catheterization. A sterile Intracath i.v. catheter (22 ga., Becton/Dickinson) with a Luer-lock injection cap (Medex) was cut to ~10cm and used as a s.c. dorsally-implanted receptacle for chronic i.v. injections. The distal end of the catheter was inserted into the jugular vein and threaded centrally. Catheter patency was maintained by daily flushing with 0.2 ml of heparinized saline. Following 1 week of surgical recovery, the mean(median) number of estrus cycles to impregnation was 2.5(2). Duration of catheter patency was limited only by completion of exposure (birth) and was in excess of 35 days for all animals (N=20). Cocaine at a dose of 3 mg/kg (GD8-14 1X/day, GD15-20 2X/day) had no significant effect on maternal weight gain during pregnancy, litter size, or birth weights. In sum, an implanted s.c. receptacle provides a procedure for the routine i.v. administration of drugs to pregnant and/or group-house rats which avoids 1) the use of anesthesia/surgery during pregnancy, 2) the acute stress of i.v. tail vein injection, 3) the difficulties of mating and single housing associated with tethered i.v. catheters, and 4) in the case of cocaine, precludes the potential confounds of any drug-induced s.c. and p.o. lesions. (Supported by the UKMCRF, THRI, & DA 06638)

757.13

THE ROLE OF DOPAMINERGIC REUPTAKE BLOCKADE IN PRODUCING COCAINE'S EFFECTS ON CEREBRAL FUNCTION IN PERIWEANLING RATS. G.S. Frick*, E.A. Grose, H.E. Hughes, L.A. Freed, D.L. Dow-Edwards Laboratory of Cerebral Metabolism, Department of Pharmacology, SUNY-Health Science Center at Brooklyn, Brooklyn, NY 11203.

Although maternal cocaine use has declined nationwide within the last few years, the burden borne by infants and children exposed to cocaine in utero still necessitates investigation into the mechanisms underlying possible long-term neurochemical sequela. Previous work from our laboratory has indicated that inhibition of serotonin reuptake does not appear to contribute significantly to the actions of cocaine on developing brain (Frick G.S. et al., Soc Neurosci Abs 18:619.8, 1992). By comparing the effects of GBR12909, a selective dopamine reuptake inhibitor, to the effects of cocaine on brain metabolism, the contribution of this pharmacologic property of cocaine to the long-term neurochemical effects of cocaine can be estimated. Sprague-Dawley rats were mated in our animal facility and on day of parturition, pups were assigned to receive subcutaneous injections of cocaine or GBR12909 at 25mg/kg or equivalent volume of vehicle during days 11-20. Local rates of glucose utilization were determined when the animals were 21 days old using the deoxyglucose method of Sokoloff et al. (J Neurochem 28:897, 1977). The final dose of drug or vehicle was administered 20 min. prior to deoxyglucose administration. Two-way ANOVA revealed a significant main effect of treatment in 36 of 56 structures evaluated. Post hoc analysis indicated that both cocaine and GBR12909 administration, resulted in increased rates of glucose utilization in several brain regions selected for analysis ($P<0.05$, Tukey HSD). Glucose utilization values in all regions examined in the GBR12909-treated animals were found to be not significantly different from values in the cocaine-treated rats. Inhibition of dopamine reuptake may therefore be an important mechanism contributing to the effects of developmental cocaine exposure on adult brain function.

Supported by NIDA Grant DA04118 to Diana Dow-Edwards

757.14

PRENATAL COCAINE EXPOSURE ALTERS POSTNATAL DEVELOPMENT OF FOREBRAIN DOPAMINERGIC FUNCTION. Catherine Leslie [1]*, Matthew Robertson [1,2], Anthony Jung [3], Jennifer Lieberman [1] and James Bennett [1,2,4]. Departments of (1) Psychiatric Medicine, (2) Neurology, (3) Neuroscience and (4) Pharmacology. University of Virginia School of Medicine, Charlottesville, VA 22908.

Maternal cocaine abuse during pregnancy remains a vexing social problem with adverse neurodevelopmental consequences for the offspring. We have determined in rats the effects in offspring of maternal cocaine treatment for the last half of gestation upon postnatal development of forebrain D1 and D2 receptor mRNA and binding sites, and DA transporter density.

Pregnant SD rats received 20 mg/kg i.p cocaine b.i.d. (or saline) from gestational day 10-11 until delivery. Frozen forebrain sections of pups from postnatal day 1-35 were examined with quantitative autoradiography for D1 receptor (D1R), D2 receptor (D2R), DA transporter (DAT), and quantitative in situ hybridization (Q-ISH) for D1R and D2R mRNA's. Q-ISH utilized external standards of 45-48 mer oligonucleotides complementary to the 45-48 mer ^{33}P-dATP-labeled probes. The standards were synthesized with U for T substitution and thus have primary nucleotide sequences identical to the mRNA species being studied.

Prenatal cocaine exposure: 1) increased DAT from days 1-5, but decreased DAT at days 14 and 35; 2) increased D2R from days 6-35; 3) had no effect on D1R; 4) increased D2R mRNA at days 7 and 14 but not day 35. We conclude that prenatal cocaine exposure produces long-lasting (up to 5 weeks) effects on pre- and postsynaptic DA activity, similar to cocaine withdrawal in adults. (Supported by NIH MH00708 and NS30024).

757.15

NEITHER EARLY SEPARATION STRESS NOR ENVIRONMENTAL ENRICHMENT SELECTIVELY REVERSES BEHAVIORAL EFFECTS OF PRENATAL COCAINE. R.F. Smith*, C.N. Medici, T.A. Rivers, D.K. Sheppard. Dept. Psychol., G. Mason U., Fairfax, VA 22030

Two experiments were conducted to determine whether postnatal manipulations could reverse behavioral effects of prenatal cocaine. In Exp. 1, pregnant Long-Evans hooded rats were dosed with 0, 10, or 20 mg/kg/d cocaine from G7-G20. At birth, litters were weighed, sexed and culled to four of each sex. Half of each litter were separated from the dam for 15 min/day from P1-P20. Separation altered development of activity and spontaneous alternation, and adult water maze performance; cocaine affected these and footshock sensitivity. Separation stress tended to ameliorate some, but not all, cocaine effects; however, stress effects seen in cocaine-dosed animals were also seen in controls.

In Exp. 2, offspring born to dams receiving 0, 20, or 40 mg/kg/d cocaine were housed in isolated or enriched conditions from P21-P50. Enrichment altered activity, spontaneous alternation, Morris maze and DRL-20 performance; cocaine altered each of these except activity. As with early separation stress, enrichment tended to ameliorate some effects of cocaine, but ameliorative effects were neither found on all behaviors, nor selective for the cocaine-dosed group.

In summary, both early separation stress and environmental enrichment alter some behaviors in rats (as previously reported), but effects in cocaine-dosed animals are no greater than those in undosed subjects. Postnatal environmental manipulations may not be effective means for selectively reversing behavioral effects of prenatal cocaine.

Support: Grant J-203, The Jeffress Trust, Richmond, VA

757.16

THE EFFECTS OF COCAINE WITHDRAWAL ON THE ONSET OF MATERNAL BEHAVIOR. **J.M. Johns*, L.R. Noonan, L.I. Zimmerman, L. Li and C.A. Pedersen. Dept. of Psychiatry, Univ. of North Carolina, Chapel Hill, N.C. 27599.**

The onset of maternal behavior has been shown to be altered by cocaine treatment. We studied the effects of chronic cocaine treatment under conditions of withdrawal and non-withdrawal on the onset of maternal behavior in rats. Gravid rats received either s.c. injections b.i.d. of saline, or 15 mg/kg of cocaine throughout gestation. Half of the saline and cocaine treatment groups were withdrawn from treatment 24 hrs. before parturition and the remaining subjects continued treatment until 10 days postpartum. Frequency, duration and latency of 11 maternal behaviors were recorded for a 15 min. period, 30 mins. following delivery of a dam's last pup. Groups did not differ with respect to the effects of withdrawal condition on the onset of maternal behavior. Cocaine treated dams had a longer latency to retrieve ($p<.05$,) and lick pups ($p<.005$) than did saline dams. Cocaine treated dams also had a shorter crouch duration ($p<.06$) and a longer latency to crouch than saline dams. Withdrawal from cocaine for 24 hrs. did not alter the effects of cocaine treatment on the onset of maternal behavior. (HD 25255)

757.17

THE EFFECTS OF LATE EMBRYONIC COADMINISTRATION OF COCAINE AND ETHANOL ON THE YOUNG CHICK. I. B. Caton*, J. M. Dose, & J. F. Zolman. Depts. of Psychology and Physiology, Univ. of Kentucky, College of Medicine, Lexington, KY 40536.

Polydrug abuse is common among cocaine addicted mothers and cocaine probably interacts with alcohol to produce aversive synergistic effects on the human fetus. We studied the effects of prehatch exposure to cocaine and alcohol during rapid synapse formation in the chick forebrain (E15-E16) on acquisition and extinction of key-pecking before and after apomorphine challenge. Viable broiler chick embryos (N=76) were randomly allocated into cocaine (300μg), ethanol (10mg), coadministration (cocaine 300μg and ethanol 10mg), vehicle control (0.9% sterile saline plus 50 μg/ml bacitracin), and normal incubative groups (all doses given/egg/day). Significantly fewer chicks from the coadministration group hatched (60%) compared with the other groups (cocaine 89%, ethanol 80%, saline 76%, normal 86%). No significant group differences in posthatch body weight or temperature regulation were found. Chicks were given key-peck conditioning trials using heat reward when 1- or 2-days old. Overall, chicks were sensitive to the conditioning contingencies and increased their key-peck responding from the first (37%) to second (48%) autoshape session and decreased their responding by 15% during extinction. All chicks except those in the coadministration group showed an increase in responding following apomorphine (.5mg/kg) challenge and the cocaine group responded at a significantly higher rate (68%) than the coadministration group (35%). Hence, late embryonic coadministration of cocaine and ethanol significantly increases chick mortality and surviving chicks show a decreased responsiveness to apomorphine challenge.

757.18

PRENATAL COCAINE ALTERS SEROTONERGIC DORSAL RAPHE NEURONAL FUNCTION DURING THE PERINATAL PERIOD: *IN VITRO* ELECTROPHYSIOLOGICAL STUDIES. J.M. Lakoski, H. Zheng, B. Haber*, G. Karp, R.E. Garfield and M.L. Boyle. University of Texas Medical Branch, Galveston, TX 77555-0498

The consequence of exposure to the stimulant cocaine during gestation on subsequent postnatal development was investigated by physiological and pharmacologic analysis of serotonergic dorsal raphe neurons (DRN). Pregnant Sprague-Dawley female rats received cocaine (COC; 40 mg/kg, 1X daily, s.c.) or vehicle (VEH; saline, 1X daily, s.c.) from E8 through E20 and delivered at term. At P7 and P21, pups were sacrificed and DRN brain slices used to assess neuronal responses to perfusion application of COC and serotonin (5-HT). DRN amine levels of 5-HT and metabolites were also determined by HPLC techniques in both treatment groups.

Prenatal cocaine exposure significantly decreased P7 neuronal sensitivity to cocaine (30μM; % inhibition, 33.6±1.7 vs 47.2±3.6, VEH) and 5-HT (30μM; 18.1±6.1 vs 42±6.4, VEH) with recovery to VEH levels at P21 for 5-HT, but not COC, responses. These results demonstrate modulation of perinatal serotonergic function produced by prenatal stimulant exposure.

757.19

INTRAUTERINE COCAINE EXPOSURE ACCELERATES CLASSICAL CONDITIONING IN ADULT RABBITS. A.G. Romano*, W.J. Kachelries, K.J. Simansky & J.A. Harvey. Department of Pharmacology, Medical College of Pennsylvania, Philadelphia, PA 19129.

Classical conditioning of the NM response was carried out using 90-day old animals exposed to either cocaine (n=12) or saline (n=12) in utero. Thirty light and 30 tone CSs were paired with an airpuff US during each of 10 conditioning sessions. Rate of acquisition to the tone CS was significantly accelerated in cocaine-exposed animals. During subsequent testing with varying tone CS intensities, cocaine-exposed animals also exhibited a greater frequency of CRs than controls. A separate experiment using different groups of animals and different training parameters 1) replicated the faster acquisition of CRs to a tone CS after cocaine exposure; and 2) established that the alteration in the CS intensity function could be abolished by training cocaine- and saline-exposed animals to a common acquisition criterion. The latter finding indicates that the altered CS intensity function observed previously was due to overtraining in the cocaine-exposed group. Thus, cocaine exposure in utero may affect associative learning abilities in later, adult life. Supported by USPHS grant DA06871.

757.20

PRENATAL EXPOSURE TO COCAINE ALTERS LATER RESPONSIVENESS TO AN UNCONTROLLABLE STRESSOR IN PERIADOLESCENT AS WELL AS ADULT RATS. R.D. Wood*, V.A. Molina, J.M. Wagner, and L.P. Spear. Center for Developmental Psychobiology, Dept. of Psychology, SUNY-Binghamton, Binghamton, NY 13902-6000

Preliminary clinical and experimental data suggest that prenatal cocaine exposure may alter later stress responsivity. Indeed, we have previously observed that adult rats prenatally exposed to cocaine show less immobility in response to intermittent footshock and forced swim exposure relative to adult offspring of pair-fed and untreated control dams. The present study examined whether a similar attenuated immobility response would be seen in periadolescent offspring exposed prenatally to cocaine. Offspring were derived from Sprague-Dawley dams given daily subcutaneous injections of 40 mg/kg/3cc cocaine HCl from gestational days 8-20 (C40); pair-fed dams given saline injections (PF); and untreated control dams (LC). Every other day beginning on postnatal day 30 (P30), periadolescent offspring were exposed to a stressor: P30 - 5 min of intermittent footshock (1 mA, 1 sec. shock on a FI 60 sec. schedule); P32 - 4 min forced swim; P34 - 1 hr white noise stress; P36 - 5 min intermittent footshock. Immobility during the intershock interval (a characteristic response to stressors) was recorded during the initial and final shock session. No differences were observed among the three prenatal treatment groups in terms of the amount of immobility exhibited during the initial footshock exposure on P30. However, C40 offpring exhibited less immobility during the last footshock exposure, failing to show the increase in immobility from the first to last shock that was evident in LC and PF offspring. Together, our data suggest that responsivity to environmental stressors is altered in both periadolescent and adult rats following prenatal exposure to cocaine. [Supported by NIDA grants R01 DA04478 and K02 DA00140]

757.21

GREATER NEGATIVE TRANSFER OF PASSIVE TO ACTIVE AVOIDANCE LEARNING IN ANIMALS PRENATALLY EXPOSED TO COCAINE. J.M. Wagner, S.M. Brasser, M.R. Kaufman, S.B. Roepe, N.E. Spear, and L.P. Spear*. Center for Developmental Psychobiology, Dept. of Psychology, Binghamton University, Binghamton, NY 13902-6000.

Prenatal exposure to cocaine has been shown to produce certain learning deficits in both preweanling (Spear et al., 1989) and adult animals (Heyser et al., 1991). The present study examined transfer of passive to active avoidance learning as a consequence of prenatal exposure to cocaine. Offspring were derived from dams that received daily subcutaneous injections of 40 mg/kg/3cc of cocaine HCl (C40) from gestational days 8-20, as well as pair-fed (PF) and ad lib (LC) offspring. Twenty-five to twenty-seven day old rats received either passive avoidance training (PA) followed by active avoidance training (AA) in succession, or equivalent shock and handling followed by active avoidance training. Confirming reports by others, cocaine exposed offspring did not differ from controls in passive avoidance or active avoidance performance alone. However, animals prenatally exposed to cocaine exhibited significantly longer latencies to escape on the first AA trial than did PF or LC controls. This transfer deficit observed in C40 subjects is reminiscent of previous alterations we have observed in the ability of these animals to learn the reversal of a conditional discrimination, and suggests that these animals may be more susceptible to proactive interference.
[Supported by NIDA Grants R01 DA04478, K02 DA00140, F31 DA05511, and NIMH Grant R01 MH35219].

757.22

THE EFFECTS OF PRENATAL EXPOSURE TO COCAINE ON HEART RATE AND NONASSOCIATIVE LEARNING IN INFANT RATS. C.J. Heyser*, D.L. McKinzie, F. Athalie, N.E. Spear, and L.P. Spear. Center for Developmental Psychobiology and Dept. of Psychology, SUNY, Binghamton, NY 13902-6000.

Nonassociative learning was assessed in sixteen-day-old male and female rats prenatally exposed to cocaine and control offspring using the rate of habituation of a heart rate (HR) orienting response (bradycardia) to a tone. Offspring were derived from Sprague Dawley dams that received daily subcutaneous injections of 40 mg/kg/3cc cocaine HCl (C40) from Gestational Day 8-20, pair-fed control dams receiving saline injections (PF), and nontreated control dams (LC). Each rat was given 10 trials of a 10-sec 2000 Hz pulsing tone (80 dB), with tone presentations separated by a 60 sec interval. To assess retention, different groups of pups were given 10 additional trials 1, 2, 4 or 6 hrs later. For all trials, HR was measured during a 5-sec pretone period and during the 10-sec tone. C40 male offspring displayed significantly lower basal HR (487 ± 9.8) than both LC (521 ± 6.6) and PF (524 ± 4.9) offspring, with no prenatal treatment differences observed among the females. Although no differences were seen in rate of habituation (i.e. rate of nonassociative learning), prenatal exposure to cocaine was observed to have an influence on retention of the habituated response. Whereas LC and PF offspring retained habituation of the orienting response for less than 4 hrs, C40 offspring exhibited no forgetting after a 4-hr interval, with a loss of the habituation response in C40 pups occurring only at the 6-hr interval. Taken together, these data suggest that prenatal exposure to cocaine lowers basal HR in male offspring and facilitates retention of the habituated autonomic HR response in both male and female offspring.
[Supported by NIDA Grants R01 DA04478, K02 DA00140, F31 DA05511, and NIMH Grant R01 MH35219].

758.1

DIFFERENTIAL EFFECTS OF COCAINE ON CHARACTERIZED RAT DORSOLATERAL SEPTAL NUCLEUS (DLSN) NEURONS. D.Simms* and J.P. Gallagher. Dept. of Pharm. and Tox., Univ. of Texas Med. Br., Galveston, TX 77555.

Neurons within the DLSN can be distinguished into at least three different types based upon their firing properties (Twery et al., Neuroscience 46:669, 1992). Features which distinguish the three different groups include a significant afterhyperpolarization (AHP), a low-threshold calcium potential/spike, and burst firing activity. We now report that cocaine acts differentially depending upon the type of DLSN neuron from which intracellular recordings were made.

Standard intracellular recording methods were used to record from 29 DLSN neurons *in vitro*. Superfusion of cocaine (10μM) hyperpolarized the membrane potential of only 7/29 (24%) DLSN neurons held at -55mV to -65mV. On the other hand, serotonin (5-HT) and the selective 5-HT_{1a} agonist, 8-hydroxy-2-[*n*-dipropylamino]tetralin (8OHDPAT) reliably hyperpolarized all DSLN neurons to which they were applied. In 3 out of 7 neurons in which cocaine induced hyperpolarizations, the hyperpolarization gradually faded during continuous superfusion suggesting that the endogenous receptor mediating this response had become desensitized. Of the 7 neurons in which cocaine caused a membrane hyperpolarization, 5 were classified as having a significant AHP, while no such AHP was present in the other two neurons. Additionally, in 4 of 10 neurons exhibiting a low-threshold calcium potential/spike, cocaine depressed the calcium potential/spike but did not hyperpolarize these neurons. None of the burster cells (n=2) were hyperpolarized by cocaine. We suggest that these different actions of cocaine may be explained by unique intrinsic membrane properties found in different neurons and by unique patterns of synaptic organization within the DLSN. Supported by DA-07190.

758.2

PHYSIOLOGICAL ACTIONS OF COCAINE IN SENSORY CIRCUITS: I. IDENTIFICATION OF MONOAMINERGIC SUBSTRATES UNDERLYING DRUG-INDUCED ENHANCEMENT OF SOMATOSENSORY EVOKED DISCHARGES IN RAT BARREL FIELD CORTICAL NEURONS. I. Bekavac* and B.D. Waterhouse, Dept. of Physiol. and Biophys., Hahnemann U., Philadelphia, PA 19102

Previous reports from our laboratory have described a selective potentiating effect of systemically administered cocaine (0.25-1.0 mg/kg, i.v.) on long latency excitatory responses (E2) of rat "barrel field" cortical neurons to mystacial vibrissae stimulation. At brainstem, thalamic and cortical levels, the rat trigeminal system receives both norepinephrine (NE) - and serotonin (5HT) - containing afferents but only minimal input from dopaminergic sources. The goal of the present study was to determine which of these monoamine systems was responsible for the previously observed facilitating action of cocaine on E2 responses of "barrel field" cortical neurons. Two approaches were used: 1) evaluation of cocaine effects on cortical neuron responses to whisker stimulation in animals pre-treated with either PCPA (5HT depletion) or DSP4 (noradrenergic neurotoxin) and 2) assessment of the effects of selective monoamine uptake blockers (fluoxetine-5HT, desipramine-NE) on cortical neuron responses to whisker stimulation. In all cases extracellular recordings were obtained from spontaneously active single units in the "barrel field" cortex of halothane-anesthetized rats. Spontaneous activity and cellular responses to mechanical displacement of a single whisker were monitored before and after systemic (i.v.) administration of either cocaine (1.0 mg/kg), fluoxetine (0.25-8.0 mg/kg) or desipramine (0.25-2.0 mg/kg). Cocaine-induced increases in the E2 response component were routinely observed in DSP4 treated animals (n = 12 cells) but were reduced or abolished in PCPA treated rats (n = 10 cells). Fluoxetine (n = 10) but not desipramine (n = 10) produced cocaine-like potentiation of the E2 response to whisker stimulation. Overall these results point to a 5HT dependent mechanism as the substrate underlying cocaine's facilitating effects on long-latency somatosensory cortical neuron responses to receptive field stimulation. Such a mechanism could involve cocaine actions at 5HT-containing cell bodies, axon terminals or a combination of both. (Supported by NIDA DA 05117)

758.3

PHYSIOLOGICAL ACTIONS OF COCAINE IN SENSORY CIRCUITS: II. EFFECTS ON POSTSYNAPTIC POTENTIALS OF RAT SOMATOSENSORY CORTICAL NEURONS. F.M. Sessler*, W. Liu, R.D. Mouradian, R.C.S. Lin and B.D. Waterhouse, Dept. of Physiol. and Biophys., Hahnemann Univ., Philadelphia, PA 19102.

In a previous report we described various actions of cocaine on intrinsic membrane properties of somatosensory cortical neurons (Sessler et al., Soc. Neurosci. Abst. 1992). These observations were indicative of a differential action of cocaine on different subpopulations of layer V neurons, suggesting that certains classes of neurons may be more sensitive to the action of the drug than others. To further examine this hypothesis and its implications for the signal processing capabilities of individual sensory neurons, experiments were conducted using an in vitro brain slice preparation from rat somatosensory cortex. Microelectrodes containing either neurobiotin (2-3%) or lucifer yellow (5%) were used for electrophysiological and morphological characterization of individual layer V neurons. Postsynaptic potentials (EPSP and IPSP) were evoked by stimulating the cortical white matter. Cocaine was applied at various concentrations (0.3-100uM) to examine the full spectrum of the drug action, i.e. from psychostimulant to local anesthetic. Bath application of cocaine at high concentrations (10-100uM) routinely produced a dose dependent decrease in EPSP amplitude, EPSP area, EPSP duration (measured at half amplitude) and evoked spiking, as well as an increase in EPSP latency, peak latency and rise time. These parameters were altered to varying degrees in different subclasses of electrophysiologically and morphologically identified layer V neurons. At lower concentrations (0.3-1uM), we observed cases where cocaine produced a clear enhancement of EPSP amplitude. In addition, bath application of cocaine (1-30uM) was found to differentially affect short and late components of EPSPs, as well as EPSP/IPSP. These results support the possibility that cocaine exerts complex influences on cells within the cerebral cortical circuitry and underscores the need to obtain specific information about the effects of this compound on different cell types in order to assess the impact of this drug on the signal processing capability of a sensory cortical network. (Supported by NIDA DA08405)

758.4

ELECTROPHYSIOLOGICAL SENSITIVITY OF AMYGDALA NEURONS TO DOPAMINE AND SEROTONIN FOLLOWING REPEATED COCAINE ADMINISTRATION. **P.M. Callahan*, E.J. Mah and K.A. Cunningham. Dept. Pharmacology, Univ. of Texas Medical Branch, Galveston, TX 77555.**

The mesolimbic dopamine (DA) region appears to be critically involved in the development and expression of behavioral sensitization to cocaine. The amygdala is an important mesolimbic brain structure with inputs from both DA and serotonin (5-HT) neurons in the midbrain. Our previous studies have indicated that iontophoretic administration of DA or 5-HT exerts prominent inhibitory actions on glutamate-activated amygdala neurons; DA and 5-HT also act in a "synergistic" manner to enhance their inhibitory actions on these neurons.

The present study used extracellular iontophoretic techniques to assess whether repeated cocaine injections (15 mg/kg, 2 x/day for 7 days, i.p.) might alter the observed inhibition of amygdala neurons produced by DA (0.1M) and 5-HT (0.04M) in urethane-anesthetized rats. Both DA and 5-HT produced a current-related (2.5-40 nA) inhibition of glutamate-activated basolateral and central amygdala neurons; maximal inhibition observed was approximately 63% and 56% for DA and 5-HT, respectively in each amygdala nuclei. Following a 24 hr withdrawal period, cocaine treatment produced a non-significant trend towards reducing the inhibitory actions elicited by both DA and 5-HT. Further assessment regarding this subsensitivity as well as possible implications in behavioral sensitization are ongoing.

Supported by DA05708 and DA06511.

758.5

COCAINE INCREASES STRIATAL SINGLE-UNIT ACTIVITY IN FREELY MOVING RATS. G.V. Rebec*, L.A. Ruble, and I.M. White, Prog. Neural Science, Dept. Psychology, Indiana University, Bloomington, IN 47405

Amphetamine produces a pattern of behavioral excitation in rats that includes locomotion, sniffing, and repetitive head movements. In the striatum, this drug activates neurons that increase firing rate in close temporal association with movement but suppresses the activity of nonmotor-related neurons (Haracz et al., Neurosci. Biobehav. Rev., 17:1-12, 1993). This divergence in striatal activity may play a critical role in amphetamine-induced behavioral effects. To assess the generality of these findings to other psychomotor stimulants, we monitored the effects of cocaine on striatal neurons in awake, behaving rats.

Cocaine (20 and 40 mg/kg) elicited a series of repetitive sniffing and head bobbing behaviors that were accompanied by frank increases in striatal neuronal activity. Thus, both motor- and nonmotor-related neurons typically increased firing rate to more than 150% of the resting baseline rate. Subsequent administration of haloperidol (1.0 mg/kg) blocked both the behavioral activation and the increase in striatal neuronal activity. Taken together, these results suggest that unlike amphetamine cocaine exerts uniformly excitatory effects on striatal neurons that may mediate some important behavioral differences between these drugs.

Supported by the National Institute on Drug Abuse, DA-02451.

758.6

THE EFFECTS OF COCAINE ON SINGLE UNITS CORRELATED WITH VERTICAL HEAD MOVEMENT IN THE LATERAL STRIATUM OF RAT DURING PERFORMANCE OF A VERTICAL HEAD MOVEMENT OPERANT TASK. M.Wolske*, C.Pederson, and M.O.West. Psych. Dept., Rutgers Univ., New Brunswick, NJ 08903.

Considerable evidence has established that the lateral striatum is a critical structure for the performance of stereotyped movements following higher doses of psychomotor stimulants such as cocaine. In order to provide an initial characterization of the effects of cocaine on single neurons in the lateral striatum correlated with vertical head movements, a prevalent stereotyped behavior in rats, an operant task was developed which reinforced with water delivery either up or down head movements, depending on the direction correlated with the neural activity of the particular recorded cell. Following approximately 1hr. of training, rats (n=7) were able to perform on a FR3 or FR5 schedule. After training, an i.p. injection of saline was followed 20 min. later by an i.p. injection of cocaine (10mg/kg). Neural and behavioral activity were continuously monitored using a Brainwave computer system. Cocaine typically increased the frequency of vertical head movements. Drug effects on firing were assessed in terms of head movements exhibiting similar form pre- versus post-injection. Preliminary results indicate that neural activity (n=10) increased, decreased, or did not change, depending on the level of movement (e.g., short vs long) at which the effect of the drug was studied. Work was supported by grant DA 04551.

758.7

ELECTROPHYSIOLOGICAL EFFECTS OF COCAINE ON THE FIRING OF MEDIAL PREFRONTAL CORTICAL (mPFC) CELLS: THE ROLE OF SEROTONIN (5-HT) AND DOPAMINE (DA). J.Y. Zhang* and R.Y. Wang. Dept. of Psychiatry and Behav. Sci. SUNY at Stony Brook, Stony Brook, NY 11794-8790.

It has been hypothesized that both the DA and 5-HT systems are of fundamental importance for the action of cocaine. It is not known where and how DA and 5-HT may interact to mediate the actions of cocaine. By using the techniques of single cell recording and microiontophoresis, we have investigated the role of 5-HT and DA in mediating the action of cocaine on mPFC cells, which have been shown to be involved in cocaine self-administration. Sprague-Dawley rats were anesthetized with chloral hydrate and put in a stereotaxic apparatus. Iontophoresis of cocaine at low ejecting currents (0.5 - 5 nA) did not have direct effect on the firing of mPFC cells but it markedly potentiated the inhibitory action of both 5-HT and DA. This potentiating effect of cocaine was blocked by the 5-HT_3 receptor antagonist granisetron. At higher ejecting currents (10 - 40 nA), cocaine induced a current (dose)-dependent suppression of mPFC cells' firing, which was blocked more effectively by 5-HT receptor antagonists (e.g. granisetron and clozapine) than DA antagonists (e.g. eticlopride, SCH 39166 and haloperidol). These results suggest that the action of cocaine cannot be explained solely by its interaction with the DA system. Indeed, cocaine's suppressant action was markedly attenuated by the pretreatment with reserpine plus either α-methyl-p-tyrosine or parachlorophenylalanine and cocaine's action could be re-instated in these rats by intavenous administration of benserazide together with L-DOPA and 5-HTP, respectively. Combined, our results indicate that both 5-HT and DA are critical in the action of cocaine on mPFC cells.

758.8

REPEATED COCAINE ADMINISTRATION INDUCES DESENSITIZATION OF THE RESPONSE OF MEDIAL PREFRONTAL CORTICAL (mPFC) CELLS TO COCAINE, DOPAMINE (DA) AND SEROTONIN (5-HT). R.Y. Wang and J.Y. Zhang. Dept. of Psychiatry and Behav. Sci. SUNY at Stony Brook, Stony Brook, NY 11794-8790.

The results from our previous study (Zhang and Wang, accompanying abstract) show that both 5-HT and DA play important roles in mediating the action of cocaine in the mPFC. The aim of the present study was to investigate the effect of repeated cocaine treatment on the sensitivity of 5-HT and DA receptors in the mPFC. Groups of rats were treated with either cocaine (15 mg/kg, i.p., b.i.d.) or saline (1 ml/kg, i.p., b.i.d.) for 7 days and withdrawn from drug treatment for 1, 15, or 30 days. The same micropipettes were used to compare the responses of mPFC neurons to cocaine, DA, 5-HT, and gamma-aminobutyric acid (GABA) in pairs of cocaine versus saline treated rats. Iontophoresis of cocaine, DA, 5-HT or GABA produced a current (dose)-dependent suppression of the firing of mPFC cells. Repeated cocaine treatment shifted the dose-response curves of cocaine, 5-HT and DA, but not that of GABA, significantly to the right, indicating a marked tolerance of the response of mPFC cells to cocaine, 5-HT and DA but not to GABA. The apparent tolerance effect lasted for more than 2 weeks following cocaine withdrawal. After 1 month of withdrawal from cocaine treatment the response of mPFC cells to cocaine, 5-HT and DA had returned to control levels. Since the mPFC is an important component of the reward circuits, the reduction of cocaine's effect on mPFC cells with repeated administration may be a mechanism of initiating or maintaining cocaine tolerance. It remains to be determined which receptor subtypes of 5-HT and DA are critically involved in the tolerance effect induced by repeated administration of cocaine.

DRUGS OF ABUSE: COCAINE—NUCLEUS ACCUMBENS

759.1

COCAINE INHIBITS MESOLIMBIC DOPAMINE RELEASE: CHRONOAMPEROMETRY IN FREELY MOVING RATS E.A.Kiyatkin[1]* and E.A.Stein. Depts of Psychiatry[1] and Pharmacology, Medical College of Wisconsin, Milwaukee, WI 53226.

Cocaine's ability to inhibit dopamine (DA) uptake into presynaptic mesocorticolimbic terminals is generally believed to provide the principal cellular mechanism of its reinforcing properties. Microdialysis, a sampling technique whose temporal resolution is approximately that of cocaine's half life, has demonstrated increased extracellular DA levels during passive cocaine injections and self-administration behavior. The present study employed high-speed chronoamperomtry (IVEC-10) with Nafion-coated carbon fiber electrodes to estimate changes in nucleus accumbens extracellular DA levels following passive IV cocaine administration (0.8 mg/kg, 1 daily injection or 20 injections/session every 6±2 min) in freely moving rats habituated to the drug environment. The initial cocaine injection led to relatively long (20-30 min), pronounced (-20-60 nM) and consistent *decreases* in DA-related signals followed by a slow increase above baseline level. The late, slow signal increase was absent upon repeated drug administration. Rapid biphasic signal fluctuations accompanied by a slow *decrease* in baseline were seen in this case. The initial decrease (15-20 nM) began to return to baseline after about 100-140 sec post injection. In contrast, when drug injections were paired to a light stimulus, a powerful increase in DA-related electrochemical signal (+100-200 nM) was seen in experienced rats after both light alone (conditioned release) and the initial cocaine injection of a session ("sensitization"). In this case, biphasic signal fluctuations associated with subsequent drug injections were superimposed upon a relatively stable tonic increase in signal. These data suggest that in addition to its reuptake inhibiting action (manifested at high doses concomitant with DA cell activation), cocaine may also inhibit impulse-dependent DA release. The combination of these two functionally opposite actions of cocaine may be involved in the mediation of its unique psychogenic properties. Finally, stimuli and events previously paired to cocaine can cause a powerful conditioned DA activation which may have significance in the development and maintenance of cocaine-taking behavior.

759.2

EXTRACELLULAR SEROTONIN AND DOPAMINE IN THE NUCLEUS ACCUMBENS FOLLOWING UNLIMITED-ACCESS TO COCAINE SELF-ADMINISTRATION. L.H. Parsons*, G.F. Koob and F. Weiss The Scripps Research Institute, Dept. of Neuropharmacology. CVN15, 10666 N. Torrey Pines Rd., La Jolla CA 92037.

Chronic cocaine exposure has been reported to result in alterations of both the dopaminergic and serotonergic systems of the rat, such as an enhanced extracellular response to cocaine challenge and changes in the sensitivity and density of receptors for both neurotransmitters. Following repeated cocaine injections or unlimited-access cocaine self-administration, basal extracellular dopamine (DA) levels in the nucleus accumbens (N ACC) are reported to be decreased from control levels. Since recent reports suggest that extracellular serotonin (5-HT) can stimulate DA release, the extracellular concentrations of 5-HT and DA were monitored in the N ACC following 12 hours of unlimited-access cocaine self-administration using in vivo microdialysis. Male Wistar rats were implanted with jugular catheters and trained to self-administer cocaine (0.25 mg/inf) on an FR-5 schedule of reinforcement in three hour limited-access sessions until stable responding for cocaine was maintained for three consecutive days (+/- 10% total rewards). Dialysate concentrations of DA and 5-HT (0.1 µl/min flowrate) were analyzed for one hour prior to, during, and for seven hours after the 12-hour unlimited access self-administration session (FR-5). Dialysate DA and 5-HT concentrations were significantly increased during the self-administration session as compared with pre-session baseline levels. In addition, dialysate concentrations of both DA and 5-HT significantly decreased below pre-session baseline levels during the seven hours following the unlimited access session. Catheterized, cocaine-naive animals displayed no significant alterations in dialysate 5-HT or DA over the same time course. These results indicate that as with DA, extracellular 5-HT is decreased in the N ACC following prolonged exposure to cocaine.

759.3

D-1 RECEPTOR ANTAGONIST INJECTED INTO THE ACCUMBENS SHELL OR CENTRAL AMYGDALA INCREASES COCAINE SELF-ADMINISTRATION IN THE RAT. S. B. Caine*, S. C. Heinrichs, C. E. Williams, V. L. Coffin[1] and G. F. Koob. Dept. of Neuropharmacology, The Scripps Research Institute, La Jolla, CA 92037, and [1]Schering-Plough Research, Kenilworth, NJ 07003.

Previous studies have demonstrated that systemic pretreatment or intracerebral injection into the nucleus accumbens with the D-1 dopamine receptor antagonist SCH23390 increases cocaine self-administration in the rat (Koob et al., Neurosci. Lett. 79:315, 1987; Maldonado et al., Pharmacol. Biochem. Behav. 45:239, 1993). This study tested the hypothesis that D-1 receptors in the nucleus accumbens shell, central nucleus of the amygdala and dorsal striatum are neuroanatomical substrates of cocaine self-adminstration. Male Wistar rats equipped with bilateral 30 ga intra-cerebral cannulae were implanted with i.v. jugular catheters and trained to self-administer cocaine (0.25 mg/injection) on an FR5 schedule of reinforcement (n=5-6/group). SCH23390 (0, 0.5, 1.0, or 2.0 µg/0.33 µl/side) increased cocaine self-administration in the first 20 min to as much as 165% of baseline values when injected into the accumbens shell or central amygdala ($p<0.01$), but not the dorsal striatum. Microinjections into all three sites increased cocaine self-administration over the entire 3 hr session. Autoradiographic studies of the diffusion of [3H]-SCH23390 from the central amygdala at 2, 10, 60, and 120 min post-injection in separate animals revealed detectable diffusion fields approximately 1.2, 1.6, 2.2, and 2.6 cubic mm in diameter, respectively, and a progressive dissipation of the signal with increased time. These results suggest that the site-specificity of intra-cerebral injections of SCH23390 is time-dependent. Moreover, based on the rapid action of intra-cerebral injection of SCH23390, D-1 receptors in the accumbens shell and central amygdala may be neural substrates of cocaine self-administration in the rat.

759.4

CELLULAR INTERACTION OF BUPRENORPHINE AND COCAINE IN RAT NUCLEUS ACCUMBENS. K.D. Nantwi*, E.P. Schoener, J. Cruz, D. Bradley, S. Hicks, T. Reed. Department of Pharmacology, Wayne State University, Detroit, MI 48201.

Buprenorphine, a mixed opioid agonist/antagonist, increases dopamine turnover in areas of the brain associated with reinforcement. The drug has attracted special interest due to behavioral, clinical, and neurochemical reports that it attenuates cocaine effects. The purpose of this investigation was to explore the cellular basis for this interaction. *In vivo* electrophysiologic experiments examined the actions of intravenous buprenorphine and cocaine, alone and in combination, on neuronal behavior in rat nucleus accumbens.

The effects of cocaine (0.25-1.0mg/kg) on the discharge rate of spontaneously-active single neurons were monitored before and after intervention with buprenorphine (0.25mg/kg). This dose of buprenorphine did not evoke reliable change in neuronal activity when tested alone. The predominant effect of cocaine was depression, although excitation and biphasic responses (excitation followed by depression) were observed. The cocaine-induced depression was diminished following intervention with buprenorphine ($p\leq0.05$). While significantly different from control, cocaine-induced facilitation was not correlated with the drug dose. In contrast to its attenuation of cocaine-induced depression, buprenorphine did not alter the excitatory response to cocaine.

These data imply that buprenorphine differentially modulates specific cellular actions of cocaine. In light of reports that buprenorphine suppresses cocaine self-administration, the current findings may prove significant in elucidating the basis of this inhibition.

This study was supported in part by a grant from the National Institute on Drug Abuse.

759.5

IN VIVO ANTISENSE BLOCKADE OF *C-FOS*-EXPRESSION IN THE NC. ACCUMBENS PREVENTS THE LOCOMOTOR STIMULANT ACTION OF SYSTEMIC COCAINE IN RATS. M. Heilig*, J.A. Engel and B. Söderpalm. Dept. of Psychiatry and Neurochemistry, and Dept. of Pharmacology, Univ. of Göteborg, S-431 80 Mölndal, Sweden.

Systemic administration of cocaine induces a transient expression of the immediate-early genes *c-fos* and *jun B* in the rat striatum through an activation of dopaminergic D_1-receptors. The functional role of this phenomenon remains unknown.

The use of antisense oligodeoxynucleotides has recently made it possible to selectively inhibit neuronal gene expression *in vivo*. We have used this approach to examine the hypothesis that *c-fos*-expression may be of importance for the locomotor stimulant action of cocaine. Rats were cannulated with bilateral chronic cannulas aimed at the Nc. Accumbens. Following recovery, a phosphorothioate modified 15-mer antisense oligodeoxynucleotide targeted at the *c-fos*-sequence immediately downstream the initiation codon was injected (5 nmoles/side). In addition to vehicle, a sense oligo injected group served as control. Eight hours later, spontaneous locomotor activity was measured for 30 min. Subsequently, cocaine (10 mg/kg i.p.) was given, and locomotor activity was measured for an additional 60 min. Cocaine induced locomotor stimulation was blocked by the antisense, but not by the sense oligo. Spontaneous locomotor activity was not affected by either treatment.

This finding implies that *c-fos* induction in the Nc. Accumbens plays a role in the psychostimulant action of central stimulants.

759.6

FIRING PATTERNS OF NUCLEUS ACCUMBENS NEURONS DURING COCAINE SELF-ADMINISTRATION AND APPETITIVE REINFORCEMENT IN RATS. R.M. Carelli*, V.C. King and S.A. Deadwyler. Bowman Gray School of Medicine, Wake Forest Univ., Winston-Salem, NC 27157.

Involvement of the nucleus accumbens in reinforcement processes was investigated in rats trained to self-administer cocaine via response contingent intravenous drug infusions (0.33 mg cocaine/infusion). 202 neurons were recorded from permanently implanted multiple electrode arrays (8 microwires) inserted bilaterally into the nucleus accumbens and/or ventral striatum (NA-VS) in animals (n=11) exhibiting stable interinfusion intervals (INT) during test sessions consisting of 16-30 drug delivery episodes. Of the 202 neurons, 74% (149 cells) showed no phasic changes (increase or decrease) in firing pattern relative to the reinforced response while 26% (53 cells) showed significant phasic changes in firing time-locked to the drug-reinforced lever press. NA-VS neurons could be classified into 6 types based on differential phasic changes in firing pattern which occurred immediately before, during or following the drug reinforced response. Anticipatory increases in firing occurring before the lever press were modified by changing the response/reward (FR) contingency. NA-VS neurons exhibiting robust increases following the lever press fired randomly during non-contingent drug delivery. In addition, the establishment of differential discharge patterns time-locked to the response for each of the 6 types did not emerge within the session until after stabilization of regular INTs. Analysis of the firing patterns of NA neurons (n=68 cells) obtained in the same subjects (n=4) trained to lever-press for water reinforcement revealed that 25% (17 cells) exhibited phasic changes in firing patterns relative to the water reinforced response. Thus, NA neurons encode specific features of reward-seeking behavior including the initiation, execution and delivery for both types of reinforcers tested. These findings are considered in terms of a common neural circuitry responsible for drug and appetitive reinforcement. *[Supported by grants NIDA DA05535 to RMC and DA06634 and DA00119 to SAD.]*

759.7

ANATOMICAL LOCALIZATION OF DOPAMINE D1 AND D2 RECEPTORS INVOLVED IN COCAINE-INDUCED LOCOMOTOR ACTIVITY. J.D. Willis*, J.C. Redmond and J.L. Neisewander. Department of Psychology, Arizona State University, Tempe, AZ 85287-1104.

Cocaine-induced locomotion is mediated, in part, by dopamine (DA) in the nucleus accumbens (NAc). The first aim of this study was to determine which DA receptor subtypes in the NAc are involved in cocaine-induced locomotion. Rats received bilateral injections into the NAc of either saline, the D1-selective antagonist SCH 23390 (0.1, 0.3, 0.5 µg/0.5 µl/side), or the D2-selective antagonist sulpiride (0.1, 0.3, 0.5 µg/0.5 µl/side). Fifteen minutes later, they received a systemic injection of cocaine (15 mg/kg, i.p.) and were immediately placed into an automated activity chamber for one hour. Cocaine-induced locomotion was dose-dependently blocked by sulpiride, but not by SCH 23390.

The second aim of this study was to develop a technique that enables visualization of the receptors occupied by the intracranially administered drugs. Rats were injected intracranially with their respective dose of selective antagonist used to assess behavior. Fifteen minutes later, they were given a systemic injection of the nonselective irreversible antagonist, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ; 10 mg/kg, i.p.). The rats were sacrificed 90 minutes later. D1 or D2 receptors were then labeled with ^{3}H-SCH 23390 and ^{3}H-sulpiride, respectively, in sections containing the NAc. The radioligands bound to the receptors protected from EEDQ-induced inactivation by the antagonist given *in vivo*. Therefore, the resulting autoradiograms allowed visualization of the precise population of receptors that had been occupied by the intracranially administered drug. This new technique provides greater anatomical control relative to techniques currently used to localize drug diffusion and provides an estimate of the density of receptors occupied by the drug. (Supported by USPHS grant DA07730 and a Faculty Grant-in-Aid Award from Arizona State University).

759.8

CHRONIC REPEATED COCAINE ADMINISTRATION RESULTS IN UPREGULATION OF D_1 DOPAMINE RECEPTORS IN SPECIFIC RAT BRAIN REGIONS. E.M. Unterwald*, J. M. Rubenfeld, and M.J. Kreek. The Rockefeller University, New York, NY 10021

Cocaine inhibits the reuptake of dopamine into presynaptic dopamine neurons thereby increasing the concentration of dopamine in the synapse. In the present study, the time course of changes in dopamine receptor densities was determined following "binge" cocaine administration. Male Fischer rats were injected three times daily at one-hour intervals with cocaine, 45 mg/kg/day, or saline for 1, 2, 7, or 14 days. The dosing regimen was selected to better mimic the way cocaine is often administered by human addicts both in terms of temporal pattern and in relation to circadian rhythm. Thirty minutes after the last injection, animals were killed and brains were processed for quantitative receptor autoradiography using selective labelling conditions for D_1 dopamine receptors. D_1 receptors, as measured with [^{3}H]SCH 23390, were found to be significantly higher in the nucleus accumbens (221.4 $\pm$ 17.9 vs. 250.4 $\pm$ 19.5 fmol/mg tissue; p=.023), olfactory tubercle (245.1 $\pm$ 10.6 vs. 275.9 $\pm$ 15.2 fmol/mg tissue; p=.002), and ventral pallidum (131.7 $\pm$ 10.8 vs. 156.3 $\pm$ 18.9 fmol/mg tissue; ,p=.02) of rats injected with cocaine for 14 days. There were no significant changes in D_1 receptors in the cingulate cortex or caudate putamen. Acute administration of cocaine (one or two days) had no effect on D_1 receptor expression in any of these brain regions. Animals injected with cocaine for 7 days had elevated numbers of D_1 receptors in the nucleus accumbens and olfactory tubercle, although these increases were not statistically significant. The results of this study demonstrate that D_1 dopamine receptors undergo upregulation in the nucleus accumbens, olfactory tubercle, and ventral pallidum following chronic, but not acute, administration of cocaine in a binge-like regimen.
(Supported by ADAMHA-DA-P5005130 and The Aaron Diamond Foundation)

759.9

ENSEMBLE RECORDING IN FRONTAL CORTEX AND NUCLEUS ACCUMBENS IN FREELY MOVING RATS DURING COCAINE SELF-ADMINISTRATION. *J.Y. Chang*, J.M. Paris, S.F. Sawyer and D.J. Woodward.* Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC 27157

The mesolimbic system, which includes the nucleus accumbens (NAc) and prelimbic frontal cortex (PFC) has been considered to be a critical circuit involved in drug self-administration. The aim of this study was to examine how PFC and NAc operate together to mediate cocaine self-administration. Our previous studies using chronic unit recording techniques demonstrated that neurons in NAc exhibit altered firing rates immediately before and after a lever press for a cocaine injection, suggesting that the NAc plays a role both in triggering and reinforcing this behavior. A total of 32 recording microwires (stainless steel, 50 µm diameter) were implanted bilaterally in both PFC and NAc. The concurrent spike activity of up to 24 isolated neurons was monitored during self-administration. As in our earlier studies for NAc, phasic spike activity was also observed in PFC in relation to lever pressing for cocaine. Of 44 neurons recorded in PFC, 9 neurons exhibited altered firing rates in the seconds before lever pressing, 6 with an increase and 3 with a decrease. Behavioral correlates with neuronal activity were assessed from videotapes of rats self-administering cocaine. While transient spike activity occurred in both NAc and PFC in relation to behaviors specific to lever pressing (e.g., turning or rearing towards lever), the changes in firing rates were not necessarily synchronized. Moreover, different neurons *within* these regions exhibited heterogeneous behavioral correlates. Our conclusion is that multiple components of the PFC and NAc become active at different times to drive the chain of behaviors that lead to cocaine self-administration. *Supported by DA-02338 (DJW).*

759.10

COMPARISON OF INTRA-ACCUMBENS COCAINE AND MUSCARINIC AGONISTS ON LOCOMOTOR ACTIVITY IN THE RAT. L.G. Sharpe*[1] and J.M. Witkin[2]. Genetics Section[1] and Drug Development Group, Psychobiology Section[2], NIDA/Addiction Research Center, P.O. Box 5180, Baltimore MD 21224.

Striatal cholinergic and dopaminergic neurons interact to regulate the release of ACh and DA but the nature of this interaction in the nucleus accumbens (NAc) to influence locomotor behavior is unknown. Bilateral cannulae aimed at the rostral pole of the NAc were chronically implanted in adult male Sprague Dawley rats. They were habituated for 1 week to the locomotor apparatus prior to testing. Oxotremorine-M (Oxo-M), carbachol (Car), bethanachol (Bet), cocaine methiodide (Coc-M), cocaine HCl (Coc), or saline were infused (0.5 µl in 2 min) bilaterally in the NAc. Locomotor activity and number of vertical movements (rearing) increased in a dose-dependent manner following Oxo-M (0.025-0.1 nmol), Car (0.3-1 nmol), Coc-M (0.3-20 nmol), and Coc (1-100 nmol). Bet (1-30 nmol) was less efficacious than the other compounds. Oxo-M and Car curves were parallel but both were steeper than curves produced by Coc-M and Coc. Methyl atropine (1 nmol) significantly antagonized the stimulant effects of Oxo-M but not that of Coc-M. Muscarinic receptors in the NAc appear to regulate dopaminergic tone involved in locomotor stimulation.

759.11

DOSE-RESPONSE EFFECT OF COCAINE HCl AND THE NOVEL TROPANE ANALOG, 2ß-PROPANOYL-3ß-(4-TOLUYL)-TROPANE (PTT) ON NUCLEUS ACCUMBENS (NACC) EXTRACELLULAR DOPAMINE AND LOCOMOTOR ACTIVITY. C. Co, S.E. Hemby, H. Davies, S.I. Dworkin, & J.E. Smith*. Center for Neurobiological Investigation of Drug Abuse, Dept. of Physiology and Pharmacology, Bowman Gray Sch. of Med., Wake Forest Univ, Winston-Salem, NC, 27157

PTT, a novel tropane analog, is known to be approximately 20 times more potent than cocaine in binding to the RTI-55 site on the dopamine uptake mechanism. Therefore, the present study was undertaken to compare locomotor activity and alterations in extracellular NACC dopamine using in vivo microdialysis following cocaine (3.0, 10.0, or 30 mg/kg; IP) or PTT (0.3, 1.0, or 3.0 mg/kg; IP). Dopamine, DOPAC, HVA, and 5-HIAA concentrations were assessed in all groups using microbore HPLC with EC detection. Cocaine concentrations were assessed in groups receiving cocaine using microbore HPLC with UV detection. Activity was monitored and dialysis samples were taken over an eight hour period (1 hr baseline, 1 hr following vehicle, and 6 hrs following drug). Cocaine and PTT elevated locomotor activity and extracellular dopamine in a dose dependent manner. The peak dopamine concentration and the locomotor activity occurred within the first hour following drug injection for cocaine and PTT. However, the duration of action was approximately 90 minutes for the highest dose of cocaine while the 1.0 and 3.0 mg/kg doses of PTT elevated dopamine concentrations for approximately 5 hours. Furthermore, the temporal profile of locomotor activity differed between cocaine and PTT but appeared to be closely related to enhanced extracellular NACC dopamine concentrations. Furthermore, extracellular dopamine levels were directly related to the NACC cocaine levels for the cocaine groups. (Supported by USPHS grants DA-6634, DA-3628, and DA-00114).

759.12

CHARACTERIZATION OF COCAINE-REGULATED GENES ISOLATED BY SUBTRACTIVE HYBRIDIZATION FROM RAT NUCLEUS ACCUMBENS. J. R. Walker* and K. A. Sevarino. Division of Molecular Psychiatry, Departments of Psychiatry and Pharmacology, Yale University School of Medicine, New Haven, CT 06508.

In rats chronically treated with cocaine, biochemical and electrophysiological evidence suggests long term changes in the nucleus accumbens (NAc) which may underlie the reinforcing and sensitizing properties of the drug. These long term changes are likely to be reflected by changes in gene expression. To detect such transcriptional differences, we have developed a subtractive hybridization procedure that identifies sequences that are upregulated by chronic cocaine administration. Subtractive enrichment was performed with target cDNA synthesized from mRNA isolated from the NAc of rats treated with twice daily 15 mg/kg i.p. injections for 14 days. Driver mRNA was isolated from the NAc of saline-treated rats. Using a target to driver ratio of 1:15, a total of 1563 clones were isolated from a cocaine-treated NAc cDNA library, and are being characterized. Thus far, we have determined that mRNAs for myelin basic protein, cytochrome oxidase subunits, and several novel proteins within the limbic system are differentially regulated by cocaine. The relationships of these findings to the known actions of cocaine are being investigated.

759.13

MODULATION OF COCAINE SELF-ADMINISTRATION BY CYCLIC AMP ANALOGUES IN THE NUCLEUS ACCUMBENS. D.W. Self*, S. Chi and E.J. Nestler. Laboratory of Molecular Psychiatry, Yale University School of Medicine, New Haven, CT.

Recent evidence suggests a role for Gi/Go proteins in the nucleus accumbens (NAc) in mediating cocaine and heroin reinforcement (Self et al., submitted), and demonstrates that adaptations occur in the G protein-cAMP system in the NAc following chronic cocaine or morphine administration (Nestler, 1992). In the present study, the possible involvement of the NAc-cAMP system in cocaine reinforcement was tested directly by infusing activators or inhibitors of protein kinase A (PKA) into the NAc of rats prior to cocaine self-administration tests. Two compounds that mimic the effects of cAMP on PKA, Sp-cAMPS (40 nmol/1ul) and dibutyryl cAMP (10-30 nmol/1ul), shortened the interinjection interval between successive cocaine injections (0.5 mg/kg/injection); this effect was greater during the second hour of a two-hr self-administration test. The shorter interinjection intervals generally reflected an increase in cocaine intake, consistent with an antagonist-like action of Sp-cAMPS and dibutyryl cAMP on cocaine self-administration. In contrast, Rp-cAMPS (40-80 nmol/1ul), which blocks the effect of cAMP on PKA, either prolonged the interinjection intervals or disrupted cocaine self-administration altogether; this effect was greatest during the first hour of the two-hr self-administration test. Studies of the effects of these compounds on heroin self-administration are underway. Opposite effects of PKA activators and inhibitors on drug self-administration suggests a role for cAMP in the NAc in modulating drug reinforcement.

759.14

DELAYED REDUCTION OF DOPAMINE TRANSPORTER BINDING IN NUCLEUS ACCUMBENS AFTER TERMINATION OF REPEATED PASSIVE INFUSIONS OF COCAINE. N.S. Pilotte*, L.G. Sharpe and M.J. Kuhar. NIDA-NIH, Addiction Research Center, Baltimore, MD 21224.

Termination of repeated intermittent IV infusions of cocaine results in a long-term reduction in the binding of the dopamine transporter (DAT) in the nucleus accumbens (NAC). In order to determine whether the binding was decreased because of the length of treatment with cocaine or the time after its withdrawal, we infused male Lewis rats IV with cocaine or saline for 5, 10 or 20 days and then measured the binding of [^{3}H]WIN 35,428 to DA transporters in the NAC 1 or 10 days after cocaine was withdrawn. One day after the last session of repeated cocaine or saline, binding to the DAT was similar in all groups of rats regardless of whether the treatment period was 10 or 20 days. In contrast, compared to saline-treated rats, significantly fewer DA transporters were measured in rats given cocaine for 10 days and assessed 10 days after cessation of cocaine. Other rats were treated for 5 days and DAT binding in the NAC was assessed 10 days later. There were no differences in the DAT binding of saline- and cocaine-treated rats. These results indicate that the reduced binding to the DAT in the NAC that occurs after cocaine is related to the withdrawal of cocaine, and not to the duration of its administration. This delayed reduction in DAT binding after cocaine may be involved with some of cocaine's long-lasting effects or lead to drug-seeking behavior.

DRUGS OF ABUSE: COCAINE—OTHER DRUGS

760.1

COCAINE-INDUCED LOCOMOTION AND STEREOTYPY ARE SELECTIVELY AFFECTED BY ETHANOL. J. Peris* & J. Scott. Dept. Pharmacodynamics, Univ. Florida, Gainesville FL 32610.

The stimulatory effects of cocaine are enhanced by daily ethanol consumption whereas parenteral ethanol administration may diminish cocaine responsivity. In the present study, male rats were divided into 3 groups (S/SC, S/EC and E/SC). For 21 consecutive afternoons, rats received either saline (Groups S/SC and S/EC) or ethanol injections (Groups E/SC). On each following morning, they received saline (Groups S/SC and E/SC) or ethanol injections (Groups S/EC) followed 10 min later by a cocaine (10 mg/kg, i.p.) injection. Locomotor crossing, headbobbing and rearing were quantified on the first, eight and fifteenth days after both the morning and afternoon injections. On the first day, ethanol (1 g/kg, i.p.) enhanced the stimulatory effect of cocaine on headbobbing but did not affect locomotor crossing or rearings. Repeated cocaine injections increased headbobbing, rearing and locomotor crossings over days indicating the development of cocaine sensitization. Ethanol injection further enhanced headbobbing on Day 8 but diminished the sensitization to cocaine-induced locomotion and rearing on Days 8 and 15. These effects of ethanol occurred regardless of administration simultaneous with cocaine or 18 hrs earlier. When all animals received a test injection of cocaine on Day 22 without ethanol treatment, Groups S/EC and E/SC showed less sensitized rearing and locomotion than Group S/SC but similar headbobbing behavior. Thus, ethanol can selectively decrease certain sensitized behavioral responses to cocaine and enhance others. This effect is fairly long-lasting in nature since it occurs regardless of whether ethanol is administered simultaneously or concurrently. Supported by PHS grant AA00135 and a grant from the Alcoholic Beverage Medical Research Foundation.

760.2

BEHAVIORAL EFFECTS OF EMBRYONIC ADMINISTRATION OF ETHANOL AND COCAINE IN THE YOUNG CHICK. J.M. Dose*, I.B. Caton & J.F. Zolman. Depts. of Psychology and Physiology, Univ. of Kentucky, College of Medicine, Lexington, KY 40536.

The effects of embryonic pretreatments given during active neurogenesis (E3-E4) were studied in 1- and 2-day-old chicks. In Experiment 1, viable embryos were randomly allocated into five treatment groups: incubative controls, vehicle (saline plus 50µg/ml bacitracin), 10mg ethanol, 300µg cocaine, or coadministration (10mg ethanol and 300µg cocaine; all doses given/egg/day). Compared with controls embryo survival in the cocaine and coadministration groups was significantly decreased. Chicks were then tested for key-peck responding using heat reward. In two autoshape sessions and in an acquisition-extinction (12 trials/phase) session all chicks responded appropriately to the changing reinforcement contingencies. In a second acquisition-extinction session following .5mg/kg apomorphine, chicks in all groups showed enhanced responding. In Experiment 2, all pretreatment groups were the same except cocaine doses were decreased from 300µg to 150µg. More drug-treated chicks survived than in Experiment 1, but embryo mortality was still higher for these chicks than controls. All chicks, except those in the coadministration group, increased responding across autoshape sessions. In acquisition-extinction, coadministration chicks increased responding (32 to 40%), whereas chicks in all other groups decreased responding. No group differences were found in ACQ-EXT responding following apomorphine challenge. Thus, early embryonic administration of ethanol and cocaine increases embryo mortality and chicks given 10mg ethanol and 150µg cocaine respond inappropriately to changing reinforcement contingencies.

760.3

SEROTONERGIC INVOLVEMENT IN COCAINE SENSITIZATION: EVIDENCE FROM BEHAVIORAL AND BIOCHEMICAL STUDIES WITH COCAETHYLENE J.D. Elsworth*, J.R. Taylor, L.M. Adams, P. Yih, M. Winston, P. Jatlow and R.H. Roth Depts. of Psychiatry, Pharmacology & Laboratory Medicine, Yale University School of Medicine, New Haven, CT 06510.

Cocaethylene (CE) is formed in vivo from cocaine (C) and ethanol. CE inhibits dopamine (DA) uptake as potently as C and has some cocaine-like behavioral properties. As repeated exposure to pyschostimulants or stress elicits a sensitized response to a subsequent challenge, and sensitization may underlie some adverse effects of continued cocaine abuse, we examined whether CE could cause sensitization and whether it cross-sensitizes with C. Sensitization was produced by daily treatment for five days with either C or CE (20 mg/kg, i.p) and a challenge dose of 10 mg/kg of C or CE given one week later.

Pretreatment with C produced a sensitized locomotor response to a challenge with either C or CE. However, when the CE was administered daily, no sensitized response was observed following injection of C or CE. Pretreatment at half the dose (10 mg/kg) of C was sufficient to produce sensitization.

Since norcocaethylene (NCE), is a metabolite of CE, we compared the potency of C, CE, NCE and norcocaine (NC) as inhibitors of binding at the DA (^{3}H-WIN 35428), 5-HT (^{3}H-paroxetine) and norepinephrine (^{3}H-nisoxetine) uptake sites.

C, NC, CE and NCE were equipotent as inhibitors of ^{3}H-WIN 35428 binding. In the ^{3}H-paroxetine binding assay, CE was nearly 10 times less potent than C, yet NC and NCE were not less potent than C. For ^{3}H-nisoxetine binding, CE was about 3 times less potent than C, and NC and NCE were more potent than C.

While other factors such as the role of NCE and different pharmacokinetics have to be considered, it is possible that the lack of potency of CE at the 5HT uptake site may have prevented the development, but not expression, of sensitization.

Support: NIDA P50DA-04060.

760.4

REPEATED COCAINE FACILITATES IMMOBILITY DURING A NOVEL STRESSFUL SITUATION. V.A. Molina*, C.J. Heyser, and L.P. Spear. Center for Developmental Psychobiology, Dept. of Psychology, SUNY, Binghamton, NY 13902-6000.

The effect of naloxone (NAL) on the behaviors exhibited during a novel and stressful situation was investigated in rats previously exposed to repeated cocaine (COC) administration. Animals were given either daily injections of COC (15 mg/kg, i.p.) or saline (SAL) for 3 consecutive days (D1 - D3). On the third day following the last COC or SAL administration (D6), all animals were exposed to one of two novel aversive experiences. COC and SAL rats were administered saline or NAL (2.0 mg/kg, i.p.) 15 min prior to placement into a cylinder containing water (25 ± 2°C) and their behavior assessed during a 10 min forced swim (FS) test. A separate group of COC and SAL rats were given SAL or NAL (2.0 mg/kg, i.p.) 15 min prior to exposure to a novel open field where the behaviors of each animal were assessed during intermittent exposure to a noise (80 dB) stressor (3 min periods of noise: off - on - off - on - off) for a total observation period of 15 min. A significant increase in immobility during the FS was observed in COC treated rats when compared to SAL rats. This increase in immobility was blocked by pretreatment with NAL. Moreover, preliminary data suggests that COC animals were more immobile during the initial exposure to the novel open field and that NAL pretreatment attenuated this increased immobility. Taken together, these findings suggest that repeated COC administration facilitates the expression of immobility when confronted with a novel stressful situation with this increase being modulated to some extent by the activation of an endogenous opiate mechanism.

760.5

LONG-TERM BENZODIAZEPINE AND MUSCARINIC RECEPTOR ALTERATIONS FROM CHRONIC COCAINE ADMINISTRATION ARE DOPAMINE DEPENDENT. J.W. Lipton*, M.S. Fanselow, R.W. Olsen. Depts. of Psychology and Pharmacology, UCLA, Los Angeles, CA 90024.

The most conspicuous neurochemical consequence of cocaine administration is a short-term rise in synaptic monoamines. However, there is little evidence of long-term dopamine (DA) receptor alterations from cocaine administration. Recently, increased benzodiazepine (BZD) and decreased muscarinic (MSC) binding were observed following chronic cocaine administration. These alterations are immediately evident and persist for several weeks. It is conceivable that the BZD and MSC receptor population changes depend upon cocaine's blockade of the DA transporter. To examine the necessity of increased synaptic DA in the production of these receptor changes, animals were implanted with subcutaneous silastic pellets filled with cocaine freebase or vehicle only. In addition, animals received a concurrent administration of alpha-methyl-p-tyrosine (AMPT; tyrosine-hydroxylase inhibitor), SCH 23390 (D1 antagonist), disulfiram (DA-beta hydroxylase inhibitor) or vehicle. Twenty-one days after the cessation of drug administration rats were sacrificed and the brains were prepared for [3H]flunitrazepam or [3H]Quinuclidinyl-benzilate autoradiography. In several brain regions, AMPT attenuated both the BZD (AMYG,CPU,CX,HIPP,NAC,VTA) and MSC (CX,CPU,HIPP,VTA) receptor changes. SCH23390 produced a similar effect, although to a lesser degree. Disulfiram had little effect, yet it did lessen the magnitude of cocaine-induced receptor alterations in some areas. These data suggest that increases in DA and norepinephrine from chronic cocaine are at least partially responsible for BZD and MSC receptor alterations.

760.6

ATTENUATED FEAR CONDITIONING FOLLOWING CHRONIC COCAINE ADMINISTRATION IS REVERSED BY FLUMAZENIL J. P. DeCola *, J. W. Lipton and M. S. Fanselow.
Dept. of Psychology, UCLA, Los Angeles, CA 90024

Chronic cocaine administration has been shown to produce long-term, increased benzodiazepine receptor binding in areas that mediate fear conditioning. These increases persist for at least 35 days post-administration in the hippocampus and amygdala of rats. Animals were implanted with subcutaneous silastic pellets filled with either cocaine freebase or vehicle. Twenty-one days after pellet removal animals were injected with either flumazenil (7 mg/kg, ip.) or vehicle and then exposed to a single electric footshock (US) in a novel context (CS). The degree of fear conditioned to the contextual cues was assessed the next day by the percentage of time spent freezing in that context. Animals previously administered cocaine showed a significant reduction in conditional fear. Flumazenil reversed this attenuated conditioning but had no effect on fear conditioning in animals not treated with cocaine. A flinch-jump test of unconditioned sensitivity to footshock indicated that the cocaine administration increased the animals' shock-reactivity threshold. This long-term alteration in pain perception can explain the reduced conditioning seen in the cocaine treated group. These findings along with the increased benzodiazepine receptor binding are consistent with fear conditioning models that propose an inhibitory, γ-Aminobutyric acid (GABA) synapse in the US input circuit located in the amygdala. This alteration in US processing suggests caution in the interpretation of learning deficits with aversive tasks following cocaine administration.

760.7

STRUCTURE-ACTIVITY RELATIONSHIPS FOR COCAINE ANALOGS INHIBITING [^{3}H]DOPAMINE AND [^{3}H]SEROTONIN UPTAKE. J.S. Bergmann[1], K.M. Johnson[1]*, A.P. Kozikowski[2], M. Roberti[2], L. Xiang[2] and D. Simoni[2]. Dept. of Pharmacology and Toxicology, University Texas Medical Branch[1], Galveston, TX 77555 and Neurochemistry Research, Mayo Foundation[2], Jacksonville, FL 32224.

Structure-activity relationships for cocaine analogs inhibiting striatal synaptosomal [^{3}H]dopamine ([^{3}H]DA) and [^{3}H]serotonin ([^{3}H]5HT) uptake were investigated. Cocaine analogs involving C2, C3 (RTI/WIN like compounds with the direct linkage of the 4-chlorophenyl to the tropane ring) and C6 modifications revealed different structure-activity properties for inhibition of [^{3}H]DA and [^{3}H]5HT uptake. Changes in substituents at the C2 position produced changes in the inhibitory potencies, expressed as Ki, at the dopamine transporter ranging from 7.81 μM to 0.238 μM (Ki for inhibition of [^{3}H]DA uptake by cocaine was 0.319 μM). These same substitutions produced compounds inhibiting [^{3}H]5HT uptake with Ki values ranging from 185.97 μM to 0.165 μM (Ki for cocaine was 0.138 μM). Modification of the C3 position along with changes to the C2 position produced some of the most potent analogs tested. These analogs inhibited [^{3}H]DA and [^{3}H]5HT uptake with Ki values ranging form 431 nM to 0.875 nM and 2.04 μM to 1.52 nM, respectively. Addition of a methoxy group at the C6 position increased the Ki for [^{3}H]DA and [^{3}H]5HT uptake to 68.27 μM and 33.16 μM, respectively. If, in addition to this C6 methoxy group the ester group at C2 is oriented in the alpha configuration, the Ki for inhibition of [^{3}H]DA and [^{3}H]5HT uptake is increased to 506.08 μM and 302.16 μM, respectively. In general, these substitutions produced changes in Ki which were similar in direction, but not magnitude, confirming the structural uniqueness of the monoamine binding sites of each transporter. Supported by DA-06856.

760.8

RATES OF OCCUPANCY OF CENTRAL DOPAMINE TRANSPORTERS BY NOVEL COCAINE ANALOGS. M. Stathis, U. Scheffel*, J.W. Boja[1] and M.J. Kuhar.[1]Department of Radiology, The Johns Hopkins Medical Institutions, Baltimore, MD 21205 and [1]NIDA/ARC, Baltimore, MD 21224.

Previous studies have shown that, after *in vivo* injection, ^{3}H-WIN 35,428 binds preferentially to striatal dopamine transporters. In this study, novel cocaine analogs and drugs known to block DA uptake were compared with (-) cocaine for their rates of displacement of ^{3}H-WIN 35,428 binding *in vivo* in mice.

Thirty minutes after tracer injection, the drugs were administered i.v. at ED_{50} levels. At different times after injection of the drugs, the animals were sacrificed and radioactivity concentrations were determined in striatal and cerebellar tissues. The rates of entry of the injected drugs were estimated by measuring their rates of competition. The rank order for the rates of the drugs was: (-) cocaine > Ritalin > Buproprion > Nomifensine > RTI-51 > RTI-32 > WIN 35,065-2 > RTI-121 > RTI-31 > RTI-55 > WIN 35,428. While the RTI analogs have proven to be behaviorally and pharmacologically more potent than (-) cocaine, their rates of entry were slower than that of (-) cocaine. Future experiments will examine correlations between the *in vivo* rates of occupancy of the different drugs and their behavioral and reinforcing properties.

760.9

QUATERNARY BENZAZEPINE ANALOGS AS POTENTIAL TOOLS FOR FURTHER ELUCIDATION OF THE ROLE OF PERIPHERAL DOPAMINE DA_1 RECEPTORS IN COCAINE TOXICITY. J. H. Shah, G. Nowak[1], J. M. Witkin*, A. H. Newman, Drug Develop. Group, Psychobiology Section, NIDA-ARC, Baltimore, MD 21224, [1]Lab.of Neurosci., NIDDK, NIH, Bethesda, MD 20892.

Several dopamine D_1 antagonists produce dose-dependent protection against the lethal effects of cocaine and the centrally inactive cocaine methiodide, in mice. Lethal effects of cocaine were previously reported to be enhanced by both centrally and peripherally-acting D_1 agonists but not by D_2 agonists. These data indicate an important role for D_1 but not D_2 receptors in the lethal effects of acutely administered cocaine and suggest that the peripheral loci may be one pathophysiological target for therapeutic intervention. In an attempt to prepare a D_1 antagonist that would not penetrate the blood-brain barrier to further elucidate the role of peripheral dopamine DA_1 sites in the lethal effects of cocaine, quaternary analogs of SCH 23390 were prepared. The benzazepine N and the *para*-position of the pendant phenyl ring were chosen as initial positions for a quaternary N-function. Methylation of SCH 23390 resulted in the methiodide salt. *Whereas total synthesis of the 4'-N,N dimethylaminophenyl-methiodide salt* was required using modifications of a published procedure to prepare the intermediate 4'-nitrophenyl-3-benzazepine. N-formylation was followed by O-demethylation, selective reduction of the NO_2 group, methylation of the resulting amine and finally mild reduction of the N-formyl group to result in the desired final product. Displacement of [^{3}H]SCH 23390 (D_1) and [^{3}H]spiperone (D_2) was evaluated in rat brain; both methiodide analogs exhibited low binding affinity ($K_i \cong 1$ μM) for the D_1 receptors, although selectivity over D_2 receptors was retained (K_i=710 μM). Since positively charged quaternary N's either at the benzazepine N or in the *para*-position of the pendant phenyl ring are not tolerated at D_1 receptors, analogs in which this moiety is extended away from the pharmacophore are in preparation.

760.10

CORTICOTROPIN-RELEASING FACTOR (CRF) POTENTIATES BENZOYL- ECGONINE (BE)-INDUCED SEIZURES AND DEATH. G.Schuelke, K.Baranek, L.C.Terry*. Department of Neurology, Medical College of Wisconsin, Milwaukee, WI 53226.

Cocaine and/or some of its metabolites cause seizures and death in humans and experimental animals, and cocaine stimulates corticotropin CRF release. Recently, Weiss et al. (Epilepsia 33(2):249-254, 1992) reported potentiation of cocaine-induced seizures and death by CRF administered intraventricularly (icv). We recently reported inhibition of cocaine and BE induced seizures by pretreatment with icv ecgonine methylester (EME) and ecgonine (EC), respectively, in subconvulsive doses (Soc. Neurosci., V.18, Abstr. No 228.11, 1992). The purpose of this investigation was to determine if icv CRF pretreatment potentiated seizures induced by cocaine metabolites BE, EME, and EC. To this end, adult male Sprague-Dawley rats, had lateral icv cannulae implanted, and icv injections were performed with a volume of 5 ul at a rate of 10 ul/min. CRF (10 ug icv) was given 30 min. prior to either icv cocaine (1.2 uM), BE (0.31 uM), EC (3.4 uM), or EME (4.2 uM). Rats were monitored for 120 min. CRF significantly ($p<.01$, N=10 animals/group) potentiated BE induced tonic/clonic seizures and seizure-associated death. Cocaine-, EME-, and EC-induced seizures were not potentiated by CRF. CRF alone did not cause behavioral change nor seizures. CRF selectively lowered the convulsive icv dose of BE. These results suggest that seizures induced by the primary metabolite of cocaine, BE, are potentiated by CRF. The release of CRF is itself stimulated by cocaine and/or its metabolites. Therefore, the toxic effects of cocaine associated with increased CRF levels appear to be primarily due to BE, rather than cocaine. The mechanism of CRF potentiation, (i.e., direct CRF action v.s. effects through secondary mediators) is currently under investigation. The results of this study may provide a mechanism to explain some apparently idiosynchratic seizures and deaths associated with cocaine use.

760.11

EFFECTS OF METYRAPONE ON INTRAVENOUS COCAINE SELF-ADMINISTRATION IN RATS. N.E. Goeders*, L.A. Wagner, S.B. Marshall and G.F. Guerin. Depts. of Pharmacology and Psychiatry, LSU Med. Center, Shreveport, LA 71130-3932.

Initial cocaine use is often reported by humans to produce profound subjective feelings of well-being and a decrease in anxiety, indicating that anxiety may be involved in the etiology of cocaine use. Recent data from our laboratory have suggested that exposure to non-contingent electric footshock stress increases vulnerability to self-administer cocaine in rats. In these rats, drug-intake was correlated with footshock stress-induced increases in plasma corticosterone. On the other hand, adrenalectomy completely prevents the acquisition of cocaine self-administration in rats, further implicating a role for corticosterone in cocaine reinforcement. These data are in agreement with reports by Piazza and co-workers on the effects of corticosterone in amphetamine reinforcement. Metyrapone decreases plasma corticosterone by inhibiting the 11-hydroxylation step during synthesis. The following experiments were therefore initiated to investigate the effects of metyrapone-induced decreases in plasma corticosterone on intravenous cocaine self-administration. Adult male Wistar rats were trained to self-administer cocaine (0.25 mg/kg per 0.2 ml infusion delivered over 5.6 sec) on a fixed-ratio 4 schedule of reinforcement. When stable baselines of drug-intake were obtained, the rats were pretreated with metyrapone (5 to 150 mg/kg, ip) 1 to 4 hrs before the start of the behavioral session. Pretreatment with metyrapone (50 to 150 mg/kg, ip) attenuated cocaine self-administration, further suggesting a role for corticosterone in cocaine reinforcement. Experiments are currently in progress to determine the specificity of these effects.

This research was supported by USPHS grant DA06013.

760.12

EFFECTS OF COCAINE ON CORTICOTROPIN-RELEASING FACTOR (CRF) IN RAT MESENCEPHALIC CULTURES. M. R. Simar*, and N. E. Goeders. Departments of Pharmacology and Psychiatry, LSU Med Center, Shreveport, LA 71130-3932.

It is well established that corticotropin-releasing factor (CRF) is the hypothalamic peptide primarily responsible for the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary following exposure to a stressor. Several studies suggest that CRF may also modulate the stress response associated with chronic cocaine abuse and withdrawal. Increases in plasma corticosterone have been detected following intracerebroventricular cocaine administration, and these increases can be blocked by pretreatment with a CRF antibody. Increases in CRF secretion have been shown in cocaine-treated cultures of hypothalamic cells. Furthermore, intravenous cocaine stimulates the secretion of ACTH in rodents, and this effect can be blocked by dopamine antagonists. Previous studies from our laboratory have demonstrated that chronic cocaine administration results in a down-regulation of CRF receptors in the mesocorticolimbic dopaminergic system of the rat and that dopamine depletion attenuates this effect. Since cocaine blocks the reuptake of dopamine, increased extracellular dopamine may be the common link between chronic cocaine administration and its stress-related effects.

This study tests the hypothesis that cocaine may have an effect on CRF secretion in cultured rodent cells from the mesencephalon, a brain region containing a major population of dopaminergic cell bodies. The culture model was chosen to enable the isolation of a discrete group of cells, thus simplifying the complexity of the central nervous system and providing an opportunity to study the direct effects of cocaine on the cells. The effects of acute and chronic cocaine treatment on CRF concentration in cultured mesencephalic cells are currently being measured using radioimmunoassay of CRF. This research was supported by USPHS grant DA04293.

760.13

CORTICOSTERONE AND SENSITIVITY TO DRUGS OF ABUSE: MODULATION OF PSYCHOMOTOR EFFECTS: V. Deroche, M. Marinelli, P.V. Piazza, S. Maccari, M. Kharouby, M. Le Moal and H.Simon*. INSERM U.259, rue Camille St Säens, 33077 Bordeaux, France.

Previous reports have suggested that corticosterone secretion may be one of the factors determining individual vulnerability to motor and reinforcing effects of amphetamine. In the present experiments we analyzed the influence of basal and stress-induced corticosterone secretion on the locomotor response to psychostimulants and opioids. Corticosterone basal levels were manipulated by means of adrenalectomy (ADX) associated with different corticosterone replacement therapies. Food-restriction was used as a model of stress since this condition sharply increases both corticosterone secretion and motor effects of psychostimulants and opioids. Food restriction-induced corticosterone secretion was blocked by means of ADX associated with the subcutaneous implantation of a corticosterone pellet, which released a fixed and constant amount of corticosterone in the range of basal physiological levels. Suppression of corticosterone basal levels by ADX significantly reduced the locomotor response to cocaine and morphine while this effect was suppressed by corticosterone replacement therapies providing levels of the hormone in the range of those observed in physiological conditions. Suppression of food-restriction induced corticosterone secretion, by ADX plus corticosterone pellet implantation, blocked the increase in locomotor response to morphine and amphetamine induced by this condition. The effects of food restriction was reinstated in ADX+pellet animals by the exogenous administration of a relative high dose of corticosterone (100μg/ml) in the drinking water. Similar results were obtained when the drugs were injected systemically (cocaine=10mg/kg, morphine=1mg/kg, amphetamine=1mg/kg) or when cocaine (50μg/side) and amphetamine (10μg/side) were injected in the n.accumbens and morphine (1μg/side) in the VTA. In conclusion, our results show that the basal sensitivity to opioids and psychostimulants and the increase in the response to these drugs induced by stress are influenced by corticosterone secretion.

760.14

CORTICOSTERONE AND SENSITIVITY TO DRUGS OF ABUSE: ROLE OF DOPAMINE RELEASE P.V. Piazza*, F. Rougè-Pont, V. Deroche, M. Kharouby, M. Le Moal, H. Simon. INSERM U.259, rue Camille St Säens, 33077 Bordeaux, France.

Behavioral evidences indicate that corticosterone secretion may modulate basal sensitivity to psychostimulants or the stress-induced sensitization to drug response. Effects of corticosterone may be mediated by the action of this hormone on mesencephalic dopamine (DA) neurons. Thus, DA neurons seem an important substrate of psychostimulants' motor and reinforcing effects and they have intracellular corticosteroid receptors. In two separate experiments, by means of microdialysis, we analyzed the influence of corticosterone on stress- and cocaine-induced increase in extracellular dopamine concentrations in the n. accumbens. The results of the first experiment show that stress-induced (10 min tail pinch) increase in DA extracellular concentrations is reduced in animals adrenalectomized and implanted subcutaneously with corticosterone pellets. Such pellets release a fixed and constant amount of corticosterone in the range of basal physiological level, but do not allow the increase in corticosterone secretion induced by stress. A stress-induced increase in DA concentration, similar to the one of control animals, is obtained in ADX+pellet animals when they are injected with corticosterone (3mg/kg i.p.) immediatly before stress. Furthermore, ADX+pellet implantation suppresses individual differences in stress-induced increase in DA accumbens extracellular concentrations. Animals vulnerable to develop amphetamine self-administration (HRs) which in response to stress show a longer corticosterone secretion and higher DA concentrations in the accumbens than resistant subjects (LRs), differ no more from LRs when submitted to ADX+pellet implantation. The results of the second experiment show that repeated treatment (100mg/kg s.c., twice a day for 7 days) with metyrapone, a blocker of corticosterone synthesis, significantly decreases the increase in accumbens DA concentration induced by an acute injection of cocaine (10mg/kg, i.p.). In conclusion these results suggest that cortticosterone action on DA neurons may mediate the effects of this hormone on behavioral sensitivity to drug of abuse.

761.1

COCAINE SELF-ADMINISTRATION UNDER A PROGRESSIVE-RATIO SCHEDULE IN RATS: INTERACTION WITH OPIOIDS. D.-H. Li, R. Y. Depoortere, and M. W. Emmett-Oglesby*. Department of Pharmacology, T.C.O.M., Fort Worth, TX 76107-2699.

These experiments tested the hypothesis that pretreatment with an opioid agonist would enhance the reinforcing efficacy of cocaine. The effects of pretreatment with the partial μ-agonist, buprenorphine, or the full μ-agonist, morphine, were investigated in rats trained to self-administer cocaine, 0.25 mg/100μl injection, under a progressive-ratio (PR) schedule of reinforcement. When pre-treated with vehicle, increasing doses of cocaine (0.028, 0.083 and 0.25 mg/injection) resulted in increasing breakpoints (responding ceased after approximately 12, 17 and 22 reinforcer, respectively). Pretreatment with morphine (1.0, 3.2 or 5.6 mg/kg, s.c., given 30 min before the session) did not enhance the breakpoint produced by any of these doses of cocaine. Indeed, at the highest dose of morphine tested, several subjects failed to initiate responding for cocaine, and of the remaining subjects, the breakpoints for all doses of cocaine was unchanged. Buprenorphine tested against the training dose of cocaine also failed to enhance breakpoint responding. These data fail to provide support for the hypothesis that pretreatment with opioids enhances the reinforcing effects of cocaine. Supported by NIDA grant RO1-4137 and Texas Advanced Technology Award 3711.

761.2

ACQUISITION OF COCAINE SELF-INJECTION IN RHESUS MONKEYS. C.A. Sannerud*, S.L. Serdikoff, & S.R. Goldberg, NIDA-Addiction Research Center, Baltimore, MD 21224.

Individual differences in the ability of intravenous (i.v.) cocaine (COC) to serve as a reinforcer were assessed in 10 drug-naive rhesus monkeys. All monkeys were trained to press a lever using an autoshaping procedure. Once responding was stable, responding was maintained under a fixed ratio (FR) schedule of reinforcement. Each of the 4 daily sessions consisted of up to 6 components or a maximum of 15 reinforcers. Each component had a 10-min pretrial followed by a 10-min trial during which the FR schedule was in operation. After a monkey successfully completed 10 ratios, the ratio requirement for each reinforcer was increased by 2 until the final FR of 50 was reached. For 6 monkeys, the autoshaping and FR training were conducted using food pellets as the reinforcer. After their response patterns were stable, these monkeys were implanted with i.v. catheters. Following surgery, response acquisition on a second lever was examined using 0.032 mg/kg/inj COC. For 4 monkeys there was no training with food pellets prior to surgery. These monkeys were trained to respond using the 0.032 mg/kg/inj COC reinforcer during both autoshaping and FR training. Extinction and reacquisition phases were conducted after each monkey met criterion (± 10% max. number of reinforcers) during 12 consecutive sessions. Rates of acquisition of cocaine- and food-maintained responding were quantified as the number of sessions to reach criterion. Correlations among baseline measures of activity, physiological measures, (e.g., levels of prolactin, corticosteroid, testosterone) and potential differences in acquisition of drug taking are discussed.

761.3

PREEXPOSURE WITH METHYLPHENIDATE HCl SENSITIZES RATS TO THE REINFORCING EFFECTS OF COCAINE. Carol G. McNamara* and Susan Schenk, Texas A&M Univ., Dept. Psychol., College Station TX, 77843.

Our laboratory has shown that pretreatment with a number of psychostimulants, including cocaine, amphetamine, caffeine and nicotine, results in shorter latencies to subsequently acquire an operant to intravenously self-administer cocaine. The present study was designed to determine whether the indirect dopamine agonist, methylphenidate, would similarly sensitize rats to cocaine's reinforcing effects. Male Sprague Dawley rats were implanted with intrajugular cannulae and received 9 daily injections of methylphenidate HCl (0.0, 5.0 or 20.0 mg/kg, IP). Twenty-four hours after the last of these treatments, acquisition of cocaine self-administration proceeded. Rats that were pretreated with methylphenidate acquired self-administration within 3 (5.0 mg/kg group) and 2 (20.0 mg/kg group) days of testing compared to 5 days for the control rats. These data suggest that intermittent exposure to methylphenidate, like other psychostimulants, predisposes rats to the positively reinforcing properties of cocaine.

761.4

REINSTATEMENT OF EXTINGUISHED COCAINE-TAKING BEHAVIOR BY COCAINE AND CAFFEINE Christina M. Worley*, Albert Valadez and Susan Schenk, Texas A&M Univ., Dept. Psychol., College Station, TX, 77843.

This study examined the effects of acute injections of cocaine or caffeine on reinstatement of cocaine appropriate responding in rats that had undergone extinction. After reliable self-administration of cocaine (0.25 mg/kg/infusion) was obtained, the infusion pumps were disconnected and behavior was monitored until a 60 min period of non-responding was obtained. Following this criterion for extinction, the rats were given an injection of either saline, cocaine (5.0, 10.0 or 20.0 mg/kg) or caffeine (10.0, 20.0 or 40.0 mg/kg). Responding of the lever that had been associated with the cocaine infusion was recorded. An injection of saline failed to reinstate responding on the cocaine lever. A non-contingent injection of cocaine induced a dose/dependent increase in the number of responses made on the cocaine associated lever. A non-contingent injection of caffeine similarly increased the number of responses made on the cocaine associated lever. The number of responses made was less than when cocaine served as the prime but was nonetheless substantially higher than when saline was administered. The basis for these priming effects is of great importance for furthering our understanding of craving and relapse in detoxified subjects.

761.5

CROSS-TOLERANCE BETWEEN CNS STIMULANTS IN A SELF-ADMINISTRATION PARADIGM IN RATS. R.L. Peltier*, M.W. Emmett-Oglesby and J.D. Lane. Department of Pharmacology, T.C.O.M., Fort Worth, TX 76107.

This experiment determined whether cross-tolerance occurs to cocaine self-administration after chronic administration of *d*-amphetamine. Rats were implanted with chronic indwelling jugular catheters. Following implantation, they were allowed to self-administer cocaine (0.25 mg/injection) on a fixed-ratio two (FR2) schedule of reinforcement, 15 reinforcers a day, until baseline responding was stable. Using a multi-dose procedure, in which three different doses of cocaine are self-administered during a single test session, a dose-response curve for each rat was then obtained. As the dose of cocaine increased, the time between each reinforcer increased in an arithmetic way. Rats were then assigned to two groups: one group treated chronically with *d*-amphetamine (3.2 mg/kg/8 hr; s.c.) and the other group treated chronically with 0.9% saline. These chronic regimens lasted for seven days, during which the rats did not have access to cocaine self-administration. Twenty-four hours after the last injection, cocaine dose-response curves were again obtained. Chronic treatment with *d*-amphetamine produced a two-fold shift to the right of the dose-response curve for cocaine self-administration, while chronic treatment with saline was without significant effects. Subjects were then left for seven days without testing or training. Subsequently, rats were once again allowed to self-administer cocaine once daily using the FR2 schedule described above. On the first training day, rats treated chronically with *d*-amphetamine had returned to baseline rates of responding. These data show that chronic administration of a CNS stimulant produces cross-tolerance to cocaine in a self-administration paradigm. Supported by NIDA RO1 4137, and Texas Advanced Technology Award 3711.

761.6

TOLERANCE STUDY OF COCAINE UNDER A PROGRESSIVE RATIO SCHEDULE IN THE RAT. M. W. Emmett-Oglesby, D.-H. Li, R. Depoortere and J.D. Lane*. Dept of Pharmacology, TCOM, Fort Worth, TX 76107-2699.

The Purpose of this experiment was to determine whether chronic cocaine would produce tolerance to cocaine self-administration under a progressive ratio (PR) schedule of reinforcement. Rats were implanted with chronic indwelling jugular catheters. Following implantation, rats were trained to self-administer cocaine, 0.25 mg/infusion, under a PR schedule. Under the PR schedule, an increasing number of responses was required to obtain each subsequent cocaine infusion. The required ratio need to be completed within 1 hr, and the last cocaine injection that was received was termed the breakpoint. When the breakpoint for each subject was stable, a cocaine dose-response curve was determined. As the dose of cocaine increased, the breakpoint increased. The subjects were then assigned to two groups. One group was treated chronically i.v. with cocaine (20mg/kg/8hr), the other group received saline (0.09%). This chronic regimen lasted for 7 days. When cocaine dose-effect data were then redetermined in both chronic treatment groups, the chronic cocaine group showed significantly decreased breakpoints. These data support the hypothesis that tolerance occurs to the motivational effects of cocaine. Supported by DA ROI 4137 and Texas Advanced Technology Award 3711.

761.7

α-CIS FLUPENTHIXOL BLOCKS COCAINE-INDUCED ACCUMBENS DOPAMINE RELEASE AND CONCURRENT COCAINE DYSFUNCTIONAL BEHAVIOR. E.P. Kornak*[1], F. Eng[1], S. Hormozdi[1], A. Cuadra[2,3] and P.A. Broderick[1,3]. Dept. Pharmacol., CUNY Med. Sch.[1], Depts. Biol. & Psychol. CCNY[2] & CUNY Grad. Sch.[3], Convent Ave. & 138 St., Rm. J910, N.Y. 10031.

Previous studies with α-cis flupenthixol (α-cis flu) have shown specific modifications on cocaine self-administration, (Ettenberg et al. *Psychopharm.* 78:204, 1982). Since dopamine (DA) is a known mediator of brain reward, the present study monitored DA release *in vivo* and within seconds, in nucleus accumbens (NAcc) of freely moving and behaving, male, virus free, Sprague-Dawley rats, after cocaine administration (10 mg/kg IP) with α-cis flu (0.3 mg/kg IP) as pretreatment. *In vivo* electrochemistry, with stearate microelectrodes was used as the method of assay; detection of DA release in concentrations as low as 5 nmole are currently possible with this microelectrode. Concomitant behavior was studied with computerized infrared photocell beams. The results showed that α-cis flu significantly increased DA release and exhibited weak psychostimulant activity immediately after injection. However, the overall enhanced DA release usually seen after cocaine administration (10 mg/kg IP), did not occur when α-cis flu was present. On the contrary, cocaine-induced DA release in NAcc was decreased to baseline values and below. Moreover, cocaine-induced psychostimulant behavior was not seen when α-cis flu was present; sedation occurred. The data suggest that the combination α-cis flu and cocaine regimen shifts the dose response curve for α-cis flu neuroleptic activity to the left. SUPP: NIDA R01 DA04755; PSC/CUNY Awards RF 669201, 661188 & 663202.

761.8

EFFECTS OF TWO BENZAMIDE ANALOGS ON COCAINE SELF-ADMINISTRATION IN RHESUS MONKEYS: COMPARISON TO HALOPERIDOL. M.A. Nader[1,2], R.H. Mach[1,3,*] & R. Ehrenkaufer[3]. Depts. [1]Physiology/Pharmacology, [2]Comparative Medicine and [3]Radiology, Bowman Gray Sch. Med., Winston-Salem, NC 27157.

The benzamide analogs 2,3-dimethoxy-N-(9-*p*-fluorobenzyl)-9- azabicyclo [3.3.1] nonan-3-ß-yl benzamide (MABN) and 2,3-dimethoxy-N-(*p*-fluorobenzyl)piperidin-4-yl benzamide (MBP), are two high-affinity dopamine receptor antagonists that readily cross the blood-brain barrier and bind to D_2 receptors *in vivo*. The goal of this study was to examine the effects of MABN and MBP on cocaine self-administration and to compare these effects to haloperidol. Rhesus monkeys (N=3) were surgically implanted with chronic intravenous catheters and trained to self-administer cocaine (0.01-0.3 mg/kg/inj) under a fixed-interval 5-min schedule during daily 4 hr sessions. Cocaine intake increased in a dose-dependent manner, while response rates were characterized as an inverted-U shaped function of dose, with peak response rates occurring at 0.03 mg/kg/inj. Administration of each compound (0.003-0.3 mg/kg, i.v.) immediately before sessions on Tuesdays and Fridays resulted in a decrease in response rates when the cocaine dose that maintained maximal rates (0.03 mg/kg/inj) was available and a 0.5-1.0 log-unit shift to the right in the cocaine dose-response curve, indicative of surmountable antagonism. The order of potency for the rate-altering effects was MABN > MBP > haloperidol, which parallels their affinity for D_2 receptors (Mach *et al.*, J. Labeled Cmpd. Radiopharm. **32:** 262, 1993). These results indicate that both benzamides can antagonize the reinforcing effects of cocaine, primarily through D_2 receptors. Supported by NIDA grant DA-06829.

761.9

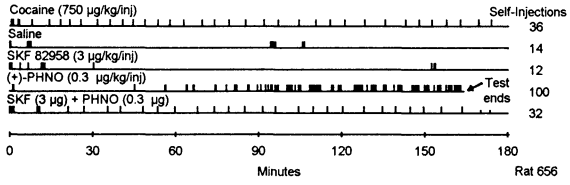
SELF-ADMINISTRATION OF BRAIN STIMULATION REWARD: THE ROLE OF AVERSIVENESS IN SETTING BASELINE. E.O. McCaskill*, J.E. Mailloux, and J.R. Stellar. Dept. of Psychology, Northeastern Univ., Boston, MA. 02115.

Recently it has been found that rats will administer a long duration, "cocaine-like" burst of brain stimulation in a manner which is strikingly similar to animals self-administering drugs (Franklin et al. NS Abstracts:15:432.12,1989 and McCaskill et al. NS Abstracts:17:489.11,1991). That is rats will increase responding to increase baseline stimulus frequency when the reward is diluted by reducing the stimulation current. Currently we are using this paradigm to investigate the relationship of aversive or toxic side-effects and reward effects of of brain stimulation in choosing the optimal stimulus level. Average self-selected brain stimulation pulse frequency was obtained for each subject and compared to average latency to turn off stimulation at the same current in the classical ON/OFF procedure (Liebman et al. Neuro. & Biobehav. Rev 9: 75-86, 1985). As average self-selected frequency decreased in the self-administration of brain stimulation paradigm across subjects, average off-latency increased. If baseline self-selected frequency in our paradigm models baseline self- selected dopamine levels in cocaine self-administration, this study shows the important role aversive or toxic effects may play in selecting and defending those baseline levels.

761.10

COCAINE SELF-ADMINISTRATION PATTERNS: DUPLICATION BY COMBINATION OF DOPAMINE D_1 AND D_2 AGONISTS. J.D. Belluzzi*, S.R. Kossuth, D. Lam, F. Derakhshanfar, A. Shin and L. Stein, Dept. of Pharmacology, College of Medicine, Univ. of California, Irvine, CA 92717.

Cocaine self-administration is characterized by precisely-spaced response patterns. Although these patterns may be duplicated in self-administration of D_1 agonists (Self & Stein, 1992), they are not in self-administration of D_2 agonists (PHNO, quinpirole, N-0923), where responding starts slowly and accelerates to rapid, erratically spaced responding (Fig). Here we report that co-administration of low doses of a D_1 agonist converts erratic D_2-agonist self-administration into cocaine-like, well-spaced response patterns. Rats were trained to bar press for i.v. cocaine (750 µg/kg/inj) in daily 3-hr sessions. After baseline rates had stabilized, D_2 agonists were substituted for cocaine. The D_2 agonists alone were self-administered erratically at high rates, but addition of D_1 agonist SKF 82958 to PHNO in particular ratios induced lower-rate cocaine-like patterns (Fig). These data indicate that well-spaced cocaine self-administration patterns are not due to D_2 receptor activation alone and may be due to joint activation of specific ratios of D_1 and D_2 receptors.



761.11

INFLUENCE OF RESPONSE-INDEPENDENT COCAINE DELIVERY ON LATER COCAINE SELF-ADMINISTRATION. S. Gleeson*, S.L. Vrana, T.R. Koves, and S.I. Dworkin. Center for the Neurobiological Investigation of Drug Abuse, Bowman Gray School of Medicine, Winston-Salem, NC 27157-1083.

Elucidation of the relative contribution of behavioral and pharmacological variables to the initiation and maintenance of drug-taking is one goal of drug-self-administration studies. A "triad" yoking procedure in which the schedule of response-independent i.v. infusions of either saline or cocaine in two rats was yoked to the pattern of infusions obtained by a third rat responding under an operant schedule of cocaine reinforcement was used to investigate how prior experience with response-independent infusions influenced the acquisition and maintenance of drug-taking. After stable drug-taking was established in cocaine self-administering rats, conditions were reversed so that the operant schedule was imposed on either the "yoked-saline" or "yoked-cocaine" rat (i.e., a rat previously receiving response-independent infusions), while the former self-administering rat was given response-independent infusions. For some of these triads, conditions subsequently were changed back to initial conditions. Drug-taking generally was lower in rats with previous exposure to response-independent infusions; there was little difference between "yoked-saline" and "yoked-cocaine". However, greater drug-taking rates were observed in "yoked-cocaine" rats that had not had access to a response lever during the initial condition. In fact, these drug-taking levels were similar to or higher than those observed in the self-administering rats in the initial phase. The results suggest that pharmacological history interacts with behavioral history to generate and maintain drug-self-administration. Supported by P50-DA 06634.

761.12

SHORT TERM COCAINE SELF ADMINISTRATION INCREASES PREPRODYNORPHIN, BUT NOT PREPROENKEPHALIN, C-FOS, OR ZIF/268 mRNAs IN RAT STRIATUM. J.B. Daunais*, D.C.S. Roberts[1], and J.F. McGinty Dept. Anat. and Cell Bio., East Carolina University School of Medicine, Greenville, NC 27858-4354, [1] Dept. Psychology, Carleton University, Ottawa, Canada K1S5B6.

Self-administration of cocaine (2-6 wk) induces increased expression of preprodynorphin (PPD), but not *c-fos*, mRNAs in patchy areas of rat dorsal striatum as determined by quantitative *in situ* hybridization (Daunais et al., NeuroReport May 1993). In contrast, following 7 days of variable free access to cocaine, PPD mRNA increased in both patch and matrix of the dorsal striatum (Hurd et al., Mol. Brain Res., 1992). In an effort to determine when PPD mRNA is upregulated, adult male Wistar rats self-administered saline or cocaine (11-40 mg/day) during 3 daily five hour sessions and were sacrificed one hour following the last injection. Brains were removed and frozen until 12µm coronal sections through the anterior striatum were cut on a cryostat. Sections were pretreated and hybridized with a 48mer oligonucleotide probe to prepro-dynorphin (PPD) or -enkephalin (PPE), or a 40mer oligo probe to *c-fos* or *zif/268*. Digital image analysis of film autoradiographs calibrated with C^{14} standards was used to quantify changes in the number of **labeled pixels per area**, **mean density** of signal in dpm/mg, and **integrated density** (ID) as previously described (Daunais et al., NeuroReport, 1993). Statistical significance in area, mean density, and ID between control and cocaine treated rats was determined by an analysis of variance with multiple observations, followed by a comparison of means based on the least squares means test. Quantitative analysis demonstrated a significant increase in PPD mRNA in patchy areas of the dorsal striatum ($p < 0.001$ for all three measurements). There were no changes in PPE, *c-fos*, or *zif/268* hybridization signals in the dorsal striatum. These data suggest that the regulation of PPD gene expression may be dissociable from that of *c-fos* and *zif/268* following cocaine self-administration. Supported by DA 03982 (JFM) and MRC of Canada (DCSR).

761.13

EFFECTS OF LEAD EXPOSURE ON COCAINE-INDUCED SENSITIZATION OF BRAIN-STIMULATION REWARD. R.T. Burkey and J.R. Nation*. Department of Psychology, Texas A&M University, College Station, TX 77843.

Adult male rats were exposed to 500 ppm lead acetate Group Lead-Treatment) or an equivalent concentration of sodium acetate (Group Control) for 80 days prior to commencing a test of brain-stimulation reward (BSR). After stable self-stimulation behavior was established, stimulation frequency thresholds were determined for a value 150 uA greater than the animal's previously established current threshold (functionally equivalent current intensity), and a set value of 600 uA (absolute current intensity). Subsequently, an ip injection 10 mg/kg dose of cocaine HCL was administered and the stimulation frequency thresholds were re-determined for both test (current) conditions. The results indicated that cocaine administration sensitized BSR,i.e., frequency thresholds were decreased for both functionally equivalent and absolute test conditions following cocaine administration. Moreover, this sensitization effect was greater for lead-treated than control animals.

761.14

FUNCTIONAL EFFECTS OF CHRONIC COCAINE SELF-ADMINISTRATION IN RATS. John H. Graham, James R. LaRosee, Steve I. Dworkin, Herman H. Samson* and Linda J. Porrino. Bowman Gray School of Medicine, Wake forest University, Winston-Salem, NC 27157

The functional effects of chronic cocaine self-administration (CSA) were examined in Fisher 344 rats using the quanitative autoradiographic 2-[^{14}C]deoxyglucose method. Rates of local cerebral glucose utlization (LCGU) were measured while animals were self-administering cocaine. Animals had been exposed to cocaine 3 hrs daily for 3 to 4 weeks, and rates of responding (on a fixed ratio 2) averaged 35 to 60 per session. The dose was 1mg/kg per infusion. Metabolism was altered in both motor circuits and the mesocorticolimbic system. LCGU was significantly elevated in the olfactory tubercle, nucleus accumbens, caudate, substantia nigra, globus pallidus, motor cortex, subthalamic nucleus, endopeduncular nucleus, cerebellum, and thalamus as compared to saline-treated controls. In addition, pronounced decreases were seen in the habenula. Moreover, preliminary data indicate that the pattern of functional activation changes across the self-administration session, with the activation within the mesocorticolimbic system more widespread and metabolism in motor circuits more enhanced later in the session as stereotypy intensifies. *(Supported by NIDA grants P50 DA 06634 and DA07522)*

761.15

COMPARISONS OF THE EFFECTS OF GBR12909 AND GBR12935 ON RESPONDING MAINTAINED UNDER SCHEDULES OF COCAINE- AND FOOD-DELIVERY. I.R. Glowa, F.H.E. Wojnicki, Brian R. de Costa, D. Matecka, K.C.Rice and R.B. Rothman*. LMC/NIDDK/NIH and NIDA/ARC/NIH.

Lever-press responding of 6-10 kg male rhesus monkeys was maintained under multiple FR 30-response schedules of food and intravenous cocaine delivery. Relatively low doses (3-10 μg/kg/inj) of cocaine maintained high rates of responding in the drug delivery components, and did not affect responding maintained by food presentation. Under these conditions, the effects of GBR12909-HCL and GBR12935-HCL (0.3-5.6 mg/kg, i.v. slow infusion) were compared. Both agents selectively decreased cocaine-maintained responding within a limited range of doses, while lower doses had no effect and higher doses decreased responding in both components. These results suggest that these GBR analogs can selectively attenuate cocaine self-administration, without affecting alternative behaviors. However, these agents differ from cocaine in significant ways. In acquisition studies, we have been unable to maintain drug-seeking behavior with GBR in cocaine-naive monkeys, in contrast to previous reports of maintenance under substitution paradigms where monkeys have a history of self-administration. These results provide additional evidence GBR-based agents may be useful in the development of drugs to treat cocaine abuse.

DRUGS OF ABUSE: COCAINE—MISCELLANEOUS

762.1

QUANTITATION OF NEUROPEPTIDE Y (NPY) AND NPY-Y1-RECEPTOR mRNA IN RAT BRAIN BY SOLUTION HYBRIDIZATION: APPLICATION TO COCAINE STUDIES. C. Bjenning*, F. Yee, D. Larhammar[1] and C. Wahlestedt. Div. Neurobiology, Dept. Neurol. & Neurosci. Cornell Univ. Med. Coll., New York, NY 10021 and [1]Dept. Med. Genetics, Univ. Uppsala, Sweden.

Considerable evidence, obtained by studies on experimental animals and man, indicates that NPY plays a role in behavior. For example, NPY appears to be an endogenous anticonflict/anxiolytic agent, whose action depends on activation of NPY-Y1-receptors (Wahlestedt *et al., Science* **259**, 528-31, 1993). We have hypothesized that the reduction of forebrain NPY levels (and stimulation of NPY-Y1-receptors) resulting from repeated cocaine treatment may be associated with increased anxiety and depression-like states that often follows cocaine withdrawal (Wahlestedt *et al., PNAS*, **88**, 2078-82, 1991). To facilitate the study of the regulation of NPY and NPY-Y1-receptor gene expression, we developed a solution hybridization method for measuring mRNA concentrations. For both gene transcripts, the assay was based on ribonuclease protection of a riboprobe prepared from 300 bp fragments of the respective rat cDNA. After hybridization, resistant riboprobe was precipitated and filtered using a cell harvester. The mRNAs were quantified by comparison with standard curves generated from sense transcripts. The hybridization conditions produced linear curves from 7.8 to 500 pg for both NPY and Y1-receptor sense transcripts. High levels of NPY mRNA were detected in many brain regions, *e.g.* cerebral cortex, nc. accumbens, striatum, hypothalamus, hippocampus and brainstem. In contrast, detectable concentrations of NPY-Y1 receptor mRNA were primarily confined to cerebral cortex, hippocampus and thalamus. Our data further indicate that treatment of rats with cocaine (10 mg/mg, twice daily for one week) resulted in a significant reduction of NPY mRNA concentrations in forebrain areas. (Supported by DA06805)

762.2

CONTINUOUS OR INTERMITTENT COCAINE ADMINISTRATION: EFFECTS OF AMANTADINE AND FLUPENTHIXOL TREATMENT DURING WITHDRAWAL. C.J. Joyner, G.R. King, E.H. Ellinwood, JR., and N. Narasimhachari*. Behavioral Neuropharmacology Section, DUMC, Durham, NC 27710.

Research indicates that daily cocaine injections produce sensitization to, while the continuous infusion of cocaine produces tolerance to, its behavioral and neurochemical effects. The present experiments examined whether amantadine or flupenthixol administrations during withdrawal from continuous or intermittent cocaine attenuate and/or eliminate the behavioral effects produced by these administration regimens. The rats were pretreated for 14 days with either continuous or intermittent daily injections of cocaine, and were then withdrawn from the pretreatment regimen for 7 days. On days 1-5 of the withdrawal period, the subjects received IP injections of amantadine, or flupenthixol. On day 7 of withdrawal, all rats were given an IP injection of cocaine, and their behavior rated. The results indicated that amantadine treatment eliminated the tolerance normally associated with the continuous infusion of cocaine. In contrast, in both the saline control and daily injection subjects amantadine treatment during withdrawal resulted in a slight, but statistically significant reduction in the behavioral effects of cocaine. Fulpenthixol also had an effect on the behavior of the treated subjects. The present results indicate that the present experimental procedures may represent a screening methodology for cocaine pharmacotherapies.

762.3

THE TIME COURSE OF REGIONAL BRAIN METABOLIC RECOVERY DURING COCAINE WITHDRAWAL, B.B. Young*, E.S. Cooke, and R.P. Hammer, Jr., Laboratory of Cellular & Molecular Neuropharmacology, Univ. Hawaii Sch. Med., Honolulu, HI 96822.

Regional brain metabolism in the rat mesolimbic forebrain is reduced during early withdrawal following chronic cocaine treatment. We examined the time course of metabolic recovery after chronic cocaine treatment with regard to the selective terminal sites of mesolimbic forebrain circuits. Adult male Sprague-Dawley rats were treated for 14 days with daily i.p. injections of either cocaine HCl (10 mg/kg) or saline vehicle followed by 3, 7, 14 or 21 days of withdrawal. Following processing for the quantitative [^{14}C]2-deoxyglucose method, regional cerebral metabolic rate for glucose ($rCMR_{glc}$) was measured by autoradiographic analysis in 63 discrete brain regions. After 3 days of withdrawal, $rCMR_{glc}$ was significantly reduced in the nucleus accumbens (NAc) core and shell, ventral pallidum, globus pallidus, central nucleus of the amygdala, rostral lateral hypothalamus and a few other regions compared to the saline group. After 7 days of withdrawal, a significant decrease still remained only in the globus pallidus. $RCMR_{glc}$ increased significantly by 21 days compared to the 3 day time point. The results suggest that metabolic activity is reduced during early withdrawal both in extrapyramidal and mesolimbic circuits, including much of the "extended amygdala" region. The selective terminal sites of NAc core projections appear to be more impaired than those from NAc shell. The time course of metabolic recovery indicates that mesolimbic regions recover sooner than do extrapyramidal regions. These regional phases of metabolic recovery could represent a biological substrate underlying the cocaine withdrawal syndrome. Supported by USPHS Award DA06645 to RPH.

762.4

CHRONIC COCAINE DIFFERENTIALLY INDUCES REGIONAL TOLERANCE, WITHDRAWAL AND SENSITIZATION IN THE RAT CNS. E.A. Stein* and S.A. Fuller Depts. of Psychiatry and Pharmacology, Medical College of Wisconsin, Milwaukee, WI 53226

In contrast to the well known opiate tolerance and withdrawal syndrome, the syndrome following chronic cocaine is less well understood. Withdrawal in man is characterized by a 'psychosis-like' paranoia. Sensitization has been reported in animals, manifest as an increase in locomotion and increased susceptibility to cocaine-induced seizures. The present study addressed the dual questions of which neuroanatomic structures develop either tolerance or sensitization to cocaine after chronic drug treatment and which become activated during withdrawal. Rats were injected with either 0, 1.0 or 10.0 mg/kg cocaine IP twice a day for 14 d and then allowed to remain in their home cage for an additional 1 or 7 d without any drug injections. On the day of rCBF determination, each group received a challenge injection of either saline or 1.0 mg/kg cocaine. Regional cerebral blood flow, an indicator of neuronal activity, was determined autoradiographically according to the method of Sakurada et al. Analysis of variance indicated: a) widespread tolerance development predominantly within such mesolimbic regions as the NAS, amygdala, and VTA; b) sensitization development was greatest in the caudate n. and such limbic areas as the ventral pallidum, olf tub and substania innominata; (there was virtually no overlap with structures displaying tolerance) and c) possible neuronal withdrawal was evident in about 40% of analyzed areas as early as 1 day post cocaine and remained prevalent for at least 7 d (the olf tub and cortical amygdala n. demonstrated withdrawal only after 7 days). These data suggest that independent, regionally selective, neuronal mechanisms may be responsible for processes leading to cocaine-induced tolerance and sensitization (Supported by grant DA 05012).

762.5

SAFETY AND EFFICACY OF BUPROPION IN COMBINATION WITH BROMOCRIPTINE FOR TREATMENT OF COCAINE DEPENDENCE. I.D. Montoya, K. Preston, R. Rothman, D. A. Gorelick*
NIH/NIDA/ARC Treatment Branch, PO Box 5180, Baltimore, MD 21224.

Bupropion (BUP) a dopamine reuptake inhibitor and bromocriptine(BRO) a dopamine agonist have been used separately for treatment of cocaine dependence, based on the hypothesis that cocaine abuse alters the dopamine transporter associated with presynaptic dopamine uptake. This 8-week open-label study used the 2 medications in combination with the goal of obtaining an enhanced therapeutic effect with less side-effects and giving lower doses than if the medications were used separately. To date, seven cocaine-dependent (DSM-IIIR criteria) males have been so far admitted (blacks: 5, mean ($\pm$ s.d.) age: 29.8 $\pm$ 6.1 , single: 6, and education: 12.9 $\pm$ 1.5 years). Lifetime cocaine use was 5.43 $\pm$ 4.4 years, use past 30 days 18.3 $\pm$ 9.8 grams. Subjects received BUP ($\leq$ 300 mg) plus BRO ($\leq$ 7.5 mg) daily plus weekly individual counseling. No subject reported any adverse event. Retention time in treatment: 25.7 $\pm$ 24.5 days. One patient completed the treatment. One patient was discharged for non-medication related medical reasons. Patients self-reported 1.75 $\pm$ 0.42 grams/week of cocaine use before treatment and 0.96 $\pm$ 1.1 grams/week during treatment. Self-reported dollar amount of cocaine use per week decreased from \$ 271 $\pm$ 360.7 before to \$ 66.3 $\pm$ 96.7 during treatment. Positive staff-observed urine toxicology tests: 63.3% $\pm$ 35.5. Data on cocaine craving and psychosocial changes as well as data from additional patients will be presented. These preliminary results suggest that the combination of bupropion and bromocriptine is safe and has potential utility in the treatment of cocaine dependence.

762.6

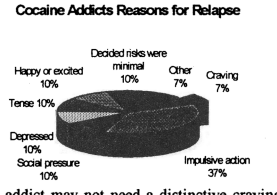
SEROTONIN AND COCAINE EFFECT IN HUMANS. C. J. McDougle*, S. C. Aronson, J. E. Black, B. E. Scanley, T. R. Kosten, G. R. Heninger, L. H. Price. Yale Univ. Dept. of Psychiatry, New Haven, CT 06519.

This study was designed to investigate the role of brain serotonin (5-HT) in the subjective and physiologic responses to cocaine in humans. Twelve cocaine-dependent subjects participated in two test sessions, separated by one week. In one session, the subjects underwent acute dietary tryptophan depletion followed by intranasal cocaine at a dose of 2 mg/kg. On the other test day, the subjects received the same dose of cocaine preceded by sham tryptophan depletion. The sequence of active and sham depletion was randomized and double-blind. Clinican and subject ratings for cocaine effect, vital signs, and serial tryptophan and cocaine blood levels, were obtained throughout each challenge. Subject ratings of cocaine "high" were significantly lower on the active depletion test day (ANOVA with repeated measures, p=0.008; paired t-test for base-to-peak change, p=0.01). A similar trend was noted in the subject ratings of positive mood (paired t-test, p=0.09). The active depletion group showed an earlier but less sustained rise in subject-rated nervousness (ANOVA, p=0.02), while there was no difference in the baseline or base-to-peak change of this variable between the two groups. No differences were noted between active and sham tests on other subjective measures of cocaine effect or vital signs. These data support the hypothesis that brain 5-HT may mediate the reinforcing and anxiogenic effects of cocaine in humans, either directly or by modulation of dopamine function.

762.7

COCAINE ADDICTION, ABSTINENCE AND RELAPSE. M.S. Gold* (1), N.S. Miller (2). (1) Depts. of Neuroscience & Psychiatry, Univ. of Florida Coll. of Med., Gainesville, FL. (2) Dept. of Psychiatry, Univ of IL at Chicago.

A dopamine (DA) hypothesis has been proposed to explain acute cocaine abstinence and chronic effects of cocaine on DA and to relate these changes to perceived need for cocaine (Dackis & Gold, 1985). We have reversed acute cocaine abstinence with bromocriptine (BROMO), further supporting a DA hypothesis. BROMO, desipramine (DMI), bupropion, and other pharmacological treatments have been reported to reduce cocaine craving. However, the focus on craving, and the assumption that withdrawal distress or craving is related to cocaine use, relapse, or recovery, has been questioned (Gold & Miller, 1993). Comparing the 2 main treatments for acute cocaine abstinence, we administered BROMO and DMI to 12 young adult, primarily crack smokers who met DSMIII-R criteria for cocaine dependence and who complained of "withdrawal." A single oral dose of BROMO (1.25 mg) and DMI (50mg) was given in a random, double-blind crossover design with craving, mood and energy self-rated. BROMO and DMI produced significant reductions in craving but only BROMO increased energy and improved depressed mood ($p<0.05$).



Subsequently, we analyzed data from 400 cocaine-dependent rehabilitation center patients, to assess the relevance of craving to continued drug use. Impulsive action was the most common reason for relapse (see figure). Drive for drug intoxication appears to be independent of the physical withdrawal intensity or the more subjective drug craving. Drug seeking/use are highly ritualized and automatic behaviors. The addict may not need a distinctive craving state to use drugs. Craving appears non-specific and dissociated from clinical relapse and other important treatment outcome measures. These conclusions are consistent with the clinical observation that DMI reduces craving but not cocaine self-adminstration.

762.8

BRAIN CORRELATES OF INDUCED COCAINE CRAVING A.R. Childress, H. F. Kung, R.T. Malison, A. Alavi, D. Mozley, J. Fitzgerald, S. Kushner, and C.P. O'Brien*. Depts. of Psychiatry and Radiology, Univ. of Pennsylvania School of Medicine, and Philadelphia VA Medical Center, Philadelphia, PA 19104

Human cocaine users experience profound craving when they encounter reminders of drug (locations, paraphernalia, etc.), but little is known about the neurochemistry of this state. Preclinical studies in rodents using electrovoltammetry and microdialysis have shown that cues which reliably signal cocaine activate brain dopamine (DA) systems, systems often implicated in cocaine's reinforcing properties. Our hypothesis is that exposure to cocaine-related cues may also produce increased DA release in humans.

Preclinical investigations with baboons have suggested the feasibility of inferring endogenous dopamine release from relative changes in brain washout of [123I]-IBZM in response to a pharmacologic probe (amphetamine). In analogous fashion, we have employed SPECT brain imaging and the reversibly binding, D2 dopamine receptor radiolgand, [123I]-IBZM, to test whether a psychological probe (i.e., cocaine-related cues known to elicit cocaine craving and arousal) may trigger dopamine release in humans.

Cocaine patients (n=7) underwent two imaging sessions using the Pickar Prism 3000 SPECT camera. After the injection of 5 mCi [123I]-IBZM, serial 10 minute images were acquired over a two hour period. Sixty minutes into each session, when specific [123I]-IBZM binding reaches "steady state", subjects were exposed to either cocaine-related or neutral cues (audiotapes, videotapes, and olfactory stimuli). Imaged activity was later analyzed, comparing activity in basal ganglia, the region of interest, to reference areas such as cerebellum or a transaxial section of whole brain at the level of basal ganglia. Though still in evolution, this approach may help elucidate the neurochemical substrates of drug craving and aid in developing "anti-craving" medications.

762.9

INDUCTION OF *C-FOS* IN RAT BRAIN BY ACUTE COCAINE AND FENFLURAMINE EXPOSURE: A COMPARISON STUDY. **Torres, G*. and C. Rivier[2]. Dept. VCAPP, Washington State University, Pullman, WA 99164-6520. [2]The Clayton Foundation for Peptide Biology, The Salk Institute, La Jolla, CA 92037.**

Cocaine and fenfluramine evoke rapid but transient increases in *c-fos* in the rat caudate putamen. Further confirmation of the similarities between cocaine and fenfluramine resides in the observation that induction of the gene signal by these two drugs can be blocked by D_1 and NMDA receptor antagonists. To better understand the postsynaptic mechanisms that may underlie gene expression induced by psychoactive drugs, we studied, by use of *in situ* hybridization and immunocytochemistry, changes in *c-fos* in brain nerve cells following cocaine and fenfluramine exposure (20 mg/kg; IP). As expected, both drugs elicited the induction of *c-fos* in the striatum (caudate putamen and nucleus accumbens). In addition, double label immunocytochemistry indicated that *c-fos* was expressed preferentially in striatal neurons containing the phenotype for DARPP-32. In sharp contrast, fenfluramine, but not cocaine, evoked *c-fos* mRNA and its protein in the neuroendocrine hypothalamus despite the fact that both drugs are known to be equally capable to stimulate the hypothalamic-pituitary-adrenal axis. This difference will be discussed in terms of serotonergic, dopaminergic and DARPP-32 input to hypothalamic neurons associated with ACTH secretion. Taken together, we identified a number of common and disparate actions of cocaine and fenfluramine in striatal and hypothalamic tissue, thereby suggesting that *c-fos* induction in these two brain drug-sensitive structures is differentially regulated by intrinsic events in addition to functional stimulation. We propose that the genomic effects produced by these two drugs represent part of a dopaminergic and glutamatergic mechanism by which monoamine reuptake inhibitor drugs affect brain function. Supported in part by DA05602.

762.10

COCAINE EXPOSURE INDUCES REGIONAL CHANGES IN FIBROBLAST GROWTH FACTOR GENE EXPRESSION IN BRAIN. D.Masco*, I.Mocchetti and K.Gale. Dept of Pharmacol. Georgetown U. Med. Ctr., Wash. DC 20007.

Cocaine exposure has been well documented to produce a marked and long lasting sensitization to the behavioral effects of subsequent cocaine challenge. It is likely that some form of neuronal plasticity is involved in this process. Because changes in expression of trophic factors often accompany neural remodeling, we examined the effect of cocaine exposure on expression of these factors in the adult rat brain. Here we report that cocaine induced changes in the regional levels of mRNAs encoding acidic and basic fibroblast growth factors (aFGF and bFGF). Rats (400 g) were injected with a single dose of cocaine (0.2 ml of a 200 mg/ml solution injected s.c.), which results in a sustained and prolonged duration of cocaine action (5-6 hr). At 5 hrs after cocaine injection, a significant increase in aFGF and bFGF mRNAs (but not in mRNA for NGF) was measured in striatum, substantia nigra and frontal cortex; this increase reached 2-3 fold over control by 8 hr, was still elevated at 16 hr, and started to decline by 24 hr. No increase in aFGF or bFGF mRNAs occurred during this time in olfactory bulbs, hippocampus or cerebellum. In rats with complete unilateral destruction of the ascending dopaminergic projections, bFGF mRNA was still increased in substantia nigra, striatum and frontal cortex in response to cocaine exposure. Moreover, the cocaine-induced increase in bFGF mRNA was not prevented by pretreatment with a potent dopamine antagonist, pimozide (2mg/kg i.p.), indicating that this effect is not dependent upon dopamine. Our results demonstrate that a single prolonged exposure to cocaine can enhance regional expression of neurotrophic factors in the adult brain, raising the possibility that these changes participate in the phenomenon of cocaine-induced sensitization.

762.11

COCAINE IN C57BL/6 MICE: EFFECTS OF GAVAGE AND SUBCUTANEOUS ADMINISTRATION. **W. Xu, S. Bingel, K. Patrick, W. Boggan,* and L. Middaugh. Medical University of South Carolina, Charleston, S.C. 29425.**

Cocaine hydrochloride (60 mg/Kg, 0.01 ml/g body weight) was administered daily for 7 days to female C57 mice either by gavage (G) or by subcutaneous injection (SC) in the suprascapular region (N = 6/group). Body weights were taken daily and skin around the injection site was examined for lesions. The animals were decapitated thirty min following the final administration. The brains were collected for cocaine assays, and skin samples, heart, lung, liver, gastrointestinal tract, urogenital tract, and adrenals were collected for pathological examination. One of the SC injected mice died of unknown cause. Cocaine reduced body weight to about the same extent for the two routes [$\bar{X}_{po}$ = 11.6%; $\bar{X}_{sc}$ = 10.3%]. Brain concentrations ($\bar{X} \pm$ SE) of cocaine at 30 min post injection were 4.22 ± 3.33 μg/g for PO and 16.96 ± 3.37 μg/g for SC. Most cocaine injected mice had increased pathology of lung (lymphocytic or lymphoplasmic infiltration) and liver (hepatocellular degeneration and necrosis) tissues. SC-cocaine mice did not have the overt dermal pathology previously described for rats (e.g., hair loss, open lesions, etc); however, were distinguished by histopathology of dermis and cutis as well as adrenal tissues. G-cocaine mice were distinguished by pathology of the kidney and by more severe liver pathology than for SC-cocaine mice. **(NIDA Grant 08034).**

762.12

COMPARISON OF THE ACUTE AND CHRONIC EFFECTS OF COCAINE ON THE IMMUNE SYSTEM. M.C. Hernandez, X.Z. Ding, R.P. Yasuda* and B.M. Bayer. Dept. of Pharmacology, Georgetown Univ. Med. School, Washington D.C., 20007.

The effect of cocaine on immune cell activity was investigated following either single or multiple injections. Animals were implanted with indwelling jugular catheters 5-7 days before being used in any experiments. Cocaine hydrochloride was administered intravenously in a 1 ml volume at 5 min intervals over a 15 min period. Two hours following cocaine administration, Concanavalin A-stimulated spleen and whole blood lymphocyte proliferation was inhibited in a dose-dependent manner. Splenic lymphocyte proliferation was inhibited by 50% at 5 mg/kg and 70% at 10 mg/kg. Similarly, at these doses, blood lymphocyte proliferative responses were inhibited by 40% and 60%, respectively. The suppressive effect of cocaine (5 mg/kg) on blood lymphocyte proliferation was found to be time dependent with maximum inhibition (50%) at 2 hours. Natural killer (NK) cytolytic activity was also measured following cocaine administration. Cocaine had no significant effect on NK activity at any of the doses or time points examined. The effect of multiple daily injections of cocaine was investigated. Animals were treated twice daily with 5 mg/kg cocaine for 4 days. On day 5, cocaine (5 mg/kg) was administered and animals were sacrificed 2 hours afterwards. Daily injections of cocaine were not found to be accompanied by a significant effect on NK cytolytic activity. In contrast to suppression observed acutely, proliferative responses of lymphocytes from animals exposed to multiple cocaine injections were similar to those of saline-injected controls. These data suggest that multiple exposure to cocaine induces the development of apparent tolerance to its immunosuppressive effects.

762.13

A COMPARISON OF THE CARDIORESPIRATORY EFFECTS OF COCAINE AND COCAINE PYROLYSIS PRODUCTS IN THE RABBIT. H. K. Erzouki, A. C. Allen, A. H. Newman, S. R. Goldberg and C. W. Schindler*. Preclinical Pharmacol. Lab., NIDA Addiction Research Center, Baltimore, MD 21224

Smoking free-base cocaine (crack) has become a serious drug abuse problem and public health concern. Anhydroecgonine methyl ester (AEME) is a major pyrolysis product of cocaine (COC) and anhydroecgonine ethyl ester (AEEE) is a product produced when "crack" cocaine and ethanol are co-administered. AEME has been detected in the urine and blood of subjects who have smoked "crack". Since cardiorespiratory arrest is a serious consequence following cocaine abuse, we administered either COC (1 mg), AEME (3 mg) or AEEE (3 mg) into either the vertebral artery (VA) or femoral vein (IV) of six different groups of anesthetized (35 mg/kg pentobarbital) rabbits while monitoring cardiorespiratory activity with the following results:

	INITIAL VALUES				PEAK CHANGES			
	MBP	HR	RR	CO2	MBP	HR	RR	CO2
COC IV	80±8	181±4	20±3	43±3	1±3	4±3	5±2	-1±1
COC VA	67±8	183±18	24±3	33±1	-25±4*	-28±6*	-24±3*	13±5*
AEME IV	89±4	230±7	26±7	31±4	-6±3	-15±5*	10±3*	-8±5
AEME VA	91±8	184±19	21±4	37±4	-12±7	-10±1*	7±1*	-5±4
AEEE IV	69±9	193±9	21±2	28±4	-5±3	-15±4*	3±2	-2±2
AEEE VA	80±3	218±15	19±2	34±3	-2±1	-11±6	12±3*	-11±5

MBP=mean blood pressure mmHg, HR=heart rate beats/min, RR=respiratory rate breaths/min, CO2= Expired CO2 mm Hg, *P<.05, values are mean±SE

Unlike IV, COC injected via VA resulted in hypotension, bradycardia and respiratory arrest. AEME and AEEE had no significant effect on blood pressure, but tended to produce decreases in heart rate via either route. No tachyphylaxis was observed for the apnea produced by cocaine. In contrast to COC, AEME and AEEE caused tachypnea. These data suggest that the central and systemic effects of COC are different. Further, COC's respiratory effects are opposite those produced by AEME and AEEE. Although tachyphylaxis quickly developed, the tachypnea produced by these pyrolysis products may initially counteract the apnea produced by COC.

762.14

CARDIOVASCULAR EFFECTS OF COCAINE IN PREWEANLING AND WEANLING RATS. F.M. Scalzo* & L.J. Burge. Dept. of Pediatrics, Arkansas Children's Hosp. Res. Ctr., Little Rock, AR 72202.

Developmental exposure to cocaine has been shown to have adverse neurobehavioral effects, however the cardiovascular effects of such exposure are poorly understood. To begin to assess the adverse effects of cocaine on cardiovascular and autonomic development, we examined the acute effects of cocaine on blood pressure (BP) and heart rate (HR) in rats at four stages of development. Rats were instrumented with a carotid and jugular cannula on postnatal day (PND) 14-15, 16-17, 18-19 or 20-21. 24 hrs later, 0.625,1.25, 2.50 or 5.00 mg/kg cocaine was administered (iv) and BP, HR and locomotor activity were recorded for one hr. On PNDs 15-16, cocaine had minor effects on BP and HR at the lowest dose tested, whereas on PND 21-22, a 10 mm Hg BP increase and a large bradycardia were observed. At 1.25 mg/kg and above, cocaine increased BP (10-20 mm Hg), with PND 17-22 rats exhibiting the largest BP increases (approx. 20 mm Hg) with the longest durations being approximately 15 min. Cocaine produced transient bradycardia at doses of 1.25 mg/kg and above after PND 17. This HR decrease was 150 bpm at some ages, lasted 5-7 min on PNDs 21-22, and was followed by a return to baseline or tachycardia, depending on the dose and age tested. The data demonstrate ontogenetic and dose-dependent changes in the cardiovascular response to cocaine that parallel the maturation of autonomic regulation of cardiovascular function. This change in responsiveness might indicate periods of differential susceptibility to the adverse effects of cocaine on cardiovascular and autonomic function (supported by DA-06319).

762.15

NEURAL MECHANISMS IN COCAINE'S CARDIOVASCULAR EFFECTS IN CONSCIOUS RATS. S.R. Tella, C.W. Schindler and S.R. Goldberg*. Preclinical Pharmacology Laboratory, National Institute on Drug Abuse Addiction Research Center, Baltimore, MD 21224 and Department of Pharmacology, Georgetown University School of Medicine, 3900 Reservoir Road, Washington, DC 20007.

The relative involvements of different neural actions of cocaine in mediating its cardiovascular effects were studied in conscious rats. Cocaine (0.03-5.6 mg/kg, i.v.) produced a dose-dependent and prolonged increase in mean arterial blood pressure and heart rate in conscious rats. The 0.3 and 1 mg/kg doses of cocaine potentiated the pressor response to exogenous norepinephrine (0.2 μg/kg), while lower (0.03 and 0.1 mg/kg) and higher (3 and 5.6 mg/kg) doses were ineffective. Desipramine (0.03-1 mg/kg), a prototype norepinephrine uptake blocker, did not alter blood pressure and heart rate. Nisoxetine (0.01-1 mg/kg), another norepinephrine selective uptake blocker, produced a small and brief (< 5 min) pressor response, but no tachycardiac response. Unlike cocaine, both desipramine and nisoxetine produced a dose-dependent potentiation of the pressor response to norepinephrine with maximal potentiation exceeding that of cocaine. Cocaine (3 mg/kg) increased plasma norepinephrine and epinephrine levels, whereas 1 mg/kg nisoxetine did not. Chemical sympathectomy by 6-hydroxydopamine selectively antagonized cocaine-induced increases in blood pressure and plasma norepinephrine levels without altering cocaine-induced increases in heart rate and plasma epinephrine levels. The converse was the case with adrenal demedullation. The combination of chemical sympathectomy with adrenal demedullation or pretreatment with chlorisondamine (10 mg/kg) antagonized cocaine-induced pressor and tachycardiac effects as well as the increases in plasma epinephrine and norepinephrine levels. These results indicate that inhibition of peripheral sympathetic neuronal amine uptake by cocaine is not critical for initiating its pressor, tachycardiac and plasma catecholamine increasing effects in conscious rats and that central stimulation of the sympathoadrenal neural axis activity plays an important role in these effects. They further suggest that the peak pressor and tachycardiac effects of cocaine are mediated by norepinephrine of sympathetic neural origin and epinephrine of adrenal medullary origin, respectively.

PSYCHOTHERAPEUTIC DRUGS: ANXIOLYTICS AND ANTIDEPRESSANTS

763.1

ALPRAZOLAM AND DIAZEPAM: COMPARED EFFECTS ON NOREPINEPHRINE AND SEROTONIN RELEASE IN CA_1 REGION OF HIPPOCAMPUS. P. A. Broderick*[1,2] and F. Eng[1], Dept. Pharmacol., CUNY Med. Sch.[1], Depts. Biol. & Psychol. CUNY Grad. Sch.[2], Convent Ave. and W. 138th St., N.Y. 10031.

The effects of the central benzodiazepine agonist anxiolytic, alprazolam (Xanax®) (1 and 3 mg/kg IP) was compared with the effects of the classical benzodiazepine anxiolytic, diazepam (Valium®) (1 and 3 mg/kg IP) on hippocampal norepinephrine (NE) and serotonin (5-HT) release in male, virus free, Sprague-Dawley rats, under chloral hydrate anesthesia. The stereotaxic coordinates for CA_1 region of hippocampus were: AP=-2.6, ML=+2.25, DV=-2.7) (Pelligrino, L.J., Pelligrino, A.S. and Cushman, A.J., 1979). *In vivo* voltammetry was used with stearate microelectrodes to detect NE and 5-HT release concurrently, in separate electrochemical peaks, within seconds, *on line* and *in vivo*. Time course studies showed that the anxiolytic alprazolam, at both the 1 mg/kg and 3 mg/kg doses, was more potent than the anxiolytic diazepam in the suppression of hippocampal NE release. Moreover, the *in vivo* neurochemical profile of hippocampal 5-HT release for alprazolam dramatically differed from that of diazepam, i.e. whereas diazepam decreased 5-HT release at the 1 mg/kg and 3 mg/kg doses in a dose dependent fashion, alprazolam produced increases in 5-HT release which occurred immediately after injection of each dose and lasted 30' and 20' respectively. Interestingly, previous data on the benzodiazepine agonist, adinazolam (Broderick, *Brain Res. Bull.*, 27:689, 1991), showed that adinazolam exhibits a neurochemical profile similar to that of diazepam. Differential effects of alprazolam, may help elucidate therapeutic approaches in anxiety and panic disorders. Supp: Upjohn.

763.2

ACUTE EFFECTS OF BENZODIAZEPINES ON REGIONAL BRAIN CRF CONCENTRATIONS: COMPARISON OF ALPRAZOLAM, DIAZEPAM, AND LORAZEPAM. M.J. Owens* and C.B. Nemeroff. Dept. Psychiatry & Behavioral Sciences, Emory Univ. Sch. Med., Atlanta, Georgia 30322.

Neurochemical, electrophysiological, and behavioral microinfusion studies suggest that CRF produces its anxiogenic effects, at least in part, by increasing activity of LC noradrenergic neurons. In view of these findings, we examined whether the clinically efficacious triazolobenzodiazepine anxiolytic, alprazolam, alters CRF neuronal function. In contrast to exposure to stress which increases LC CRF concentrations, both acute and chronic alprazolam administration resulted in decreases in LC CRF concentrations. Clinical studies suggest that alprazolam may possess unique properties in comparison with other benzodiazepines in the treatment of certain psychiatric illnesses such as panic disorder. In order to determine whether the alterations in CRF neurons are specific to triazolobenzodiazepines such as alprazolam, or are common to all anxiolytic benzodiazepines, we compared the acute effects of three commonly prescribed benzodiazepines on brain CRF concentrations in the LC.

Alprazolam (1 mg/kg) and diazepam (10 mg/kg) both produced significant decreases in CRF concentrations with the alprazolam effect of a significantly greater magnitude. Lorazepam (1 mg/kg) produced a decrease in CRF concentrations which did not attain statistical significance. This lack of effect of lorazepam may be dose-related or due to pharmacokinetic differences. Indeed, it has been shown that iv lorazepam has a slower onset of action than diazepam due to its relatively slower entry into the brain. Dose-response studies will be necessary to further clarify these findings, though at present it appears that alprazolam does not possess any unique properties, as related to its actions on CRF neurons, compared to other anxiolytic benzodiazepines. Supported by MH-42088 and BRSG S07 RR05364.

763.3

AN ETHOLOGICALLY BASED, STIMULUS AND GENDER-SENSITIVE NONHUMAN PRIMATE MODEL OF ANXIETY. J. D. Newman* and M. J. Farley. Laboratory of Comparative Ethology, NICHD, NIH, Poolesville, MD 20837-0529.

Behavioral testing in suitable animal models is generally regarded as an obligatory step toward establishing the efficacy and risk/benefit attributes of drugs being screened for possible treatment of behavioral disorders in humans. While the ideal testing paradigm may never be fully achievable, its characteristics would likely include: differential sensitivity to various etiologies, ability to reveal gender differences in models for human disorders demonstrating gender differences in incidence or symptoms, testable in animal models most relevant to the human disorder, efficient in terms of time to completely test a full range of drug doses in an adequate sample of subjects. We have refined a behavioral testing paradigm, using adult squirrel monkeys permitted to range freely inside an observation cage, that measures natural behavioral responses to the anxiety states underlying social separation and external threat. The entire test requires a maximum of 15 minutes/animal/drug dose, and, following an initial pretest acclimation period, may be administered to each subject on a weekly basis without altering baseline performance levels. The model exhibits sensitivity to stimulus (social isolation vs. external threat from humans) and to gender in terms of behaviors expressed and drug efficacy, and may be useful in screening drugs developed to differentially treat separation anxiety, panic attack disorder, and phobias.

763.4

U-93385, A HIGH INTRINSIC ACTIVITY 5-HT1A AGONIST WITH GOOD ORAL ACTIVITY. M.F.Piercey*, K.A.Svensson*, C.H.Lin, S.R.Haadsma-Svensson, R.B.McCall, M.W.Smith, P.A.Broderick# and A.Carlsson*, The Upjohn Co., Kalamazoo, MI, *Pharmacology, Dept., Goteborg, Sweden, and #Pharmacology Dept., CUNY Medical School, New York, NY.

U-93385 is a tricyclic carboxamide analog of 8-OH DPAT with the amido group in the 8-position of the aminotetralin. U-93385 has nanomolar affinity for the 5-HT1A receptor site *in vitro*. Its affinity for a broad range of additional CNS receptors (adrenergic, cholinergic, serotonin, opioid, dopamine) is greater than 1 μM. In mice, U-93385 is as potent and as effective in depressing body temperature as 8-OH DPAT, a high intrinsic activity 5-HT1A agonist. It is approximately twice as effective as 5-HT1A partial agonist anxiolytics such as buspirone, gepirone, and ipsapirone. In contrast to 8-OH DPAT and the partial agonist anxiolytics, U-93385 is a potent agonist following oral as well as subcutaneous administration. Oral bioavailability in the rat is 46%. U-93336, the (+)-optical isomer of U-93385, is much weaker as a 5-HT1A agonist, both *in vitro* and *in vivo*. The racemate, U-91770, has *in vivo* potencies intermediate between the two enantiomers. U-93385E potently depresses 5-HT neuron firing, 5-HTP synthesis, and 5-HT release. It depresses glucose metabolism in a majority of brain areas. It is concluded that U-93385 is a potent and highly-selective 5-HT1A agonist which, by virtue of its high intrinsic activity and good oral activity, could be an anxiolytic with greater efficacy than other 5-HT1A agonists under development.

763.5

U-93385: AN ORALLY ACTIVE ANXIOLYTIC WITH SELECTIVE 5-HT_{1A} AGONIST ACTIVITY. P.J.K.D.Schreur*, M.P. Stone, N.F.Nichols, C.-H.Lin and S.R.Haadsma Svensson. Upjohn Laboratories, Kalamazoo, MI 49001.

U-93385(*cis*-(3a*R*)-(-)-2,3,3a,4,5,9b-hexahydro-3-(*n*-propyl)-1*H*-benz[*e*]indole-9-carboxamide) is a high intrinsic activity agonist with excellent 5-HT_{1A} selectivity (C.-H.Lin *et al.*, 1993; also M.F. Piercey *et al.*, R.A.Lahti *et al.*, this meeting). U-93385 was active in mice in 3 tests for anxiolytic activity. It was orally active against isolation-induced aggression (3 and 10 mg/kg) and in a social interaction test, the face-to-face test (10 mg/kg). It was also active i.p. in mice against isolation-induced aggression (0.3-3 mg/kg) and against shock-induced aggression (10 mg/kg). The *cis*-(3a*S*)-(+)-enantiomer of U-93385 (U-93336) and the *trans*-(3a*S*)-(+)-enantiomer (U-94109) were inactive in all 3 tests, while the *trans*-(3a*R*)-(-)-enantiomer (U-94110) was weakly active in the isolation-induced aggression assay and inactive in the other 2 assays.

In rats, U-93385 (1-10 mg/kg s.c.) or gepirone (10 mg/kg s.c.) was inactive acutely in the center test (in which benzodiazepine anxiolytics antagonize thigmotaxis). However, 16 days of U-93385 (22 mg/kg/day) or gepirone (67 mg/kg/day) when given chronically in chow had an anxiolytic effect in this test. In contrast, diazepam (10 mg/kg s.c.) was active acutely, but inactive when given for 16 days in the diet (67 mg/kg/day).

763.6

ANXIOLYTIC ACTIVITY OF THE 5-HT1A AGONIST U-93385. ATTENUATION OF STRESS-INDUCED INCREASES IN RAT CORTICOSTERONE LEVELS. R.A. Lahti*, D.L.Evans, N.F.Nichols and L.M.Figur. Upjohn Laboratories, Kalamazoo, MI 49001.

Studies based on the premise that anxiety and/or stress result in elevated plasma corticosteroid levels have provided insight into the dosing parameters, mechanism of action, and potency for U-93385, a serotonin 5-HT_{1A} receptor agonist with "anxiolytic" activity. Investigation into the dosing regime determined that acute dosing at 3 and 10 mg/kg (IP) resulted in the elevation of corticosteroids; however, this acute response could be alleviated by dosing subchronically. Attenuation of stress-induced increases in corticosteroids was observed following subchronic dosing, and tolerance did not develop to this anxiolytic effect of U-93385. Several serotonin 5-HT_{1A} receptor agents were tested in this rat model and showed varying effects. Studies with the 5-HT_{1A} receptor antagonist, pindolol, indicated that the acute corticosteroid-elevating effect was exerted through the serotonin 5-HT_{1A} receptor, whereas the anxiolytic effect observed following subchronic dosing was not affected by pindolol and, thus, probably not via a 5-HT_{1A} mechanism. The inability of U-93385 to block the effects of CRF- or ACTH-induced corticosteroid increases indicated that it does not act at the pituitary or by antagonizing the effects of ACTH, respectively. U-93385 did attenuate the corticosteroid-increasing effect of FG-7142, a benzodiazepine inverse agonist, in rats. When comparing the potency of U-93385 to diazepam, the results indicated that U-93385 is a unique anxiolytic agent with an efficacy and potency better than or equal to diazepam.

763.7

BUSPIRONE, BUT NOT FLUOXETINE OR ZATOSETRON, ATTENUATES INCREASES IN SENSORIMOTOR REACTIVITY RESULTING FROM WITHDRAWAL OF CHRONIC NICOTINE. D. Helton*, K. Rasmussen, D. Modlin, and J. Czachura. Lilly Research Laboratories, Eli Lilly and Company, Greenfield, IN 46140.

Cessation of chronic nicotine (NI) in rats leads to increased sensorimotor reactivity (as measured by auditory startle responding) during the first 5 days of nicotine withdrawal. We have previously reported that 5-HT_{1a} agonists exacerbate this increase in reactivity. The present study evaluated the effects of pretreatment with 1) the selective 5-HT reuptake inhibitor fluoxetine, 2) the 5-HT_3 antagonist zatosetron, or 3) the partial 5-HT_{1a} agonist buspirone, on auditory startle responding following NI withdrawal. NI (6 mg/kg/day) was continuously administered for 12 days in rats by surgically implanting osmotic pumps (sc). Fluoxetine (5, 10, 20 mg/kg, ip), zatosetron (.1, .3, 1 mg/kg, sc), or buspirone (.1, .3, 1, 3, 10 mg/kg, sc) was given 60, 30, or 15 minutes, respectively, before daily evaluation of startle responding through 5 days following cessation of NI exposure. Buspirone (.3 mg/kg) attenuated the increased reactivity following the termination of chronic NI for 5 days. In contrast, higher doses of buspirone exacerbated increases in reactivity through 5 days at doses which did not alter startle responding in naive rats. Both fluoxetine and zatosetron failed to attenuate withdrawal. These results suggest that the attenuation of withdrawal symptoms by buspirone may not be related to its 5-HT_{1a} agonist properties.

763.8

PHARMACOLOGICAL PROFILE OF HT-90B, A PUTATIVE ANXIOLYTIC WITH POTENT ANTIDEPRESSIVE ACTIVITY. T.Miyauchi, K. Inagawa, H. Uchida, C. Tameda and M. Sakakibara*. Fuji Gotemba Research Labs., Chugai Pharmaceutical Co., Ltd., Gotemba 412, *Dept. of Biol. Sci. and Tech., Tokai Univ., Numazu 410-03, Japan.

A number of studies have suggested that 5-HT1A and 5-HT2 receptors have opposing effects in the CNS. This provides a possibility that a 5-HT1A agonist which has 5-HT2 antagonist profile as well produces more effective anxiolytic and antidepressive actions than does a simple 5-HT1A agonist. HT-90B ((–)-N-{[2-(8-methyl - 1,4- benzodioxane - 2- ylmethyl) amino] ethyl}tricyclo [3, 3, 1, 1 (3, 7)] decane -1-carboxamide) had high affinities for the 5-HT1A (IC_{50}=0.4 nM) and 5-HT2 (IC_{50}=20 nM) receptors. HT-90B (1 nM - 1 μM) inhibited forskolin activated adenylate cyclase in rat hippocampal membrane as a 5-HT1A full agonist, and the potency of the drug was higher than that of 8-OH-DPAT, a standard 5-HT1A agonist. On the other hand, HT-90B (0.1 - 30 mg/kg, s.c.) behaved as a weak partial 5-HT1A agonist in the serotonin syndrome test in reserpinized rats. HT-90B (100 nM - 10 μM) showed 5-HT2 antagonistic action in rabbit platelet aggregation. In a Vogel conflict model in rats, HT-90B (3 - 30 mg/kg, p.o.) was more effective than buspirone in abolishing the response suppression. In the forced swim test in rats, HT-90B (3 - 30 mg/kg, p.o.) reduced the duration of immobility. In particular, the compound was active after a single oral dose, which contrasts with the requirement of multiple doses for standard antidepressants to produce a stable anti-immobility effect. The anticonflict and anti-immobility effects of HT-90B (20 mg/kg, p.o.) were still evident even 4 hr after the administration, and no tolerance was observed for these effects after repeated oral administration (10 mg/kg, b.i.d., 2 weeks). Similar to the effect of various antidepressants, repeated administration of HT-90B produced a down regulation of 5-HT2 receptors in the rat cerebral cortex. HT-90B (up to 100 mg/kg, p.o.) did not produce benzodiazepine-like sedation, ataxia, muscle relaxation and barbiturate-potentiation, nor had buspirone-like antidopaminergic action. These results suggest that HT-90B is a potent antidepressive anxiolytic agent with minimal side effects.

763.9

ACUTE EFFECT OF WY-48723, A NOVEL ANTIDEPRESSANT, ON THE SPONTANEOUS ACTIVITY OF SEROTONERGIC AND DOPAMINERGIC NEURONS. C. W. Uzzle*, D. E. Jones, J. T. Haskins, K. L. Marquis, G. P. Stack and T. H. Andree . Wyeth-Ayerst Research, CN 8000, Princeton, NJ 08543-8000

WY-48723 (Decahydro-3-[4-[4-(2-pyrimidinyl)-1-piperazinyl] butyl]-1,5-methano-6,7,9-metheno-2H-pentaleno[1,2-a]azepin-2,4(3H)-dione dihydrochloride quarter hydrate), a compound displaying preclinical antidepressant activity was evaluated to determine its effect on the spontaneous activity of both 5-HT and DA neurons. The effect of WY-48723 was compared to those of 8-OH-DPAT and gepirone on 5-HT dorsal raphe neurons, and to that of buspirone on A9 and A10 dopaminergic neurons. Standard neurophysiological methods were used for recording. The rank order of potency of these compounds for inhibiting the spontaneous activity of 5-HT neurons was found to be: 8-OH-DPAT > WY-48723 > gepirone (ID_{50}'s = 1.9, 17, and 28.9 ug/kg i.v., respectively). WY-48723 produced an activation of A9 DA neurons and was slightly greater in potency than buspirone (ED_{125}'s = 45 and 69.7 ug/kg i.v., respectively).

These findings suggest that WY-48723 possess characteristics similar to those of other azapirones in affecting both 5-HT and DA spontaneous neuronal activity. Additional testing is underway to examine the effects of WY-48723 on A10 DA neurons and to compare these data with those observed on A9.

763.10

REPEATED ADMINISTRATION OF THE ANTIDEPRESSANT FLUOXETINE, BUT NOT DESIPRAMINE OR MIANSERIN, PRODUCES DESENSITIZATION OF 5-HT_{1A} AUTORECEPTORS. D.S. Kreiss* & I. Lucki. Institute of Neurological Sciences, Depts of Pharmacology & Psychiatry, University of Pennsylvania, Phil., PA 19104.

The regulation of serotonin (5-HT) release by 5-HT_{1A} autoreceptors was investigated following repeated treatment with the 5-HT uptake inhibitor fluoxetine, the norepinephrine uptake inhibitor desipramine, and the 5-HT/α-adrenergic receptor antagonist mianserin. Animals were pretreated with these antidepressant drugs (each at 15.0 mg/kg) for 1 or 14 days. The ability of the 5-HT_{1A} receptor agonist 8-OH-DPAT to decrease 5-HT release in the striatum and hippocampus of rats maintained under chloral hydrate anesthesia was examined 48 hours after the last antidepressant drug injection using *in vivo* microdialysis. Repeated treatment with fluoxetine, but not desipramine or mianserin, markedly attenuated the ability of 8-OH-DPAT to decrease 5-HT release. 14 day pretreatment with fluoxetine increased basal levels of 5-HT release in the striatum and hippocampus, whereas 14 day pretreatment with desipramine increased basal levels only in the striatum.

This study demonstrates that the 5-HT_{1A} autoreceptors regulating 5-HT release were desensitized by chronic treatment with fluoxetine. In addition, this study demonstrated that mechanisms regulating basal 5-HT release can be altered independently from the sensitivity of 5-HT_{1A} autoreceptors.

This work was supported by MH 36262 and MH 48125.

763.11

BLOCKADE OF THE ANTIDEPRESSANT-LIKE EFFECTS OF SEROTONIN$_{1A}$ AGONISTS AND DESIPRAMINE IN THE FORCED SWIM TEST. M. J. Detke*, S. Wieland and I. Lucki. Departments of Psychology, Psychiatry and Pharmacology, University of Pennsylvania, Philadelphia, PA 19104.

In order to determine whether the antidepressant-like effects of serotonin (5-HT) $_{1A}$ agonists in the Forced Swim Test (FST) are mediated by the 5-HT$_{1A}$ receptor, several 5-HT$_{1A}$ receptor antagonists were studied for their abilities to reverse the effects of the 5-HT$_{1A}$ receptor agonists 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) and buspirone. Rats were given a 15-min pretest swim session followed 24 h later with a second swim session for 5 min. Drugs were administered 0.5, 19 and 23 h after the first swim session. NAN-190, BMY 7378 and pindolol were inactive when tested alone. Pretreatment with each of these compounds blocked the antidepressant-like effects of 8-OH-DPAT and buspirone in the FST. For comparison, the effects of pretreatment with the 5-HT$_{1A}$ receptor antagonists were examined on the antidepressant-like effects of the norepinephrine (NE) selective uptake inhibitor desipramine. Pretreatment with these 5-HT$_{1A}$ receptor antagonists also blocked the antidepressant-like effects of desipramine in the FST.

These results provide evidence that the antidepressant-like effects of the 5-HT$_{1A}$ receptor agonists are mediated through activation of the 5-HT$_{1A}$ receptor. The finding that 5-HT$_{1A}$ receptor antagonists also reversed the effects of desipramine lead to considerations of how the NE and 5-HT systems interact to produce antidepressant-like behavioral effects in the FST.

Supported by USPHS grant MH 36262, NIH fellowship 5-T32-GM-071770, and NIMH fellowship 5-T32-MH-18902 and the Benjamin and Mary Siddons Measey Foundation.

763.12

CHRONIC ANTIDEPRESSANT TREATMENT DOES NOT ALTER THE LEVELS OF Gs and Gi α-SUBUNIT TRANSCRIPT AND IMMUNOREACTIVITY IN RAT CORTEX. P.P. Li*, M. Emamghoreishi, D. Sibony and J.J. Warsh. Clarke Institute of Psychiatry, Toronto, Ontario, Canada, M5T 1R8.

Recent evidence indicates that chronic antidepressant treatment in rats modifies the CNS β-adrenoceptor signaling pathway at multiple sites including receptor, G-protein, adenylyl cyclase and protein kinase A. In the present study we examined the postreceptor effect of chronic antidepressant treatment on the levels of $G\alpha_s$, $G\alpha_{i1}$ and $G\alpha_{i2}$ mRNA and immunoreactivity in rat cortex. Male Wistar rats were infused with desipramine (10 mg/kg/d), amitriptyline (10 mg/kg/d), tranylcypromine (7.5 mg/kg/d) or saline via osmotic minipumps for 21 days. G protein α-subunit mRNA levels were determined with specific cDNA probes by hybridization blot analysis. Cortical membrane G protein immunoreactivities were estimated by Western blotting. Chronic administration of desipramine, amitriptyline and tranylcypromine did not significantly affect the levels of $G\alpha_s$, $G\alpha_{i1}$ and $G\alpha_{i2}$ transcript in rat cortex. Similarly, the levels of cortical $G\alpha_s$ (both 45- and 52-kDa species), $G\alpha_{i1}$ and $G\alpha_{i2}$ immunoreactivity remained unchanged following these drug treatments. Our data do not support the earlier findings of $G\alpha_s$ and $G\alpha_i$ down-regulation by chronic imipramine (Duman et al., Pharmacologist, 31:182, 1989) or desipramine (Lesch et al., Eur. J. Pharmacol. Mol. Pharmacol., 207:361, 1991) treatment, respectively. These results suggest that the adaptive changes of the β-adrenoceptor-adenylyl cyclase system following chronic antidepressant treatment might not involve regulation at the level of $G\alpha_s$ or $G\alpha_i$ protein, at least in rat cortex. (Supported by a grant from Canadian Psychiatric Research Foundation).

763.13

EFFECTS OF THE CALCIUM ANTAGONIST NIMODIPINE IN ANIMAL MODELS OF DEPRESSION AND ALCOHOLISM. J. De Vry, R. de Beun and T. Glaser* Institute for Neurobiology, Troponwerke, Berliner Strasse 156, 51063 Köln 80, FRG

Besides the well known vasodilatory and antiarrhythmic properties of calcium channel inhibitors (CCIs), and their therapeutic potential in the treatment o0f some CNS disorders such as stroke, migraine, subarachnoidal hemorrhage and age-related disorders, recent evidence suggests that CCIs may also be beneficial in the treatment of mood disorders and drug abuse (for a review, see: Pucilowski, Psychopharmacol. 109, 12, 1992). The aim of the present study was to investigate the behavioral profile of nimodipine (NIM), a 1,4-dihydropyridine with weak cardiovascular effects, in rodent models of depression and alcoholism. In rats, NIM reversed the behavioral deficit in a learned helplessness procedure (0.5 - 5 mg/kg, p.o.) and reduced immobility in a behavioral despair test (forced swimming test, 3 - 30 mg/kg, p.o.). In the latter test, sensitization of the anti-immobility effects of NIM were observed after subchronic application (3 mg/kg, 19 applications, p.o.), a phenomenon which is also observed with classical antidepressants. Also in mice, NIM (3 - 50 mg/kg, p.o.) reduced immobility in a behavioral despair test. In AA rats, a rat line selected for high ethanol (EtOH, 10 % V/V) preference, NIM (1-50 mg/kg, p.o.) completely blocked EtOH preference in a two-bottle 12 h choice test. Also in normal rats which developed a preference for EtOH (5 % V/V) in a two-bottle continuous access procedure, NIM (15 mg/kg, p.o.) was able to reduce EtOH preference. Although NIM has stimulus properties (as assessed either in a two-lever procedure in which rats were trained to discriminate 15 mg/kg NIM, p.o., from vehicle, or in a cross-familiarization conditioned taste aversion procedure), they appear to be qualitatively different from the stimulus properties of EtOH. It is therefore unlikely that the EtOH preference reducing effect of NIM is due to a simple substitution for alcohol. Although antidepressive effects may contribute to the EtOH preference reducing effects of NIM, differences in the shape of the dose response curves in models of depression (inverted U-shaped) and alcoholism (monotonous), suggest that NIM has specific anti-craving effects.

763.14

AN ANIMAL MODEL FOR FLUOXETINE INDUCED AKATHESIA M. H. Teicher*, P. J. Wallace Department of Psychiatry, Harvard Medical School, Mailman Laboratories for Psychiatric Research, McLean Hospital, Belmont, MA, 02178

A common and potentially significant side effect of treatment with the antidepressant fluoxetine is a state of inner agitation and distress referred to as akathesia. Not only can akathesia contribute to non-compliance, but it has also, more significantly, been anecdotally linked to suicidal attempts and ideation. It has been observed that the most severe cases of akathesia occur in response to the selective serotonin uptake inhibitors while the tricyclic antidepressant produce milder forms of 'jitteriness.' Cessation of antidepressant treatment or co-administration of propranolol has been found to ameliorate akathesia. However, the basis of and treatments for this condition have, to our knowledge, not been fully explored. We have developed an animal model for akathesia to address these and other questions. Sprague-Dawley rats (250-330 g) were injected with 30 mg/kg (+/-)-Fluoxetine (s.c.) and monitored with a MacReflex infrared tracking system during the diurnal, resting, phase of their activity cycle. Monitoring began 2 hours following drug administration in order to allow the animals to fully habituate to the test environment and to recover from any agitation produced by handling and injection. The total locomotor displacement during the first hour of monitoring was 7.65±0.89 (N=8) and 2.88±0.79 (N=8) meters for the fluoxetine and vehicle treated groups, respectively. This 266% increase in activity consisted of a non-stereotypic, non-exploratory agitation and an inability to maintain the typical resting posture. Restlessness was maximal at two hours following injection and persisted for four hours. With this model it should be possible to investigate the biological bases and pharmacological specificity of this important but poorly understood phenomenon.

763.15

ALPHA-METHYL-PARA-TYROSINE (AMPT) DEPLETION OF CATECHOLEAMINES IN TREATED DEPRESSED PATIENTS. **P.L. Delgado*, H.L. Miller, R.M. Salomon, J. Licinio, G.R. Heninger, A.J. Gelenberg, D.S. Charney. Dept.'s of Psychiatry, Tucson and West Haven VAMC, Yale University School of Medicine, and University of Arizona College of Medicine, 1501 N. Campbell Avenue, Tucson, AZ 85724**

Depletion of plasma tryptophan (TRP) causes a transient depressive relapse in depressed patients treated with selective serotonin (5-HT) reuptake inhibitors (SSRI's) but rarely in patients treated with desipramine (DMI), suggesting that the antidepressant response to DMI is less acutely dependent on brain 5-HT content than that to SSRI's (Delgado et al., 1991). Brain norepinephrine and dopamine are reduced by inhibiting their synthesis with alpha-methyl-para-tyrosine (AMPT). Given our findings with TRP depletion, we wanted to assess the effects of catecholamine depletion in antidepressant-treated depressed patients. **METHOD**: AMPT challenges were administered in a double-blind, placebo-controlled, crossover fashion to 14 depressed patients having maintained a therapeutic antidepressant response (predetermined criteria) for ≥ 2 weeks (3 DMI, 2 mazindol, 5 fluoxetine, 4 sertraline). Each patient participates in two challenges one week apart. Each challenge includes a baseline day, two days of either AMPT 1 gm TID or diphenhydramine (active placebo) 50 mg TID and a follow-up day. Antidepressant drugs are continued throughout testing. Ratings (Ham-D) and plasma for MHPG and HVA levels are obtained prior to, during and after testing. **RESULTS**: The 3 DMI- and 2 mazindol-responders had a rapid increase in Ham-D score during AMPT but not placebo (diphenhydramine) challenge while only 1/9 SSRI-treated patients did. **IMPLICATIONS**: The antidepressant response to DMI may be more acutely dependent on brain catecholeamine content than the response to SSRI's. In the context of our work with TRP depletion, these results suggest that the neurobiological mechanisms underlying the antidepressant responses to different drugs involve alterations in the functioning of different neurotransmitter systems and reinforce the importance of changes in both the 5-HT and catecholeamine systems in successful antidepressant responses.

763.16

4-PHENYLPIPERIDINES AND -SPIROPIPERIDINES WITH SUB-NANOMOLAR AFFINITY FOR SIGMA BINDING SITES AND WITH POTENT ANXIOLYTIC ACTIVITY. J.Perregaard, E.K.Moltzen, E.Meier, C.Sánchez and J.Hyttel*. Research & Development, H.Lundbeck A/S, Ottiliavej 9, DK-2500 Copenhagen-Valby, Denmark.

The functional role of sigma binding sites within the central nervous system has been studied intensively during recent years. The selective sigma ligand (+)-pentazocine is claimed to be anxiogenic in humans[1] and rats[2]. We have developed a series of 4-phenylpiperidines and spiro[isobenzofuran-1-(3H),4´-piperidines] substituted with 1-phenylindol-3-ylalkyl groups at the piperidine nitrogen atom. Sigma affinities with IC_{50} values below 1 nM (inhibition of ^{3}H-DTG binding to rat brain homogenates) were found for key derivatives such as 1´-[4-[1-(4-fluorophenyl)-1H-indol-3-yl]butan-1-yl]spiro[isobenzofuran-1-(3H),4´-piperidine], Lu 28-179 (sigma binding: IC_{50} = 0.12 nM) and 1-(4-fluorophenyl)-3-[4-[4-(4-fluorophenyl)piperidin-1-yl]butan-1-yl]-1H-indole, Lu 29-253 (sigma binding: IC_{50} = 0.11 nM). These compounds show potent anxiolytic activity in the light/dark exploration test in rats as benzodiazepines such as diazepam. In a further series of related structures the 3-(1-phenylindole) substituent was replaced by another 4-phenylpiperidine or spiro[isobenzofuran-1-(3H),4´-piperidine] group resulting in symmetrical and more simple "dimeric" structures. Selectivity and high sigma affinity were retained in these "dimers" such as eg 1,4-bis-spiro[isobenzofuran-1(3H),4´-piperidin-1´-yl]butane, Lu 29-252 (sigma binding: IC_{50} = 0.64 nM). Structure-affinity relationships including results from the series of dimers will be presented as well as anxiolytic effects of key compounds.

[1]Belville and Forrest. *Clin.Pharmacol.Ther.* (1968)9:142-151.
[2]Lai et al. *Soc.Neurosci.* (1989)15: abstract 270.9

764.1

ONTOGENY OF FIRING PATTERNS SEEN IN STIMULUS-EVOKED ELECTROGRAPHIC SEIZURES RECORDED IN HIPPOCAMPAL SLICES.
S. Clark*[1], W. A. Wilson[1,2,5] D. V. Lewis[3,4], Duke Univ. Depts. of Pharmacology[1], Medicine[2], & Pediatrics[3], Neurobiology[4] and Veterans Administration Medical Center[5], Durham, NC 27705, USA

Young animals and humans are at greater risk of having seizures. While there are numerous ontological differences that could promote seizures, it is not clear which of these are critical for seizures. We have begun to explore age-related differences in seizure expression with our ***in vitro*** model of epilepsy: stimulus train induced-electrographic seizures (EGSs) in hippocampal slices.

We found that the firing pattern of the EGSs were age-dependent. In slices from 10-30 day old (DO) rats, EGSs had a tonic-clonic pattern. The firing frequency of the tonic phase decreased linearly with age, whereas total EGS duration peaked between 15 and 25 days of age (35 sec.). (Unlike either of the seizure parameters, pop spike amplitude increased from 10 to 30 days.)

In contrast, the tonic-clonic firing pattern was not seen in either younger or older rats. In 60 DO rats, the stimuli evoked only brief, low-frequency afterdischarges which lacked a tonic phase. In 5 DO rats the activity varied widely; most strikingly, many slices exhibited only a brief tonic-like discharge with high burst firing frequency and a low amplitude.

We also found that spontaneous interictal-like burst activity varied with age. It only appeared at ages ≥ 15 DO. Their appearance may contribute to the age-related decrease in EGS intensity. (Swartzwelder, et. al. Brain Res. 410:362-366)

This ontological model of seizure expression could have several benefits. It may permit the identification of mechanisms underlying the tonic phase of EGSs and it may facilitate the development of epilepsy therapies which target certain age-specific processes.

764.2

SELECTIVE ACTIVATION OF HIPPOCAMPAL INTERNEURON SUBPOPULATIONS BY METABOTROPIC GLUTAMATE RECEPTOR STIMULATION. H.B. Michelson* and R.K.S. Wong, State Univ. of N.Y. Health Science Ctr., Brooklyn, NY 11203.

We have been investigating the activation of the inhibitory circuit in the transverse hippocampal slice in the presence of 4-aminopyridine (75-80 uM) and the excitatory amino acid blockers CPP and CNQX (both 10 uM). The purpose of the present experiments was twofold: (1) to test whether distinct postsynaptic GABA responses were activated by separate groups of interneurons and (2) to evaluate whether subgroups of interneurons can be distinguished by their different pharmacological profiles. Under the above conditions, synchronized IPSPs spontaneously occurred in pyramidal cells, as a result of synchronized burst firing of interneurons. Bath application of the metabotropic glutamate receptor (mGluR) agonist trans-ACPD (20-30 uM) decreased the amplitude, increased the frequency, and disrupted the rhythm of the synchronized IPSP. The interneurons which burst fired to generate the synchronized IPSP depolarized and exhibited large amplitude oscillatory depolarizations. They no longer consistently burst fired simultaneous with the synchronized IPSP in pyramidal cells. In other experiments, picrotoxin was added to the bath along with 4-AP, CPP and CNQX. A synchronized $GABA_B$ IPSP was generated under these conditions. 30 uM trans-ACPD did not significantly alter the frequency or amplitude of the synchronized $GABA_B$ IPSP. The results of this study indicate that interneurons show differential sensitivity to mGluR agonists. In addition, the IPSPs mediated by $GABA_A$ and $GABA_B$ receptors are probably generated by different subpopulations of interneurons.

764.3

INTRACELLULAR CALCIUM AND EPILEPTOGENESIS. L.R. Merlin* and R.K.S. Wong. Depts. of Neurology and Pharmacology, SUNY/Health Science Center, Brooklyn, NY 11203

Elevation of intracellular calcium concentration ($[Ca^{2+}]_i$) has been shown to cause a suppression of $GABA_A$ receptor-mediated responses in hippocampal cells (Chen et al., *J. Physiol.* 1990). We are interested in the effect of $Ca^{2+}{}_i$ on synaptic transmission and epileptogenesis in the hippocampal circuit.

Experiments were carried out using hippocampal slices prepared from guinea pigs. Caffeine concentrations above 0.7 mM elicited epileptiform discharges in the CA3 region of the slice. These consisted of spontaneous burst discharges of greater than 100 ms duration occurring once every 5-10 sec and followed by a pronounced afterhyperpolarization. Such discharges were generally not observed in the CA1 region. Instead, phasic IPSP's were the most prominent event seen there. In the presence of ionotropic glutamate receptor blockers (CNQX and CPP), application of caffeine resulted in hyperpolarizations in CA3 pyramidal cells. These events were associated with a conductance increase, and were not blocked by bath application of tetrodotoxin. They are most likely the result of Ca^{2+}-activated K^+ currents secondary to caffeine-induced elevation of $[Ca^{2+}]_i$. This finding is consistent with the previous report that ryanodine receptors are densely concentrated within CA3 neurons (Sharp et al., *Soc. Neurosci. Abstr.* 1992). At present, the relevance of release of calcium from intracellular stores to epileptogenesis remains to be explored.

764.4

INHIBITION OF EPILEPTIFORM ACTIVITY IN HIPPOCAMPAL CA1 NEURONS VIA ACTIVATION OF 5-HT1A RECEPTOR SUBTYPE. Delanthi Salgado* and Karim A. Alkadhi, Department of Pharmacology, University of Houston, Houston, TX 77204-5515 USA.

Presently, there is a lack of strong evidence linking serotonin to the inhibition of epilepsy. The purpose of this investigation was to examine the role of serotonin in the inhibition of epileptiform activity and more importantly to determine the serotonergic receptor involved in this response. For this purpose we have employed conventional techniques for intracellular recording of CA1 neurons in the rat brain slice preparation. Initial investigations have demonstrated that serotonin inhibits bicuculline induced epileptiform bursts in CA1 neurons of Sprague-Dawley rats. Concomitantly, there was a membrane hyperpolarization and a decrease in membrane input resistance. Similar results were obtained with the selective 5-HT1A agonist, 8-OH-DPAT. The changes in membrane properties seen in association with the inhibition of epileptiform bursts is characteristic of the activation of the 5-HT1A receptor. Serotonin inhibited the bicuculline induced epileptiform bursts in genetically epilepsy-prone rats as well. Kainic acid (KA) treated brain slices were used as a third model of epilepsy. KA (10 μM), when administered alone, produced epileptiform activity followed by neurotoxicity. Serotonin (20 μM) in the presence of KA (10 μM) prevented epileptiform activity but did not prevent the neurotoxicity. The results obtained thus far strongly suggest that activation of 5-HT1A receptors in hippocampal CA1 neurons can suppress epileptiform activity.

764.5

DYNAMICS OF CYTOSOLIC CALCIUM RESPONSES IN CORTICAL MIXED CULTURES TO KAINATE STIMULATION IS ENERGY-DEPENDENT T. Meier *, S. Brooke, A. de Haas-Johnson, R. Sapolsky. Dept. Biol. Sci., Stanford University, Stanford, CA 94305

Excessive mobilization of free cytosolic calcium is central to excitotoxicity. Excitotoxic insults are energetic in nature, insofar as they disrupt the capacity of neurons to generate energy (e.g., in hypoglycemia), or cause pathologic over utilization of energy (e.g., seizure), and a paucity of energy transforms glutamate from an excitatory neurotransmitter to an excitotoxin. A way in which energy availability can alter the toxicity of glutamate is via the magnitude of the calcium response it evokes; this is because numerous steps in the influx, sequestration and extrusion of calcium are energy dependent. In this study, we examine which parameters of excitotoxin-induced calcium mobilization are sensitive to glucose availability.

Free cytosolic calcium concentrations were measured with fura-2 in fetal mixed cortical cultures exposed to the glutamatergic excitotoxin kainate; cells had been exposed for 4 hours to either 20, 5, 1, 0.5 or 0.25 mM glucose. "Responsiveness" to kainate was defined as a greater than 50% increase in free cytosolic calcium concentrations within 200 seconds.

We observed the following: 1) glucose availability did not alter calcium concentrations prior to kainate exposure. 2) Decreased glucose availability was associated with a greater percentage of neurons responding to kainate, and with a faster and larger response; the speed of response was more sensitive to energetics than the magnitude. 3) Glucose availability did not alter the percentage of neurons which recovered from the kainate, or the magnitude of recovery. Thus, a paucity of energy exacerbates the calcium response to kainate (and the likely degenerative consequences); however, different components of calcium trafficking are differentially sensitive to energetics.

764.6

EPILEPTIFORM ACTIVITY IN RAT HIPPOCAMPAL SLICE IS INHIBITED BY NEUROPEPTIDE Y. G.J. Klapstein* and W.F. Colmers. Dept. of Pharmacology, Univ. of Alberta, Edmonton, Alberta, CANADA T6G 2H7.

Neuropeptide Y (NPY) potently and selectively inhibits feedforward excitatory synaptic transmission in rat hippocampus via a presynaptic Y_2 receptor. We have hypothesized that the role of endogenous NPY in normal hippocampus is to regulate excitability by this presynaptic action. A direct test of this hypothesis awaits the development of a selective antagonist to the Y_2 receptor. However, we have been able to test a correlate of this hypothesis, namely, that exogenously-applied NPY can control the epileptiform discharges induced in a number of *in vitro* brain slice models of electrographic seizure.

Perfusion of a hippocampal slice with magnesium-free artificial cerebrospinal fluid (ACSF) results in the appearance of spontaneous, synchronous population bursts, which, when recorded extracellularly in the CA3 cell body layer, resemble the interictal bursts seen in EEG recordings of human epilepsy patients. Bath application of 1 μM NPY potently and reversibly inhibits the frequency of these events, without obviously altering their morphology.

Ictaform afterdischarges can be induced by stimulation of the stratum radiatum of CA3 with trains of 30V stimuli at 60 Hz for approximately 1 second (STIB, or stimulus train induced bursting) or in groups of 4 stimuli at 100 Hz repeated 15 times at 5 Hz (FRED, or frequency regulated electrographic discharge). Repeated stimuli also lead to the development of small, synchronous GABAergic potentials, which in turn can lead to the development of interictal-like breakthrough bursts. Bath application of 1 μM NPY potently and reversibly inhibits both the afterdischarges and the breakthrough bursts, without affecting the small inhibitory potentials.

These observations support the hypothesis that the role of NPY in the hippocampus is to regulate excitability, and suggest that it may also be used exogenously for this purpose.

764.7

ANTIEPILEPTIC ACTIONS OF DYNORPHIN AND NALOXONE ON CA3 PYRAMIDAL CELLS OF GUINEA PIG HIPPOCAMPUS. N.A. Moy, Z.J. Aguirre, A.M. Flores and M.F. Pacheco*. Centro Universitario de Investigaciones Biomédicas, Universidad de Colima. Colima, Col. México.

We determined whether dynorphin A 1-17 (DYN) acts to suppress epileptic activity in hippocampal CA3 pyramidal cells, using conventional intracellular recordings, on transverse slices from adult guinea pigs. Epileptic activity was induced by continuous perfusion of the slices with either 3.4 mM penicillin or 10 µM bicuculline in artificial cerebrospinal fluid. Addition of DYN (10-100 nM, 15 min) into the perfusion medium, resulted in a (concentration-dependent) gradual decrease on the amplitude and duration of the paroxysmal depolarizing shift (PDS) and afterhyperpolarization (AHP), as well as a reduction on the number and amplitude of action potentials triggered by PDS (AP-PDS), and the amplitude of spontaneous action potentials (SAP). The epileptic activity was totally blocked after 7 to 15 min of DYN application, and recovered completely after 25 to 40 min of DYN removal from the perfusion medium. DYN actions were without significant change on resting membrane potential (> 56 mV) or input resistance (>80 MW); were mimicked by dynorphin A 2-13 (10-100 nM); and resulted insensitive to naloxone (0.1-1 µM). Furthermore, naloxone alone showed similar antiepileptic actions than DYN, except for no effects on the amplitude of both SAP and AP-PDS. Our data are indicative that in this preparation, DYN exerts a potent antiepileptic action of nonopioid nature, which involve predominantly the regulation of calcium-dependent components of the interictal discharges. The results obtained on the antiepileptic actions of naloxone are indicative as well of a modulation of calcium-dependent components of the interictal discharge, however, the mechanisms remain to be elucidated.

Supported by CONACYT DO780-M9201, México (M.F.P.)

764.8

EXTRACELLULAR pH AND EPILEPTIFORM ACTIVITY IN RAT HIPPOCAMPAL SLICES. J. H. Lee, T. L. Vollmer*, and B. R. Ransom, Dept. of Neurology, Yale Medical School, New Haven, CT 06510

The physiological factors that influence seizure initiation and cessation are poorly understood but may include alterations in extracellular ion concentrations. We have begun to test the hypothesis that extracellular pH (pH_o) has a regulatory effect on neural excitability that may be important in controlling epileptic discharge (B.R. Ransom, Prog. Brain Res., 94: 37-46, 1992).

Double-barreled, pH-selective microelectrodes (4-6 µm tip diameter) were used to record the effects of exogenous shifts in pH_o on epileptiform activity in rat hippocampal slices. Rat hippocampal slices (400 µm thick) were maintained in a perfusion chamber of interface design and equilibrated with a 70% O_2/25% N_2/5% CO_2 gas mixture. Epileptiform activity in the form of spontaneous, regular, epileptiform spikes was elicited by bathing in 50 µm bicuculline. pH_o was controlled by altering the CO_2 content of the gas mixture; total gas flow and PO_2 were kept constant via compensatory changes in N_2 content. Spontaneous activity and pH_o were recorded from stratum radiatum of the CA-1 region of the slices.

Extracellular acid shifts of as small as 0.1 pH units were associated with an average decrease in spontaneous event frequency of 46 +/- 8% (N=4); this pH_o effect appeared to occured rapidly and was completely reversible. Spontaneous epileptiform events were reversibly abolished by an average acid shift of 0.25 +/- 0.05 pH units (N=5). The results suggest a quantitative relationship between pH_o and epileptic activity; acid shifts decreased the rate of epileptiform discharge and alkaline shifts increased this rate. Given that activity-induced acid shifts of 0.1 pH units and more have been observed in mammalian hippocampal slices, these data lend further support to the hypothesis that seizure-induced acid shifts in pH_o can act in the manner of a negative feedback signal to inhibit further epileptic discharge. (Supported by N.I.H. grant NS15589 to BRR)

764.9

Epileptogenesis In Immature Neocortical Brain Slices Induced By 4-aminopyridine. S.N. Hoffman* and D.A. Prince, Department of Neurology & Neurological Sciences, Stanford University School of Medicine, Stanford CA 94305.

Results from adult neocortical brain-slice models of acute chemically-induced and chronic post-traumatic epileptogenesis have identified layer V as the site of origin of interictal epileptiform discharges (Connors, Nature, 1984; Hoffman et al., Neurosci. Abstr., 1992). This finding has been ascribed to the presence of a subset of neurons with intrinsic bursting (IB) properties in this lamina that are hypothesized to initiate the discharge. However, neurons with IB properties are unusual in immature neocortical slices (McCormick & Prince, J. Physiol. 1986), and cells with clear IB behavior do not appear until ~P14-21 in rat (Avanzini et al., Epilepsy Res. Suppl. 9, 1992). Therefore, epileptiform discharges in immature tissue must be initiated by alternative mechanisms, and might not originate in layer V. To further explore the laminar source of epileptiform discharges in immature rat neocortical tissue (P8-10), we bathed slices in the convulsant 4-aminopyridine (4-AP, 50-200 µm) and examined the distribution of activities with an array of 2-4 extracellular electrodes. Spontaneous "ictal" and "interictal" discharges began in layer V and spread to supragranular layers. However, synchronous and occasional independent interictal discharges were also observed in layers III and V. Whole-cell patch clamp recordings (K-gluconate, EGTA free) in deep layer V did not identify any neurons with IB characteristics (P8, n=10). These findings suggest that network interactions among layer V neurons, rather than IB properties, are responsible for the initiation of epileptiform discharges in immature neocortical brain slices bathed in 4-AP. Supported by NIH grants NS12151, NS07280 from the NINDS and Dana and Pimley Postdoctoral Fellowships.

764.10

SEIZURES PRODUCED IN NEONATAL RATS BY STEREOTAXIC INJECTION OF TETANUS TOXIN (TT): *IN VIVO* AND *IN VITRO* MODELS OF SEIZURES IN EARLY INFANCY. C. Lee[1*], R. Hrachovy[2], K. Smith[1], J. Frost, Jr.[2] and J. Swann[1]. [1]Cain Fndn. Labs., Dept. Pedi., and [2]Dept. Neurol., Sect. Neurophys., Baylor Coll. Med., 1 Baylor Plaza, Houston, TX 77030.

We are developing *in vivo* and *in vitro* experimental models to study the effects of neonatal seizures on brain development. The hippocampal CA_3 subfield of 9-11-day-old Wistar rats was injected with the convulsant, TT (0.25-4 ng). *In vivo*, surface and depth EEG electrodes were placed bilaterally in the cortex and hippocampus. Behavioral and EEG activities were monitored 1-4 h per day for up to 8 days. Seizures (wet dog shakes, running seizures, forelimb clonus and arrest episodes) began 48-72 h following injections. Epileptiform EEG activity was evident by 48 h. Interictal and ictal discharges originated independently from the cortex or hippocampus and could be unilateral or bilateral. Frequently, EEG seizures were recorded without accompanying behavioral seizures. Seizures were infrequently observed after one week although interictal spikes were still present. With lowest doses, EEG activity could consist solely of interictal spikes in the side ipsilateral to the injection. *In vitro*, electrophysiology was performed on hippocampal slices (3-4 weeks after TT injection) from the injected and contralateral hippocampus as well as littermate controls. Spontaneous extracellular interictal discharges were recorded in CA_3 of 100% of the contralateral and 55% of the ipsilateral slices. Occasionally, spontaneous prolonged seizure discharges occurred or could be evoked by electrical stimulation. The interictal discharges correlated with intracellular paroxysmal depolarization shift (PDS) of 50-150 msec duration and 10-40 mV amplitude. These results suggest that seizures in the neonatal period can produce abnormal activity at least one month later. Thus the TT model is potentially valuable for studying the chronic effects of neonatal seizures. (Supported by NIH Grant NS-18309).

764.11

PROPAGATION OF EPILEPTIFORM ACTIVITY IN THE PIRIFORM CORTEX IN VITRO FOLLOWING AREA TEMPESTAS STIMULATION. J. Doherty* and D.A. Eagles. Dept. of Biology, Georgetown University, Washington, D.C. 20057.

We have previously reported that the rostral piriform cortex (rPC) is a primary target in vitro for the epileptiform activity generated through focal stimulation of the area tempestas (AT), a functionally defined epileptogenic site located in the rostral deep prepiriform cortex of the rat (Neurosci. Abs., 517.20, 1992). The current study has been undertaken to describe the neuronal circuitry by which area tempestas stimulation propagates through the piriform cortex. Using whole cell patch and field potential techniques in coronal and horizontal slices of rat brain containing the AT, we have demonstrated that epileptiform activity originating in the AT propagates to discrete neuronal populations in both layers II and III of the rPC. This focally evoked activity is strongest in the cortex immediately superficial to the AT. This activity is transmitted to the caudal piriform cortex (cPC), in both layers II and III. Activation of the neurons in the rPC is mediated by recurrent excitation among cells in the seizure focus, driven through either the local blockade of GABAergic inhibition or through high frequency electrical stimulation. These results indicate that rPC is an initial target of AT and suggest that propagation to the cPC occurs through multiple synaptic pathways and at least two neuronal populations.

764.12

NMDA RECEPTORS MEDIATE ENHANCEMENT OF EPILEPTIFORM DISCHARGES IN DENTATE GYRUS FOLLOWING *IN VITRO* ETHANOL WITHDRAWAL. R.A. Morrisett* and G. Zhang. Dept. Pharmacol., Univ. Nebraska Med. Ctr., Omaha, NE, 68198-6260.

Alterations in N-methyl-*D*-aspartate (NMDA) receptor function may contribute to epilepsy associated with ethanol withdrawal. We assessed the effects of acute ethanol exposure and withdrawal on epileptiform discharges (EDs) in the rat dentate gyrus and evoked by short, high frequency trains of electrical stimuli.

Slice patch recordings revealed a slow current which corresponded with the timecourse of the EDs. This current reversed at about -60 mV, was DNQX and *D*-APV insensitive but was antagonized by picrotoxin. We concluded that a slow, depolarizing GABAergic current was the predominant current responsible for ED induction.

NMDA receptors did contribute to ED expression since NMDA receptor and channel antagonists blocked EDs. Ethanol also inhibited EDs evoked at identical stimulus intensities and in a dose-dependent manner (25-100 mM). When slices were withdrawn from *in vitro* ethanol exposure, both the duration and firing frequency of EDs were significantly enhanced. This *in vitro* withdrawal effect was dependent upon an enhancement of the NMDA receptor-mediated component of the ED. However, the processes responsible for induction of this withdrawal effect were insensitive to block of NMDA receptors or channels during the period of ethanol exposure and withdrawal.

These data suggest that acute ethanol exposure and withdrawal may increase epileptiform discharges via enhancement of NMDA receptor-mediated responses. (Supported by NIAAA #9230 and the Alcoholic Beverage Medical Research Foundation).

764.13

SPONTANEOUS "BURSTS" ELICITED IN THE MEDIAL ENTORHINAL CORTEX IN NORMAL AND LOW-$[Ca^{2+}]_o$ SOLUTIONS

A. Copus, P.R. Patrylo*, and F.E. Dudek. Dept of Anatomy and Neurobiology, Colorado State University, Fort Collins CO 80523

Previous work has demonstrated that CA1 and the dentate gyrus can elicit epileptiform activity by nonsynaptic mechanisms in low-$[Ca^{2+}]_o$ solutions. Furthermore, these regions have an increased susceptibility for generating bursts of activity in low-$[Ca^{2+}]_o$ solutions at early stages of development (Roper et al., 1993, *J. Neurophysiol.*, in press). The aim of the present experiments was to determine whether regions in the CNS that have less densely packed neuronal laminae (*vs* that in CA1 and the dentate gyrus) can also elicit epileptiform activity in low-$[Ca^{2+}]_o$ (i.e., 0-added Ca^{2+}) solutions and if so, whether they also show an increased susceptibility early in development. Simultaneous multi-unit and field potential recordings were performed from the medial entorhinal cortex of slices (400 μm) from postnatal 2-3 week old and adult rats. In 1.3 mM $[Ca^{2+}]_o$ solutions, the medial entorhinal cortex from young (n=7 of 7), but not adult (n=5 of 5) rats elicited periodic bursts of action potentials recorded with the multi-unit electrode. These "multi-unit bursts" slightly preceded and corresponded with small negative DC shifts in the field potential recordings. In the low-$[Ca^{2+}]_o$ solutions, the medial entorhinal cortex from both young (n= 6 of 6) and adult (n= 2 of 5) rats elicited periodic bursts of action potentials, as observed with the multi-unit recording. The corresponding field potential recordings displayed small negative DC shifts (0.25-1 mV), which were occasionally superimposed with small population spikes. The onset of the "multi-unit bursts" preceded the field potential responses. Our data support the hypothesis that the medial entorhinal cortex can also generate epileptiform activity in low-$[Ca^{2+}]_o$ solutions, suggesting that nonsynaptic mechanisms may be important in cortical structures other than the hippocampus. Supported by NIH grant HD05958 and NRSA NS08993.

764.14

RESPONSES OF THE ENTORHINAL CORTEX IN VITRO.

J. Bear, J. Bekenstein*, and E.W. Lothman. Dept. Neurology, U.Va. Health Sci. Ctr., Charlottesville, VA 22908.

As the "gateway" to the hippocampal formation, the entorhinal cortex (EC) is of interest for its role in both health and disease. Less is known of the function of the EC than its anatomy. To characterize the intrinsic physiology of the EC, 500 μm thick slices were prepared from adult male Sprague-Dawley rats that included the EC and hippocampal complex. Protocols were developed to consistently evoke antidromic and orthodromic responses in layers II and IV. Responses were characterized as orthodromic or antidromic based upon their susceptibility to blockade by glutamatergic antagonists. Connectivity between the hippocampus and EC was established by activation of dentate granule cells by stimulation of EC layer II and antidromic activation in the reverse direction, as well as activation of EC layer IV by subicular stimulation. Slices in which connectivity was present exhibited clonic epileptiform discharges, lasting tens of seconds and involving both deep and superficial layers of the EC, in response to stimulus trains to the angular bundle. In summary, protocols were developed to consistently obtain orthodromic and antidromic responses in layers II and IV from sites within and without the EC. It was demonstrated that the EC can exhibit clonic ictal-like activity under physiological conditions in an in vitro slice preparation where connectivity is maintained between hippocampus and EC. This preparation offers the possibility of investigating both normal and epileptic responses in the hippocampal-parahippocampal "loop" in vitro. By characterizing EC responses induced by stimulation *within the EC*, these results provide insight into the intrinsic physiology of this region.

764.15

AUGMENTATION OF SUBTHRESHOLD SODIUM CURRENT BY VERATRIDINE RESULTING IN EPILEPTIFORM DISCHARGE IN RAT HIPPOCAMPAL CA1 NEURONS.

L. M. Tian* and K. A. Alkadhi, Department of pharmacology, University of Houston, Houston, TX 77204-5515.

A subthreshold sodium current has been shown to be important in generating burst-firing activity from individual neurons (Llinas, Science, 242:1654-64,1988). In a previous study we demonstrated that veratridine induced a slow depolarizing after-potential (SDAP) which triggered epileptiform activity or even seizure-like events in rat hippocampal CA1 neurons. We report here results showing that veratridine at low doses enhances subthreshold sodium current in a voltage dependent manner. Single electrode voltage clamp techniques were employed. Step current in response to a 5 mV step depolarization (250 ms duration) was recorded at clamped levels of membrane potential between -90 mV and -60 mV in the absence or presence of TTX (0.5 μM). Subthreshold TTX-sensitive sodium current ($I_{Na(sub)}$) was calculated by subtracting the step current in the absence of TTX from that in presence of TTX. The outcome was an inward component. This TTX-sensitive component was small when membrane potential was clamped at levels more negative than -65 mV and became steeply augmented at more positive levels (n=6). Step current became net inward in the absence of TTX when membrane potential was clamped at subthreshold levels (about -63 mV). In the presence of veratridine (200-300 nM), there were no changes in RMP (Control: -68.5 ± 1.2 mV; Veratridine: -70.8 ± 1.5 mV, n=18) or firing threshold (Control: 10.0 ± 0.8 mV; Veratridine: 10.2 ± 0.9 mV, n=16). A significant increase of $I_{Na(sub)}$ was noted after the neurons were exposed to veratridine for 30 minutes. When membrane potential was clamped at -70 mV, $I_{Na(sub)}$ was 6.7 ± 2.1 pA in the absence and 14.4 ± 3.8 pA in presence of veratridine (n=8, $p<0.05$). When membrane potential was clamped at -65 mV, the $I_{Na(sub)}$ was 15.7 ± 3.5 pA and 35.7 ± 5.7 pA in the absence and presence of veratridine (n=6, $p<0.05$). The voltage-dependency of $I_{Na(sub)}$ is similar to that seen for the amplitude of veratridine-induced SDAP. These results indicate that augmentation of $I_{Na(sub)}$ may be responsible for epileptiform activity induced by veratridine and that an augmented $I_{Na(sub)}$ could be responsible for certain forms of epilepsy.

764.16

ROLE OF K^+ IN GABA (γ-AMINOBUTYRIC ACID)-MEDIATED SYNCHRONOUS POTENTIALS EVOKED IN RAT HIPPOCAMPUS BY 4-AP (4-AMINOPYRIDINE).

M.E. Morris*, G.V. Obrocea and M. Avoli. Dept. of Pharmacology, University of Ottawa, Ottawa, Canada K1H 8M5 & Montreal Neurological Institute, McGill University, Montreal, Canada H3A 2B4.

To determine the role of K^+ in relation to GABA-ergic long-lasting depolarizing (LLD) potentials in the 4-AP model of epilepsy, ion-selective microelectrodes have been used to measure changes in $[K^+]_o$ and field potentials in rat hippocampal slices, perfused with 100 μM 4-AP. Focal potentials ≤6 mV, ≤10 s occurred at 1-2' intervals in association with $[K^+]_o$ ↑s of ≤8.5 mM, ≤20 s. $[K^+]_o$ ↑s were >er with progression from stratum oriens to stratum radiatum, >er in CA1 cf. CA3, and largest in the perforant path region of the dentate. ↑s persisted in the presence of CNQX (≤10 μM) and APV (aminophosphonovaleric acid) (50 μM), which blocked the more frequent inter-ictal events. The $GABA_A$ antagonist, BMI (bicuculline methiodide) (100 μM) -- with/without CNQX and APV -- produced reversible block (or attentuation to 10-20%) of both $[K^+]_o$ and focal potential changes. The BMI-resistant residual K^+ potential could be blocked by PTX (picrotoxin) (100 μM); while the $GABA_B$ antagonist, saclofen, appeared to enhance excitability. These potentials could also be reversibly blocked by the $GABA_B$ agonist, baclofen (100 μM). These data demonstrate the presence of GABA receptor-mediated accumulations of $[K^+]_o$ in association with the occurrence of LLDs and support the hypothesis that this ionic mechanism may importantly contribute to synchronization and propagation of neuronal activity in the hippocampus.

Supported by The Medical Research Council of Canada

764.17

TIME COURSE OF CHANGES IN INHIBITORY POSTSYNAPTIC CURRENTS IN RAT HIPPOCAMPUS MADE CHRONICALLY EPILEPTIC BY TETANUS TOXIN

J.G.R. Jefferys* & M.A. Whittington , Dept. Physiology & Biophysics, St.Mary's Hosp. Med. Sch., Imperial College, London W2 1PG, UK.

Injecting tetanus toxin into one rat hippocampus induces epileptic foci in both hippocampi, which discharge intermittently over the following 8+ weeks. The dose used here (3-5 ng, Wellcome Biotech, UK) was given under general anaesthesia (3.3 $ml.kg^{-1}$ of a mixture of fluanesone and midazolam, comprising 5 $mg.ml^{-1}$ Hypnorm and 2.5 $mg.ml^{-1}$ Hypnovel). The rats were allowed to recover, and subsequently developed epileptic seizures, but suffered neither loss of condition nor increased mortality.

Transverse slices of dorsal hippocampus (400 μm thick) were prepared 1, 2, 4, 8, and 16 weeks after injection and maintained in an interface chamber at 35°C. None of these slices showed evidence of gross neuronal loss, which is compatable with our previous histopathological data. Once the slices had been confirmed epileptogenic, monosynaptic fast IPSCs were isolated pharmacologically by bathing the slice in 20 μM CNQX, 50 μM APV and 100-200 μM 2-OH saclofen. IPSC's decreased to <10% in the injected hippocampus at 1 and 2 weeks, but only to 50% in the secondary focus in the contralateral hippocampus. In neither case was the response to exogenous GABA affected. Subsequently the IPSCs recovered in both hippocampi, returning to normal before the cessation of epileptic activity at 8-16 weeks; thus slices with apparently normal monosynaptic IPSCs could be epileptogenic in both the primary and secondary foci.

Supported by the Wellcome Trust

764.18

TEMPERATURE-DEPENDENT EFFECTS ON ASTROCYTIC POTASSIUM CURRENTS IN RAT ORGANOTYPIC BRAIN CULTURES.

C. Fink, R. Wehby, T. Donta, J. London*, and R. Davidson. Neuroscience Program and Dept. of Periodontology, Univ Conn Health Center, Farmington, CT 06030.

Recent evidence (Tanaki et al., 1992) suggests that organotypic brain cultures incubated at elevated temperatures display spontaneous neuronal activity thought to resemble activity in epileptic tissue. To examine the response of astrocytes in these cultures, we used the whole-cell patch clamping technique to investigate temperature-dependent differences in membrane properties of migrating astrocytes from rat brain organotypic slices. Slices were made by transverse sectioning of rat pup brain, and were maintained for up to 24 days in minimum essential medium supplemented with 25% horse serum in a 5% CO_2 humidified incubator at 37° or 34° C. All recordings were made at room temperature.

With NaCl in the bath and KCl in the pipette, step depolarizations ranging from -75 to 150 mV evoked a voltage-dependent, outwardly rectifying current in most cells (65/109). This current was blocked by tetraethylammonium (TEA), 4-aminopyridine (4-AP), and $BaCl_2$, and in symmetric solutions of KCl, the reversal potential shifted to more depolarized potentials, indicating selectivity for potassium. Two classes of current could be distinguished: 1) current that activated (V_{act}) at ~-35mV, reached maximum amplitude at ~80mV, and subsequently inactivated to ~60% of the peak current, and 2) current that displayed a wide variability in V_{act} (-50 mV to 57 mV) and did not inactivate at more positive potentials.

For cultures incubated at 37° C, 80.5% (33/41) of the cells exhibited inactivating type currents. By contrast, for cultures incubated at 34° C, only 50% (12/24) of the cells exhibited currents of the inactivating type ($p < 0.02$; χ^2). Further, the kinetic behavior of inactivating currents differed as a function of temperature; in 34° C cultures, currents inactivated less profoundly and at more positive potentials than in cultures maintained at 37° C. Our results suggest that modest differences in temperature during incubation may alter the kinetics and/or membrane properties of potassium currents of astrocytes found in organotypic cultures. These changes could play a role in the development of epileptiform behavior seen at the higher temperature in these preparations. Supported by NIH DE09662 and the Klingenstein Foundation.

764.19

Spontaneous low Ca^{2+} bursting can be blocked or induced by applied fields. T.L. Richardson* and C.N. O'Reilly. Sch. of Kinesiology, Simon Fraser Univ., Burnaby, B.C. Canada, V5A 1S6

The hippocampal CA1 region is known to exhibit spontaneous epileptiform activity when slices are perfused with a low or zero calcium medium. Characteristic of these low Ca^{2+} bursts is an abrupt and sustained negative extrasomatic potential with overlying population spikes and a corresponding positive extradendritic potential in the region of the apical but not the basal dendrites. We have found that these sustained DC shifts are associated with voltage gradients in the range of 20 to 40 mV/mm along both the apical and basal dendrites. These gradients have the correct polarity to induce somatic depolarization and thereby contribute to burst initiation and maintenance. Externally applied fields in the range of 5 to 30 mV/mm were found to block low Ca^{2+} bursts when the field was hyperpolarizing with respect to the apical dendrites. Fields in this same range initiated robust bursts when the field polarity was reversed. These findings support the hypothesis that field effects associated with the sustained DC shift of low Ca^{2+} bursts contribute to burst generation and that apical dendrites of pyramidal neurons play a key role in this process.

764.20

Antidromic bursting in the dentate gyrus during low Ca^{2+} with applied fields. C.N. O'Reilly* and T.L. Richardson. Sch. of Kinesiology, Simon Fraser Univ., Burnaby, B.C. Canada V5A1S6

Extracellular mechanisms contribute to the epileptiform activity generated in the CA1 pyramidal cell population when Ca^{2+} is removed from the perfusing medium of hippocampal slices. Under these conditions spontaneous bursts of population spikes occur on a sustained negative extracellular potential and multiple population spikes follow a single antidromic stimulation. These forms of epileptiform activity are seldom reported in the dentate gyrus unless the $[K^+]_o$ is markedly increased (>9.0mM). In the present study, $[K^+]_o$ was within normal range ($[K^+]_o$ 5.0mM). Small external uniform fields (range 1-70mV/mm) were applied parallel to the dendrosomatic axis of the dentate granule cell population for durations of 100ms. During applied fields of a depolarizing polarity (negative extrasomatic, positive extradendritic) the dentate was antidromically stimulated. Bursting was recorded in all slices studied (n=16) with a field threshold to induce bursting in the range of 10-20mV/mm. Antidromic stimulation not accompanied by applied fields did not result in bursting activity. This study supports the theory that field effects contribute to epileptogenesis and re-emphasize the need to understand the role of non-synaptic mechanisms in neuronal interactions.

TRAUMA: CORD

765.1

ELEVATED MACROPHAGE DENSITY AND INCREASED LEVELS OF QUINOLINIC ACID FOLLOWING CONTUSION INJURY TO THE RAT SPINAL CORD. P.G. Popovich[1], J.F. Reinhard, Jr.[2], E.M. Flanagan[2], and B.T. Stokes[1]. [1]The Ohio State University, College of Medicine, Columbus, OH 43210; [2]The Wellcome Research Laboratories, Division of Pharmacology, Research Triangle Park, NC 27709

Elevated concentrations of the NMDA agonist and neurotoxin quinolinic acid (QA) have been demonstrated in models of CNS injury and neuropathology known to be accompanied by an accumulation of activated macrophages and/or microglial cells. Such cell types have also been implicated as potential effector cells of secondary degenerative events following spinal cord injury. Here we have demonstrated that QA is increased following contusion injury to the thoracic spinal cord. Tissue QA concentrations were assayed from three separate regions of the injured spinal cord by GC/MS at 3, 7, 14, and 18 days post-injury (PI). Peak QA levels were obtained by 3 days PI at the lesion epicenter and remained elevated above control values at 18 days PI.

Histological and immunocytochemical analysis of this lesion area also revealed a high density of blood-derived macrophages and/or activated microglia. Thus, the neurotoxin QA, appears to be produced acutely in the injured spinal cord tissue as a result of immunological activation and therefore could mediate some of the secondary neuronal degeneration associated with traumatic spinal cord injury. Supported in part by grant NS 10165-21.

765.2

UBIQUITIN EXPRESSION IN DEGENERATING AXONS OF EQUINE CERVICAL STENOTIC MYELOPATHY. B.S. Jortner*, W.K. Scarratt, P.D. Modranksy, S.K. Perkins. Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA 24061

Equine cervical stenotic myelopathy is a neurological disease of young horses manifest by ataxia and paresis of the limbs (hind > fore), which produce gait abnormalities of such a nature that affected animals are colloquially termed "wobblers." An important cause of the condition is a genetically conditioned (it is most common in male thoroughbred horses) malarticulation - malformation of some cervical vertebrae. This causes articular instability and flexion-induced focal narrowing of the cervical spinal canal. Such intermittent compromise of the canal's capacity produces regional compression of the cervical spinal cord. A prominent resulting myelopathic change is swollen, degenerating myelinated axons most prominent in lateral and ventral white matter funiculi. In a neuropathological study of horses with cervical stenotic myelopathy (n=5), we confirmed the axonal degeneration at and distal to the compressive site. Sections of this lesion from paraffin-embedded spinal cord were immunostained to detect the presence of ubiquitin, using a polyclonal rabbit antibody to this heat-shock protein (Biomeda). Ubiquitin has been detected in damaged neurons in a variety of human chronic neurological diseases. In our study of horses with cervical stenotic myelopathy, a prominent reaction product to this protein was seen in swollen, obviously degenerating axons, as well as some normal sized ones (possibly earlier stages of the axonopathy). It was not found in control fibers. A reported cellular function of ubiquitin is its conjugation to altered proteins, "marking" them for lysosomal or non-lysosomal degradation (Johnson et al., EMBO J. 11:497). Our study suggests it also plays such a role in the trauma-induced axonal degeneration which is so prominent in equine cervical stenotic myelopathy.

765.3

EFFECT OF ANTI-INFLAMMATORY DRUGS UPON CALPAIN IN SPINAL CORD INJURY. N.L. Banik*, E. Terry, D. Lobo, E.L. Hogan. Neurology Dept, MUSC, Charleston, SC 29425

Methylprednisolone (MP) has been found to reduce neurofilament protein degradation in experimental spinal cord injury (SCI) and has beneficial effects in SCI, we believe that one of the actions of MP is inhibition of calpain activity. We therefore examined the effect of MP in SCI animals in vivo as well as on purified mcal-pain in vitro. SCI was induced in rats using 40g-cmf by weight drop technique. MP (165mg/kg body wt) was given IV for 24 hrs. Lesion and sham cord protein were separated by SDS-PAGE and immunoblotted using NFP antibodies. The extent of loss of protein was taken as a measure of calpain activity. For in vitro studies calpain activity was assayed using ^{14}C-azocasein as substrate. Our in vivo results indicate a substantial reduction in protein loss (NFP) in the lesion of MP treated vs untreated animals. MP also significantly inhibited calpain's activity in vitro. The calpain inhibition with MP was concentration-dependent and a 50% inhibition was obtained with 200μg of MP while indomethacin and ketorolac were more potent inhibitors and did not inhibit another neutral proteinase, multicatalytic proteinase complex. These results suggest that the use of corticosteroid and other anti-inflammatory drugs in SCI may prevent degradation of cytoskeletal protein by inhibiting calpain activity and provide neuroprotection. Supported in part by grants from NIH (NS11066) and NMS Society (RG2130, PP0297).

765.4

ALTERATIONS IN THE H-REFLEX BY GLYCINERGIC COMPOUNDS AFTER *SPINAL CORD INJURY*. R.K. SIMPSON*, A.A. LEIS, M.M. GONDO, C.S. ROBERTSON, AND J.C. GOODMAN, Neurosurgery Department, Baylor College of Medicine, Houston, Tx. 77030

Spasticity is a frequent and complex sequel to spinal cord injury. The neurochemical basis for the origin of spasticity is largely unknown. Neurotransmitters such as γ-amino butyric acid (GABA) may play a role. Drugs like baclofen mimic GABA activity and can reduce spasticity but are limited by side effects. Glycine is among the most abundant neurotransmitters in the spinal cord. However, the role of glycine and related compounds in spasticity have received little attention. We suggest that glycine and related compounds may modify spasticity as measured by the H-reflex.

A complete spinal cord injury was produced in rabbits by a percutaneous, mid-thoracic, radio frequency heat generator. The animals were studied after stabilization of spasticity as determined clinically by the Ashworth score (average score was 3). A catheter was inserted into the cisterna magna and the spinal cord was bathed with either 100mmol/l solutions of glycine, strychnine, D-serine, β-alanine, MK801, or artificial CSF for 4 hours at a rate of 5-10 µl/min. H-reflexes were periodically monitored before and during infusion by stimulating the posterior tibial nerve at intensities ranging 0.5 to 20 mA and recording from the plantar surface of the foot. Amplitudes of the H waves were measured and compared between groups.

Glycine and D-serine depressed the H wave in spastic animals after 90-120 minutes of infusion compared to artificial CSF. Strychnine and β-alanine produced heightened H waves compared to artificial CSF infusion. The influence of each of these compounds on the H wave was most prominent using intensities ranging 0.5-4 mA. No changes in H wave amplitudes were seen by any infused compound when higher intensities were used, compared to artificial CSF.

Our results indicate that glycine and related compounds may influence spasticity. Further study of these compounds may yield information that will enhance current treatment modalities.

765.5

EFFECTS OF IL-1 RECEPTOR ANTAGONIST PROTEIN (IRAP) IN SPINAL CORD-TRANSECTED RATS. J.B. Gelderd*, N.R.S. Hall+, J. Oliver+ R.A. Menzies+ & M.P. O'Grady+. Department of Human Anatomy & Neurobiology*, Texas A&M University, College Station, TX 77843 and Department of Psychiatry+, University of South Florida College of Medicine, Tampa, FL. 33613.

We have previously shown that a significant increase in IL-1 levels occurs with time in the neuropil adjacent to transected rat spinal cord. The purpose of this study was to ascertain the biological significance of this injury-induced increase in IL-1. A laminectomy was performed at the T5-T6 vertebral level in male, Sprague Dawley rats, ranging in age from 40 to 50 days, and the spinal cord was transected with a scalpel. Sham animals were subjected to the same surgery without the transection. A group of unhandled control rats was also included. A sub-group of transected animals received a subcutaneous osmotic mini-pump which dispensed IL-1 receptor antagonist protein (IRAP) over a 7 day interval and in close proximity to the site of transection. Another sub-group was fitted with a pump that infused the vehicle only. IRAP treated rats displayed a significant reduction in body temperature ($p<0.05$) compared with vehicle treated rats. They also were less active when assessed for locomotor behavior using a HVS computerized tracking system ($p<.01$). IRAP treatment had no impact upon Con-A, PHA or LPS induced splenocyte mitogenesis when compared with vehicle treated animals. However, spleen weight, but not thymus weight, was significantly reduced by this treatment. No significant changes in either serum corticosterone or beta-endorphin were detected. The lack of an effect of the IRAP treatment upon traditional immunologic measures was probably due to the infusion of this drug directly into the site of injury rather than systemically. These data will be discussed in the context of observed morphologic changes in spinal neuropil adjacent to the transection in these same animals.

765.6

ENDOTHELIN AND BLOOD-SPINAL CORD BARRIER BREAKDOWN IN SPINAL CORD INJURY. A. L. McKenzie*, J. J. Hall, N. Aihara and L. J. Noble. Department of Neurosurgery and the Graduate Program in Physical Therapy, University of California, San Francisco, CA 94110.

Endothelin (ET-1) is a prominent vasoactive agent which may contribute to barrier breakdown after spinal cord injury. The purpose of this study was to determine the relationship between ET-1 and breakdown of the blood-spinal cord barrier following a moderate spinal cord injury. We hypothesized that: 1) initial, direct effects of trauma are exacerbated by subsequent barrier breakdown, which results in the extravasation of plasma constituents and secondary injury; 2) the diffusion and accumulation of plasma proteins, specifically IgG, follows an axial pattern and; 3) the expression of ET-1 increases and corresponds to patterns of IgG diffusion after injury.

Adult (300-350 g), male, Sprague-Dawley rats were sacrificed 24 hours after spinal cord injury. The distribution of IgG and ET-1 in the spinal cord was evaluated using immunohistochemical techniques. Immunoreactivity for IgG and ET-1 was more intense in the injured as compared to the control cords. Staining for both IgG (n=9) and ET-1 (n=4) was most intense within 1.0 cm of the epicenter of the injury, with less intense staining within 2.0 cm. Minimal staining was observed within 3.0 cm distal to the injury site.

In conclusion: the diffusion and accumulation of both IgG and ET-1 followed a corresponding, axial pattern at 24 hours post moderate spinal cord injury. (Supported by UCSF Academic Senate Shared Equipment Grant to ALM and NIH NS 23324 to LJN.)

765.7

A MODEL OF GRADED CONTUSIVE CERVICAL SPINAL CORD INJURY (SCI) IN RATS. A. Martinez-Arizala*, D.H. Hesse, A.A. Marcillo, O. Llorente, D.I.Santiago, S.M. Onifer. The Miami Project, Department of Neurology, University of Miami School of Medicine, Miami, Fl 33136

Most human SCI occur in the cervical spine and these lesions are the most neurologically devastating. We have previously shown that a chronic survival SCI of moderate severity can be produced in the C7 spinal cord level in the rat. Morphologically this lesion is centered at C7, and extends from C5 to T1. The present study was designed to produce a **graded** model of cervical SCI in the rat using the Allen (weight drop) technique. Injuries of graded severity were produced at C7 by dropping a 10g weight from 1.0, 2.0, 3.5 or 5 cm. Strain gauge generated force tracings revealed a high degree of correlation between peak force and injury severity ($r^2=0.81$; $p < 0.001$), as well as between impulse and injury severity ($r^2=0.72$; $p < 0.001$). Tarlov scores showed significant recovery from an initial quadraparesis in all animals, and graded decreases, which corresponded to injury severity, were noted in proximal forelimb and hindlimb function. Distal forepaw function remained significantly impaired in the more severe injury group. A decrease in inclined plane performance occurred acutely post-injury in all rats, and graded recovery, according to severity of injury, was seen in all groups. Preliminary data indicates that the head down testing position in the inclined plane was the most sensitive for discriminating between the different injury groups. The righting reflex was initially abolished in all animals and it remained abnormal in 90% of the most severe injury group. Marked deficits in the response to paw pinch were also present initially following injury, however, this was followed by good recovery in all but the most severely injured rats. We conclude that clinically relevant graded cervical injuries are produced in this SCI model. Behavioral tests more specific for quantifying neurological deficits in this cervical lesion model are currently being utilized (see Onifer et al.).

765.8

CERVICAL SPINAL CORD INJURY (SCI) IN THE RAT: CHARACTERIZATION OF GRADED FORELIMB DEFICITS. S.M. Onifer*, B. Calancie, D.H. Hesse, J.C. Benitez, D. Kim, O. Llorente, A.A. Marcillo, J. Perrone, J.F. Rodriquez, D.I. Santiago, A. Martinez-Arizala. The Miami Project, Departments of Neurology and Neurological Surgery, University of Miami School of Medicine, Miami, FL. 33136.

Traumatic contusion injury to the human spinal cord most frequently occurs at the cervical level and produces chronic deficits in the hands and arms. The present study was designed to characterize forelimb deficits in a **graded** rat survival model of lower cervical SCI (see Martinez-Arizala et al.) for investigations into transplantation therapies. Contusive SCI was produced with the Allen technique in anesthetized rats by dropping a 10 gm weight from varying heights onto the C7 spinal cord. Visual and Tactile Forelimb Placing Tests revealed acute deficits in proximal extension, distal extension, and distal flexion which increased with the severity of the SCI. By 20 weeks post-injury, significant, graded deficits were still evident in tests of distal extension. A Forelimb Grip Strength Test demonstrated acute and chronic decreases that correlated with severity of the SCI. A Forehead Adhesive Sticker Removal Test showed an acute increase in removal time for all SCI groups, however, at 20 weeks graded increases were evident only in the 3.5 and 5 cm SCI group. Food retrieval was examined using the Staircase Test. A graded decrease in total number of pellets retrieved was seen initially after injury and persisted up to 20 weeks. Well clearance scores at 20 weeks were similar for the SCI groups indicating deficits in grasp but not reach. EMG recording of forelimb extensor and flexor muscles during the Staircase Test showed graded alterations in EMG pattern. Graded decreases in fall time during a Beam Balance Test were observed acutely in all SCI groups, however, by 20 weeks graded deficits were evident in the 2, 3.5 and 5 cm SCI groups. These results demonstrate that, similar to humans, chronic forelimb deficits occur in the rat after cervical SCI and that the extent of the deficits depends on the severity of the SCI.

765.9

RECOVERY OF INTERLIMB AND SPINO-BULBO-SPINAL (SBS) REFLEX POTENTIALS IN CHRONICALLY SPINAL-LESIONED RATS. T. Imai*, and M. Aoki. Departments of Physiology and Neurology, School of Medicine, Sapporo Medical University, Sapporo 060, Japan

This study was performed to determine which descending pathways play the most important role in the recovery of coordinated four-legged locomotion in chronically spinal-lesioned rats. Partial spinal lesions sparing only right ventral (VQ) or dorsal quadrant (DQ) of the spinal cord at the lower thoracic (T9-10) levels were performed aseptically under Nembutal anesthesia. Coordinated four-legged locomotion reappeared within 2-3 weeks after the initial operations in VQ rats. However, no recovery of hindlimb movement was observed in DQ rats. In terminal experiments, the right brachial plexus (C6-T1) was dissected and mounted on a bipolar stimulating electrode. Interlimb reflex potentials and SBS reflex potentials were recorded from bilateral hindlimb muscles under Nembutal anesthesia and urethane-chloralose anesthesia, respectively. In VQ rats, threshold intensities for evoking interlimb and SBS reflexes were elevated for a week after the initial operation and returned gradually to the normal range within 2-3 weeks. In DQ rats, on the other hand, the early threshold elevation for interlimb and SBS reflexes persisted over the one month observation period. These results demonstrated that the propriospinal interlimb reflex pathway and reticulospinal (SBS) pathway are essential for the functional recovery of coordinated four-legged locomotion after spinal cord injury in rats.

765.10

AN EXPERIMENTAL MODEL FOR EXPLORING MECHANISMS OF SECONDARY DAMAGE IN SPINAL CORD INJURY: EFFECTS OF POTASSIUM. D. Liu* and D.J.McAdoo. Marine Biomed. Inst., Univ. Texas Med. Branch, Galveston, TX 77555

We present an experimental model for characterizing effects of agents suspected of causing secondary damage upon spinal cord injury. Microdialysis is used to administer candidate damaging agents and to sample the release of other substances in response to administered agents. Damage is assessed by monitoring the amplitudes of evoked potentials during candidate administration and by post-mortem histological examination. This approach enables us to correlate electrophysiological, histological and neurochemical parameters in the same experiment. Potassium was chosen as a candidate damaging agent, as it kills neurons at high concentrations and its concentration rises substantially following impact injury to the spinal cord. Administration of 100 mM KCl, 50 mM K_2HPO_4 or 100 mM potassium glucuronate blocked electrical conduction and destroyed cell bodies. Releases of the neurotransmitter amino acids (aspartate, glutamate, glycine, GABA) and the possible neurotransmitter taurine were dramatically increased by administration of 100 mM KCl. Levels of nonneurotransmitter amino acids increased to lesser degrees. Impairment of conduction, destruction of cell bodies, and release of excitotoxins are all consistent with elevated K^+ being a secondary damaging agent upon injury to the spinal cord.

765.11

THE ROLE OF K^+ CHANNELS IN MEDIATING AXONAL DYSFUNCTION AFTER ACUTE SPINAL CORD INJURY M. Fehlings*, R. Seth, D. Anthes, E. Theriault, C. Tator Playfair Neuroscience Unit, University of Toronto, Toronto ON

The mechanisms underlying conduction failure of acutely injured spinal cord axons are not clearly understood. We examined the hypothesis that activation of K^+ channels by posttraumatic demyelination contributes to conduction block after acute spinal cord injury (SCI).

Recordings of axonal field potentials were made from the spinal cord of rats in vivo (n=23). After acute SCI at T1 (30 g X 1 min clip compression injury), there was a significant decrease in the amplitude of the somatosensory evoked potential (SSEP) (81.2 ± 18.2 %; $p<0.002$), the motor evoked potential (MEP) (74.4 ± 14.4 %; $p<0.0001$) and field potentials recorded from the cord at C3 ($p<0.001$) and T10 ($p<0.001$). Topical application of 5 mM 4-aminopyridine (4-AP), a blocker of fast K^+ channels, significantly enhanced the amplitude of the SSEP ($p<0.05$) and C3 response ($p<0.05$) when compared with cords superfused with artificial CSF. Application of 10-20 mM tetraethylammonium (TEA), a blocker of kinetically slow K^+ channels, also enhanced conduction in the injured, but not in the normal cord. Superfusion of the normal cord with 4-AP or TEA did not result in any significant electrophysiological effects. The ultrastructural features of axons were examined 15 minutes (n=3), 2 hours (n=3) and 4 hours (n=3) after SCI to correlate the physiological effects with structural changes. We observed evidence of myelin disruption, periaxonal swelling, vesicular changes in the myelin, lamellar separation and myelin invagination as early as 15 minutes after SCI.

We conclude that acute SCI results in early posttraumatic demyelination which appears to contribute to axonal dysfunction by exposure of 4-AP and TEA sensitive K^+ channels normally confined to submyelinic regions.

765.12

THE EFFECTS OF TRAUMA ON SPINAL CORD AND CAUDA EQUINA AXONS DIFFER. **M.Jayachandra and V.E.Amassian*. Dept. of Physiology, SUNY-HSCB, Brooklyn, NY 11203.**

Our previous study (*J.Physiol.438,41P,1991*) showed that a graduated weight drop could temporarily abolish direct conduction in spinal cord axons with virtually complete recovery, implying that axons were not disrupted. We now compare these effects of trauma on cauda equina. In cats under pentobarbital anesthesia, after a lumbar laminectomy, the dura was incised over the cauda equina and under a dissecting microscope, individual roots were elevated onto a perspex platform. A 15gm cylinder, centered in a guiding tube, was dropped on the root. Killed-end responses to bipolar, electrical, dorsal column stimulation were recorded from the caudal part of the isolated root or from the posterior tibial nerve; a second stimulus, below the trauma site, was sometimes used to monitor recording conditions. Trauma affected cauda equina axons differently from central axons:

1.Recovery from submaximal drops was never complete as in spinal cord axons (eg.dorsal columns and lateral corticospinal).

2.Cauda equina axons were most sensitive to the initial weight drop; subsequent drops being less effective.

Applying a cotton pledget soaked in >20mEQ K^+, on the root, blocked conduction in most axons. In the dorsal columns, slow sub-pial infusions of K^+ (>40mEQ) also resulted in conduction block. In both cases the block induced by K^+ depolarization was entirely reversible. Assuming conservative values for various parameters, an increase in $[K^+]_o$ to blocking levels is many orders of magnitude smaller than maximal efflux possible from nodal membranes of undisrupted cord axons.The differences in effects of trauma can best be explained by invoking a role of glia (eg. astrocytes) in spinal cord injury.

765.13

EXPRESSION OF mRNA FOR MYELIN PROTEINS AFTER CONTUSIVE SPINAL CORD INJURY. **Jean R. Wrathall* and Lynn D. Hudson. Dept. of Anatomy and Cell Biology, Georgetown Univ., Washington, DC 20007 and Lab. of Viral and Molecular Pathogenesis, NINDS, NIH, Bethesda, MD 20892.**

Contusive spinal cord injury (SCI) results in loss of tissue and consequent functional deficits. Nearly half of patients with SCI appear to have incomplete injuries with some function below the level of the lesion. In animal models of incomplete SCI the residual tissue that is spared has been found to be abnormal in several respects. These include abnormal myelination and reduced conductance velocity of axons in the residual white matter. To examine the molecular basis of the abnormal myelination after SCI we used a standardized rat model of reproducible contusive injury in which a weight drop device is used to produce an incomplete lesion at the T8 vertebral level. Spinal cord tissue was removed at 1, 4 and 7 days to study the acute response to injury and at 2 and 6 months to study the chronic lesion site. The relative expression of mRNA for myelin proteins was compared using *in situ* hybridization with radioactive or digoxigenin labelled antisence 48mer oligonucleotide probes to proteolipid protein (PLP), a major protein in central myelin, myelin basic protein (MBP), a major component of central and significant minor component of peripheral myelin, and protein zero (P0), the major structural protein of peripheral myelin. The results suggest a down-regulation of the expression of genes for PLP and MBP, not only at the injury epicenter where there is significant tissue loss, but also in the spinal cord both rostral and caudal to the lesion. Further, by 2 months after injury, P0, normally expressed only in the peripheral nervous system, is expressed both at the epicenter and in regions of spinal cord rostral and caudal to it, presumably due to invasion of Schwann cells. Thus, after SCI the abnormal myelination of residual, spared, axons may be due, at least in part, to changes in transcriptional regulation of genes for myelin structural proteins and an altered distribution of myelin-producing cells. [Support: NIH- NS28130].

765.14

SEQUENTIAL EXPRESSION OF C-FOS, TNF-ALPHA AND PREPRODYNORPHIN GENES IN SPINAL CORD FOLLOWING EXPERIMENTAL TRAUMATIC INJURY. A. Yakovlev and A.I. Faden*. Departments of Neurology and Pharmacology, Georgetown University Medical Center, Washington, DC 20007.

Delayed biochemical changes play an important role in tissue damage resulting from traumatic injuries to the central nervous system. Identification of such secondary injury factors at the level of gene expression and their regulation may lead to the development of more effective treatment strategies. We used the reverse transcription-polymerase chain reaction to estimate dynamic changes in levels of c-fos, tumor necrosis factor (TNF)-alpha, and preprodynorphin mRNA isolated from individual segments (T1-T12) of spinal cord following graded impact trauma (50 or 100 g-cm) to the T9 segment of pentobarbital-anesthetized rats. Levels of mRNA were assessed at 30 min, 4 hrs, 24 hrs, and 1 wk after injury.

Trauma caused elevation of c-fos mRNA at the trauma site by 30 min after injury. At this time, increased levels of TNF-alpha, but not of preprodynorphin, mRNA were also found. By 24 hrs, c-fos and TNF-alpha mRNA had returned to normal levels at the trauma site, but were now increased at more distal segments (T5 and T12). At 4 hrs after trauma, induction of preprodynorphin mRNA was detected at the trauma site; levels continued to be elevated at 24 hrs after trauma, at which time they were also detected at T5 and T12. Increases for each mRNA were greater in severe, as compared to moderate, trauma.

The injury dose-dependent and time-dependent changes in c-fos, TNF-alpha and preprodynorphin mRNA expression suggest that the respective proteins are synthesized in response to trauma and may participate in the secondary injury response. Later accumulation of message distant from the trauma site may reflect a progression of delayed damage along the spinal cord.

765.15

ELECTRICAL STIMULATION ENHANCES SLOW AXONAL TRANSPORT IN THE CORTICOSPINAL TRACT AFTER SPINAL CORD INJURY. J.A. McLane* and T. Khan. Rehab. R&D Center, Edward Hines Jr. DVA Hospital, Hines, IL 60141.

Unlike neurons from the peripheral nervous system, injured neurons of the adult central nervous system seldom undergo a functional regeneration. However, recent animal studies have shown that electrical stimulation not only enhances neurite outgrowth, but also stimulates directed neurite growth. Direct current stimulation through contusion or transection injuries in the cat has produced histological and electrophysiological evidence of regrowth of axons into and through the lesion site.

It has been reported that young, growing rats transport more material by slow axonal transport along the corticospinal tract than adults. A T8 spinal cord transection in adults temporarily increased the level of slow transport to that of young rats (Feringa et al., J. Neurol. Neurosurg. Psychiat. 47:917, 1984). This study was designed to determine whether electrical stimulation could enhance this period of increased slow axonal transport following spinal cord injury.

The spinal cords of adult rats were completely transected at the T8 level. Half of the animals had miniature stimulators implanted at the time of transection with platinum leads placed epidurally so that the cathode was placed distal and ventral while the anode was placed proximal and dorsal. The stimulators provided a constant 15 uA of DC current. Slow axonal transport in the corticospinal tract was labelled with ^{35}S-methionine one week later by injecting 100 uCi of radioisotope bilaterally into the sensorimotor cortex. Three weeks after the isotope injection the animals were perfused with formalin, the entire spinal cord dissected, and the radioactivity in 5 mm segments of the spinal cord determined by scintillation counting.

We have found that the amount of radiolabel accumulating at the injury site was increased by 39% to 62% in the animals with stimulators compared to animals receiving the spinal cord transection but no stimulator. This data supports our hypothesis that electrical stimulation enhances spinal cord regeneration by prolonging or amplifying the period of increased delivery via axonal transport of critical materials needed for axonal elongation after injury to the spinal cord. Supported by funds from the Rehabilitation R&D Center, VA Hines Hospital, Hines, IL 60141.

765.16

HIGH DOSE METHYLPREDNISOLONE INCREASES BOTH SYNAPTIC ACTIVITY AND FIRING FREQUENCY IN MURINE SPINAL CORD CELL CULTURE. A. Foroutan , M. Behbehani, T. Jonas, and D.K. Anderson*. Dept. of Vet. Affairs Med. Ctr, Dept. of Physiology, Univ. of Cincinnati Coll. of Med., Cincinnati, OH, 45267.

In this study, the whole-cell patch clamp technic was used to characterize the acute effect of methylprednisolone (MP) on murine spinal cord culture. Exposure of 10-18 day-old dissociated spinal cord cultures to 25, 50, 100, and 133μM MP did not cause any detectable changes in the membrane potential, the leak current (at -55mV), the number of EPSPs or action potentials (APs) in more than 90% of the cells. However, in less than 10% of the cells (4 cells out of 50), MP (133μM) caused a mean hyperpolarization of 15mV. Higher concentrations of MP such as 266 and 500μM as well as 1, 10, and 20mM all caused cellular depolarization ranging from 2 to 20mV, while at the same time, decreasing the threshold by 5 to 15mV and increasing the number of EPSPs and APs in a dose dependant fashion. The leak current (at -55mV) did not change even in response to such high doses. Addition of the Ca^{2+} chelator, EDTA, prior to MP treatment prevented any cellular response to the drug. Based on these observations, the elicited effect of MP on the murine spinal cord neurons appears to be an excitatory one and dependant upon extracellular Ca^{2+}.

766.1

HOLE BOARD PERFORMANCE OF RATS AFTER SEPTO-HIPPOCAMPAL LESIONS AND TREATMENT WITH NIMODIPINE. C. Weichman, P. McMurray, G. Knuttingen, P. Mudd, E. Foley, and S. Finger*, Psych. Dep't., Washington Univ., St. Louis, MO 63130.

Rats were taught to select 8 holes in a 4 x 4 hole board for food reinforcements. Upon reaching criterion, 23 were given electrolytic lesions of the anterior hippocampus (including the septo-hippocampal pathways) and 15 received sham operations. Within 24 hours of surgery, approximately half of the rats in each group began daily oral treatments for 10 days with the central calcium channel blocker, nimodipine, while the others received vehicle alone. Retention testing began the day after the drug treatments ended. The means were Sham (combined) = 4.5 days, Lesion/Drug = 6.4 days, and Lesion/Vehicle = 7.6 days to criterion. An ANOVA revealed a significant lesion effect ($p < .05$), and additional analyses showed that only the Lesion/Vehicle group differed from the Sham group. Additional evidence for nimodipine improving postoperative performance came when lesions from the two lesion groups were matched and the scores of the paired animals were analyzed with a sign test ($p < .05$). The findings show that hole board performance can be disrupted by septohippocampal damage. The data also extend previous findings from this laboratory demonstrating that nimodipine can enhance recovery on higher cognitive tasks (e.g., DRL, 8-arm radial maze) after hippocampal damage.

766.2

CYCLOHEXIMIDE REDUCES SPONTANEOUS ACTIVITY OF CULTURED MAMMALIAN SPINAL NETWORKS. J.H. Lucas*[1] R.S. Jordan,[2] and G.W. Gross,[2] [1]Dept. of Physiology, Ohio State Univ., Colombus, OH 43210 and [2]Center for Network Neuroscience, Univ. of North Texas, Denton, TX 76203-5218.

Protein synthesis inhibition (PSI) by cycloheximide (CHX, 1.0 µg/ml) or puromycin (0.05 µg/ml) increases survival of spinal cord (SC) neurons subjected to transection of a primary dendrite 100 µm from the soma (Lucas et al., Soc. Neurosci. Abst. 18, 1992). Proposed mechanisms of PSI protection are: (1) reduction of cell metabolism and (2) prevention of the synthesis of specific proteins which may mediate cell death. Neuronal survival after dendrotomy is also increased by barbiturates (Wang and Lucas, Soc. neurosci. Abst. 17, 1991) which reduce activity-dependent metabolism in nervous tissues. The present study examined whether PSI affects spontaneous electrical activity in monolayer cultures of mouse SC.

Microcultures (approx. 1.5 mm diameter, 100-500 neurons) were grown on multimicroelectrode plates (MMEPs) which contain 64 photoetched electrodes on their surfaces. The MMEPs allow simultaneous recording of spontaneous SC network activity (c.f. Gross et al., Neurobionics, M. Samii and H.W. Bothe eds., Elsevier, 1993). Stripchart recordings of integrated spike activity (rectified and integrated with a time constant of 300 ms) were used to monitor changes in burst activity after application of 1.0 µg/ml CHX.

CHX caused an average decrease in burst frequency of 17% by 1h and 42% by 2h (N=5 cultures). Internal controls with carrier medium showed no similar effects. As the fate of neurons after dendrotomy is decided within 2h, protection of lesioned neurons by CHX may be related to decreased activity within the surrounding network. Experiments will be performed to determine: (1) whether puromycin also reduces activity, and (2) specific circuits affected by PSI. NS 29683-02.

766.3

ANTI-INTERCELLULAR CELL ADHESION MOLECULE (ANTI-ICAM-1) ANTIBODY REDUCES MYELOPEROXIDASE ACTIVITY IN RAT HEAD INJURY

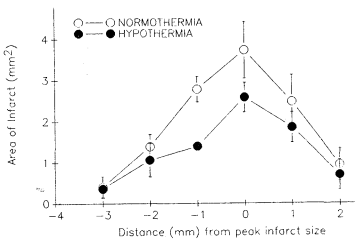
D. Hines, L. Fritz, T. Yednock, P. Setler, and H. Horner*
Athena Neurosciences, South San Francisco CA 94080

A myeloperoxidase (MPO) assay was used as a measure of neutrophil infiltration into the brain of head injured Sprague Dawley rats (275-320grams). The peak time of MPO activity has been determined to be 16 hours post-injury (a 10 gm weight dropped from 10 cm onto the exposed dura). This correlates with the apparent peak of neutrophil infiltration as assessed by immunohistochemistry. A single 1 mg injection (iv) of a monoclonal anti-ICAM antibody (developed at Athena) 5 minutes prior to injury decreased MPO activity by 37% (0.229 units/gram tissue ± 0.027 vs. 0.145 units/gm tissue ± 0.046 N=7,P=0.0012). Similar results were obtained with injection of the ICAM antibody 5 minutes post-injury.An isotype control antibody (IgG_1) had no effect on MPO activity. The anti-ICAM antibody also significantly reduced neutrophil migration in an oyster glycogen induced peritonitis model in the Sprague Dawley rat. Rats were initially injected (iv) with PBS or 1 mg of anti-ICAM followed by the injection (ip) of 20 mls of oyster glycogen in PBS (1mg/ml). 4 hours later the peritoneal exudate was collected and cell counts and differentials were done. The peritoneal exudate from the anti-ICAM treated rats showed an 85% reduction in total number of neutrophils when compared with the PBS controls (22x10E6 vs 145x10E6 N=6 p=0.0001). These rats also showed a marked increase in the number of circulating neutrophils (8.7x10E6 vs 3.6 x10E6 neutrophils/ml blood).

766.4

HYPOTHERMIA REDUCES INFARCT SIZE AFTER TRAUMATIC BRAIN INJURY IN IMMATURE RATS. R.T. Mansfield, J.K. Schiding, E.M. Nemoto, and P.M. Kochanek*. Depts. of Anesthesiol/CCM and Peds, Univ. of Pittsburgh, Pittsburgh, PA 15213

Cerebral edema and hyperemia are more prominent in immature than in adult animals after traumatic brain injury. Hypothermia (H) is beneficial after trauma in adults. We hypothesized that 4 h of H after traumatic brain injury reduces injury in an immature rat model. Anesthetized Wistar rats (3-4 wk, 90-140 g) were traumatized (10 g x 4.2 cm weight-drop) on the exposed parietal cortex. Ten min posttrauma, brain temperature (BT) was decreased to 32°C for 4 h (n=4). BT was 37°C in controls (n=6). At 5 d posttrauma, infarct area was measured in thionin-stained coronal sections. H reduced infarct size ($p<0.05$ vs normothermia, two-way ANOVA, Fig). We conclude that a brief period of moderate H ameliorates traumatic brain injury in the immature rat.



766.5

HYPOTHERMIA IS CYTOPROTECTIVE WITHOUT ATTENUATING TRAUMATIC BRAIN INJURY-INDUCED ELEVATIONS IN INTERSTITIAL CONCENTRATIONS OF GLUTAMATE M.L. Botscheller*, D.W. Marion, E.E. Redd and A.M. Palmer Departments of Psychiatry and Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

Moderate hypothermia has previously been shown to reduce mortality and improve behavioral outcome following fluid-percussion injury (*J. Cereb. Blood Flow Metab.* 11:114-121). Using a controlled cortical impact model, we assessed the influence of moderate hypothermia on both lesion volume and injury-induced increases in interstitial concentrations of aspartate and glutamate. Rats were randomized to groups of normothermic (37°C) and hypothermic (32°C) temperatures. *In vivo* microdialysis was used to collect serial measurements of aspartate and glutamate in rat frontal cortex before and after impact (3.0 mm of deformation at a velocity of 4.0 ± 0.1 m/sec). Animals were perfused 14 days after injury for lesion volume determination. Cooling the brain to 32.0-32.5°C 30 min before injury and maintaining this temperature 2 h after injury significantly reduced the mean lesion volume (mm^3) in 9 hypothermic animals (8.2 ± 1.3) when compared with 8 normothermic animals (13.2 ± 1.7). However, unlike cerebral ischemia (*Stroke* 20: 904-911; *Neuroscience* 42: 661-670), hypothermia did not attenuate the marked elevation of dialysate concentrations of glutamate and aspartate caused by severe cortical impact. Under normothermic conditions glutamate content (nmol/10 min) increased from 0.13 ± 0.03 to 3.08 ± 0.52 (n = 6) and from 0.19 ± 0.06 to a peak value of 3.09 ± 0.26 under hypothermic conditions (n = 6); similar data was obtained for aspartate. These data suggest that: 1) the cytoprotective action of hypothermia is mediated by postsynaptic mechanisms, and 2) traumatic brain injury-induced elevations in dialysate concentrations of glutamate occur by a different mechanism from that associated with cerebral ischemia.

766.6

POST-TRAUMATIC BRAIN HYPOTHERMIA REDUCES HISTOPATHOLOGICAL DAMAGE FOLLOWING CONCUSSIVE BRAIN INJURY IN THE RAT. W. D. Dietrich*, O. Alonso R. Busto, M.Y-T. Globus, M.D. Ginsberg. Univ. of Miami School of Medicine, Miami, FL

This study documented the histopathological consequences of moderate traumatic brain injury (TBI) and determined whether post-traumatic brain hypothermia would protect. Normothermic (37.5°) Sprague-Dawley rats were injured with a fluid percussion pulse ranging from 1.7-2.2 atmospheres. In one group (n=9), brain temperature was maintained at normothermic levels for 3 hrs after injury, while in a second group (n=9), brain temperature was reduced to 30°C at 5 min post-trauma and maintained for 3 hrs. Although histopathological damage at the impact site was seen in only 1 of 9 normothermic rats three days after TBI, all normothermic animals displayed necrotic neurons within ipsilateral cortical regions lateral and remote from the impact site. Intracerebral hemorrhagic contusions were also present at the gray-white interface underlying the injured cortical areas. Selective neuronal necrosis was present within the CA3 and CA4 hippocampal subsectors and thalamus. Post-traumatic brain hypothermia significantly reduced the overall sum of necrotic cortical neurons (519 ± 122 vs. 952 ± 130, mean ± SE, $p=0.03$, Kruskal-Wallis test) as well as contusion volume (0.50 ± 0.14 vs. 2.14 ± 0.71 mm^3, $p=0.004$). These data document a consistent pattern of histopathological vulnerability following normothermic TBI and demonstrate hypothermic protection in the post-traumatic setting.

766.7

ADENOSINE PROTECTS RAT HIPPOCAMPAL CELLS FROM TRAUMATIC CELL DEATH

H.L. Mitchell, K.-W. Yoon and T. Pittman*. Division of Neurosurgery and Surgical Research Institute, Saint Louis University, St. Louis, MO 63110-0250.

Dispersed rat hippocampal cell cultures were used as a model for traumatic neuronal injury. The cultured cells were injured using a sterile needle tip to produce neuronal and glial monolayer disruption (Tecoma, et al, Neuron, 1989). The cell death in the regions far from the physical disruption (5mm) was assessed by Trypan Blue staining of the dead neurons. Cell death was attenuated by MK801 (10μM) (46.1% ± 11.3 less than injury control, $p<0.001$, n=6) added into the buffered electrolyte solution suggesting that at least some of the cell death is mediated by glutamate. A specific adenosine A1 receptor agonist N6-cyclopentyladenosine (100nM to 10μM) dose dependently attenuated the cell death (44.7% ± 13.5 less than control at 10μM, $p<0.001$, n=4). On the other hand, A1 receptor antagonists, 8-cyclopentyl-1, 3 dimethylxanthine (1μM) significantly increased the cell death suggesting that endogenous adenosine release may be involved in modulating traumatic cell injury. These findings suggest that adenosine may have a protective effect on traumatic cell injury mediated by glutamate.

766.8

TRAUMATIC INJURY OF SPINAL CORD CELLS *IN VITRO* REDUCED BY GM1 GANGLIOSIDE

J.L. Bonheur, H. Laev, C.Vorwerk, and S.E. Karpiak.* Div. Neuroscience NYSPI, & Dept. of Psychiatry, Columbia U. (P & S). NY,NY 10032.

GM1 ganglioside is a significant endogenous component of CNS cellular plasma membranes thereby contributing to their integrity and function. Exogenous GM1 can incorporate into plasma membranes, and, can exert neuroprotective effects on damaged neuronal tissue(s). An *in vitro* method of physical injury (trauma) was adapted using cultures derived from fetal mouse spinal cord to assess GM1's neuroprotection. Injury was induced by uniformly cross-hatching spinal cell cultures with a 1mm plastic pipette tip. The extent of injury and effect of GM1 post-treatment (80μM) was assessed at 48 hrs by measuring lactate dehydrogenase (LDH) release and chronicling changes in the plasma membrane surface distribution of endogenous GM1 using cholera toxin/antitoxin/fluorescent antibody immunohistochemistry. A *gradient* of injury was seen to occur from the zone of maximum injury to partially traumatized or noninjured areas. The primary injury zone was characterized by areas of swollen or dead cells and abnormal or degenerating processes. At further distances, cells were nearly normal with intact fibers. This injury gradient likely reflects proximate and distant effects of released neurotoxic levels of endogenous glutamate and other excitatory amino acids. GM1 treatment resulted in reduced (***>75%***) LDH release and enhanced cell and process integrity indicative of reduced injury. These preliminary results indicate that GM1's previously documented neuroprotective effects using cortical culture systems can be generalized to injured spinal cells *in vitro* wherein there is evidence for preservation (rescue) of cellular plasma membranes. These data parallel clinical studies that report efficacy of GM1 treatment for spinal cord injury.

766.9

THE EFFECT OF GM1 ON RECOVERY AFTER SPINAL INJURY.

F.Roisen*, D.Burke, S.Guo, J.Johnson, D.Linden, C.Lu, C.Shields, G.Yorke, P.Zhang. Depts. of Anat. Sci. and Neurobio., Orthopedic Surg. and Surg. (Div. Neurosurg.), University of Louisville, School of Medicine, Louisville, KY 40292.

We and others have reported that gangliosides have neuronotrophic effects on primary neurons and established neuronal lines *in vitro*. *In vivo* studies suggest that gangliosides may be beneficial in the treatment of neuronal degenerative diseases. This study evaluated the therapeutic utility of the ganglioside GM1 in enhancing functional recovery after spinal lesion. Adult Wistar rats (200 g) were given a series of behavioral tests that served to indicate sensory/motor function. Following a pre-injury intravenous injection (IV) of GM1 (1 mg) or ceramide (0.36 mg solubilized with phosphatidyl choline), anesthetized rats were given a T3 weight drop injury (10 g x 2.5 cm) and the test agent was injected subdurally. Ceramide or GM1 were given IV on alternate days for 2 wk; the animals were maintained for 8 wk. Weekly behavioral testing on coded, randomized animals was performed to assess functional recovery. Compared to sham operated or normal animals, all groups exhibited significant functional deficits over the course of this study. However, animals treated with GM1 generally exhibited a slight, but consistently higher level of recovery over the ceramide controls for the first 3 wk. These differences declined in the remaining 5 wk, perhaps reflecting the cessation of GM1 or its relatively low dosage. At 8 wk, no significant differences were found between the ceramide or GM1 treated animals, except the mean weight of rats receiving GM1 was not different from the sham operated controls, while those treated with ceramide were significantly reduced. Histological studies on representative segments of the lesioned spinal cords are in progress. Although this study did not directly support the use of GM1 for spinal trauma, it did suggest that GM1 may be of benefit if given until functional recovery. Supported by Alliant Community Trust Fund, Louisville, Ky.

766.10

AN IN VITRO MODEL OF TRAUMATIC BRAIN INJURY WITH PROTECTION WITH POST-TRAUMA MAGNESIUM TREATMENT.

J.M. Girard*, K.L. Panizzon and R.A. Wallis, Dept. of Neurology, UCLA, Los Angeles, CA 90024 and sepulveda VAMC, Sepulveda, CA 91343.

Traumatic brain injury is a leading cause of death in the United States today. We developed an in vitro fluid-percussion model of neuronal injury using the hippocampal slice to study the ionic mechanisms involved in traumatic neuronal injury. Rat hippocampal slices, 475 μ thick, were prepared and placed in a recording chamber perfused with ACSF. Each slice was then transferred into a chamber sealed by a rubber piston and filled with 7.0 ml of oxygenated ACSF. Slices were traumatized by the dropping of a 1 kg weight from a height of 62.3 cm onto the rubber piston. After trauma, slices were returned to the recording chamber and monitored electrophysiologically. Paired sham slices underwent the same procedure without dropping of the weight. After 60 mins. of recovery, mean CA1 orthodromic PS recovered to 14 ± 13% of original amplitude, with a mean CA1 antidromic PS recovery of 16 ± 8%. These recoveries differed significantly from sham slices which showed orthodromic recovery of 104 ± 6%, and antidromic recovery of 102 ± 4% ($p<.05$).

Treatment after trauma with ACSF containing 10 mM magnesium for 35 mins. provided significant protection from this injury. Traumatized slices receiving magnesium treatment demonstrated CA1 orthodromic and antidromic PS recoveries of 114 ± 13% and 103 ± 19%, compared to traumatized slices not given this treatment, which showed recoveries of 24 ± 22 and 24 ± 14 ($p<.05$). These results indicate that traumatic neuronal injury can be studied in the hippocampal slice. They additionally indicate that magnesium given after trauma can provide significant protection from traumatic neuronal injury.

766.11

ELECTROPHYSIOLOGICAL AND ULTRASTRUCTURAL CONSEQUENCES OF *IN VIVO* CALCIUM IONOPHORE EXPOSURE IN THE RAT SPINAL CORD.

David L. Anthes*, Michael G. Fehlings, Elizabeth Theriault, Runjan Seth, Charles H. Tator. Playfair Neuroscience Unit, The Toronto Hospital Neurological Centre, University of Toronto, Toronto, Ontario M5T 2S8 Canada

Traumatic and ischemic injuries to the CNS are accompanied by secondary cellular injury mediated in part by elevated intracellular calcium ($[Ca^{2+}]_i$). It is not clear to what extent calcium-mediated events (as opposed to direct mechanical compression or vascular disruption) account for the subsequent anatomical and functional deterioration. Therefore, the current study investigates ultrastructural and electrophysiological changes associated with increased $[Ca^{2+}]_i$ induced by the application of calcium ionophore to the normal uninjured rat spinal cord. Calcium ionophore induces elevations in $[Ca^{2+}]_i$ by enhancing membrane calcium permeability, allowing calcium to flow down its large concentration gradient (10^4M) into the cell. Following cervical laminectomies in adult male Wistar rats (n=12), exposed spinal cords (with dura removed) were irrigated with artificial cerebrospinal fluid (CSF) with or without the inclusion of 20μM calcium ionophore A23187 (administered blinded). For 4 hours following administration of the perfusate, somatosensory and motor evoked potentials (SEPs and MEPs) were recorded. As well, direct spinal cord stimulation and recording (at C3 and T10) was performed. Immediately following the 4 hours of recording, animals were sacrificed and prepared for electron microscopy. Electrophysiological conduction deficits were observed in the form of increased response latencies for MEPs ($p=0.0175$) and C3 spinal recordings ($p=0.005$) in the calcium ionophore group but not in the control animals. The calcium ionophore group also demonstrated structural axonal degeneration in the form of periaxonal swelling, organelle accumulation, lamellar separation and vesicular myelin formation. Our data suggest that a rise in $[Ca^{2+}]_i$ alone mimics many of the ultrastructural and electrophysiological features of traumatic spinal cord injury. This data provides further evidence implicating calcium influx as a major event in the pathophysiology of traumatic nervous system injury.

766.12

POSSIBLE INDUCTION OF NITRIC OXIDE SYNTHASE IN PURKINJE NEURONS FOLLOWING INJURY.

S. Chen* and G.Aston-Jones. Div. of Behavioral Neurobiology, Dept. of Mental Health Sciences, Hahnemann Univ., Philadelphia, PA 19102.

Nitric oxide (NO) has been recently implicated as an interneuronal messenger in the brain and periphery. Neurons that stain for markers of NO have been found to be resistant to various brain insults, leading to proposals that induction or increase of NO activity could be involved in neuronal response to injury. This idea was tested using NADPH-diaphorase histochemistry as a possible marker of NO-producing neurons following injury to the cerebellar cortex. Adult male Sprague Dawley rats were anesthetized with pentobarbital and lesions of the cerebellum were performed with a blade. After survival for 10 -15 days, the animals were re-anethetized and perfused with 4% paraformaldehyde. NADPH-diaphorase histochemistry was performed by incubating sections in a solution containing 0.01% NADPH, 0.02% nitro blue tetrazolium, and 0.3% Triton X-100 in 0.1 M phosphate buffer. Intense NADPH-diaphorase reactivity was seen in both cell bodies and dendrites of Purkinje neurons around the lesion site, while Purkinje neurons in control animals that sustained lesions in other brain areas, or in adjacent non-lesioned areas of the cerebellar cortex were unstained . It has been reported that sciatic nerve transection induces NOS in rat dorsal root ganglion neurons (Fiallos-Estrada et al., 93). The present study is the first report indicating that lesion may induce NOS in central neurons. Supported by PHS grant NS24698.

766.13

A ROLE FOR NITRIC OXIDE IN DELAYED DAMAGE AFTER SPINAL INJURY? R.J. Weinberg[1]*, J. Valtschanoff[1], and A. Blight[2], [1]Dept. of Cell Biology & Anatomy, and [2]Dept. of Neurosurgery, University of North Carolina, Chapel Hill, NC 27599.

Besides the direct effects of trauma, secondary effects may contribute to the severity of spinal injury. Evidence has accumulated that these delayed effects are mediated by glutamate excitotoxicity, especially via activation of NMDA receptors. Other lines of evidence suggest that inflammatory responses by macrophages and neutrophils may contribute to this delayed damage. Neuronal and immune responses may share a common mechanism: release of the free radical nitric oxide (NO). Glutamate is likely to activate constitutive NO synthase (NOS) in spinal neurons, while inflammation may trigger synthesis of inducible NOS in phagocytes. We thus hypothesize that high levels of NO at the site of spinal injury contribute to the delayed damage.

To study this, female Hartley guinea pigs (300-450 g) are anesthetized with a ketamine/xylazine/acepromazine mixture. Following laminectomy, the spinal cord is compressed at T13 to a thickness of 1.2 mm for 15 sec, and the animal allowed to recover. During the 3 days survival (shown previously to be maximal for delayed injury in this model), an osmotic pump delivers either of two NOS antagonists: L-nitroarginine (selective for constitutive NOS), or *N*-methyl-L-arginine (which blocks both constitutive and inducible NOS). Both agents are dissolved in 5% dimethylsulfoxide in normal saline (pH adjusted to 7.2). Control animals receive vehicle only. To investigate effects of these antagonists, we assess (blindly) the cutaneus trunci muscle reflex, the vestibular placing response, and record evoked potentials over the somatic sensory cortex. Histological studies of neuronal loss and white matter damage are also being performed. This work is supported by the American Paralysis Association and the Paralyzed Veterans of America.

766.14

PRE- AND POST-SYNAPTIC INHIBITION OF GLUTAMATE ATTENUATES CEREBRAL EDEMA FOLLOWING EXPERIMENTAL BRAIN INJURY. DH Smith*[1], K Okiyama[1], R Simon[2], TK McIntosh[1]. Div. Of Neurosurgery, Univ. of Pennsylvania[1], Philadelphia, PA 19104 and Dept. of Neurology, Univ. Of Calif.[2], San Francisco, CA. 94143.

It has been postulated that following traumatic brain injury (TBI), cerebral edema formation occurs due, in part, to a massive release of the excitatory amino acid (EAA) neurotransmitter, glutamate, and to its subsequent excitotoxic effect. In the present study, we examined the effects of 1) magnesium, a non-competitive antagonist of the *N*-methyl-D-aspartate glutamate receptor subtype and 2) BW1003C87, a novel pre-synaptic glutamate-release inhibitor, on cerebral edema formation following parasagittal fluid-percussion (FP) brain injury in the rat. Animals (n=33), were subjected to FP brain injury of moderate severity (2.5 atm). Fifteen minutes after injury, the animals received a constant infusion over 15 minutes (2.75 ml/kg/15 min) of either $MgCl_2$ (300 µmol/kg, IV), BW1003C87 (10 mg/kg, IV), or saline. Forty-eight hours following injury, regional cerebral edema was determined using the wet weight/dry weight technique. Edema formation observed in saline treated animals was significantly reduced in the left (ipsilateral to injury) hippocampus ($p<0.01$) by both MgCl2 and BW1003C87, while BW1003C87 additionally reduced regional edema in the cortical area adjacent to the site of maximal injury ($p<0.001$). These results suggest that an excitotoxic response to brain injury may play an important role in post-traumatic cerebral edema formation, and that pre- or post-synaptic blockade of the glutamate receptor system may attenuate this excitotoxic effect. This study was supported, in part, by NS 26818, and the Brain Trauma Foundation.

766.15

KYNURENATE IS NEUROPROTECTIVE FOLLOWING EXPERIMENTAL BRAIN INJURY IN THE RAT. R.R. Hicks*, D.H. Smith and T.K. McIntosh. Neuroscience Training Program, Univ. of Conn. Health Ctr., Farmington, CT 06030 and Div. of Neurosurgery, Univ. of Penn., Philadelphia, PA 19104.

Pharmacologic inhibition of excitatory amino acid (EAA) neurotransmission improves physiologic, metabolic, and neurobehavioral outcome following experimental brain trauma, however, no studies to date have demonstrated an attenuation in the histopathologic sequelae of traumatic central nervous system injury. The present study examined the effects of kynurenate (KYNA), a broad spectrum EAA amino acid antagonist, on neuronal survival in the hippocampus after experimental fluid-percussion (FP) brain injury in the rat. Animals (n=10/treatment) received either an intravenous injection of KYNA (300 mg/kg) or buffer (equal volume) 15 min following lateral FP brain injury of moderate/high severity (2.5 atm.). Two weeks after injury, animals were sacrificed and neuronal cell loss in the hippocampus was examined with Nissl staining. KYNA significantly increased the number of surviving neurons in the CA3 region of the hippocampus ($p<0.05$), but not in the hilus of the dentate gyrus. These results support existing findings that pharmacological intervention with an EAA receptor antagonist may be neuroprotective in the treatment of traumatic brain injury.

766.16

Intracerebral Administration of basic Fibroblast Growth Factor Blocks Recovery Following brain Damage and May Be Tumorigenic R. Duvdevani*, R.L Roof, I. Becher and D.G. Stein, Brain Res. Lab., Inst. Anim. Behav., Rutgers Univ., Newark, NJ 07102

Fibroblast growth factor (FGF) has been reported to promote survival of injured neurons, induce cerebral angiogenesis and improve memory. We examined whether intraventricularly infused b-FGF would enhance recovery of maze performance after contusion of medial frontal cortex (MFC). Our previous studies have shown that bilateral MFC contusion in rats is followed by a pronounced deficit in spatial learning, as well as significant gliosis and neuronal loss.

Immediately after contusion, cannulas were implanted into the left lateral ventricle, and basic FGF or saline (vehicle) was infused via a mini osmotic pump for 14 days. Beginning 21 days after surgery, rats were tested for their spatial learning in the Morris water maze (MWM) for 10 consecutive days. Rats with contusions were impaired in MWM performance compared to shams. FGF-treated rats showed an initial improvement relative to vehicle-treated rats on the first 5 days of testing, but then showed a significant deterioration in performance over last 5 days. By the end of testing, FGF-treated rats performed as poorly as the brain-injured vehicle-treated controls. These data suggest that FGF can be detrimental to recovery following brain injury. Morphological examination revealed that 3 out the 7 rats receiving FGF developed brain tumors in their left lateral ventricles, an event never seen in vehicle-treated, injured animals, or intact controls. Such tumors might be the cause of the behavioral deterioration. Counts of blood vessels in frontoparietal cortex (near the injury site) did not show any b-FGF related angiogenic effect. Supported by GENRE Inc. and the Graduate School, Newark.

766.17

PROGESTERONE REDUCES MAZE IMPAIRMENT AND SECONDARY CELL LOSS FOLLOWING BILATERAL MEDIAL FRONTAL CONTUSION. R.L. Roof*, R. Duvdevani, L. Braswell, and D.G. Stein. Brain Res. Lab, Inst. of Anim. Behav., Rutgers Univ., Newark NJ 07102

We recently demonstrated that progesterone (P) significantly reduces cerebral edema associated with cortical contusion. Edema can have serious consequences, including intracranial swelling, and secondary neuronal loss. However, if edema is not present for an extended period of time, residual fluid and electrolytes are eventually removed, restoring the neuropil to a relatively normal state. The effective control of post-injury edema could result in the elimination of many of the functional deficits associated with traumatic brain injury. The following experiment was done to determine if P-induced reductions in edema can reduce cell loss and behavioral impairments caused by bilateral medial frontal contusion.

Male Sprague-Dawley rats were given bilateral medial frontal cortical contusions or sham surgery. One hour later, P (4 mg/kg, i.p.) or the oil vehicle was injected. Four additional injections (s.c.) were given at 24 h intervals. Beginning 7 days after surgery, each animal was tested for 10 days in the Morris water maze. Contused rats took significantly more time and used a longer path to find the hidden platform compared to shams. Contused rats receiving P injections performed as well as shams (also P injected) on all days except Day 2. Cell density measures demonstrated significant cell loss associated with the contusion in the medial dorsal thalamus (MD)as well as in cortical areas adjacent to the contusion area. Reduction of the MD cell loss was seen in P treated lesion rats.

We conclude that progesterone can reduce some of the secondary damage associated with traumatic brain injury and has potential as a treatment for traumatic brain injury.
We thank Genre for financial support.

766.18

GINKGO BILOBA EXTRACT (EGb761) IMPROVES SPATIAL PERFORMANCE IN THE MORRIS WATER MAZE AFTER CORTICAL CONTUSION IN THE RAT. S. W. Hoffman* and D. G. Stein. Brain Res. Lab., I.A.B., Rutgers, The State Univ. of New Jersey, Newark, NJ 07102.

We previously reported that (Hoffman et al, 1992) contusion injury to the medial frontal cortex (MFC) results in profound impairments of spatial navigation performance. In the present study we administered EGb761 or vehicle following a bilateral MFC contusion. Male rats (90d of age) received contusion-injury after which they were injected i.p. with a 100 mg/kg dose of EGb761 (L+EGb) or an equal volume of saline (L+sal). The rats then received one injection/day for the first 7 postinjury days, for a total of 8 injections. On the 8d postinjury, the rats were tested on a Morris Water Maze (MWM) task for 10 days (2 trials/d; 20s intertrial interval). On the 18th day postinjury the rats were perfused for histological analyses. ANOVA of body weights indicated a significant main effect. Rats treated with EGB761 increased their body weight to a level intermediate to shams and L+sal on postinjury days 14,15,16,17,and 18. ANOVA's for the MWM revealed significant differences on the 2nd daily trials in latency, distance, and in swim strategy to the platform. Post hoc analyses indicated that L+EGb rats performed better than L+sal rats on latency and distance measures ($p's<0.05$). Post hoc analysis of swim strategy revealed that the L+sal rats spent a larger percentage of their swim time closer to the wall of the pool than the shams ($p<0.05$), while the L+EGb rats were not significantly different from either group. Histological analysis revealed no differences between the two injured groups in cavity size ($p>0.05$). However, EGb761 treatment resulted in ventricular dilatation that was intermediate between that of shams and L+sal rats. These results suggest EGb761 reduces cerebral edema and may serve to reduce the behavioral and anatomical impairments caused by traumatic brain injury. Supported by IPSEN Research Foundation.

766.19

EFFECTS OF AMPHETAMINE ON BEAM-WALK RECOVERY FOLLOWING RIGHT OR LEFT SENSORIMOTOR CORTEX CONTUSION IN RAT. A.E. Kline, R.A. Salazar, E.A. Bustos, D.M. Feeney, and E.C. Benzel*. Depts. of Psych., Physiol., and Division of Neurosurgery, Univ. of New Mexico, Albuquerque, NM 87131.

Previous studies examining the effect of amphetamine (AMPH) following sensorimotor cortex (SMCX) contusion, or ablation, on BW recovery have exclusively utilized right hemisphere injury (CRC Critical Reviews in Neurobiol, 13:135-197, 1987; Canadian J. Psych, 44:233-252, 1990). However, there may be a differential effect of AMPH on right compared to left SMCX injury because marked decreases of catecholamine (CA) levels follow right, but not left, cortical injury in rat (Science, 205:707-710, 1979). To test this hypothesis the current study compared two dosages (2mg/kg or 3.5mg/kg) of AMPH on BW recovery after right or left SMCX contusion or sham operation (N=53). At 24 hours following contusion or sham surgery a single administration of drug or saline was given and BW testing conducted for 15 days using our standard paradigm. The results indicated that the 2 mg/kg dosage significantly facilitated BW recovery for the left, but not the right, SMCX contused animals compared to the saline controls. In contrast the 3.5 mg/kg dosage facilitated BW recovery for the right, but not the left, SMCX injured group. These results suggest the optimal dosage of AMPH for promoting functional recovery is dependent upon the hemisphere injured. This variable may also be important for other drugs.

Supported by MBRS SO6 RR08139-17.

766.20

THE RED NUCLEUS MEDIATES RECOVERY FROM HEMIPLEGIA AFTER SENSORIMOTOR CORTEX ABLATION IN THE RAT. K.A. Krobert*, D.M. Feeney, and G.K. Weiss. Depts. of Physiology and Psychology, Univ. of New Mexico, Albuquerque, NM 87131.

A series of experiments were conducted to test the hypothesis that the red nucleus is involved in the "spontaneous" recovery from hemiplegia after sensorimotor cortex (SMCX) ablation. Locomotor ability was evaluated using a beamwalking (BW) task [Science, (1982) 217:855]. Lesion of the SMCX, rubrospinal tract (RST) or the red nucleus produced transient BW deficits lasting an average of 11, 17, and 25 days respectively. However, enduring BW deficits ensued after SMCX ablation (> 90 days) only in rats recovered from prior complete red nucleus or RST lesions (> 90% damage). Rats SMCX ablated infused with 2% lidocaine (2 ul) into the red nucleus immediately prior to a single BW trial 1,2,4,6,10, and 12 days postinjury were significantly impaired on the BW task tested 8 and 14 days postinjury (no infusion) compared to saline infused controls. Inhibition of red nucleus neural activity by infusion of 2% lidocaine, 1M GABA, or 75 mM kynurenine (precursor of kynurenic acid) transiently (5-10 min) reinstated unilateral BW deficits in recovered SMCX ablated rats but not uninjured controls. These results indicate that rubrospinal neuronal activity is necessary for recovery and maintenance of BW ability in rats with SMCX injury.

Supported by Army Grant DAMD17-91-Z-1006.

766.21

THE EFFECT OF AN ENRICHED ENVIRONMENT ON RECOVERY OF COGNITIVE FUNCTION AFTER TRAUMATIC BRAIN INJURY. M.D. Temple, R.J. Hamm*, D.M. O'Dell, B.R. Pike, B.G. Lyeth, and L.W. Jenkins. Depts. of Neurosurgery and Psychology, Virginia Commonwealth Univ., Richmond, VA 23284.

This study was designed to determine whether exposure to an enriched environment would promote the recovery of cognitive function following traumatic brain injury (TBI) in rats. The rats were injured at a moderate level of fluid percussion injury (2.1 atm.) or were prepared for injury but were not injured (sham injury). Immediately after the traumatic injury was delivered, one group of rats (n=8) was placed as a group into the enriched environment. The enriched environment was 89 x 89 cm with a painted wood base and clear plexiglass walls 45.5 cm in height. Inside, there were four separate compartments interconnected by openings in the dividers. Each compartment consisted of different types of bedding and toys providing various olfactory, tactile, and visual stimuli (e.g., running wheel, wire grid, hollow tubes). In addition, the enriched environment was housed in the laboratory, giving the rats more exposure to a changing external environment. The other injured group of rats (n=8) and the sham-injured group (n=8) were returned to the animal room where they were housed individually in standard metal cages (24 x 20 x 18 cm). On days 11-15 performance in the Morris water maze was assessed. Analysis of variance indicated that animals raised in the enriched environment performed significantly better than injured animals raised in the standard isolated cages ($p<.01$). In fact, injured animals in the enriched environment performed as well as the sham injured animals. These results indicate that exposure to the enriched environment enhances recovery of cognitive function after traumatic brain injury.

Supported by NS 12857.

TRAUMA: MISCELLANEOUS I

767.1

FLUID-PERCUSSION BRAIN INJURY SELECTIVELY DESTROYS PARVALBUMIN CONTAINING CELLS IN RAT PARIETAL CORTEX. K. Querido, S.M. Lee*, D.A. Hoyda and D.P. Becker. Division of Neurosurgery, UCLA School of Medicine, Los Angeles, CA 90024

Parvalbumin (PV) is a member of Ca^{++}-binding proteins (CaBPs) which may help to regulate the levels of intracellular Ca^{++} by buffering free Ca^{++}. In adult neocortex, cells immunoreactive (IR) to PV are likewise IR-positive for the inhibitory transmitter GABA. In this study, we determined whether the presence of a CaBP protects neurons from fluid-percussion (F-P) injury and assessed the selective vulnerability of GABAergic neurons. Nine adult rats (250-275 g) were F-P injured (2.3-2.6 atm) as described previously under ethrane anesthesia. Two sham-injured animals served as controls. Animals were survived for 2 weeks after which they were perfused transcardially with 100 ml PBS followed by 200 ml 4% paraformaldehyde. Frozen sections (40 µm for PV-IR, 20 µm for cresyl violet) were cut through parietal cortex (site of F-P injury). Free-floating sections were incubated in primary antibody (dilution 1:1000, Sigma Immuno) overnight and visualized with the ABC kit (Vector) using DAB as the chromogen. PV-IR cells and adjacent cresyl violet sections were quantified by counting cells in 450 µm vertical strips 3.0 to 5.35 mm away from midline. Cell counts are expressed per 100 $\mu m^2 \pm$ SEM.

	Ipsilateral	Contralateral
PV-IR (Injured)	7.51 ± 0.31 ($p < 0.001$)	10.92 ± 0.19
PV-IR (Sham-injured)	10.15 ± 0.84	11.3 ± 0.77
Cresyl violet (Injured)	154.1 ± 6.83	160.9 ± 4.63

The loss of PV-IR cells was seen throughout the depth of cortex with the most extensive loss being between 450-600 µm (61.5% of contralateral values). These results confirm previous findings that F-P injury does not induce extensive cell loss in parietal cortex and indicate that parvalbumin-containing GABAergic neurons are particularly vulnerable to traumatic brain injury. (supported by NS30308, HD07416 and Lind Lawrence Foundation)

767.2

IMMUNOLOCALIZATION OF MICROGLIA AND MACROPHAGES AFTER MILD HEAD INJURY. N. Aihara*, J. J. Hall, L. H. Pitts and L. J. Noble. Department of Neurosurgery, University of California, San Francisco General Hospital, San Francisco, CA 94110.

Glia are particularly sensitive to traumatic injury and may therefore serve as biologic markers for assessing the extent of neural damage. In this study microglia were studied after mild head injury. Animals (n=4/time point) were sacrificed at 1, 3, and 7 days post injury. Sham operated animals (n=4) served as surgical controls. Microglia were examined by immunocytochemistry using the antibody OX42, which is directed against the CR3 complement receptor. Since OX42 does not distinguish macrophages from microglia, ED1, an antibody to a cytoplasmic antigen of macrophages, was immunolocalized in adjacent sections of brain. We report the regional changes in immunoexpression that were consistently noted in all animals.

In sham operated animals no immunostaining with OX42 was noted and ED1-labeled cells were restricted to the subarachnoid space. Consistent immunostaining for OX42 was observed at 3 days post injury in the substantia nigra, medial and lateral geniculate nuclei, superior colliculus, hippocampus, external capsule, and thalamus. At 7 days staining was also apparent in the striatum and cortex. Immunostaining for ED1 differed from that observed for OX42 in its more limited distribution. ED1-labeled cells at 3 and 7 days post injury were restricted to the cortex, external capsule, superior colliculus, and medial and lateral geniculate nuclei.

These findings demonstrate a widespread microglial reaction after mild head injury and the infiltration of macrophages into the injured hemisphere. (Supported by NIH NS14543 to LJN).

767.3

ASTROCYTES DIFFERENTIALLY EXPRESS *trk* A, B, C FOLLOWING FOCAL CORTICAL CONTUSION IN RAT BRAIN. S.D. Styren*, S.T. DeKosky, D.R. Kaplan, G. C. Styren, P. Kochanek, D. Marion. Depts. of Psychiatry, Neurology, Pittsburgh Brain Trauma Research Center, Univ. of Pitt. Sch. of Med., Western Psychiatric Inst. & Clinic, Pittsburgh, PA 15213. and NCI, Frederick, MD 21702

Reactive astrocytes, present following brain injury, produce nerve growth factor (NGF) in culture and may provide trophic support to damaged or dying neurons. Following entorhinal cortex and fimbria fornix lesions, astrocytes also express a truncated form of the neurotrophin receptor, *trk* B. To examine the role and distribution of *trk* following brain injury we examined cortex from rats which underwent a standardized focal cerebral contusion 4 to 14 days previously. We utilized a pan *trk* antibody and antibodies to extracellular epitopes of *trk* A, B, and C, and intracellular epitopes of *trk* A and B. In control animals astrocytes only weakly and rarely stained with any *trk* antibodies. In trauma, *trk* staining was mainly in highly reactive astrocytes, as well as some dystrophic neurons and fibers in the lesion penumbra. Pan *trk* antibody intensely stained reactive astrocytes around the lesion. *Trk* A extracellular (*trk* Ae) predominantly stained astrocytic fibers while *trk* A cytoplasmic (*trk* Ac) was localized to both fibers and cell bodies. *Trk* Be (like pan *trk*) intensely stained reactive astrocytes located in the penumbra, as did *trk* Bc. *Trk* C immunoreactivity was also present on astrocytes surrounding the lesion, but was restricted principally to cell bodies and peri-somal fibers. *Trk* expression on astrocytes suggests a novel role for neurotrophins following brain injury. The presence of both extracellular and intracellular domains for both *trk* A and B on astrocytes following brain injury suggests that these are functional receptors.

767.4

ASTROCYTIC RESPONSE FOLLOWING ENTORHINAL LESION IN THE RAT. S.A.Baldwin*, and S.W.Scheff. Center On *Aging, Dept. Anatomy & Neurobiology, Univ. of Kentucky, Lexington,* KY 40536-0230

In the normal brain, astrocytes regulate ion concentrations, amino acid uptake and play a key role in the blood brain barrier. Their response to brain injury is complex as well as the role they play in CNS repair. Astrocytes hypertrophy in response to a perturbation and up regulate astrocytic specific intermediate filament GFAP. These cells also show a positive signal for the intermediate filament vimentin, a protein primarily found in developing astrocytes.

The entorhinal cortex has a major input to the ipsilateral hippocampus. This innervation is very specific to the outer molecular layer of the hippocampal dentate gyrus. A unilateral entorhinal cortex denervates the molecular layer triggering synaptogenesis and the replacement of lost synaptic connections.

Fisher 344 rats were subjected to a unilateral entorhinal cortex lesion. Coronal sections showing the hippocampus were stained with antibodies against GFAP and vimentin 2, 10, and 15 days after the lesion. By 2 days there is a dramatic increase in GFAP in almost all areas of the hippocampus both ipsilateral and contralateral to the lesion. Astrocytes which normally have no detectable amounts of vimentin show a positive vimentin signal in both ipsilateral and contralateral hippocampii. By 10 and 15 days the GFAP signal decreased in the contralateral hippocampus and in nondenervated areas of the ipsilateral hippocampus. GFAP signal remained high in the ipsilateral denervated molecular layer. Numerous vimentin positive astrocytes were still observed throughout the ipsilateral and contralateral hippocampus.

767.5

GLIAL RESPONSES FOLLOWING CLOSE AND DISTANT AXONAL INJURY OF MAMMALIAN CNS NEURONS. G.-F.Tseng*, and K.-C. Lai
Dept. Anatomy, Col. Medicine, National Taiwan Univ., Taipei, Taiwan, R.O.C.

Adult rat rubrospinal neurons(RSN) surviving distal axotomy(DA) had less profuse dendritic arbors as compared to those after proximal axotomy(PA)(Tseng & Hu,'92). Here we studied glial responses following similar manipulations. Fast blue was applied during axotomy to retrogradely label lumbar-projecting RSN(*l*-RSN). Astrocytes and microglia were visualized following histochemical staining with an antiserum to glial fibrillary acidic protein(GFAP) and a lectin, GSA-IB_4 respectively in alternating sections of 30 μm thickness. Stained GFAP processes reconstructed were measured using an image analyzer. Stained microglia were counted and both were expressed as amount in unit corresponding nuclear area, defined by the location of the retrograde tracer in each section.

Results show that GFAP-staining increased and peaked at 6 days, then dropped slowly till 4 weeks after PA. Interestingly, DA caused an earlier(peaked 3-4 days) and much higher degree increase, 3-5 times, than that caused by PA. In contrast, microglia increased and peaked in 3-4 days and declined to control levels in a week following both PA and DA, and the reaction was higher following PA than DA. Substantial increase of both glial staining was observed in the rest of the contralateral and ipsilateral nuclei indicating that diffusible factor(s) may be involved. Sham-operated animals also displayed a similar pattern of increases, although of slightly lower intensity, indicating that CNS microglia can respond to trauma outside CNS. Since PA removed a longer segment of axon from *l*-RSN, presumably more injury, than DA, the responses of microglia were expected. In contrast, the seemingly contradictory responses of astrocytes observed may relate to that PA, but not DA, increases mRNAs encoding structural proteins (Tetzlaff et al., '90) and maintains or increases the dendritic profuseness of surviving RSN.(supported by NSC 81-0412-B002-03 & 82-0142-B002-036, Taiwan, R.O.C.)

767.6

MODERATE TRAUMATIC BRAIN INJURY ALTERS MUSCARINIC CHOLINERGIC RECEPTOR AFFINITY AND BINDING SITES IN RAT HIPPOCAMPUS AND NEOCORTEX. J.Y. Jiang, B.G. Lyeth*, L.C. Vaughan, L.W. Jenkins, T.M. Delahunty, L.L. Phillips, E.T. Belardo, R.J. Hamm. Division of Neurosurgery, Virginia Commonwealth University, Richmond, Virginia 23298

Excessive activation of muscarinic cholinergic receptors significantly contributes to the pathophysiological consequences of traumatic brain injury (TBI) (Lyeth et al.,1988). We examined the muscarinic cholinergic receptor binding in rat hippocampus and neocortex following moderate (1.9 ATM) fluid percussion TBI. Three groups were examined: Sham TBI, 1 hr post-TBI, and 24 hr post-TBI.

The affinity (Kd) and binding sites (Bmax) of muscarinic cholinergic receptors were determined by [^{3}H]QNB-binding methods (Yamamura 1974). Specific binding exceeded 95% at all [^{3}H] QNB concentrations. In hippocampus, Kd values were higher in 1 hr post-TBI rats (0.201 ± 0.018 nM) and 24 hr post-TBI rats (0.192 ± 0.018 nM) compared to shams (0.158 ± 0.012 nM). Bmax values were also higher in 1 hr post-TBI rats (492.6 ± 21.8 fmol/assay) and 24 hr post-TBI rats (450.8 ± 28.0 fmol/assay) compared to shams (397.6 ± 19.4 fmol/assay). In neocortex, Kd values were higher in 1 hr post-TBI rats (0.105 ± 0.01 nM) and 24 hr post-TBI rats (0.097 ± 0.002 nM) compared to shams (0.089 ± 0.01 nM). Bmax values were also higher in 1 hr post-TBI rats (227 ± 26 fmol/assay) and 24 hr post-TBI rats (218 ± 15 fmol/assay) compared to shams (189 ± 19 fmol/assay). These results show that traumatic brain injury decreases the affinity and increases binding sites of muscarinic cholinergic receptor in hippocampus and neocortex, which may be related to the pathophysiology of traumatic brain injury.

Supported by NIH NS 29995, NS 12587.

767.7

MUSCARINIC AND METABOTROPIC GLUTAMATE RECEPTOR-STIMULATED INOSITOL PHOSPHATE PRODUCTION IS ENHANCED IN RAT HIPPOCAMPUS 15 DAYS FOLLOWING MODERATE TRAUMATIC BRAIN INJURY. T.M.DELAHUNTY*, L.W.JENKINS, L.L.PHILLIPS, R.J.HAMM, J.Y.JIANG, B.G.LYETH. Division of Neurosurgery, Medical College of Virginia, Richmond, VA 23298.

We have previously reported that carbachol-stimulated inositol phosphate production is enhanced by up to 200% at I hour following both mild (1 atm) and moderate (1.9 atm) traumatic brain injury (TBI). We now extend that finding to 15 days following moderate TBI, at which time the response to carbachol is enhanced by 27%. In addition, at this time point we measure a 19% enhancement in inositol phosphate generation stimulated by the metabotropic glutamate receptor agonist, trans-ACPD. Male Sprague Dawley rats were injured by fluid percussion impact following isoflurane anaesthesia and after 15 days survival were sacrificed. Hippocampal miniprisms were prepared from injured and sham-injured controls, labelled with [^{3}H]-myoinositol and challenged with 50μM Carbachol, 250μM Glutamate, trans-ACPD, AMPA, or NMDA. Reactions were terminated after 1 hour and inositol phosphates extracted and separated on dowex columns. The response to glutamate was minimally enhanced and no response to AMPA or NMDA was observed. These data suggest that at 15 days post-TBI, both muscarinic and glutamate receptors linked to PI hydrolysis remain hypersensitive. These biochemical abnormalities may contribute to deficits in memory present at 15 days after moderate fluid percussion TBI. Supported by NIH grants NS 12587 and NS 19550.

767.8

IL-1α, IL-6 AND TNFα IMMUNOREACTIVITY FOLLOWING STAB INJURY TO THE RAT NEOSTRIATUM. J. T. Hansen*, K. Sakai, and J. Finkelstein. Departments of Neurobiology and Anatomy and Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642.

Following neural transplantation, the host brain undergoes an inflammatory reaction in response to both the mechanical trauma of grafting and the implantation of cells. The acute reaction of the host brain involves a cascade of events that includes a breakdown in the blood brain barrier, the infiltration of blood-borne cells, and the activation of microglia and astrocytes. This response is probably mediated by cytokine and neurotrophic molecules released at the site of injury. To study the early events in this injury response, we examined adult rat brain sections 24 and 48 hours following stereotactic stab wound penetrations into the neostriatum. Sections were stained with antibodies to the inflammatory cytokines IL-1α, IL-6 and TNFα. All sections showed significant immunostaining in monocytes adjacent to the injury site. Vascular cuffing was evident adjacent to and some distance from the stab site. At 48 hours, IL-6 immunostaining was present in astrocytes, and the overall staining intensity of IL-1α appeared to diminish compared to 24 hours. Interestingly, faint IL-1α and TNFα immunostaining was observed in large neurons of the cerebral cortex adjacent to the stab site. The presence of an inflammatory cytokine network in the injured brain may play a key role in the host brain's response to the trauma of neural grafting, irrespective of the presence of implanted cells which may elicit its own reaction. How these cytokines affect a host sprouting response to neural implantation remains to be determined. Additionally, the possibility that neurons themselves may release cytokines suggests an intriguing role for them, perhaps separate from that played by activated microglia and astrocytes. (Supported by NS 25778)

767.9

EXPERIMENTAL TRAUMATIC BRAIN INJURY INDUCES EXPRESSION OF INTERLEUKIN-1ß mRNA IN THE RAT BRAIN. L. Fan*[1], K. G. Perlman[1], P. C. McDonnell[2], P. R. Young[2], F. C. Barone[3], G. Z. Feuerstein[3], D. H. Smith[1], T. K. McIntosh[1]. Div. of Neurosurgery, Univ. of Pennsylvania[1], Philadelphia, PA 19104 & Dept. of Molecular Genetics[2] and Pharmacology[3], SmithKline Beecham Pharmaceuticals, King of Prussia, PA 19406.

Because cytokines have been shown to be induced following central nervous system injury, in the present study we examined the expression of interleukin-1ß (IL-1ß) mRNA in specific brain regions following experimental traumatic brain injury (TBI) in rats. Adult Sprague-Dawley rats (n=42) were anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to lateral fluid-percussion (FP) brain injury of moderate severity (2.4 atm.) or "sham" treatment (surgery with no injury). Animals were sacrificed at 1, 6 and 24 hr post injury, brains removed and ipsilateral (injury site) left cortex (LC), contralateral right cortex (RC), ipsilateral adjacent cortex (LA), contralateral adjacent cortex (RA), left hippocampus (LH) and right hippocampus (RH) were dissected. Total RNA was isolated and Northern blot hybridization was performed and quantitated relative to an IL-1ß positive RNA (R=100). High expression of IL-1ß mRNA was observed in LH (R=26.4), LA (R=23.2) and LC (R=22) on the injury side 1 hr following injury. IL-1ß mRNA was also found in LC (R=4.2), LH (R=3.8) and LA (R=3.6) 6 hr and in LA (R=1.9) 24 hr following injury. On the contralateral side, only low expression of IL-1ß mRNA was observed in RA (R=5.5), RH (R=3.5) and RC (R=1.5) 1 hr following injury with no expression at later times. No IL-1ß mRNA was detected in any of the 6 brain areas at 1, 6, and 24 hr following sham surgery or in naive animals. These results indicate that following TBI, the expression of IL-1ß mRNA is stimulated in injured brain regions. Since IL-1ß is able to induce nerve growth factor (NGF) in brain, post-traumatic expression of IL-1ß might play a role in the regeneration of injured neurons via the release of NGF or other cytokines.

767.10

INTERLEUKIN-1 RECEPTOR ANTAGONIST PROTEIN (IRAP) ADMINISTERED FOLLOWING PENETRATING CORTICAL INJURY REDUCES MICROGLIAL RESPONSE WITHOUT DIMINISHING REACTIVE ASTROCYTOSIS. S.T. DeKosky*, S.D. Styren, M.E. O'Malley, C.H. Evans, P. D. Robbins. Depts. of Psychiatry, Neurology, Orthopedic Surgery, Molecular Genetics and Biochem, Univ. of Pittsburgh Sch. of Med. and Western Psychiatric Inst. & Clinic, Pittsburgh, PA 15213.

Astrocytes and microglia become reactive and may increase in number following brain injury. To examine the role of IL-1 in reactive gliosis, we anesthetized rats and induced a stereotatic cortical stab wound with a needle. Group 1 received 50,000 rabbit synovial fibroblasts transfected with a replication-deficient murine leukemia virus, with the viral envelope gene replaced by the IRAP gene. Groups 2 received the same number and type of non-transfected fibroblasts; Group 3 received the vehicle. Three days later all rats were immunohistochemically assessed for reactive microglia (OX-42) and astrocytic changes (GFAP). In the vehicle and non-transfected groups, reactive microglia were intensely OX-42 positive in ipsilateral cortex and in underlying hippocampus. Equivalent regions in IRAP-injected brain contained significantly fewer microglia, most of which were morphologically unreactive. All groups exhibited intense astrocytic staining for both GFAP in the ipsilateral cortex and hippocampus, with slightly less intense staining in the lesion penumbra (relative to equivalent contralateral regions or non-operated animals). The suppression of inflammatory cells and presumably IL-1 may be significant in reducing IL-1-mediated edema and other adverse effects of IL-1 following brain injury, and illustrates the potential role for gene therapy in human brain trauma.

767.11

DIMINISHED MAP2 IMMUNOREACTIVITY FOLLOWING CORTICAL IMPACT BRAIN INJURY. W.C. Taft*, P. Varahrami, J. Bao, R.L. Hayes and C. E. Dixon. Dept. Neurosurgery, Univ. Texas-Houston Health Science Center, Houston TX 77030.

MAP2 antigenicity decreases following ischemic insults and excitotoxic lesioning in CNS, implicating aberrant activation of neuronal proteases as a common feature of CNS injury. We have recently reported that moderate levels of traumatic brain injury (TBI) produced by midline fluid percussion injury, which produces no overt histopathological cell death in the hippocampus, cause a 44.3% decrease in hippocampal MAP2 levels measured 3 hrs post-injury (Taft et al., *J. Neurotrauma 9:* 281, 1992). In this report we investigated the effects of a more severe magnitude of TBI on MAP2 immunoreactivity, employing a lateral cortical impact injury device that produces significant cortical neuronal death at the contusion site (Dixon et al., *J. Neurosci. Meth. 39:* 253, 1991). We observed a 68.0% loss of hippocampal MAP2 immunostaining at 3 hrs post-injury. The loss of MAP2 protein levels was greater in ipsilateral hippocampus (74.8%) than in contralateral hippocampus (61.2%). In contrast to the absence of cortical MAP2 loss following moderate fluid percussion injury, we report significant (30.9%) MAP2 loss in cortices from severely injured animals. Again, MAP2 loss was greater in ipsilateral cortex (59.1%) than on the contralateral side (2.7%). We conclude that increased magnitudes of TBI produce increased levels of MAP2 protein loss in hippocampus, a region which is particularly vulnerable to neuronal death after CNS injury. Further, the presence of MAP2 loss following severe TBI in cortical samples associated with neurons destined to die at the contusion site may be a harbinger of pathological destruction of the cytoskeleton which these neurons cannot survive. Supported by NIH NS-21458.

767.12

INDUCTION OF HEAT SHOCK PROTEIN (hsp72) AND c-*fos* mRNA FOLLOWING FLUID PERCUSSION BRAIN INJURY IN THE RAT. R. Raghupathi, F.A. Welsh, E. Flamm* and T.K. McIntosh, Div. of Neurosurgery, Univ. of Pennsylvania, Philadelphia, PA 19104

To better understand the cellular response to traumatic brain injury (TBI), the expression of hsp72 and c-*fos* mRNA was evaluated using *in situ* hybridization in rats subjected to lateral fluid percussion brain injury of moderate severity (2.2 atm). Two hours after injury, a mild and patchy induction of hsp72 mRNA was observed in the cortex ipsilateral to and surrounding the site of maximal injury; by 6 hrs, expression of mRNA was confined to the cortical layers immediately below the site of necrosis. No expression was noted in the hippocampal and other subcortical regions at either 2 hrs or 6 hrs post injury. In contrast, at 2 hrs, robust expression of c-*fos* mRNA was observed throughout the ipsilateral cortex, except at the site of necrosis, suggestive of spreading depression; interestingly, a low level of induction was also observed in the contralateral cortex. In addition, mild, bilateral induction of c-*fos* mRNA was noted in the selectively vulnerable CA2/CA3 subfields of the hippocampus, and in the pyramidal cells of the dentate gyrus; induction was also observed in the ipsilateral thalamus. By 6 hrs, a low level of c-*fos* mRNA was noted in the ipsilateral subcortical white matter and ependymal cells; c-*fos* in other regions had returned to basal levels. Levels of both hsp72 and c-*fos* mRNA had returned to baseline by 24 hrs. These results suggest that stress protein genes and immediate-early genes may influence cellular response to TBI. (This study was supported, in part, by a VA Merit Review grant 74R to TKM).

767.13

TEMPORAL AND REGIONAL PROFILE OF C-FOS mRNA EXPRESSION AFTER CORTICAL IMPACT INJURY IN RAT BRAIN. K.Yang*, J.J.Xue[2], W.C.Taft[1], J.Bao[1], C.E.Dixon[1], C.Y.Hsu[2], R.L.Hayes[1]. Neurosurgery[1], UT Houston Health Science Center, Houston TX 77030; Restorative Neurology[2], Baylor College of Medicine, Houston, TX 77030.

We have reported that hippocampal protein kinase C (PKC) activity increase following moderate levels of traumatic brain injury (TBI: Yang et al., 1992). PKC activation may mediate immediate early gene expression, and immunostaining has shown increased c-fos protein positive neurons in rat hippocampus after TBI (Phillips et al., 1991). Thus using *in situ* hybridization methods, we initiated the study of c-fos mRNA expression in a lateral cortical impact model of more severe TBI (Dixon et al., 1991). Sprague-Dawley rats were subjected to cortical impact or sham injury. At 20 min, 1 h, 3 h and 4 h after injury or sham injury, animals were anesthetized and sacrificed by intracardiac perfusion with 4% paraformaldehyde. After cryoprotection in 10 % sucrose, rat brains were sectioned coronally at 20 µm on a cryostat. Hybridization was performed with ^{32}P-labeled RNA probes at 56°C. After washing, the slides were exposed to KODAK XAR-5 film. TBI induced c-fos mRNA in the ipsilateral cortex and hippocampus at 20 min, 1 h, 3 h and subsided at 4 h after injury. TBI also induced c-fos mRNA in the contralateral hippocampus at 1h post injury, although the induction was less than in the ipsilateral hippocampus. These data indicate that more severe levels of TBI can produce regionally restricted increases in c-fos mRNA. The prominent bilateral involvement of the hippocampus is consistent with the preferential vulnerability of the hippocampus to mechanical injury. (Supported by NIH grant NS21458 to RLH).

767.14

INCREASED BASIC FIBROBLAST GROWTH FACTOR mRNA FOLLOWING CONTUSIVE SPINAL CORD INJURY. P. Follesa, M. Riva, J.R.Wrathall and I. Mocchetti*. Dept. Anatomy & Cell Biology, Georgetown Univ. Sch. of Med. Washington DC 20007.

Neurotrophic factors appear to be crucial for the survival and potential regeneration of injured neurons. Injury of the peripheral nervous system results in the induction of a number of neurotrophic molecules. Less is known about the response of central nervous tissue to injury. We have examined changes in levels of mRNA for three trophic factors, basic and acidic fibroblast growth factor (bFGF and aFGF), and nerve growth factor (NGF), after a standardized incomplete thoracic contusive spinal cord injury (SCI). RNase protection assays showed a rapid increase (three-fold) in the content of bFGF mRNA by 6 hours after SCI in tissue that included the injury site. No effect of injury was seen in segments of cervical or lumbar cord. bFGF mRNA at the injury site remained significantly increased at 1 and 7 days after SCI. Further, at 7 days, the increase was anatomically restricted to the rostral portion of the injury site suggesting the involvement of specific pathways in the maintenance of high levels of bFGF mRNA. No change in the levels of aFGF mRNA was seen after SCI. Similarly, no difference in the expression of the mRNA for NGF or its high affinity receptor (*trk*A), were observed at 6 hr, 1 or 7 days following SCI. Our observation of a specific effect of SCI on bFGF mRNA expression supports a speculative hypothesis that bFGF may play a role in the partial recovery of function seen following incomplete contusive spinal cord injury. Supported by American Paralysis Association grant MB1-9104-1, by HHS grants NS 29664 and NS 28130.

767.15

INCREASED PHOSPHORYLATION OF CREB FOLLOWING TRAUMATIC BRAIN INJURY (TBI). P. K. Dash*[1], A. N. Moore[1], D. Ginty[2], C. E. Dixon[3]. [1]Depts. of Neurobiology and Anatomy and [2]Neurosurgery, University of Texas Houston-Health Science Center, Houston, Texas, and [3]Dept. of Microbiology and Genetics, Harvard Medical School, Boston, Mass.

Acute pathophysiologic responses following experimental TBI in rodents include 1) acute neurotransmitter release, 2) excessive neuronal excitation, and 3) physical alterations to neurons. These changes can alter intracellular signal transduction pathways which may contribute to chronic neuronal disfunction. The cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) mediates expression of several immediate-early genes including *c-fos* in response to agents that increase intracellular concentrations of cAMP or Ca^{2+}. These signals trigger phosphorylation of CREB on Ser^{133}. This phosphorylation event leads to activation of transcription of genes containing CREB binding sites. To identify the signalling pathways that trigger gene expression following TBI, we have used antibodies which specifically detect phosphorylated CREB. Increased phosphorylation of CREB was examined at 15 min, 30 min, 1 hr and 3 hr following cortical impact injury (6 meters/sec, 1.7 mm compression) in Western blots. Phosphorylation of CREB was increased in the cortical and hippocampal areas 15 min after cortical impact and decreased to basal levels after 30 min. This finding was corroborated by gel-retardation assays and immunohistochemistry. Moreover, the expression of immediate early genes (e.g. c-Fos) were enhanced subsequent to CREB phosphorylation. These data suggest that chronic post-traumatic disturbances may be related to CREB mediated gene activation. Supported in part by CDC-R49 CCR606659.

767.16

THE EFFECTS OF VARYING DOSES OF CDP-CHOLINE ON RECOVERY OF SPATIAL MEMORY FUNCTION FOLLOWING CONTROLLED CORTICAL IMPACT INJURY IN RATS. S. J. Liu, C. E. Dixon, and R. L. Hayes*. Dept. Neurosurgery, Univ. Texas-Houston Health Science Center, Houston, Texas 77030.

Recent findings suggest that chronic spatial memory deficits following experimental traumatic brain injury may, in part, be attributable to deficits in central cholinergic neurotransmission. Supplementing central cholinergic tone chronically may accelerate recovery of spatial memory deficits following TBI. The purpose of this study was to examine the effects of varying doses of CDP-choline, a precursor to choline, on post-traumatic spatial memory performance. A total of 50 rats were randomly assigned to one of five treatment groups. The treatment groups (n=10 each) included injured animals that received one of three doses of CDP-choline (100 mg/kg, 300 mg/kg, or 500 mg/kg) or an equal volume of saline. Ten additional sham animals were surgically prepared, but not injured. Starting one day after injury, drug treatments were administered daily. CDP-choline was administered by intraperitoneal injection 15 minutes prior to spatial memory testing. Spatial memory performance was assessed using the Morris water maze on days 14-18 post injury. The data demonstrates that animals treated with 100 mg/kg of CDP-choline had significantly better post-traumatic spatial memory performance that all of the other injury treatment groups. Additionally, animals treated with the 100 mg/kg dose of CDP-choline did not differ significantly from uninjured controls. These observations indicate that post-injury spatial memory deficits are amenable to pharmacological intervention and that cholinergic supplementation post-injury improves neurobehavioral outcomes. Supported by CDC-R49 CCR606659 to CED.

767.17

CAUDATE DOPAMINE LEVELS AFTER CORTICAL CONTUSION IN THE RAT. R. L. Sutton* Surgery Dept., Hennepin County Medical Center and Dept. of Neurosurgery, Univ. of Minnesota, Minneapolis, MN 55415 U.S.A.

It has been reported that peripheral catecholamines are elevated after traumatic brain injury (TBI) and increased dopamine (DA) contributes to striatal damage after ischemia. Microdialysis combined with HPLC was used in halothane-anesthetized rats to determine if DA is acutely elevated in regions of the caudate that atrophy 1 month after TBI. Dialysis probes were inserted bilaterally into the head of the caudate nucleus and dialysates were collected at 20 min intervals. Mean (± SD) basal levels of DA ranged from 1126 ± 207 to 1178 ± 259 pg. After a 2 hr baseline probes were removed, 1/2 of the animals (N=4) received TBI to the right cortex, probes were reinserted, and sampling continued for 4 hr. The DA levels in initial and final samples post TBI/reinsertion of probes, expressed as percent of basal levels of DA, are shown below.

	20 minutes		240 minutes	
Group	Right	Left	Right	Left
Sham:	89± 22.9	96±12.7	105±11.7	93±17.3
TBI:	88±25.1	110±14.5	108±4.3	105±11.7

Results indicate that: 1) caudate DA is not significantly altered acutely after TBI and, 2) probes did not disrupt the blood-brain barrier and/or TBI did not alter peripheral DA release.
Support: U.S. Army Grant DAMD17-91-Z-1006 and Minneapolis Medical Research Foundation.

767.18

DIRECT ELECTRON PARAMAGNETIC RESONANCE (EPR) EVIDENCE OF FREE RADICAL GENERATION IN CLOSED HEAD INJURY IN RATS. H. Goldman*, S. Sen, M. Morehead, S. Murphy and J.W. Phillis. Department of Physiology and Pharmacology, Wayne State Univ. Sch. of Med., Detroit, MI 48201.

Traumatic head injury is one of the important causes of mortality and morbidity. The pathogenesis of the underlying brain dysfunction is poorly understood. Recent data have suggested that oxygen free radicals play a key role in the primary and secondary process of acute traumatic head injury. We are the first to report direct electron paramagnetic resonance (EPR) evidence of hydroxyl radical (·OH) radical generation in closed-head injury of rats. Moderate brain concussion was produced by controlled and repeatable mechanical, fixed, closed-head injury. Cortical cups were placed over cerebral hemisphere within 20 min of the concussion; perfused with artificial cerebrospinal fluid (aCSF) containing the spin trap agent pyridyl-N-oxide-t-butylnitrone (POBN, 100mM) and superfusate samples collected at 10 minute intervals for a duration up to 120 min post brain trauma. In addition POBN was administered systemically (50 mg/kg body wt.) 10 min pre trauma to improve our ability to detect free radicals. EPR analysis of the superfusate samples revealed six line spectra (α_N=15.4 G and α^{β}_H= 2.5 G) characteristic of POBN-OH radical adducts, the intensity of which peaked 40 min post trauma. The signal was undetectable after 120 min. Administration of α-phenyl-tert-butyl-nitrone (PBN) a spin adduct forming agent systemically (100 mg/kg body wt. IP 10 min prior to concussion) and topically (100 mM) in aCSF completely attenuated the ESR signal, suggesting its possible role in treatment of brain trauma.

767.19

NEURONS SURVIVE FOR DAYS IN CONTUSED RAT CORTEX. D.M. Feeney*, H.M. Bramlett, and A.E. Kline. Depts. of Psychology & Physiology, University of New Mexico, Albuquerque, NM 87131.

Traumatic brain injury (TBI) can produce a focal cortical contusion causing a cavitation which in the rat first appears 1 day after TBI and expands over the subsequent 15 days. Impact force determines volume and general shape of the cyst which is stable for months (Brain Res., 211, 67-77,1981). We tested the hypothesis that in the cortex which evolves into a cavitation, many neurons survive the impact and die days later as the cyst expands. All rats received a 400g/cm impact under halothane anesthesia, brains removed after perfusion under barbituate, and 40µ coronal sections cut on a cryostat. Sections were stained by Fink-Heimer, thionin or counterstained with acid fuschin and thionin. Six rats were killed at 25-30 days after TBI and a rectanglar sampling grid (3 mm long) drawn at the center plane of impact fitting within the necrotic area common to all rats. The grid was then superimposed on coronal sections from rats killed at 6, 24, 48 and 72 hrs. The proportion of apparently normal cortical neurons (not argyrophilic, nor acidophilic but having well stained Nissl substance) was rated for each of three 1 mm grid blocks of cortical lamina. In 14 of the 15 animals studied at least one of the nine sample points had 25-100% of neurons rated as normal. At 6-24 hrs after TBI there was greater neuronal death in the upper lamina and lateral samples than other grid points. At 72 hrs after TBI a few neurons appeared to be in an early stage of argyrophilic reaction. The data suggests that secondary cell death in contused cortex begins days following TBI.
Supported by NIH MBRS Grant SO6RR08139-19.

767.20

IDENTIFICATION AND CHARACTERIZATION OF APOLIPOPROTEIN E IN PERIPHERAL NERVE DAMAGE AND ALZHEIMER'S DISEASE. D.M. VanderPutten[1,2*], B.M. Cameron[3], and C.R. Merril[2]. [1]Monoclonetics International Inc., Houston, TX 77027 [2]Laboratory of Biochemical Genetics, NIMH, Washington, DC 20032 [3]Baylor College of Medicine and St. Luke's Hospital Houston, TX 77067

Non-biased screening of plasma proteins by two dimensional gel electrophoresis from individuals suffering from nerve root compression due to low back syndrome was performed to test the hypothesis that molecular markers of nerve damage would be present. A polypeptide spot was found to be increased two to five fold over the concentration in normal control individuals. The apparent molecular weight (34-36kD), pI (5.7), immune reactivity with anti-apolipoprotein E antibodies and N-terminal amino acid microsequence confirmed the identity of this polypeptide as apolipoprotein E (Apo-E). We have shown that the elevated plasma levels of Apo-E are found in individuals suffering from nerve damage and chronic inflammation. Changes in Apo-E were also observed in neurodegenerative diseases of the CNS including Alzheimer's disease (AD). We have characterized Apo-E forms present in AD individuals and also confirmed previous observations of an over representation of the Apo-E4 phenotype in sporadic AD patients (16/28 AD patients vs 3/16 normal individuals).

768.1

TNF-α AND DIFFERENT KIND PERIPHERAL NERVE INJURIES. S. Zhao†, R. W. Beuerman‡, D. Nguyen‡, H. W. Thompson‡ and D. G. Kline†,* †Dept. of Neurosurgery, LSU Medical School and ‡Lab. of Molecular Biology of the Ocular Surface, LSU Eye Center, New Orleans, LA 70112.

The Sprague-Dawley rats were anesthetized by intraperitoneal injection of ketamine and peripheral nerve injury was made in two different manners: 1) Sciatic nerve of the rats were severed below the sciatic notch. The proximal and distal ends of the severed nerve were sutured to the adjacent muscle. Distance between the two ends were kept at about 0.5 mm. 2) The brachial plexus of the rats was isolated and avulsioned above the dorsal root ganglia. Control rats received same type of surgery except for lesions of the nerves. The rats were sacrificed 2 days, 5 days and 10 days postoperatively. The sciatic nerves in group I animals and spinal cord in group II animals were taken out. Total cellular RNA was obtained, slot blotted, and probed with ^{32}P labeled TNF-α cDNA. The results showed that TNF-α mRNA increased in the proximal and distal end of severed sciatic nerve, and in the C5 to C8 spinal cord compared to the controls. The rats with 5 days of nerve injuries showed a higher increase of TNF-α mRNA than those with 2 or 10 days.

768.2

ASSESSMENT OF COGNITIVE PERFORMANCE IN THE MORRIS WATER MAZE FOLLOWING TRAUMATIC BRAIN INJURY. S.M. Lee , F. Velarde, D.A. Hovda, A. Karimi and D.P. Becker.*Division of Neurosurgery, UCLA School of Medicine, Los Angeles, CA 90024

Morris Water Maze (MWM) task was used to assess cognitive performance following a lateral fluid-percussion (F-P) brain injury (2.3 - 2.6 atm) in rats under ethrane anesthesia. Performances were assessed in two ways: 1) cued task (goal platform raised 3 cm above water) tested animals' ability to swim toward a visible target and climb onto a platform (max search time =10 sec), and 2) spatial task (goal platform submerged) tested their ability to use extramaze cues to locate a hidden platform (max search time = 45 sec). Eight male rats (290-350 g) were trained before F-P injury until they reliably located a hidden platform in < 5 sec from all 4 release points ("criterion"). Animals reaching criterion were tested for their cued performance after which they were injured as described previously. Histological analysis indicated that at this level of injury severity, there was no detectable loss of neurons in the hippocampus or neocortex. The average number of trials needed to reach criterion before injury was 41.8 ± 12.7 (± SD). Following injury, animals were unable to locate the platform whether it was visible (cued task) or submerged (spatial task). The mean number of trials required for cued performance to return to preinjury levels was 21.0 ± 9.5 (~72 h after injury). Although spatial performance times after the recovery of cued task was significantly better than the first day of pre-injury training (8.4 vs. 28.4 sec, $p < 0.001$, Student's t-test) injured animals required an additional 31.9 ± 14.5 trials to again reach criterion. During this period of cognitive deficit, animals were primarily unable to maintain their spatial performance overnight (mean times for last trial vs. first ensuing trial the next day was 4.3 vs. 11.7 sec, respectively, $p < 0.001$). These results suggest that cognitive deficits may reflect a state of metabolic dysfunction in the hippocampus and neocortex following F-P injury.

(supported by NS30308, HD07416 and Lind Lawrence Foundation)

768.3

CHANGES IN THE PATTERN OF ACTIVITY-DRIVEN METABOLISM AFTER TRAUMATIC BRAIN INJURY (TBI) TO THE SOMATOSENSORY (S1) CORTEX IN ADULT MALE RATS. A. Dunn-Meynell* and B.E. Levin, Neurol.Svc., VA Med.Ctr., E.Orange, NJ 07018

We examined the brain's capacity to reorganize its functions after TBI. Anesthetized rats received open-cranium TBI by a rapid 3mm depression of the left S1 cortex using an air-driven rod of tip diameter 5mm. Weekly behavioral testing after TBI showed a persistent deficit in a lateralized motor/sensory task. At 2 months, the 2-deoxyglucose method was used to show the pattern of brain metabolism during stimulation of the right mystacial vibrissae. The range of glucose utilization was represented by pseudocolor imaging of the autoradiographs. The area of activation was defined as the percentage of the total S1 cortex area in which activation fell in the highest 75% of this range. TBI caused almost total degeneration of the left S1 cortex. In the intact right cortex, the area of activation (24.0±1.8%) was 2.75 times as great as that seen in the unstimulated controls with TBI (8.7±3.5%,P<.005) and 1.89 times that seen in the unstimulated right cortex of sham TBI controls (12.7±3.5%,P<.025). However, the area of activation in the stimulated, left cortex of sham TBI controls (25.9±5.8%) was similar to that in the intact right cortex of stimulated TBI rats, suggesting reorganization of somatosensory information processing after TBI. Supported by the Research Svc. of the DVA.

768.4

NEUROPSYCHOLOGY OF POST-TRAUMATIC STRESS DISORDER. A.M. Horton, Jr.* Psych Associates, Neuropsychology Clinic, Towson, MD, 21204

This paper discusses the role of neuropsychological testing in PTSD. After a brief review of the symptoms of PTSD, three perspectives or models of PTSD and neuropsychological impairment are outlined. The first postulate is that PTSD can cause neuropsychological impairment, or PTSD = NPI. The second postulate is the null version of the first; that is, PTSD does not cause neuropsychological impairment. Put briefly, PTSD ≠ NPI. The third postulate simply proposes that the two conditions may coexist in a non-interacting fashion; or simply put, PTSD can coexist with neuropsychological impairment, or PTSD + NPI. Each of these perspectives are discussed in turn. It is thought that a neuropsychological perspective will prove to be quite valuable as researchers attempt to further understand the complex nature of PTSD.

768.5

SPATIAL DISTRIBUTION OF VISUAL EVOKED POTENTIALS DURING STATES OF DECREASED AROUSAL AFTER BRAIN INJURY. **A.K.Sestokas*, D.Vancova, N.Knoller, Div. of Neurotrauma, Maryland Institute for Emergency Medical Services Systems (MIEMSS), Univ. of Maryland at Baltimore, Baltimore, MD 21201**

The purpose of this study was to determine how visual evoked potentials (VEPs) recorded over different regions of the scalp vary during states of decreased behavioral arousal secondary to brain injury. The study involved a retrospective review of VEPs from 1058 patients tested over a 4 year period (89% traumatic head injuries, 4% vascular lesions, 3% anoxic injuries, 4% other). Visual evoked responses to stimulation of each eye with 100 flashes of diffuse light at 1.1 Hz were recorded from 21 scalp locations using a linked ear reference. Grand average VEPs for each recording location were calculated from the evoked responses of individual patients grouped by their Glasgow Coma (GC) score (3 to 15). Peak amplitudes and total power were measured for each grand average VEP.

Responses recorded over different regions of the scalp showed nonuniform changes with decreasing GC level. Those response peaks recorded over the central and frontal regions between 150 and 300 msec after stimulus onset showed progressive attenuation as GC level decreased from 15 to 7, and were often missing at lower GC levels. By comparison, changes in peak amplitudes over the occipital regions were generally less consistent. The results suggest that spatially distributed VEPs are differentially sensitive to changes in behavioral arousal after brain injury and that evoked responses over the central and frontal regions of cortex may provide a more reliable index of arousal level than responses over the occipital regions.

768.6

ANALYSIS OF PREFRONTAL TISSUE VOLUMES FOLLOWING CLOSED HEAD INJURY IN CHILDREN AND ADOLESCENTS. M.A. Lilly, P. Berryhill, G.R. Hillman, H.S. Levin*, T.A. Kent, and D.B. Brunder. University of Texas Medical Branch, Galveston, Texas 77555

A volume averaging program written in C language was used to measure prefrontal tissue volumes (white matter (WM), gray matter (GM), and CSF) for a group of four children with severe closed head injuries (CHI) and four with mild CHI (ages 5.4 to 14.5 years) matched one-to-one for gender and age (±1 year). All of the children studied were without focal prefrontal lesions.

Our program classifies tissue types based on the intensity of pixels from MRIs acquired 3 months post-injury (Hillman GR et al. J Comp Assist Tomogr 15:640-646; 1991). Comparisons between the severity groups were made for WM, GM and CSF volumes for the left, right and total prefrontal area. Gray matter volumes were also examined for prefrontal subregions, including the orbitofrontal (OF) region (inferior, orbital and rectal gyri), dorsolateral (DL) region (middle and superior frontal gyri) and the cingulate gyrus (CG).

T-tests indicated a significantly greater amount of CSF (as a percentage of total prefrontal volume) in the severe group for the entire prefrontal region ($p<.01$), and for each hemisphere measured separately ($p<.01$). The severe group also tended to have lesser amounts of WM and GM as a percentage of the total intracranial volume as compared to the mild CHI group ($p<.10$). White matter differences were significant only for the left hemisphere ($p<.05$). While all differences in subregional gray (OF, DL, and CG) volumes were in the expected direction (subregional gray constituted a greater amount of the total prefrontal area in the mild group), none of these differences were significant.

Our present findings of substantially larger amounts of CSF in the severe group suggests greater neuropathology and tissue loss among the severely injured children, even in the absence of focal lesions. Follow-up analyses, which will focus on better delineating the extent and source of tissue loss and examining this subsequent relationship to neuropsychological outcome measures, have the goal of clarifying the functional specificity of developing prefrontal regions.

768.7

TRAUMATIC BRAIN INJURY ENHANCES THE AMNESIC EFFECT OF A GLUTAMATERGIC ANTAGONIST AND PRE-INJURY TREATMENT BLOCKS THE EFFECT. *B.R. Pike*, R.J. Hamm, D.M. O'Dell, B.G. Lyeth, and L.W. Jenkins.* **Depts. of Neurosurgery and Psychology, VA Commonwealth Univ., Richmond, VA 23284.**

This experiment examined the effect that traumatic brain injury (TBI) has on the amnesia produced by the NMDA antagonist MK-801. Rats were either injured at a moderate level of fluid percussion injury or were prepared for injury but not injured (sham injury). Nine days following injury or sham injury, rats were either injected with saline (Sham/Saline n=9; Injured/Saline n=9) or 0.1 mg/kg of MK-801 (Sham/MK-801 n=9; Injured/ MK-801 n=8) 30 min before being trained on a passive avoidance (PA) task. Twenty-four hr later, rats were tested for retention of the PA task. Results revealed that the low dose of MK-801 did not significantly effect the retention of the PA task in the sham injured group. In injured animals, MK-801 produced a profound amnesia compared to sham animals treated with MK-801 ($p<0.001$) and injured animals treated with saline ($p<0.001$). To further investigate the enhanced sensitivity to the amnesic effects of MK-801 that was exhibited by injured animals, injured (n=9) and sham-injured rats (n=8) were injected with 0.3 mg/kg of MK-801 15 min before injury. Nine days after injury, these animals were injected with 0.1 mg/kg of MK-801 30 min prior to training on the PA task. Twenty-four hr later all animals were tested for retention of the PA task. Results indicated that the animals treated with MK-801 before injury did not significantly differ from sham-injured animals in retention of the PA task. In addition, animals treated with MK-801 before injury and injected with MK-801 before PA testing did not differ from untreated injured animals injected with saline before PA testing. These findings indicate that MK-801 treatment before injury prevented the enhanced sensitivity to MK-801-induced amnesia that follows TBI.

Supported by NS12587

768.8

A NEW NON-IMPACT MODEL OF EXPERIMENTAL BRAIN INJURY IN THE RAT. M.S. Grady*, T.J. Stewart, D.O. Maris, M.A. Howard, R.H. Schmidt. Dept. of Neurological Surgery, Univ. of Washington, Seattle, WA 98104.

Diffuse axonal injury (DAI) in human traumatic brain injury (TBI) is associated with prolonged coma, severe cognitive deficits, and high mortality. While angular acceleration of primate heads accurately models DAI, current rodent models utilize cortical impact or fluid percussion and do not produce either extended unconsciousness or extensive DAI.

In an effort to model DAI in rodents we developed a device to rapidly and precisely accelerate a rodent head in the coronal plane with the center of rotation adjustable through different levels of the head and neck. Animals are anesthetized with halothane, intubated, and subjected to average tangential accelerations of hundreds of G's through 90 degrees centered at the interaural line (acceleration is measured 1 cm from axis of rotation). Animals were ventilated to pCO_2 levels of 35 - 40 mm Hg before injury. Mild to moderate injury was seen with hypotonicity and unresponsiveness lasting from 7 to 65 minutes. Animals subjected to larger forces consistently showed longer periods of unconsciousness with a corresponding longer loss of pinna, corneal, paw pinch and righting reflexes. Some animals showed occasional extensor spasms and transient dystonic intorsion of the lower extremities. After awakening, all animals demonstrated a period of incoordination, circling behavior, and weakness which was largely resolved in 24 hours.

Sparse axonal retraction balls were seen in the corpus callosum of animals subjected to larger accelerations with a corresponding longer period of unconsciousness. Through future design modifications we will determine if greater accelerations are capable of producing longer periods of unconsciousness and if the typical histopathological changes of DAI can be produced.

768.9

COMBINED FLUID PERCUSSION BRAIN INJURY AND ENTORHINAL CORTICAL LESION: A NEW TRAUMA MODEL FOR ASSESSING BEHAVIORAL MORBIDITY AND SYNAPTIC PLASTICITY. **L.L. Phillips*, B.G. Lyeth, E.T. Belardo and J.T. Povlishock.** **Div. of Neurosurgery and Dept. of Anatomy, Medical College of Virginia, Richmond, VA 23298.**

Laboratory studies suggest that excitotoxicity and deafferentation can contribute to long-term morbidity following human head injury. Since no current animal model of traumatic brain injury (TBI) combines excitotoxicity and deafferentation, we developed a rat model combining excitotoxicity of fluid percussion TBI with subsequent entorhinal cortical (EC) deafferentation. Moderate TBI was induced first in each rat, and then 24 hrs later bilateral EC lesions were performed. Two experimental groups were utilized to: 1) assess motor deficits (with beam balance, beam walk, rotorod testing) and cognitive deficits (with the Morris water maze) and 2) examine the brain morphology of the combined injury (with immunocytochemistry and electron microscopy). Control groups included TBI and EC alone, as well as surgical shams. Motor deficits were greater in the combined injury than in TBI alone, however, no significant difference was observed between the motor dysfunction after combined injury and that of EC injury alone. Cognitive deficits were more pronounced in the combined injury model relative to each individual insult and persisted for longer postinjury intervals (11-15 days postinjury). These cognitive deficits were additive for the two injuries, EC deafferentation producing deficits intermediate between TBI and combined insult. Morphological analysis of the dentate gyrus suggested that synaptic input was reduced after the combined insult, specifically at postlesion intervals coinciding with the greatest deficits in spatial memory. Our results suggest that axonal injury and its attendant deafferentation contribute to behavioral morbidity after TBI. Moreover, they indicate that this model can be used to study the interaction between excitotoxicity and synaptic plasticity. Support: BTF and NIH NS12587.

768.10

CEREBRAL HEMODYNAMIC EFFECTS OF CONTROLLED CORTICAL IMPACT INJURY IN RATS. L. Cherian, R.M. Bryan, Jr., C. Robertson and R.G. Grossman*; Dept. of Neurosurgery, Baylor College of Med., Houston, TX 77030.

The controlled cortical impact injury is widely used as a model of traumatic brain injury. There is little information about the effects of this type of injury on intracranial pressure (ICP) and cerebral blood flow. Twenty seven Long Evans rats were randomly assigned to the following groups: sham (n=10); moderate impact of 6 m/sec, 2 mm deformation (n=9); or severe impact of 6 m/sec, 3 mm deformation (n=8). The animals were anesthetized with 2% isoflurane and mechanically ventilated throughout the entire experiment. Physiological variables, including ICP from an intraparenchymal microsensor, blood pressure (BP), cerebral perfusion pressure (CPP), cortical perfusion contralateral to the impact measured with laser Doppler, rectal temperature, arterial blood gases, blood glucose and lactate concentrations, were monitored for 8 h. after the cortical impact. Both immediate and sustained hemodynamic effects of the cortical impact were observed, and the changes were more severe with the 3 mm deformation impact. The moderate impact had minimal effect on ICP, but the severe impact caused an immediate rise in ICP that peaked at 38± 9 mm Hg. The moderate impact caused a transient decrease in BP that recovered within seconds; severe impact caused a transient increase in BP followed by a decrease that was sustained throughout the entire 8 h. CPP was lowest immediately after the severe impact injury (29±3 mm Hg), and intermediate in the moderate impact injury (61±6 mm Hg) compared to the sham impact group (81±3 mm Hg). Cortical perfusion was reduced by an average of 52% in the severe impact group compared to 12% in the moderate impact group. There were no significant differences in arterial pO_2, temp., or blood lactate concentrations between the groups. From the 3rd h. after impact, the arterial pCO_2 was higher and pH was lower in the severe impact animals than in the other 2 groups even though all animals were ventilated.

768.11

DYNAMICS OF BLOOD FLOW AND IONIC SHIFTS DURING LOCAL COMPRESSION ISCHEMIA OF RAT CORTEX

AZ Hassan*, T. Moriya, W. Zhang, W. Young & M Chesler. Dept. of Neurosurgery NYU Med. Ctr., 550 1st Ave., NY, NY 10016.

Rapid, focal compression of cortex is a complication accompanying a variety of traumatic brain insults. We developed a model of such injury in which local blood flow (LBF) and microelectrode recordings may be obtained from within the compressed cortex. Long Evans rats were anesthetized, paralyzed & ventilated. Arterial blood pressure, rectal temp. & arterial blood gas variables were monitored. Pressure was applied to the cortex with intact dura, using an insulated, box-shaped (5 mm) brass cup with a perforated floor, attached to a micromanipulator. Laser Doppler and ion-selective microelectrode (ISM) recordings were obtained via the cup floor. ISM penetration of dura was facilitated by brief application of collagenase which had no effect on baseline $[K^+]_o$. Compression of 1, 2, & 3 mm over 30 sec. caused decreases in LBF to 32 ± 11, 17 ± 7 & 6.8 ± 2.0 % of control. LBF recovered in 1 hr. despite continued cortical displacement. Following 3 mm compression only, ISMs revealed marked extracellular ion shifts confined to the first 1000 µm. These consisted of an early (0-5 min.) rise in $[K^+]_o$ (57-71mM) which recovered in 1 hr., and a fall in $[Ca^{2+}]_o$ (to ~100 µM), and pH_o (to ~ 6.9) which recovered over 2 hrs. Atomic absorption analysis (after 1 hr) revealed a significantly greater [Na], and lower [K] in compressed vs contralateral cortex. Histology after 24 hr. survival revealed a local infarct of the upper cortex. Our results indicate that sustained compression produces transient, severe ischemia of the upper cortical layers with modest acidosis. This may favor injury mediated by NMDA receptors, in view of their high density in upper cortex and their steep sensitivity to extracellular pH.

Supported by NIH Grant NS 30309. .

768.12

LASER-DOPPLER FLOWMETRY MEASUREMENT OF SUBCORTICAL BLOOD FLOW AFTER FLUID PERCUSSION BRAIN INJURY IN RATS. S.L. Bolt[1], J.A. Bettencourt[1] and J.B Long*[2]. [1]Anesthesia & Op. Svc., Walter Reed Army Med. Ctr., and [2]Neuropharm. Br., Dept of Med. Neurosci., Div. of Neuropsych., Walter Reed Army Inst. of Res., Wash., D.C. 20307.

Compromised autoregulation of cerebral blood flow (CBF) following traumatic brain injury (TBI) has been proposed to play an important role in the secondary pathophysiological events leading to neuronal damage and persistent neurological impairment. Evaluations of CBF following TBI have been hampered by the inherent limitations of the various blood flow measurement techniques employed. Laser-Doppler flowmetry (LDF) uniquely permits the continuous monitoring of blood flow in discrete brain regions of rats that can then be neurologically and histopathologically evaluated. In these experiments we evaluated LDF as a means to monitor subcortical CBF during and following fluid percussion injury. Male S-D rats (300-400g, n=14), pretrained in beam walking and beam balancing tasks, were surgically prepared with a guide cannula for the LDF probe and a luer adapter for attachment to the fluid percussion device. After a 24 hour recovery, rats were anesthetized with halothane (1.0-1.5%) and a tail artery catheter was implanted. The LDF probe was stereotaxically placed in the hippocampus contralateral to the injury, and after baseline CBF and cardiovascular data were recorded, TBI (2.58 ± 0.15 atm) was induced. After a transient hyperemia at 1 minute post-injury, a 31% decrement in CBF was seen at 5 minutes and was sustained through 60 minutes post-injury. Consistent neurologic deficits were noted on both tasks, with partial recovery noted by 2 weeks post-injury. Histologic examination revealed moderate to severe cortical damage. These results indicate that LDF is a viable means to continuously monitor acute TBI-induced changes in CBF in rats maintained for subsequent long-term evaluation.

769.1

MAJOR DEPRESSION AND DYSTHYMIA FOLLOWING SEROTONIN REUPTAKE BLOCKADE: MODIFICATION OF STRESSOR PERCEPTION AND COPING STYLE. A. Ravindran*, J. Griffiths, C. Waddell, Y.D. Lapierre and H. Anisman. Royal Ottawa Hospital and Carleton University. Ottawa, Ontario, Canada.

Both major depression and dysthymia (chronic, low grade depression) were associated with increased reports of major life events, minor stressors (daily hassles), and feelings of loneliness, as well as the use of inappropriate coping strategies (i.e., emotion-focussed rather than problem-focussed coping). Treatment with serotonin reuptake inhibitors over an 8-week period resulted in a marked alleviation of the depressive symptoms in patients suffering from major depression, and to a slightly lesser extent in dysthymic patients. The effectiveness of the drug was unrelated to basal cortisol levels, cortisol suppression by dexamethasone, or stressor reactivity. The altered natural killer cell number associated with major depression was, however, reduced with the alleviation behavioral symptoms. The amelioration of the depressive symptoms were also accompanied by an increase in the frequency of positive events encountered coupled with a modest diminution in reports of minor stressors. Significantly, recovery from depression was associated with a marked change in coping style, such that patients were less likely to use inappropriate coping strategies (i.e., emotion-focussed coping). Data are considered in terms of the stress-depression topography, and the impact of antidepressants on coping styles.

769.2

EFFECTS OF AMPT IN DRUG-FREE DEPRESSED PATIENTS. H.L.Miller* P.L.Delgado, R.M.Salomon, M.Wong, D.S.Charney. Dept. of Psychiatry, Yale University & West Haven VAMC, West Haven, CT 06516.

A variety of biological studies demonstrate abnormal regulation of the norepinephrine (NE) system in patients with major depression, suggesting a role for NE in the etiology of depression. Brain NE and dopamine can be rapidly reduced by blocking synthesis with the tyrosine hydroxylase inhibitor alpha-methyl-para-tyrosine (AMPT). We gave AMPT to drug-free depressed patients to evaluate the effects on mood of decreasing catecholamine levels. **Method:** In an ongoing study, drug-free patients meeting DSM-III-R criteria for Major Depression were tested with AMPT and placebo. Testing was accomplished in a double-blind, placebo-controlled, crossover fashion, with random assignment to test conditions. Each test included baseline evaluation, two days with administration of either AMPT 1 gm TID or diphenhydramine 50 mg TID, and a follow-up day. Diphenhydramine was used as an "active placebo" because of the significant sedation associated with AMPT. Behavioral ratings of mood, including the Hamilton Depression Rating Scale (HDRS), and plasma for MHPG and HVA levels were obtained. **Results:** 2 of 17 drug-free depressed patients experienced an exacerbation of depressive symptoms (increase in HDRS score $\geq$ 10) during AMPT but not control testing. A trend of decreasing HDRS scores during diphenhydramine testing was noted, but the change was small and was not clinically apparent. These findings contrast with earlier reports of exacerbation of depression after AMPT, and with our own findings that depressed patients in remission after desipramine treatment relapse when challenged with AMPT. A larger sample and more complete data analyses will be presented.

769.3

DECREASED CORTICAL 5-HTT BINDING IN DEPRESSED HUMANS. Karley Y. Little*, F. Ivy Carroll, Gary E. Duncan. Dept. of Psychiatry, Univ. North Carolina, Chapel Hill, NC 27599

Earlier work in this laboratory suggested that there is a regional loss of 5-HT terminals in older depressed subjects as well as a decrease in citalopram affinity for the 5-HTT in younger subjects. In order to clarify if there are changes in affinity specific to one type of radioligand, binding to brain 5-HTT sites in depressed subjects was examined using [^{125}I]RTI-55, [^{3}H]citalopram, and [^{3}H]imipramine. Tissue was obtained at autopsy from 8 suicides meeting the DSM-3R criteria for major depression (HAM-D= 20 + 2.2, no antidepressant treatment), and 8 matched controls dying suddenly. Binding experiments were performed using quantitative autoradiography. Depressed subjects exhibited slightly decreased binding in several hippocampal and midbrain regions. However, cortical serotonergic binding was markedly decreased as determined with [^{125}I]RTI-55 (50 pM, non-specific +100 nM citalopram): Broadman area 10-medial aspect: .24 $\pm$ .08 vs .63 $\pm$ .14 nCi/mg tissue equivalents, p= .01; Broadman area 10-lateral aspect: down 62%, p= .03; Broadman area 11: down 62%, p= .006; temporal cortex-Broadman area 20: down 41%, p= .15. [^{3}H]citalopram binding (3 nM, non-specific +100 nM sertraline) was also decreased in these same cortical regions. Results of the [^{3}H]imipramine binding experiment and further experiments clarifying the nature of the binding changes are pending and will be presented.

769.4

IDENTIFICATION OF A POLYMORPHIC (GT)n MARKER NEAR THE HUMAN ß-ADRENERGIC RECEPTOR KINASE GENE. Mark H. Grossman*, James B. Littrell and Ronald Weinstein. Dept. of Pediatrics, Temple Univ. Sch. of Med., St. Christopher's Hosp. for Children, Phila., PA 19134.

Desensitization of the ß-adrenergic receptor may be caused by specific phosphorylation of the receptor through the protein kinase, ß-adrenergic receptor kinase (ßARK). This enzyme has the ability to recognize and phosphorylate the receptor only when the receptor is in its active conformation. Alteration of the normal process of receptor desensitization may be involved with a number of neurologic disorders. The identification of a highly polymorphic genetic marker [microsatellite/(GT)n repeat] nearby the ßARK gene may prove useful in studies of hereditary psychiatric and neurologic diseases. Several microsatellite-containing cosmid clones have been isolated through screening of a human cosmid library in pCos2EMBL vector with a partial cDNA for human ßARK. Fragments of these clones, designated 2B-2, 4B-2a, 5C-2, 6B-2 and 7B2a have been subcloned into M13mp19 vector and sequenced by the dideoxy chain termination method. Sequence analysis identified a stretch of DNA containing 15 perfect GT/AC repeats within the 5C-2 clone. Synthetic nucleotide primers (42% G/C content) flanking the repeat sequence were used for PCR amplification of DNAs from unrelated individuals in order to determine the usefulness of this (GT)n repeat by allelic typing. Typing of 32 individuals indicates alleles ranging in size from 118 to 128 bp. The calculated heterozygosity of this microsatellite is 76%, indicating that it will likely be a useful polymorphic genetic marker for future linkage studies in diseases such as bipolar illness, schizophrenia and panic disorder.

769.5

INHERENT VARIABILITY IN EEG: A MEASURE OF PSYCHOLOGICAL FUNCTIONING. N.Lexow, P.Zaleski, D.Topol, G.Maislin, A.Winokur*. Dept. of Psychiatry, Univ. of Pennsylvania, Philadelphia, Pa. 19104.

Variability is an essential feature underlying the brain's ability to respond to diverse challenges. We examined the EEG of 15 normal subjects (18-50 y.o.) during resting and activating states to identify patterns of variation within EEG rhythms across the neural axis. To determine if variation is altered in affective disorder a clinically depressed group, at three stages of Sertraline treatment -pretreatment(DP), acute posttreatment(DA), chronic postreatment(DC) - was also examined.

EEG was measured from 20 scalp electrodes (10-20 system) under four conditions - eyes closed, eyes open, verbal task, numerical task - at 9AM, 11AM, 1PM, and 3PM. EEG was Fourier analyzed into four spectral bands: delta (0.0-3.5Hz), theta (4.0-7.0Hz), alpha (8.0-13.0Hz), and beta (13.5 -23.5Hz). We assessed variation within each band, at each electrode site, by calculating the coefficient of variation (CV) of relative power across condition and time for each subject. Within each group, individual CVs were then averaged across subjects.

Our results revealed discrete patterns, in terms of range, distribution, and symmetry, of variation across the neural axis within each EEG rhythm. Furthermore, these patterns differed markedly across subject groups. For example, relative to controls, DP exhibited a severely reduced beta variability and increased delta variability. Additional group specific findings will be presented.

These observations suggest that the brain possesses a complex pattern of 'resonance' - a capacity for response variation revealed by perturbing the system - and that changes in this resonance may mirror changes in psychological functioning.

769.6

SELF INDUCED WATER INTOXICATION: PREVENTING HYPONATREMIA WITH ENALAPRIL. C.S. Sebastian*, D. Sinha and N.K. Gulati. Georgia Regional Hospital at Augusta, 3405 Old Savannah Road, Augusta, GA 30906

In an open trial, enalapril stabilized serum sodium levels in a patient with self induced water intoxication (SIWI). This controlled study investigated the prophylactic sodium stabilizing effect of angiotensin-converting enzyme (ACE) inhibitor enalapril in a normonatremic (serum sodium > 136 meq/L) subject with a known history of SIWI. Experiment I: Serum sodium levels were monitored on placebo or 10 mg enalapril/day, on a randomized, double blind, crossover basis for 21 days. Experiment II: At the end of each 21 days of treatment, the subject was challenged with a water load of 20 mls/kg. Serum sodium was obtained at hourly intervals for five hours. Results: In Experiment I, the mean serum sodium of 140.111 meq/L on enalapril was significantly higher than 137.25 meq/L on placebo (p=0.0015). In Experiment II, after water loading, the mean serum sodium on enalapril was 137.6 meq/L and on placebo 133.833 meq/L (p=0.0015).

Enalapril maintained higher serum sodium levels over 21 days and prevented hyponatremia when challenged with a water load.

769.7

NEURAL NETWORKS IN THE PATTERN RECOGNITION ANALYSIS OF FUNCTIONAL BRAIN IMAGES AND SYMPTOMATOLOGY.
J. D. Hidary*, J. Hsiao, R. Litman, C. Smyser, W. Hong, D. Pickar, ETB, NIMH, NIH, Bethesda, MD 20892.

We have previosly reported the utility of neural networks in the analysis of functional brain images. In this study we extend that work in two ways. First, we train and apply the networks on raw pixels as well as meaned ROI data. Second, we couple metabolic data with symptomatology as reflected in the subject's BPRS scores. As in our previous work, we utilize both O^{15} and F^{18}-deoxyglucose data of schizophrenic and normal subjects. We first place each PET scan segment into a canonical space so that group comparisons can be made without region of interest analysis. These scan values serve as input to various types of neural networks. Once each network is trained, a number of scans are input to test it. Finally, we extract the hidden layer and weighting information from the network to determine which patterns serve to discriminate pathological and non-pathological states and medicated and non-medicated conditions. This hidden information also allows us to find patterns of metabolic and behavioral coupling.

769.8

FUNCTIONAL IMAGING WITH SPECT OF COGNITIVE ACTIVITY IN SCHIZOTYPAL PERSONALITY DISORDER.
RL Trestman, M Losonczy, B Siegal, M Buchsbaum, E Pavell, LJ Siever*. Bronx VAMC & the Mt. Sinai School of Medicine, Bronx, NY 10468.

Schizophrenic patients have demonstrated a reduced rCBF (by SPECT) in the prefrontal cortex during prefrontal lobe cognitive activation with the Wisconsin Card Sorting Test (WCST) versus a control task; this contrasts with normal controls, who demonstrate an increase in prefrontal rCBF (Weinberger et al 1986, 1988). Schizotypal Personality Disorder (SPD) patients are hypothesized to be able to compensate for cognitive/ perceptual impairment by alternative strategies that are less efficient than those used by normal controls. Subjects are medically healthy males, with IRB informed consent, and are DSM-III-R SPD (n = 8) or normal controls (n = 8). Subjects are studied on 2 days, one week apart at the same time of day, with tasks counterbalanced. An automated WCST is used; 99mTc- HMPAO is infused and registered on a Medimatic 564. In this preliminary analysis, consistent with previous studies (Weinberger), the normal controls demonstrate an increase in frontal activity during WCST compared to the control task. However, in contrast with the findings of decreased prefrontal rCBF in schizophrenic patients (Weinberger), we find a greater increase in the SPD patients compared to normal controls. This takes place in the context of an increase in parietal and occipital flow in the SPD patients, compared to decreases in the controls. These results are consistent with the possibility that SPD patients use inefficient strategies to compensate for an underlying prefrontal neurocognitive deficit; these strategies may rely on increasing prefrontal rCBF, along with a recruitment of normally uninvolved cortical areas.

769.9

EVENT RELATED DESYNCHRONIZATION (ERD) ANALYSIS OF RHYTHMIC BRAIN FUNCTIONS IN NORMAL AND AUTISTIC PEOPLE.
J. Panksepp*, P. Lensing, W. Klimesch, H. Schimke, and M. Vaningan Dept. of Physiological Psychology, Univ. of Salzburg, Salzburg, Austria and Dept. of Psychology, Bowling Green State University, Bowling Green, OH 43403.

Past work has shown that event related desynchronizations (ERDs) are a sensitive index of brain information processing. ERDs and event related synchronizations (ERSs) within the alpha range of the EEG (8-13 Hz) were analyzed from 19-29 electrode arrays as a function of several forms of exteroceptive stimulation, including music and visual stimulation, in normal as well as several autistic individuals.

The music work analyzed topographic brain changes in adults to 1) repeated ~5 seconds of a single segment of music (opening bars of Beethoven's Fur Elise), and 2) to continuous pieces of happy and sad music presented in 10 sec on and 10 sec off patterns. ERDs and ERSs were quantified by averaging artifact-free data over a one second reference interval, and 4 second interval following music onset. The first procedure led to consistent and relatively selective left frontal ERDs in all 4 subjects. The second procedure led to consistent ERD's over many areas of the cortex in all subjects, with sad music having a stronger effect than happy music. ERDs, as opposed to ERSs were the predominant cortical response to music in adults.

Topographical brain responsivity of two autistic children and a normal child were evaluated in response to visual stimulation (0.25 sec flash of light or the mother's picture) before and after treatment with naltrexone (0.5 mg/kg). While visual stimulation produced widespread ERDs in the normal child, both autistic children exhibited predominantly ERS responses which suggested the failure of their brains to actively process incoming information. Two hours after naltrexone, pockets of ERDs were evident in frontal and occipital areas, suggesting that opioid blockade was facilitating brain functioning. This was confirmed by parallel behavioral analyses which indicated increased visual attention following naltrexone.

769.10

LOCUS COERULEUS NEURON NUMBER IS REDUCED IN SUICIDE VICTIMS.
M.D. Underwood, R.W Smith, J.J. Mann and V. Arango.* Laboratories of Neuropharmacology, University of Pittsburgh, Pittsburgh, PA 15213.

We sought to determine whether the increase in β-adrenergic receptor binding in the prefrontal and temporal cortex of suicide victims might be due to changes in the neuromelanin-containing, noradrenergic neurons of the locus coeruleus (LC).

Computerized mapping of neuron distribution and morphometry was performed using commercial software (MicroBrightfield, Inc.; Imaging Research, Inc.). Within a section, the x, y and z coordinate of pigmented neurons with nucleoli were identified and marked. Controls (n=8; ages: 19-65 y) and suicide victims (n=5; ages 23-75 y) were drug-free by toxicological screen and did not have known psychiatric or neurologic disorders. Bilateral LC volume, cell number, density and distribution were determined every 500 µm. In both groups, the right and left distribution of neurons was symmetrical, therefore the bilateral number of neurons was used in the analyses. LC length and volume in controls were 16.3±0.8 mm and 19.4±1.9 mm^3, respectively. The total number and density of neurons were 42,726±1,270 and 1,173±120 cells/mm^3. In the suicide group, neither the LC length (15.9±1.0 mm) nor the LC volume (25.6±3.6 mm^3) differed from controls. However, the total number (35,419±2,247; p=0.03) and density (761±132 cells/ mm^3) of LC neurons was lower than controls with the reduction localized to the middle third of the LC. The reduction in the number of neurons in suicide victims was independent of age. In suicide victims, neurons had a similar range in size as controls; however, at 2.5 mm rostral to the decussation of the trochlear nerves, but not at the level of the decussation or 5 mm caudal, neurons were smaller and had a shorter diameter than controls (p=0.05). Altered noradrenergic neurotransmission in suicide victims may be due to reduced numbers of, or pathological changes involving, noradrenergic neurons in the LC. Further studies are needed to determine whether this noradrenergic neuron loss is associated with major depression or suicidal behavior. (American Suicide Foundation, AA09004 and MH46745)

769.11

A MORPHOMETRIC STUDY OF MAGNETIC RESONANCE BRAIN IMAGES IN SCHIZOPHRENIA.
Jin-Sook Cheon*. Dept. of Neuropsychiatry, Kosin Univ. Sch. of Med., Pusan 602-702, Korea.

Since Johnstone et al(1976) had discovered ventricular enlargement in the CAT of chronic schizophrenics, structural brain abnormalities have been focus of interest in relation with the pathophysiology of schizophrenia. In this study, some neuroanatomical structures presumed to be involved in schizophrenia were evaluated in the MRIs of 13 schizophrenics in comparison with 15 neurotic controls. All MRI scans were obtained with a 1.0T SMT-100 scanner using high-resolution spin echo technique, with 5mm contiguous sections in sagittal plane(TR/TE=500ms/20ms) and 7mm contiguous sections in coronal plane(TR/TE=3000ms/90ms). Transferring the raw data stored in the magnetic tape to the optical disk, the area and the mean of the image signal intensity of free ROI including prefrontal cortex, corpus callosum, amygdala-hippocampal complex, septum pellucidum, thalamus, caudate and lentiform nuclei, and cerebellum were measured by the image analysis system. In schizophrenics, as compared with controls, the area of septum pellucidum was larger(P<0.05), and the areas of thalamus, amygdala-hippocampal complex and cerebellum were smaller(P<0.01). There were no significant differences in basal ganglia and corpus callosum. Prefrontal cotices were smaller in schizophrenics to be more prominent in the left (P<0.01). In conclusion, the structural brain abnormalities of schizophrenics seemed highly responsible for the pathophysiology of schizophrenia.

769.12

PREFRONTAL EEG FRACTAL STRUCTURE IN SCHIZOPHRENICS AND NORMAL CONTROLS.
R.E. Hoffman,* M.S. Buchsbaum, R.V. Jensen, and S.M. Guich. Yale Psych. Inst., Yale Univ. Sch. Med., New Haven CT 06520.

Fractal structure detected in normal and schizophrenic scalp EEG recordings was characterized. Twelve neuroleptic-free schizophrenic patients and 11 normal controls were studied. EEG recordings reflected two experimental conditions: (A) subjects passively viewing degraded visual continuous performance task stimuli, (B) subjects actively participating in this perceptual task. Laplacian filtered EEG epochs referable to prefrontal areas underwent dynamical analysis based on extensions of the Grassberger-Procaccia algorithm. Correlation exponents of EEG waveforms were compared to correlation exponents of their phase-randomized surrogates in order to estimate fractal structure (Theiler *et al* 1992). Schizophrenics demonstrated significantly greater fractal structure relative to normals during condition A ($p < .005$). Comparing condition B to condition A, task engagement produced significant increases in fractal structure in normals but not in schizophrenics ($p < .02$). These data suggest that: (i) perceptual task engagement is normally associated with increased fractal structure in prefrontal systems; (ii) schizophrenia may be a dynamical disorder whereby prefrontal systems are episodically "captured" by excessive, spontaneous fractal orderliness.

769.13

INCREASED N-CAM-IMMUNONOREACTIVE GLYCOPROTEINS IN THE CSF OF PATIENTS WITH SCHIZOPHRENIA AND OTHER NEUROPSYCHIATRIC DISORDERS.

M. Poltorak, J.R. Williams, J.J Hemperly, R. El-Mallakh, and W.J. Freed*. Neuropsychiatry Branch, NIMH Neuroscience Center at St. Elizabeths, Washington, DC 20032 and Becton Dickinson Research Center, Research Triangle Park, NC 27709

The neural cell adhesion molecule (N-CAM) is involved in cell-cell interactions during development and regeneration of the nervous system. Although the pathogenesis of schizophrenia is unkown, there are data which indicate that the disease may be due to neurodevelopmental disturbances. Using the Western blot technique and antibodies against human N-CAM, we found several N-CAM immunoreactive polypeptides of 70-180 kD MW in human CSF and serum. The heavy chains of human IgG (60-65 kD) were also recognized by the detection system, but were excluded from the assay on the basis of MW. We found significant increases in N-CAM immunoreactive glycoproteins in the CSF of schizophrenic patients, as compared to the CSF of normal controls. Neuroleptic treatment did not significantly change N-CAM concentrations in CSF. Additionally, in small samples, we observed indications of an increase in N-CAM immunoreactive glycoproteins of patients with bipolar mood disorder and Huntington's disease, but not in normal pressure hydrocephalus or in patients with Parkinson's disease and adrenal medulla grafts. The source of these N-CAM immunoreactive glycoproteins in CSF is unknown. It is possible that these CSF proteins are derived from CNS cells as secreted soluble N-CAM isoforms or degradation products. Nevertheless, our results are consistent with the possibility of defects in CNS synaptogenesis or morphogenesis in schizophrenia.

769.14

REDUCED BRAIN 5-HT AND ELEVATED NE TURNOVER AND METABOLITES IN BIPOLAR AFFECTIVE DISORDER

J.J. Warsh*, L.T. Young, S.J. Kish, K. Shannak, O. Hornykeiwicz. Section of Biochem. Psychiat., Clarke Institute of Psychiatry, Toronto, Ontario, Canada M5T 1R8.

Norepinephrine (NE), serotonin (5-HT), dopamine (DA) and their major metabolites were determined by HPLC with electrochemical detection in postmortem brain obtained from 10 subjects with antemortem histories meeting DSM-IIIR criteria for bipolar affective disorder. As compared with controls, no statistically significant differences were found in mean levels of NE, 5-HT, or DA in any brain area. We found, however: 1) significant increases in levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) in temporal cortex (+71%) and MHPG/NE ratios (an index of NE turnover) in frontal (+69%), temporal (+120%) and occipital (+66%) cortex; 2) significant decreases in 5-hydroxyindoleacetic acid (5-HIAA) in parietal cortex (-50%) and caudate nucleus (-41%), and in 5-HIAA/5-HT ratio in temporal cortex (-53%), caudate nucleus (-43%) and cerebellar cortex (-53%); and 3) significantly decreased (-39%) levels of homovanillic acid (HVA) in parietal cortex and HVA/DA ratios (-64%) in occipital cortex, in bipolar compared with control subjects. Taken together with previous findings regarding monoamines in postmortem brain of depressed and suicide subjects, decreased 5-HT metabolites and turnover may be common to major depression. The increased cortical NE turnover in bipolar disorder may reflect an imbalance in 5-HT-NE interactions posited to occur in affective disorders. It is also possible that the increased NE turnover is a more selective pathophysiological change in bipolar disorder, since such alterations have not been consistently demonstrated in earlier postmortem brain studies of depressed subjects or those who died by suicide.

NEUROTOXICITY III

770.1

PRETREATMENT WITH GM1 GANGLIOSIDE DID NOT PREVENT SOMAN-INDUCED BRAIN DAMAGE IN RATS.

G. P. Ballough, F. J. Cann, J. V. Wade*, C. E. Kling, J. S. Forster, S. Phann and M. G. Filbert. *Neurotoxicology Branch, Pathophysiology Division, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland 21010-5425.*

Soman (pinacolylmethylphosphonoflouridate) is an irreversible acetylcholinesterase (AChE) inhibitor which produces seizure-related brain damage in animals; extensive neuropathology has been observed in the pyriform cortex, amygdala, hippocampus and thalamus of rats and guinea pigs. There is evidence that these effects are initiated by an elevation in brain acetylcholine concentration, culminating in NMDA receptor mediated excitotoxicity. Pretreatment with gangliosides has been shown to produce "receptor abuse dependent antagonism" (RADA) of excitotoxicity in a variety of in vitro and in vivo models. In the present study, we examined possible ameliorative effects of ganglioside pretreatment on brain damage resulting from soman administration. Male Sprague-Dawley rats, chronically instrumented for electrocorticogram (ECoG) recordings, were given i.p. injections of either GM1 ganglioside (60 mg/kg; FIDIA) or isotonic saline 1 hour prior to 1.5 X LD_{50} soman (i.e., 100 µg/kg, i.m.). All rats were administered pyridostigmine (0.13 mg/kg, i.m., 30 min prior to soman), atropine methylnitrate (4 mg/kg, i.m., 5 min prior to soman), and 2-PAM (25 mg/kg, i.m., 5 min following soman administration). Control subjects were divided into three groups: those receiving GM1 as well as the adjunct treatments, those receiving the adjunct treatments but no GM1, and those receiving saline alone. ECoG recordings were monitored for 6 hours following soman or saline injections. Twenty-seven hours after soman/saline administration, rats were placed under deep pentobarbital anesthesia and euthanized via transcardial perfusion with 4% paraformaldehyde in 0.1M phosphate buffer. Sucrose-saturated brains were cryostat sectioned and processed for H&E, cresyl violet and AChE histochemistry, as well as GFAP and MAP-2 immunohistochemistry. Preliminary analysis of the results indicates that, under the above experimental paradigm, GM1 administration did not alter the incidence or severity of soman-induced seizures, nor did it diminish neuropathologies observed in the above brain regions of rats which underwent seizures.

770.2

LONG-TERM EXPOSURE TO CORTICOSTERONE AGGRAVATES AF64A-INDUCED CHOLINOTOXICITY IN RAT HIPPOCAMPUS.

D. Amoroso, A. El Tamer*, E. Wülfert, and I. Hanin. Loyola Univ. Chicago Sch. Med., Maywood, Il 60153 USA, and UCB s.a., Pharmaceut. R&D, Brussels, Belgium.

Intracerebroventricular (ICV) AF64A decreases choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) activities in hippocampus in a dose and time dependent manner (El Tamer et al., Neuropharm., 1992). Since an excessive exposure to glucocorticoids can damage hippocampal neurons (Sapolsky et al., J. Neurosci., 1985), we investigated whether long-term exposure to corticosterone (CORTS), prior to the ICV injection of AF64A in rats, further reduces ChAT and AChE activities in the hippocampus. Male Sprague-Dawley rats were bilaterally adrenalectomized and CORTS substituted as subcutaneous pellets in two groups of animals: low- (L-CORTS: 1x25 mg pellet) or high-level of CORTS (H-CORTS: 4x100 mg pellet). The table shows the time (2, 4 and 7 days post-injection) and dose (0.5 and 1.0 nmol/side, ICV) dependent effects of AF64A on ChAT and AChE activities in L- and H-CORTS animals. The values are expressed as percentages of inhibition of the enzymatic activity, compared to their respective vehicle-treated groups. Number of animals used: 5-8 per group.

	Inhibition of ChAT activity		Inhibition of AChE activity	
	0.5 nmol L-/H-CORTS	1.0 nmol L-/H-CORTS	0.5 nmol L-/H-CORTS	1.0 nmol L-/H-CORTS
2 days	0%/ 0%	0%/ 0%	0%/ 0%	0%/ 0%
4 days	21%/39%	0%/41%	0%/20%	0%/35%
7 days	0%/19%	14%/60%	0%/20%	14%/53%

These data indicate that: (1) long-term exposure to high levels of CORTS enhances the cholinotoxicity induced in hippocampus by AF64A, at doses of 0.5 and 1.0 nmol/side; and (2) high circulating plasma CORTS concentrations may impair hippocampal cholinergic neuronal capacity to recover from damage.

770.3

SELECTIVE BEHAVIORAL TOXICITY OF CHRONIC DIDEOXYCYTIDINE TREATMENT IN THE RHESUS MONKEY

M.G. Paule', R. Rountree, R.R. Allen and W. Slikker, Jr. Division of Neurotoxicology, National Center for Toxicological Research/FDA, Jefferson, AR 72079-9502.

In order to study the effects of chronic treatment with the anti-HIV compound 2',3'-dideoxycytidine (ddC) on brain function, studies were designed to monitor several operant behaviors in monkeys used to model learning (LRN), short-term memory (STM), time estimation (TE), color and position discrimination (CP) and motivation (MOT). Adult males (n = 3/group) were given ddC orally at doses of 0.06, 0.6 or 1.5 mg/kg, 3 x day, 7 days/week for 3-6 months. Doses of 0.06 and 0.60 mg/kg were well tolerated: no significant effects on behavior were seen. The 1.5 mg/kg dose selectively disrupted TE, LRN, and CP behaviors: STM and MOT were not affected. Accuracy of responding was disrupted in the CP and TE tasks, but not in the LRN task; response rate was decreased in the LRN and CP tasks but not in the TE task. Thus at doses resulting in ddC plasma levels approximately 5-times human therapeutic values, several signs of toxicity, as evidenced by significant but selective behavioral alterations, were present in the rhesus monkey. Some of these effects appeared to be irreversible or only slowly reversible. Few, if any, signs of toxicity were noted at doses yielding plasma levels considered appropriate for humans infected with HIV. (supported in part by NIEHS IAG YO1-ES-10187).

770.4

PYRIDOSTIGMINE READILY ENTERS THE CENTRAL NERVOUS SYSTEM OF THE CAT.

A.W. Kirby*, A.T. Townsend, C. Pope, T. Clarke, G. Evans, and S. Arroyo. U.S. Army Aeromedical Res. Lab, Ft. Rucker, AL 36362.

Last year at this meeting we reported that pyridostigmine (pyr), a reversible inhibitor of acetylcholinesterase (AChE), provides significant protection to the visual system of the cat when administered before soman, an irreversible inhibitor of AChE. Pyr is a quaternary compound and should not readily enter the central nervous system (CNS). These studies were done to investigate CNS changes following pyr.

Baseline visual evoked responses (VER) and blood AChE assays were completed before and after pyr in anesthetized adult cats. Cortical samples were collected from each animal for neurochemical analysis. Two animals had both tissue and microdialysis samples collected from visual cortex before and after pyr.

Both animals with pre- and postcortical samples showed up to 40% inhibition of cortical AChE within one hour after pyr. VERs were not affected. HPLC analysis of microdialysis and tissue samples suggests changes in NE and 5HIAA. Pretreatment with pyr prior to soman results in less cortical AChE inhibition than that found with soman alone. These results strongly support the rapid entry of pyr into the CNS of the cat.

770.5

AMYGDALA KINDLING IN IMMATURE RATS: EFFECTS OF THE ORGANOPHOSPHATE INSECTICIDE - CHLORPYRIFOS

John N.D. Wurpel*, Patrick C. Hirt and Jesse H. Bidanset. Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, NY 11439

Recent reports indicate that chlorpyrifos (CPF) causes behavioral neurotoxicity (Muto et al., 1992). Besides behavioral effects the organophosphates (i.e. CPF) may elicit convulsions on toxic overdoses. These experiments determine the effects of low doses of CPF and xylene (XYL - the vehicle in commercial preparations of insecticide sprays) and their interaction on amygdalar kindling in immature (16 or 17 day old) rats. Electrodes were implanted into the right or left amygdala on postnatal day 14, after a 2-3 day recovery period kindling was performed. Afterdischarge threshold (ADT) was determined for vehicle, CPF or XYL treated pups. Kindling was performed by delivering a 400 uA current every 15 minutes & recording the seizure stage elicited. All drug injections were performed one hour prior to kindling paradigms. CPF lowered the ADT in a dose-dependent manner, XYL (0.2%) reduced the ADT as well. CPF (1, 3 and 10 mg/kg, s.c.) shifted the kindling response to the right accelerating the kindling rate of immature rats. XYL (0.2%) also shifted the kindling response rate to the right (proconvulsant effect). The combination of XYL (0.2%) with CPF (either 0.3 or 1.0 mg/kg, s.c.) demonstrated additivity of these two compounds. CPF 0.3 mg/kg did not demonstrate a proconvulsant effect when administered alone, yet was proconvulsant when coadministered with XYL. These results indicate that CPF has a proconvulsant effect on amygdala kindling of immature rats, in addition XYL may be proconvulsant and displays additivity with CPF.

770.6

EVIDENCE FOR HISTAMINE-MEDIATED THALAMIC LESIONS IN ACUTE THIAMINE DEFICIENT RATS.

S.X. Zhang*, G.S. Weilersbacher, S.W. Henderson, L.B. Hough, P.J. Langlais. Depts. of Psychology, SDSU, San Diego, CA 92182 and Dept. of Pharmacol. & Toxicol., Albany Med. Coll., Albany, NY.

Disturbances of brain histamine in acute thiamine deficiency (TD) are suggested by the following observations: several of the thalamic nuclei damaged by TD contain either histamine nerve terminals or mast cells; and TD-induced hypothermia is associated with increased levels of histamine in anterior and posterior hypothalamus (Onodera et al., Japan J. Pharmacol., 54:339-343, 1990). In the present study, the release of histamine into medial thalamus was measured by in vivo microdialysis in groups of pyrithiamine (0.25 mg/kg, i.p., daily) induced thiamine deficient rats (PTD) and pairfed controls (CT). Histamine levels in PTD compared to CT animals were significantly elevated (180 %) on Day 12, prior to pathologic lesions, and further elevated (380%) on Day 14 , during onset of pathologic lesions. To further investigate the role of histamine in PTD-induced diencephalic lesions, groups of PTD and CT rats were infused continuously with either alpha-fluoromethylhistidine (30mg/day, i.p.,), an irreversible inibitor of histamine synthesis, or saline and the brains perfused 6 hrs after onset of seizures. Neuronal loss and gliosis were observed in the gelatinosus, anteroventral ventrolateral (AVVL) , ventrolateral and posterior thalamic nuclei of both PTD groups but the midline intralaminar nuclei, i.e., central medial, anteromedial, interanteromedial, were damaged only in the PTD+saline group. No pathological changes were observed in CT+FMH brains. These observations suggest that histamine may play an important role in the production of midline thalamic damage seen in PTD rats. Supported by NINDS grant #NS2948101 and VA Merit Award to PJL.

770.7

PATTERN AND PROGRESSION OF THIAMINE DEFICIENCY-INDUCED DIENCEPHALIC LESIONS IN THE RAT.

P.J. Langlais*, S.W. Henderson, and S.X. Zhang. Dept. of Psychology, SDSU, San Diego, CA, 92182 and VA Medical Center, San Diego, CA 92169.

The present study examined the site of first damage, progression of lesions, and their relationship to neurologic symptoms in acute thiamine deficiency. Separate groups of male SD rats were subjected to an acute bout of pyrithiamine (0.25 mg/kg, i.p., daily) induced thiamine deficiency (PTD), reversed prior to or at varying intervals after onset of seizures (SZ), and the brains perfused transcardially 7 days later. In animals reversed after losing righting reflexes and prior to SZ, extensive neuronal loss and gliosis were present in the gelatinosus (G) nucleus and to a lesser extent in the anteroventral ventrolateral (AVVL) nucleus. All other diencephalic structures were unchanged. In animals reversed after 10 min-1 hr SZ, the entire AVVL was destroyed, and mild gliosis and neuronal loss were observed within ventrolateral (VL) and ventral posterolateral (VPL) nuclei of midthalamus and VPL and posterior nuclear group (Po) of posterior thalamus. In the 3 hr SZ group, mild gliosis and neuronal loss were present within midline central medial, anteromedial, paracentral, centrolateral, and mediodorsal nuclei. These changes were more severe in the 5 hr SZ group. Gliosis was evident in mammillary body nuclei of the 3 hr SZ group whereas moderate neuronal loss was observed only in the 5 hr SZ group. These observations suggest: i) gelatinosus is the first thalamic nucleus damaged by PTD; ii) there are two separate zones of damage - one containing the VL group and bordered by the internal and external medullary laminae; and a second region containing the intralaminar nuclei and medial to the internal medullary lamina; and iii) the gelatinosus and VL nuclei are affected prior to seizure onset whereas damage to midline areas occurs after 3 or more hrs of seizures. Supported by NINDS grant #NS2948101 and VA Merit Program Award to P.J.L.

770.8

INFLUENCE OF PRE- AND/OR POST-WEANING POLYCHLORINATED BIPHENYL (PCB) ON BASAL FOREBRAIN AND HIPPOCAMPAL CHOLINE ACETYLTRANSFERASE (CHAT) ACTIVITY IN 60 DAY OLD RATS.

D.A. Corey, L.M. Juárez de Ku, B.W. Seo, V. Bingman and L.A. Meserve*. Dept. of Biol. Sciences and Psychology, Bowling Green State University, Bowling Green, OH. 43403.

Improper disposal of polychlorinated biphenyl, which was used widely for many industrial purposes, resulted in extensive contamination of the environment. Symptoms in humans exposed to PCB are similar to those in rats and include hypothyroidism and neurophysiological and behavioral abnormalities. Since a depression in choline acetyltransferase (ChAT) has been demonstrated in the hippocampus and basal forebrain of 15 day old rats exposed to PCB pre- and postnatally, we were interested in similar measures at 60 days and determining whether withdrawal of the toxin at weaning would normalize these effects. Behavioral abnormalities were also monitored.

Pregnant rats were fed 0, 125, or 250 ppm Aroclor 1254 (PCB) from day one of pregnancy through weaning. Young rats were weighed daily and either left on the PCB diet or given regular lab mash at weaning (28 days of age). At 60 days of age, ChAT activity, and circulating T_3 and T_4 levels were determined. Radial arm maze performance was determined for one litter from each diet between days 45-55.

Growth rates were subnormal in rats given 125 or 250 ppm, and removal of PCB at weaning normalized the weights. As previously shown, PCB depressed T_4 and, to a lesser extent T_3, in a dose dependent manner, and PCB withdrawl at weaning restored both levels. Hippocampal ChAT was depressed by 125 or 250 ppm, whereas basal forebrain ChAT was depressed by 125 ppm only. Removal of PCB at weaning returned ChAT activity to normal or above. Maze performance to criterion required more trials in PCB-fed than control animals. The mechanisms by which PCB influences ChAT activity and behavior remain unclear, but may depend upon altered thyroid status.

770.9

EFFECTS OF POLYCHLORINATED BIPHENYLS ON DOPAMINE RELEASE FROM PC12 CELLS.

WGR Angus and ML Contreras*. Department of Pharmacology and Toxicology, Neuroscience Program and the Institute for Environmental Toxicology. Michigan State University, East Lansing, MI 48824.

Exposure to polychlorinated biphenyls (PCBs) has been associated with decreases in the levels of cellular dopamine in PC12 cells and *in vivo*. To determine if the decrease in cellular dopamine results in a reduction of stimulated release of dopamine, PC12 cell were exposed to either a PCB mixture (Aroclor 1254) or PCB congeners for 3 days. Spontaneous and evoked release of dopamine was examined by exposing the cells to a saline buffer without or with 56 mM potassium, respectively, for 5 minutes. High pressure liquid chromatography (HPLC) coupled to electrochemical detection was used to quantitate dopamine levels in cells and in the release buffers. Results were normalized to DNA levels. Aroclor 1254 appeared to decrease evoked release of dopamine from PC12 cells. At 10 μg/ml, Aroclor 1254 caused a decrease in evoked release of approximately 44%. At 50 μg/ml, evoked release of dopamine was not detectable. Spontaneous release of dopamine was unaffected by Aroclor 1254. Cellular levels of dopamine decreased in a parallel fashion to the decrease in evoked release of dopamine. PCB congeners varied in their ability to alter cellular dopamine levels and evoked release of dopamine. Supported by USDA 59-0500-2-183.

770.10

DIFFERENTIAL RECOVERY OF EXCITATORY AND INHIBITORY NEUROTRANSMITTER RELEASE FOLLOWING TETANUS TOXIN-INDUCED SYNAPTIC BLOCKADE.

L.C. Williamson*, S.C. Fitzgerald and E. A. Neale. Lab. Develop. Neurobiol., NICHD, NIH, Bethesda, MD 20892.

Tetanus toxin (TnTx) initially blocks neurotransmitter release at inhibitory synapses in murine spinal cord cell cultures, but eventually blocks all transmitter release (Williamson et al., J. Neurochem., 1992). We have examined the recovery of both inhibitory and excitatory neurotransmitter release following TnTx-induced synaptic blockade. Spinal cord cell cultures were incubated in 6 pM TnTx. After 24 and 48 hr in toxin, cultures were radiolabeled and K^+-evoked Ca^{++}-dependent release of [^{3}H]-glycine and [^{3}H]-glutamate was assayed to confirm synaptic blockade. Additional cultures were processed for electron microscopy of synaptic terminals. At this low toxin concentration, glycine release was blocked in 24 hr but glutamate release was not blocked completely until 48 hr. Cultures were rinsed, maintained in toxin-free medium, and monitored weekly for recovery of synaptic function. At 1 wk after toxin removal, transmitter release remained suppressed. At 2 wk, glutamate release was restored to 24% and glycine to 9.8% of the release evoked in cultures not exposed to toxin. Glutamate release recovered completely within 4 wk. However, glycine release was only 57% of controls at 4 wk, and did not reach control levels until 7 wk after toxin removal. The fine structure of synapses after 48 hr in TxTn was consistent with a lack of synaptic activity. Synaptic vesicles lined the active zones and there were no coated pits or coated vesicles to signify vesicle recycling. By 7 wk after the removal of toxin, when assays indicated that neurotransmitter release was restored, evidence for vesicle recycling was observed. Thus, in addition to a difference in the time course of TxTn-induced synaptic blockade, excitatory and inhibitory synapses differ with respect to the time course of recovery of synaptic function. Inhibitory synapses are blocked more quickly and recover more slowly than excitatory synapses.

770.11

CYSTEINE BLOCKS PEROXYNITRITE TOXICITY IN CEREBELLAR GRANULE CELLS TREATED WITH BUTHIONINE SULFOXIMINE (BSO). G.J.Fici, J.S. Althaus, H.M.Scherch and P.F.VonVoigtlander*. Upjohn Laboratories, Kalamazoo, MI 49001.

Glutathione (GSH) is an important cellular constituent thought to control and maintain the oxidative status of cells. Dysfunction of the GSH-synthesizing machinery of the CNS has been identified as a possible contributing factor to disorders such as Parkinson's Disease (Jenner *et al.*, Ann. Neurol., V32,S82, 1992). Our study was carried out to investigate the role of GSH in two cerebellar granule cell models of oxidative stress.

Cells were exposed to BSO, an inhibitor of γ-glutamyl-cysteine synthetase, for 24 hrs. Cellular GSH levels measured by HPLC with fluorometric detection fell by as much as 90% following BSO treatment (1-1000 μM). In the first model, BSO alone at 300 and 1000 μM was toxic to the cells as measured by aminoisobutyric acid (AIB) uptake and LDH release. In the second model, sublethal concentrations of BSO (100 μM) potentiated peroxynitrite (thought to be a nitric oxide-related toxin) toxicity. In both models, thiol-containing compounds were investigated as protectants of cytotoxicity.

L-cysteine (100 μM) blocked the toxicity of 300 and 1000 μM BSO and resulted in significantly higher cellular GSH levels throughout the BSO concentration range. It also inhibited the BSO-potentiated toxicity of peroxynitrite (50 μM) with an EC_{50} of ~50 μM.

The results show that GSH is a vital component in the maintenance of cell function under conditions of oxidative stress.

770.12

AN *IN VITRO* ASSESSMENT OF PEROXYNITRITE TOXICITY. H.M. Scherch, J.S. Althaus, G.J. Fici, P.F. VonVoigtlander, and E.D. Means* CNS Diseases Research and *Clinical Research II, The Upjohn Company, Kalamazoo, MI 49001.

Nitric Oxide (NO) has recently gained attention regarding its action as a neurotransmitter and as a neurotoxin. Theoretically, NO toxicity is due in part to its interaction with superoxide to form peroxynitrite, a highly reactive intermediate. This may be relevant to ischemic stroke, where large quantities of NO are released in an environment of superoxide formation following reperfusion. In this study using spinal cord neurons, peroxynitrite toxicity was characterized in terms of cell viability and cellular levels of oxidized glutathione and vitamin E.

Neurons were cultured from embryonic (E13-E15) mouse spinal cords. Cells were pretreated with drug or vehicle and then exposed to peroxynitrite (.3 to 10 mM) for one minute followed by a 30 minute incubation in buffer. Viability was assessed utilizing the uptake of ^{3}H-aminoisobutyric acid, found previously to be a direct measure of cell survival.

Peroxynitrite was toxic to cells in a dose dependent manner (EC_{50}=300μM). A 1 mM dose of peroxynitrite caused a decrease in vitamin E of 30%. Levels of oxidized glutathione increased by approximately 100%. Cysteine, a known peroxynitrite scavenger, and related compounds partially blocked the toxicity.

NO is becoming widely recognized as a therapeutic target. Drugs which scavenge peroxynitrite have an advantage over drugs which interfere directly with NO function. Therefore, we have adapted a spinal neuron toxicity assay to screen for drugs which block peroxynitrite toxicity.

770.13

GLUTATHIONE DEPLETION AND CADMIUM-INDUCED BIOGENIC AMINE CHANGES IN RAT BRAIN. H. R. Bahng, C. Kim and K. H. Kim*. Dept. of Pharmacology, Yonsei Univ. College of Medicine, Seoul 120-752, Korea.

Temporal effects of Cd on the central nervous system were studied. The levels of monoamine neurotransmitters (NTs) (NE, DA, 5-HT) and their metabolites were measured in various brain regions at 6, 12, 24 and 48 hours after i.c.v. injection of $CdCl_2$(10 μg). The levels of monoamine NTs and their metabolites were increased time-dependently. These effects were prominent at 48 hour after i.c.v. Cd while only minimal changes were observed during the first 12 hours. This phenomenon occurred almost invariably in various brain regions and monoamines with their metabolites. To examine the role of glutathione(GSH) for the Cd toxicity, tissue GSH was depleted by i.c.v. injection of L-buthionine-[S,R]-sulfoximine (BSO; 3.2 mg), a selective inhibitor of γ-glutamylcysteine synthetase, at least 24 hours before Cd. This dose of BSO depleted brain GSH about 60% of the control level. When BSO was pretreated before Cd, three phases of temporal effect was observed. Increased levels of the monoamines and their metabolites occurred up to the first 12 hours after Cd while Cd itself caused minimal changes. At 24 hours after Cd, those levels were variable. However, increased levels of those reappeared at 48 hours after Cd. It is noteworthy that increased levels of monoamines and their metabolites at 48 hours after i.c.v. Cd, were not changed by BSO pretreatment. These results suggest that expression of Cd toxicity may have different phases, and that GSH exerts its protective effects in the early phase of Cd toxicity.

770.14

Brain Oxidative Stress Induced Neuropathology - tertiary Butylhydroperoxide. J.D. Adams,* L.K. Klaidman, M.L. Chong, M.H. Nguyen and Z.J. Wang. Dept. Molecular Pharmacology and Toxicology, School of Pharmacy, University of Southern California, Los Angeles, CA 90033.

We have previously reported that ICV t-butylhydroperoxide damages neurons in the cortex, hippocampus and cholinergic neurons in the striatum, GABA neurons in the midbrain, and dopaminergic neurons in the midbrain. Electron microscopic examination demonstrates that t-butylhydroperoxide induces nuclear swelling and rupture in astrocytes, pericytes, endothelial cells and neurons within 2 h of administration. Capillaries occasionally had blebs and ruptured cytoplasmic membranes. Astrocytic and capillary damage produced possible extracellular edema. Mitochondria in many cells were swollen or, in some cases, condensed. The neuropil occasionally had swollen nerve terminals. Different changes were found in mice treated ICV with the antioxidant t-butanol, the major metabolite of t-butylhydroperoxide. t-Butanol treated mice demonstrated nuclear convolutions in some cells, vacuolation of the endoplasmic reticulum and occasional swollen or condensed mitochondria. t-Butylhydroperoxide is toxic to nuclei and other cellular structures. This neuropathology may correlate with biochemical changes in glutathione, lipid hydroperoxides and t-butylhydroperoxide elimination from the brain.

770.15

ACUTE VACUOLIZATION STUDY OF SUBCUTANEOUSLY ADMINISTERED D-CYCLOSERINE (DCS) IN SPRAGUE DAWLEY RATS. G. C. Haggerty*, V. Charles and T. H. Lanthorn. G.D. Searle & Co., Skokie, IL 60077.

Antagonists of the N-methyl-D-aspartate (NMDA) receptor, such as MK-801, have been shown to induce 1) vacuolization of the cell body of neurons of the posterior cingulate and retrosplenial cortices and 2) a hypermetabolic state (as measured as a large increase in [^{14}C]-2-deoxyglucose (2-DG) uptake) in these neurons. DCS, a potential cognitive enhancer, is a partial agonist at the glycine site of the NMDA receptor. Because DCS could conceivably reduce NMDA receptor activity in the presence of fully efficacious concentrations of glycine, it was of importance to determine the potential of DCS to trigger vacuolization and increase 2-DG uptake. Rats received s.c. doses of 2, 500 and 1000 mg/kg DCS and were killed 4, 12 and 48 hours later. MK-801 (1.5 mg/kg, s.c.) was used as a positive control. Cytoplasmic vacuolization was seen in the cell bodies of both cortical regions at 4 and 12 hours in the MK-801 treated animals but not in any DCS dosage group at any evaluation time. DCS (10-500 mg/kg, iv) did not increase 2-DG uptake in these cortical regions. In conclusion, these results indicate that DCS does not produce NMDA antagonist-like effects under the conditions tested.

770.16

EFFECT OF γ-HEXACHLOROCYCLOHEXANE IN CALMODULIN GENE EXPRESSION IN THE CENTRAL NERVOUS SYSTEM.
S. Barrón*, J.M. Tusell[1] and J. Serratosa.
Departament of Pharmacology and Toxicology and [1]Departament of Neurochemistry C.S.I.C. Jordi Girona 18-26, 08034 Barcelona, Spain.

The expression of calmodulin genes (CaM I and CaM II) in the central nervous system after administration of the organochlorine pesticide γ-hexachlorocyclohexane (γ-HCH, Lindane) has been studied.

A dose response and a time course of CaM II gene expression in cerebral cortex of rats treated with lindane has been studied using Northern blot analysis after total RNA isolation and *in situ* hybridization. The onset of CaM II expression was 24h after administration of a convulsive dose of 30mg/kg of lindane. We observed a signidicative decrease of about 60% in the expression of this gene. CaM I expression also decrease at this dose of lindane however this modification is not so important.

This pattern of differential CaM gene expression produced by lindane has been previosly shown , by other authors, in different experimental situations as virally induced transformations in cells, in the chemically induced rat Morris hepatomes and during prolifelation or differentiation stadies in several cell lines.

We report here, changes in calmodulin gene expression in a neither proliferative nor differentiation model. This finding, seen after lindane administration could reveal the implication of calmodulin in the mechanism of action of this neurotoxic agent.

771.1

INCREASE IN MAP5 IMMUNOREACTIVITY IN DORSAL RAPHE CELL BODIES FOLLOWING NEUROTOXIN-INDUCED DAMAGE TO SEROTONIN AXONS. K.J. Axt* and M.E. Molliver. Dept. Neurosci., Johns Hopkins Univ. Sch. Med., Balto., MD 21205

Substituted amphetamines produce a marked and long-lasting loss of fine 5-HT axons in forebrain. Despite the extensive denervation, however, little to no effect on cell bodies in the dorsal raphe nucleus (DRN) has been reported. Many types of neurons express robust changes in cytoskeletal proteins following axotomy: levels of phosphorylated neurofilaments (P-NF) increase and/or levels of MAP2 decrease in the somata of the damaged axons. Monoamine neurons respond differently to axonal damage; we have found that in rats treated 3 days or 2 weeks previously with the neurotoxic amphetamine p-chloroamphetamine (pCA), 5-HT neurons in DRN exhibit no change in P-NF or MAP2 immunoreactivity (IR). In addition, lesioning medial forebrain bundle with 5,7-dihydroxytryptamine (5,7-DHT) causes no change in P-NF-IR or MAP2-IR in DRN, despite an obvious decrease in 5-HT-IR and tryptophan hydroxylase-IR and loss of staining of Nissl substance. Three days after pCA or 5,7-DHT lesions, one cytoskeletal protein was clearly affected: neurons in DRN expressed a robust increase in MAP5-IR in dendrites and peripheral perikaryon. Curiously, the response was limited to neurons in the dorsomedian and ventromedian regions of DRN; the lateral cell groups expressed no MAP5. This increase in MAP5-IR was transient: it was not observed at 2 weeks survival. To our knowledge, no *increase* in MAP5 has been reported in other models of axotomy. MAP5 is up-regulated during development and is not expressed in most mature neurons; its re-expression in 5-HT neurons after chemical axotomy may be a response to injury which is related to the regenerative capacity of 5-HT neurons. [Support: DA04431, NIDA 271-90-7408]

771.2

DEVELOPMENTAL EFFECTS OF PERINATAL EXPOSURE TO DEXAMETHASONE AND OXYGEN DEFICIENCY. E-M. E. Montgomery* and C. R. Almli. Lab of Developmental Neuropsychobiology, Washington Univ. Sch. of Med., St. Louis , MO 63110.

This study is aimed at assessing the developmental effects of early postnatal exposure to dexamethasone (DEX) and oxygen deficiency (OD). These two variables are being scrutinized because the hippocampus is known to be a primary target of insult by both variables. An animal model, consisting of rats, was used in analyzing the effects of neonatal DEX and OD on CNS damage and neurobehavior performance. The three experimental groups assessed were: an OD group (OD), a DEX group (D), and an OD plus DEX group (OD-D). OD consisted of 3 treatments each separated by 30 minutes conducted on P0 (day of birth). DEX treatment was given for 7 consecutive days (P0-P6) at a 1mg/Kg body weight dosage. Preliminary results show that, in comparison to the control group, experimental groups demonstrated reduction in body weights, disruptions of some reflexive measures, as well as open field behaviors and spatial task performance. (Conducted under NIH Guide for care and Use of Laboratory Animals).

771.3

PROTEIN KINASE C (PKC) MODULATES RHODANESE ACTIVITY. E.U. Maduh and S.I. Baskin. US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland 21010-5425.

Cyanide intoxication is characterized by impairment of cellular respiration principally in the central nervous and cardiovascular systems. Detoxification of cyanide is catalyzed by a sulfurtransferase, rhodanese, a phosphoprotein regulated by unknown protein kinases (*Ogata et al., J. Biol. Chem. 264: 2718, 1989*). In this study, we determined if a Ca^{2+}/phospholipid modulated phosphotransferase (PKC) could modify rhodanese activity. Thiocyanate (SCN^-) production as an indication of rhodanese activity *in vitro* was measured in the presence or absence of exogenously added purified PKC which could either donate or accept phosphate. HI-6 (1-(2-(hydroximino)methyl))pyridinium-2-(4-(aminocarbonyl)pyridinium dimethylether) is an oxime that may dephosphorylate phosphoproteins due to the known phosphatase-like activity of oximes (*Chapman, Pflügers Arch. 422: 325, 1993*). We examined HI-6's effect on rhodanese-catalyzed SCN^- production. Bovine kidney rhodanese (0.40 mg/ml protein) was reacted with varying concentrations of KCN and SCN^- production determined spectrophotometrically, OD at 460 nm in accordance with Westley (*Meth. Enzymol. 77: 281, 1981*). Preincubating rhodanese with 20 or 100 ng of purified PKC (α,β,γ isozymes) for 5 min before initiating the reaction with 4 mM KCN as the substrate increased SCN^- production respectively by 17 or 40% over the control ($P < 0.05$). When HI-6 at 1 or 10 μM was used in place of PKC, rhodanese activity was enhanced by 6 or 14%, respectively, ($P<0.05$) compared to control. Under the conditions tested, exogenous PKC acting as a possible phosphate acceptor, and HI-6, a potential dephosphorylating compound, increased rhodanese activity. These initial data are consistent with the observation that rhodanese can exist as a phosphorylated enzyme which is not active and a dephosphorylated form which is active. It is suggested that addition of purified, exogenous PKC may accept phosphate from phosphorylated rhodanese or by HI-6 may dephosphorylate rhodanese, both of which stimulate the conversion of cyanide anion to the less toxic SCN^-. The observations support the possibility that rhodanese may be regulated by protein phosphorylation and compounds that increase the dephosphorylation of rhodanese may affect cyanide detoxification.

771.4

γ-RADIATION IMPAIRS NEURONAL FUNCTION IN GUINEA PIG HIPPOCAMPUS, D.L. Lepinski and T. C. Pellmar*, Physiology Dept., AFRRI, Bethesda, MD 20889-5603

Guinea pigs were exposed to 5 and 10 Gy γ-radiation. Hippocampal slices were isolated 30 min, 1 day, 3 days and 5 days after radiation or sham-radiation and input-output curves in field CA1 were evaluated.

Radiation elicited dose, dose-rate and time dependent changes. 5 Gy produced a decrease in synaptic efficacy at 30 min and day 1 with recovery by day 5. With 10 Gy, the PSP was potentiated at day 1 but decreased by day 3 and did not recover by day 5. Synaptic efficacy was minimally dose-rate dependent. The ability of the synaptic potentials to generate spikes (E/S coupling) was potentiated within 30 min after exposure to 5 Gy at 1 Gy/min and persisted through day 3, with recovery at day 5. Similar potentiation did not occur with a dose-rate of 20 Gy/min, at both 5 and 10 Gy. Rather, within 30 min and after 5 days, E/S coupling was significantly depressed by these exposures. E/S coupling showed significant dose-rate sensitivity. Both synaptic efficacy and E/S coupling contribute to the net input-output relationship of field CA1. This relationship was profoundly decreased within 30 minutes with recovery at 1 day and subsequent decline with the higher dose-rate in a dose-dependent manner.

The persistent changes in neuronal function are likely to be a consequence of the actions of ionizing radiation on the physiological processes that influence the neuronal environment.

771.5

EFFECT OF MASTOPARAN ON BOTULINUM TOXIN A (BoTx) INHIBITION OF STIMULATED ACETYLCHOLINE (ACh) RELEASE. P. Ray*, W. Middleton, J.D. Berman and S. Mott. Walter Reed Army Inst. Res., Washington DC 20307-5100.

BoTx blocks stimulated ACh release from presynaptic nerve terminals at neuromuscular junctions. We showed that arachidonic acid, bee venom phospholipase A_2 (PLA_2), and a PLA_2 activator melittin can prevent BoTx inhibition of 80 mM K^+-stimulated [^{3}H]ACh release in PC12 cells in vitro (Ray et al., JBC **268**: 11057-11064, 1993). We report here that mastoparan (3-30 μg/ml), a basic tetrapeptide isolated from wasp venom can also prevent BoTx inhibition of K^+-stimulated [^{3}H]ACh release in PC12 cells in a concentration-dependent manner. This mastoparan effect is inhibited completely by a PLA_2 inhibitor p-bromophenacyl bromide (20 μM), but partially (45%) by pertussis toxin (200 ng/ml). These results demonstrate that mastoparan can prevent the effect of BoTx in PC12 cells via mechanisms involving PLA_2 and pertussis toxin sensitive GTP-binding protein(s).

771.6

BRAIN GLUCOSE USE, METABOLITE CHANGES AND GRADE OF ENCEPHALOPATHY IN ACUTE HEPATIC FAILURE. A. M. Mans* and R. A. Hawkins. Department of Physiology and Biophysics, University of Health Sciences/Chicago Medical School, North Chicago, IL 60064.

Acute hepatic failure is associated with brain dysfunction, decreased brain oxidative metabolism, and many biochemical abnormalities in both brain and plasma. Because changes that correlate highly with the degree of behavioral impairment may be important in the development of encephalopathy, we determined correlations between these abnormalities. Rats underwent portacaval shunting and hepatic artery ligation (or sham operation), and were kept normoglycemic and normothermic thereafter. Two, four or six hours later we sampled blood and whole brain (by near-instantaneous freeze-blowing) for metabolite measurement, or measured glucose use and blood-brain barrier integrity. There were no alterations in high-energy phosphate metabolites or most other intermediary metabolites in the brain, but glucose use was decreased. Blood-brain barrier integrity remained intact. The highest correlation coefficients with behavioral impairment ($r^2>0.42$) were obtained with plasma ammonia and brain glutamine, which were increased, and with brain aspartate (decreased).

Supported by NIH grant NS 16389.

771.7

DEVELOPMENT OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODEL FOR 2,4-DICHLOROPHENOXYACETIC ACID (2,4-D) DOSIMETRY IN DISCRETE AREAS OF THE BRAIN FOLLOWING A SINGLE INTRAPERITONEAL DOSE. C.S.Kim*[1], W. Slikker[2], Z. Binienda[2], M.L. Gargas[3] and M.E. Andersen[3], FDA, Washington, DC 20204[1] & Jefferson, AR 72079[2] and CIIT, RTP, NC 27709[3].

A PBPK model for the dosimetry of organic acids in discrete areas of the brain was constructed using 2,4-D as a model compound. The PBPK model accounted for distribution of 2,4-D throughout the body as well as within discrete areas of the brain. This strategy is preferred to treating the entire brain as a single isolated compartment because the effects are likely to be associated with concentration in specific regions of brain. The brain compartments in the model were the hypothalamus, caudate nucleus, hippocampus, forebrain, brainstem and cerebellum. The remainder of the model consisted of two-body compartments and venous and arterial blood compartments. In the model, chemical uptake by the brain was membrane-limited by the blood-brain barrier with saturable clearance from the cerebrospinal fluid (CSF) into the venous blood by the choroid plexus. The body has both a central and a deep compartment with saturable clearance from the central compartment. The model was used to examine the brain and CSF concentrations of 2,4-D as a function of plasma 2,4-D as well as plasma time-course behavior by using experimental data from rabbits given 2,4-D by IP(40 or 100 mg/kg) administration. Model parameters were adjusted to fit the observed 2,4-D concentrations in blood and brain regions. This generic PBPK model should be a very useful tool for evaluating the safety of this class of organic acids.

771.8

INTERACTION OF DIETARY β-ALANINE AND TAURINE IN CATS. P. Lu*, W. Xu, H. Imaki, J.M. Messing and J.A. Sturman. Institute for Basic Research in Developmental Disabilities, Staten Island, NY 10314.

β-Alanine and taurine utilize the same uptake system in most, if not all, mammalian tissues. We have reported that β-alanine and taurine interact differently with cultured cat and mouse cerebellar granule cells, prompting us to examine their relationship in adult cats (Trenkner and Sturman, Int. J. Devl. Neurosci. 1991, 9:77-88). Adult female cats were fed a completely defined taurine-free synthetic diet alone or supplemented with 0.05% taurine for at least 2 years and then provided with 5% β-alanine in the drinking water for 20 weeks. During this period each cat consumed approximately 500 g β-alanine. As noted in other species, β-alanine reduced taurine concentrations globally in all cats. Large amounts of β-alanine accumulated in non-neural tissues of all cats and in neural tissues of taurine-deficient cats, but only small amounts accumulated in taurine-supplemented cats. Using an antibody against β-alanine, its localization in Purkinje cells and their dendrites, Golgi II cells and basket cells of the cerebellum was demonstrated, with greater staining in taurine-deficient cats. The latter also showed staining in granule cells. Using an antibody against taurine, heavy staining of Golgi II cells was evident, with little labelling elsewhere. The number of granule cells in taurine-deficient cats is reduced, and many appear pyknotic. Such cells are rare in taurine- supplemented cats. Thus it appears that β-alanine is neurotoxic to taurine-deficient cats, although less so to taurine-supplemented cats.

771.9

EOSINOPHILIA-MYALGIA SYNDROME: MULTI-ELECTRODE ANALYSIS OF CONTROL AND CONTAMINATED TRYPTOPHAN SAMPLES. E. R. Ryan, I. N. Acworth, G. J. Gleich[1], P. H. Garnache and A. N. Mayeno[1]. ESA Inc., 45 Wiggins Ave, Bedford, MA 01730. [1]Mayo Clinic, 401 Guggenheim Bldg., Rochester, MN 55905.

Ingestion of toxin contaminated food or food supplements has been responsible for a variety of aggressive, debilitating and often lethal diseases. Many of the substances thought to be the toxin are highly modified amino acids or amine containing compounds and include: domoic acid (from contaminated blue mussels), ß-N-oxalylamino-L-alanine (Lathyrism), ß-N-methylamino-L-alanine (Guam amyotrophic lateral sclerosis with secondary Parkinsonism and Alzheimer's dementia) and anilides (Toxic Oil Syndrome). More recently ingestion of contaminated manufactured tryptophan (Trp) resulted in many cases of eosinophilia-myalgia syndrome (EMS). Although it is still not clear which contaminant(s) caused EMS, interest has focused on two key analytes - 1,1'-ethylidenebis[tryptophan] (EBT) an aminal formed by condensation of tryptophan with acetaldehyde, and 3-phenylaminoalanine (3PAA). We have developed a sensitive gradient HPLC-electrochemical array method capable of measuring Trp, EBT, 3PAA and a variety of other electrogenic contaminants within 40mins. Analytes eluted in the order: 3PAA (14.80±0.04 mins.), Trp (17.00) and EBT (29.80±0.06) with maximum oxidation occurring at 480, 540 and 660 mV respectively. Both control (n=8) and contaminated (n=6) samples of Trp contained between 350-400 unknown analytes: 92% of these were <0.01% of the level of the Trp peak; the remainder were <0.1%. Using conventional UV detection less than 100 peaks were detected. In case samples levels of EBT were 60±20ng/mg Trp compared to 3±1 in control samples. 3PAA levels were 102±59ng/mg Trp in case samples and 15±6 in controls. Principal component analysis clearly differentiated the case from the control Trp batches. Multi-metabolite analysis is a very powerful approach to study the presence of environmental toxins and contaminated food.

771.10

NORADRENERGIC LESIONING USING anti-DBH IMMUNOTOXIN. M.J.Picklo, R.G. Wiley, D. Lappi, D. Robertson*. Depts. of Pharmacology and Neurology, Vanderbilt University and DVAMC, Nashville, TN 37232 and Whittier Institute, La Jolla, CA 92037.

Current methods of lesioning noradrenergic neurons have significant drawbacks due either to incompleteness, partial specificity, or reversibility. We sought to determine if an immunotoxin to dopamine ß-hydroxylase (DBH) would efficiently destroy noradrenergic neurons in vivo. The MAB308 monoclonal antibody to bovine DBH was obtained from Chemicon International (Temecula, CA). Antibody was disulfide coupled to the ribosome inactivating protein, saporin, using SPDP. The resulting immunotoxin was injected into anesthetized adult, male Sprague-Dawley rats. Injection sites in individual animals were the submandibular gland (3.1-12.5 µg), intravenous (6-31 µg), and intraventricular (1.8-4.8 µg). Three days after systemic injections, rats were reanesthetized and transcardially perfused with aldehyde fixative. Frozen sections of peripheral ganglia were processed for Nissl staining. In sections from sympathetic ganglia, most neurons showed severe chromatolysis characteristic of the cytotoxic effect of immunotoxins containing saporin. Sensory ganglia showed small numbers of similarly poisoned neurons. Eleven days after intraventricular injections, rats were sacrificed and brain sections stained either with cresyl violet (Nissl) or for tyrosine hydroxylase (TH) using indirect immunoperoxidase technique. Nissl staining of the locus coeruleus showed a decrease in the numbers of neurons as was confirmed by staining for TH. Dopaminergic neurons in the midbrain appeared unaffected as did catecholaminergic neurons in the caudal brainstem. We conclude that anti-DBH-saporin efficiently destroys noradrenergic neurons in the CNS and PNS. This immunotoxin may be a valuable lesioning tool with greater selectivity than has been previously available.

771.11

QUANTITATIVE GLIAL MODIFICATIONS IN THE CENTRAL NERVOUS SYSTEM BY CHRONIC INTOXICATION WITH 2-4 DICHLOROPHENOXY-ACETIC ACID THROUGHOUT LACTATION. A. Brusco(*), G.García, E. de Duffard, D. Duffard, P. Tagliaferro and J. Pecci Saavedra. Instituto de Biología Celular, Facultad de Medicina, UBA, Paraguay 2155, (1121) Buenos Aires; Lab. Toxicología Experim., Fac. Cs. Bioquímicas y Farmac., U.N. Rosario, República Argentina.

In a previous study we demonstrated that 25-day old rat pups exposed to 70 mg/kg/day of 2,4-dichlorophenoxyacetic acid through mothers' milk expressed morphological and biochemical changes in the central serotonergic system. Behavior alterations were also studied; they were expressions of the "serotonergic syndrome."

In order to determine whether this chronic intoxication also produced a gliosis, and the degree and specificity of such gliosis, an immunocytochemical study was performed. Sternberger's Peroxidase-Anti-Peroxidase technique was used, with anti-GFAP, anti S-100 and anti-vimentine antisera as primary antibodies.

A significant glial reaction was detected at serotonergic nuclei level and fundamentally, extreme gliosis at hippocampus and cerebellum levels were also observed.

Quantitative analysis of "reactive astrocytes" showed statistically significative increase in their size, number of processes, and density of immunostaining as well as in their number/µm² in intoxicated animals.

(Supported with grants from CONICET and SECYT, Argentina).

771.12

Dose-related effects of 192 IgG-saporin on basal forebrain cholinergic neurons: biochemical, immunocytochemical and behavioral studies on neonatal and adult rats.

G. Leanza*, O.G. Nilsson, R.G. Wiley[1] and A. Björklund

Dept. of Medical Cell Research, University of Lund, Lund, Sweden and (1) Neurology Service, DVAMC, Nashville, TN 37212-2637, USA

Highly selective and efficient depletions of the NGF receptor-positive cholinergic neurons in the basal forebrain, associated with profound behavioral changes, have been reported after treatment with 192 IgG-saporin, a recently introduced immunotoxin. In the present study, the effects of different doses of the toxin-conjugate were compared following bilateral injections in the lateral ventricles of infant (2-3 days post-natal, 0.2 to 0.8 µg dose-range) and adult rats (1.25 to 10 µg dose-range). Five to eight weeks post-injection, dose-related behavioral effects of the lesion were evaluated in water maze, passive avoidance and locomotor activity tests, followed by biochemical and histologic analyses performed on tissue specimens. In the adult rats, the immunotoxin produced severe dose-dependent cognitive deficits in water maze task performance and passive avoidance retention that correlated with decline in choline acetyltransferase (ChAT) activity in neocortical and hippocampal areas (up to 95% reduction) and depletion of NGF receptor-positive neurons in the septal-diagonal band area and nucleus basalis (>95%). Similar dose-related patterns of ChAT activity reduction and neuronal loss throughout the basal forebrain were seen in rats neonatally injected with the immunotoxin. ChAT levels in other regions such as brainstem, cerebellum or the spinal cord were found largely unaffected in both adult and neonatally lesioned rats.

The present results confirm 192 IgG-saporin as a powerful tool to induce specific and robust cholinergic lesions either during development or adulthood and emphasize the crucial role of the forebrain cholinergic system in cognitive functions.

771.13

EFFECTS OF DDC AND AZT ON LOCOMOTOR ACTIVITY IN RATS. H.D.Davis[1*], D.E.Morse[1], K.J.Brown[2], E.J.Popke[2], M.A.Ussery[1] and N.E.Grunberg[2]. [1]FDA, Antiviral Research Laboratory, Rockville, MD 20857. [2]Uniformed Services University of the Health Sciences, Medical Psychology Department, Bethesda MD 20814.

Dideoxycytidine (ddC) and azidothymidine (AZT) are nucleosides used in the treatment of HIV infection. ddC, but not AZT, is associated with an increased incidence of peripheral neuropathy in adult patients receiving repeated dosing. In order to examine and compare the behavioral toxicities of these drugs, locomotor activity was monitored in female Sprague-Dawley rats after a single IG dose of ddC (0-1250 mg/kg) or AZT (0-250 mg/kg). Locomotor activity was decreased in animals that received the lower doses of ddC, while higher doses were comparable to control, thus suggesting an inverse dose-response relationship. No behavioral changes were observed in AZT treated animals. The fact that locomotor activity effects clearly differed between these anti-HIV drugs, which also differ in neuropathic effects, suggests that the further examination of behavioral responses in animals may provide a valuable preclinical screening tool. The implications of these results for behavioral tests designed to predict neurotoxicity will be discussed.

771.14

Exposition of striatal synaptosomes to the couple ascorbic acid/Fe^{2+} alters ^{3}H-dopamine uptake and ^{3}H-GBR 12783 binding without reducing the K^+-induced dopamine release. C. RAMASSAMY*[1], F. GIRBE[1], J. PINCEMAIL[2], Y. CHRISTEN[3] and J. COSTENTIN[1]. [1] Unité de Neuropsychopharmacologie CNRS URA 1170 Faculté de Médecine et de Pharmacie de Rouen 76803 Saint-Etienne-du-Rouvray, France; [2] Centre de Pathologie de l'Oxygène 4000 Sart-Tilman, Belgium ; [3] Institut IPSEN , 30 rue Cambronne 75015 Paris, France.

Incubation of synaptosomes, at 37°C during 1 hour, prepared from mouse striatum in a Krebs-Ringer medium containing ascorbic acid (0.1 mM) and Fe^{2+} (1 µM) resulted in an almost complete suppression of their ability to take up ^{3}H-dopamine (DA) and to bind the specific DA uptake inhibitor ^{3}H-GBR 12783. These effects seemed to depend on a lipid peroxidation since we simultaneously evidenced an increase (≈+300%) in malondialdehyde level (measured with the thiobarbituric acid reagent by spectrofluorimeter), as well as a decrease (≈-70%) in alpha tocopherol level (measured by HPLC). Moreover, these alterations were prevented by the Ginkgo biloba extract (EGb 761, 10 µg/ml) a free radical scavenger. On the other hand, the ^{3}H-DA release elicited by K^+ (40 mM, in the presence of Ca^{2+} 1 mM) from synaptosomes incubated in the previously indicated conditions was higher than in controls. This effect seemed, for its part, independent from the lipid peroxidation since it was not prevented by the free radical scavengers trolox C (0.1 mM) and EGb 761 (10 µg/ml). In conclusion, these peroxidative conditions selectively altered the ability of synaptosomes to take up ^{3}H-DA by especially affecting the DA uptake complex, but left unaltered the K^+-induced exocytotic DA release.

771.15

TOXIC EFFECTS OF REPIN, A SESQUITERPENE LACTONE FROM *CENTAUREA REPENS*, ON PC-12 CELLS IN CULTURE. M. Robles, E. Rodriguez, S. Yee, and B. H. Choi*, Neuropathology, University of California, Irvine, Irvine, CA 92717

Russian knapweed (*Centaurea repens*) is a perennial weed found in many parts of the U.S. including California. Ingestion of this plant in the horse has been reported to cause degeneration of nigro-pallidal system associated with signs and symptoms similar to those of Parkinson's disease in human. Preliminary studies in our laboratory demonstrated that repin, a sesquiterpene lactone isolated from Russian knapweed, is highly toxic to rodents (approximate LD 50, 50 mg/kg in C57BL/6J mice). The nature and pathogenesis leading to such toxic effects remain unclear. As a part of an ongoing investigation to elucidate pathogenesis of neurotoxic effects of repin, PC 12 cells were exposed to different doses of repin for 3 hours and the effects evaluated. Control cultures received the vehicle (DMSO) in place of repin. The results showed dose-dependent decreases in cell viability following repin exposures (i.e., 25% and 40% cell death at 40 and 80 µM repin, respectively). Withdrawl of the processes associated with shrinkage and peripheral vacuolization of the cytoplasm, pyknosis of the nuclei and eventual cell loss characterized the cytotoxic changes. Immunoperoxidase staining for tyrosine hydroxylase (TH) demonstrated equivocal loss in TH immunoreactivity in repin exposed cells. Also noted was a marked reduction in the concentration of reduced glutathione (GSH) following exposures to repin (up to 95% of control at 80 µM repin). However, the reduction in GSH was not accompanied by proportional decrease in cell viability, suggesting that GSH reduction may not be the sole factor responsible for repin-induced cell death. (Supported in part by NIEHS grant # ES 02928)

771.16

MODE OF ACTION OF *HELODERMA HORRIDUM* VENOM (HHV) IN GUINEA PIG ILEUM. R. K. Gordon, T. C. Chapman, R. R. Gray, and P. K. Chiang*. Walter Reed Army Institute of Research, Division of Biochemistry, Washington DC 20307-5100.

Since the observation that HHV (Gila monster) contains pancreatic secretagogues, several bioactive peptides and proteins have been isolated from this venom. We demonstrated (Arch. Int. Pharmacodyn. 305:14) that several VIP and helodermin peptides induced the release of acetylcholine (ACh). Next, we investigated the toxic mechanism of a phospholipase A_2 (PLA_2) component in this venom. Longitudinal muscle-myenteric plexus preparations were preincubated with [^{3}H]choline, and the release of [^{3}H]-metabolites were measured. HHV PLA_2 induced a maximum of 2.5-fold increase in the release of [^{3}H]ACh, while [^{3}H]choline increased about 1.5-fold over basal levels. HHV-induced released of ^{3}H could not be reversed by washing. No ^{3}H release above basal levels was found with pancreatic PLA_2, or HHV PLA_2 in the absence of Ca^{2+}, or when Sr^{2+} replaced Ca^{2+}, implying a non-neuronal release mechanism. When the ileum was incubated with HHV PLA_2, erratic and spontaneous contractions were observed. Anatoxin-a-, DMPP-, or nicotine-induced ileum contractions were inhibited 75-95% after HHV PLA_2 treatment for 10 min, whereas ACh- and oxotremorine-induced ileum contractions were inhibited only about 20-30% when compared to controls. These results suggest that HHV PLA_2 specifically blocks neuromuscular transmission in the ileum by preferentially inactivating ganglionic interneurons containing nicotinic receptors.

771.17

ONTOGENY OF SUSCEPTIBILITY TO CONVULSIONS INDUCED BY ALARM SUBSTANCE IN RATS. E.L. ABEL*. Dept. of Ob/Gyn, W.S.U., Detroit, MI 48201.

Water previously swum in by another rat contains an alarm substance that attenuates the immobility response in the forced swim test (PHYSIOL. Behav. 1990, 48, 233; 1991, 49, 321; 1991, 50, 151, 723; 1992, 51, 345) and precipitates convulsions in rats primed with imipramine (Pharm. Bio. Behav. 1992, 4, 599). This study determined the age onset for this convulsive effect. Male S.D. rats, 23-78 days old (5-10/group), were injected (i.p.) with imipramine 20 or 30 mg/kg, at 24 hr, 5 hr, and 1 hr prior to testing in water previously swum in by another rat. Convulsions were not observed until rats were 44 days of age for those treated with the 30 mg/kg dose, or 49 days for those given the 20 mg/kg dose. Convulsions did not begin to occur reliably, i.e., at least 40% per group, until rats were 54-55 days of age.

The induction of convulsions in imipramine-treated rats represents a new model for studying both alarm substances and their biological effects, and neurochemical factors underlying convulsions. The present results extend previous studies by showing that these effects are age-dependent.

771.18

NEUROTOXIC AND NEUROPROTECTIVE ACTIONS OF INTERLEUKIN-1β ON CORTICAL NEURONS IN CULTURE. P. J.L.M. Strijbos, B.A. Wilde and N.J. Rothwell*. Neuroscience Division, School of Biological Sciences, University of Manchester, Oxford Road M13 9PT, United Kingdom.

Previous data indicate that various cytokines, including the interleukins (IL) have differential effects on neuronal survival depending on the interleukin subtype, culture conditions, concentration and time of exposure. In the present study we examined the effects of hrIL-1β on the survival of mature primary rat cortical neurons (14-16 days in culture) and on glutamate-induced neuronal death. Neuronal death was assessed by lactate dehydrogenase release into the culture medium and confirmed by immunocytochemistry. Exposure of cultures to high doses (0.5-5μM) of hrIL-1β caused neuronal death in a dose- and time dependent manner, with maximum effects (~30%) observed after 72h exposure to 5μM hrIL-1β. At low doses (50pM-500nM), hrIL-1β protected cortical neurons (~45%) against toxicity induced by 5min exposure to 1mM glutamate, this effect was accompanied by gliosis. These data indicate that IL-1β can either act as a neurotoxic or neuroprotective agent depending on the concentration and time of exposure.

771.19

NEUROTOXIC EFFECTS OF INTERLEUKIN-1 (IL-1) IN VIVO. S. Toulmond, J.K. Relton*, C. Lawrence, S. Loddick, J. Benavides[1] and N.J. Rothwell. Neuroscience Division, School of Biological Sciences, University of Manchester, M13 9PT UK and[1] Synthelabo Recherche, 41 rue P. Valliant Couturier, 92220 Bagneux, France.

IL-1 is expressed in the mammalian CNS and is rapidly induced following ischaemic, traumatic or excitotoxic brain damage. We have shown that central injection of IL-1 receptor antagonist (IL-1ra) markedly inhibits neuronal death resulting from focal cerebral ischaemia or activation of NMDA receptors in the rat brain in vivo. Central injection of IL-1ra (10μg) in the rat inhibits infarct volume measured 24h after middle cerebral artery occlusion by 72% compared to a reduction of 66% in animals treated with MK801 (4mg/kg ip). Direct neurotoxicity of recombinant human IL-1β was tested in vivo. Infusion of IL-1β (10-100U) into the rat striatum caused extensive, local neuronal damage (histological examination after 7 days), a significant reduction (34 $\pm$ 6%) in glutamic acid decarboxylase activity , but no change in choline acetyl transferase activity. In a separate study, IL-1 infusion caused a dose dependent gliosis (up to 90% increase in the density of peripheral benzodiazepine binding sites). These data indicate that IL-1β can cause neurodegeneration which is accompanied by gliosis and selective loss of neuronal function.

NEUROTOXICITY V

772.1

ONSET AND RECOVERY OF NEUROMOTOR DYSFUNCTION IN F344 RATS FED DIETS CONTAINING THE ANTHELMINTIC LY274537. J.L.Buelke-Sam*, A.S. Fix, K.I. Griffey, T.L. Smalley and M.N.Novilla. Toxicology Research Labs, Lilly Research Laboratories, Eli Lilly & Co., Greenfield, IN 46140.

This study compared the onset and recovery patterns of motor deficits and neuropathological findings in rats exposed to a new anthelmintic agent. F344 rats (20 males/group) were fed diets containing 0, 0.01, 0.06, or 0.10% LY274537 for 2 weeks, followed by a 12-week period off treatment. Hind limb grip strength, acoustic and tactile startle were measured after 1 and 2 weeks of treatment, and 1, 4 and 8 weeks after removal from treatment. After startle testing, brain, spinal cord and peripheral nerve from 4 rats/group were taken for neuropathology. Daily intake of LY274537/group averaged 0, 6.5, 41 or 61 mg/kg during the 2-week treatment period. Dose-related decreases in grip strength occurred during the treatment period, and acoustic and tactile startle amplitudes progressively decreased in the mid- and high-dose groups. Dose-related spongy degeneration of myelin, characterized by myelin splitting and edema, was evident after 1 week of treatment. Dose-dependent recovery of neuromotor function occurred during the first post-treatment week; moderate impairment remained in grip strength, but startle was no longer reduced. Further recovery in grip strength was seen at 4 weeks. Thus, onset of neuromotor deficits occurred rapidly, followed by a slower recovery after removal of LY274537 treatment.

772.2

CARBAMAZEPINE INDUCES DNA FRAGMENTATION BY A NMDA-REVERSIBLE MECHANISM IN RAT CEREBELLAR GRANULE CELLS. X.-M. GAO*, R.L. MARGOLIS, R.M. POST and D.-M. Chuang Biological Psychiatry Branch, NIMH, NIH, Bethesda, MD 20892, U.S.A.

We have reported that long-term carbamazepine (CBZ) treatment is toxic for rat cerebellar granule cells, as demonstrated by both morphological examination and by a decrease of [^{3}H]-ouabain binding to Na^+, K^+-ATPase (Gao and Chuang, Neurosci. Lett. 135 : 159, 1992). Moreover, this CBZ-induced neurotoxicity is completely prevented by NMDA. Since DNA fragmentation has been implicated in programmed cell death (also known as apoptosis), we examined whether DNA fragmentation occurs during CBZ-induced neurotoxicity. Cerebellar granule cells prepared from postnatal rats were treated with 100 μM CBZ for 3 days after 5 days in culture. Cells were then lyzed with a detergent and DNA was extracted with phenol-chloroform-isoamyl alcohol. DNA fragments were electrophoretically separated in a 1.5% agarose gel and visualized by staining with ethidium bromide. CBZ treatment markedly increased the intensity of small DNA fragments, which appeared as multiple bands with a length of less than 2 Kb. This DNA laddering was completely blocked by inclusion of 100 μM NMDA during CBZ exposure. NMDA alone did not influence DNA fragmentation. CBZ-induced DNA fragmentation was detectable after 1 day of treatment, but maximal fragmentation occurred after 3 to 4 days of treatment. The effect of CBZ was dose-dependent, and more than 20 μM of CBZ was required for the induction of fragmentation. These results suggest that DNA fragmentation may contribute to CBZ-induced neurotoxicity in cultured rat cerebellar granule cells.

772.3

EFFECT OF gp120 AND CD_4 ANTISENSE ON HUMAN FETAL NEURONAL CULTURES.

F. Gremo*, S. Torelli, M.G. Ennas, V. Sogos, S. Angioni
Dept. Cytomorphology, School of Medicine, Cagliari, Italy.

It has been shown that both neuronal and glial injury are involved in neurologic manifestations of AIDS. In particular, the envelope protein (gp120) of HIV-1 can cause injury to rodent neurons in culture and to astrocytes in human brain cell aggegrates, even if the mechanism(s) of cell damage is still unknown. We consequently treated human fetal neuronal cultures with different doses (1-10 nm) of gp120. At different intervals, cells were fixed, neurons stained for neurofilaments and counted.

No morphological changes or neuronal loss occurred in treated cultures with respect to controls until the 7th day after treatment. At this time, astrocytes showed lack of confluence, morphological alteration and decrease in GFA-P staining, whereas neurons appeared unaffected and their percentage only slightly diminished. Since we have previously shown that human fetal neurons in culture expressed CD4, we also treated human fetal neuronal cultures with CD4 antisense (10-30 µm). At different intervals, cells were fixed, stained for neurofilaments and counted. Results demonstrated no significant changes in the first 24 hours. However, after 2-3 days a significant loss of neurons was observed in treated cultures whereas no changes were observed in controls or in cultures treated with other proteins. Whether this effect was due to alteration in neuronal adhesiveness, cell death or cell detachment from substratum is presently under investigation.

(Supported by AIDS Grant 1993).

772.4

PROTEIN KINASE C (PKC) ACTIVITY IS INCREASED IN PERIPHERAL NERVE FROM ACRYLAMIDE (ACR) TREATED RATS. J. Mathew*, E.J. Lehning , R.M. Lopachin and J. Eichberg . Dept. Biochem. Biophys. Sciences, University of Houston, Houston, TX 77204 and SUNY Stony Brook, Stony Brook, NY 11794.

Our previous studies have shown that exposure *in vivo* to ACR causes changes in Na and K content of rat tibial axons consistent with the loss of Na-K ATPase activity (LoPachin et al, 1992). Since Na-K ATPase activity is decreased by PKC phosphorylation (Bertorello et al, 1991), we investigated the effect of ACR (50 mg/kg/d x10d, ip and 2.8 mM in drinking water x30d) on PKC activity in rat sciatic nerve. In the absence of Ca^{2+} and added lipids, the protein kinase activity expressed as pmoles/min/mg protein was significantly reduced in nerve homogenate (control=30.9$\pm$3.2; ACR ip=16.3$\pm$0.8; ACR oral= 21.7$\pm$2.1, $p<0.05$) following either ip or oral ACR administration. In both treatment groups, PKC activity measured as the difference between added Ca^{2+} and Ca^{2+} plus lipids was significantly higher in homogenate (control=16.1$\pm$4.3; ACR ip=28.3$\pm$2.9; ACR oral= 27.3$\pm$3.3, $p<0.05$) and cytosol (control=1.2$\pm$1.6; ACR ip=6.1$\pm$1.6; ACR oral=9.9$\pm$1.3, $p<0.05$) and tended to be elevated in the 105,000g pellet. The results suggest that the decreased Na-K ATPase activity observed in ACR-treated animals (see Lehning et al, this Meeting) may be related to the elevated PKC activity found in peripheral nerve. (Supported by NIH grants ES03830 and DK30577).

772.5

ACRYLAMIDE EXPOSURE DECREASES NA-K ATPASE ACTIVITY IN DESHEATHED RAT SCIATIC AND TIBIAL NERVE. E.J. Lehning*, E.C. Stack, J. Eichberg and R.M. LoPachin. SUNY Stony Brook, Stony Brook, NY 11794 and Univ. Houston, Houston, TX 77204.

Previously we have shown that in vivo exposure to acrylamide (ACR) causes progressive changes in Na and K content of tibial axons consistent with loss of Na-K ATPase activity (LoPachin et al., Toxicol. Appl. Pharmacol. 115:35, 1992). In initial studies (Lehning and LoPachin, The Toxicologist 13:126, 1993), we found that ACR intoxication does not alter Na-K ATPase activity when measured in intact rat peripheral nerve. Because Na-K ATPase activity in nonneuronal components may have masked an effect, the study was repeated using nerves stripped of the epineurium. Rats were exposed to ACR subacutely (50 mg/kg/d x10d, ip) or subchronically (2.8 mM in drinking water x30d), and Na-K ATPase activity was measured in desheathed sciatic and tibial nerves using a continuous recording method. Subacute treatment with ACR decreased ($p<0.01$) Na-K ATPase activity (mean μmoles Pi/hr/mg protein ± SEM) 40% in sciatic nerve (control = 2.8 ± 0.2, ACR ip = 1.7 ± 0.3), but did not affect this activity in tibial nerve. Subchronic ACR treatment reduced ($p<0.01$) Na-K ATPase activity 19% in sciatic nerve (control = 3.1 ± 0.2, ACR oral = 2.5 ± 0.2) and 36% in tibial nerve (control = 2.6 ± 0.2, ACR oral = 1.7 ± 0.3). Na-K ATPase activity was not affected by in vitro exposure to ACR (1.0 mM). Results suggest decreased Na-K ATPase activity is involved in ACR-induced perturbation of axoplasmic Na and K and that loss of activity is not due to direct chemical inhibition of the enzyme. (Supported by NIH grants ES03830 and DK30577).

772.6

SYSTEM TO DETECT AND ANALYZE RAT ULTRASONIC VOCALIZATIONS FOR TOXICOLOGICAL ASSESSMENT M.R. Murphy*, S.A. Miller, S.C. Baker, C.J. Sherry, & B.E. Mulligan. U.S. Air Force Armstrong Laboratory, Brooks AFB, TX 78235.

Ultrasonic vocalization (UV) by rats to a threatening situation (e.g., shock, noise, human touch) is viewed as an indicator of fear or anxiety. An automated system to detect and analyze UVs during acoustic startle testing was developed. The compressed 20-200 kHz output of an S-25 Bat Detector was digitally recorded (1000Hz) direct to PC hard drive and analyzed to detect UV start time, duration, and relative intensity. Tests were 30 min long, with 20 startle exposures (108 dB, 40ms). Validation was by comparison with hand calculations and by sonographic analysis (Kay) done on 250kHz digital recordings. The UVs and startle responses of 160 rats, were tested 1 to 3 times each. Focus was on UVs that were at least 120 ms long, with at least 120 ms between UVs. Mean signal to noise ratio was 7.7 ± 0.2. The mean UV rate of rats that had been handled daily in a Functional Observational Battery was much higher than that of rats handled less frequently (924 ± 60 vs 237 ± 39), suggesting a difference in sensitivity to fear evoking stimuli. Mean UV length did not differ between these groups (825 ms ± 38 vs 836 ms ± 43). Few UV and startle parameters were correlated, suggesting startle and UV reflect independent measures. Across repeated tests, UVs declined; however, UV parameters correlated highly with the same parameters in later trials, suggesting these parameters reflect individual rat characteristics. Automatically detected acoustic startle evoked UVs may be a useful and efficient indicator of stress resulting from toxic exposures or experimental procedures.

772.7

PALYTOXIN CHANGES $[Ca^{+2}]_i$ IN PHEOCHROMOCYTOMA (PC-12) CELLS. F. Serrano, M. Cordero, G. Escalona de Motta and J.G. Ortiz*,. Departments of Pharmacology and Biology, University of Puerto Rico, San Juan, Puerto Rico 00936-5067.

Palytoxin (PTX) is one of the most potent marine toxins isolated from the zoanthid Palytoha species. In PC-12 cells, 1 minute of exposure to PTX (10^{-8} M) causes an irreversible effect leading to cell death. Thirty minutes of exposure to PTX (10^{-8} M) result in an apparent loss of organelles and by 3 hrs. cell death is observed (Trypan blue exclusion). It has been postulated that PTX binds to the Na^+/K^+ ATPase (Habermann, 1989 and Tosteson, 1991). However, cell death is observed in cells exposed to a solution containing Ouabain (10^{-6} M) and PTX (10^{-8} M). In contrast, Ouabain (10^{-6}-10^{-5}M) alone does not affect the cells. On the other hand, in cells incubated with PTX (10^{-9}-10^{-7} M), a dose dependent increase in the intracellular calcium concentration $[Ca^{+2}]_i$ was obtained. These results suggest that the toxicity of PTX involves the influx of calcium and may not be mediated by the Na^+/K^+ ATPase. (Supported by MBRS/SUBE Programs).

772.8

PREVERTEBRAL AND PARAVERTEBRAL NEURONAL DEPLETION IN ADULT GUANETHIDINE-TREATED RATS. I. L. Smithson, E. E. Benarroch*, P. J. Zollman, J. D. Schmelzer and P. A. Low. Neurophysiology Laboratory, Mayo Clinic, Rochester, MN 55905.

Guanethidine (Gu) produces depletion of sympathetic neurons in neonatal and adult rats. In neonates, there is a differential susceptibility for Gu sympathectomy (GuSx) with relative sparing of prevertebral (celiac/superior mesenteric, CSMSG) as compared to paravertebral (superior cervical, SCG) ganglia (Schmidt RE et al., Brain Res. 460:214-226, 1988). We sought to determine whether differential susceptibility also occurs in adult GuSx rats. Guanethidine (40 mg/kg i.p.) was administered daily for five weeks to adult (250-350 g) Sprague-Dawley rats. One to 24 weeks after treatment, GuSx and control rats were anesthetized and the SCG and CSMSG processed for Nissl and neuropeptide Y (NPY) and calcitonin gene-related peptide (CGRP) immunocytochemical staining. Cell numbers were determined using an MCID image analysis system. Some ganglia were processed for radioimmunoassay of NPY and CGRP. At one week following treatment, there was depletion of NPY (114±20 vs. 4461±289 pg/ml, $n=5$, $p<0.01$) and increase of CGRP (534±54 vs. 31±1 pg/ml, $n=5$, $p<0.01$) in the SCG; these persisted after 24 weeks. Guanethidine also produced about 90% neuronal depletion in the CSMSG. There was preservation of CGRP-fibers. Thus, chronic Gu treatment in adult rats depletes sympathetic neurons in prevertebral, as well as paravertebral ganglia. This may reflect age-related differences in neuronal plasticity and resistance to injury.

772.9

ESCALATING DOSES OF FENFLURAMINE PREVENT THE LONG-LASTING 5-HYDROXYTRYPTAMINE DEPLETION IN THE RAT. S. Rose, J.G. Hindmarsh, P. Collins, D.B. Campbell* & P. Jenner. Pharmacology Group, King's College, Manresa Rd, London, UK.

The monoamine-depleting effect of amphetamine analogues can be prevented by gradual escalation of dose. In the present study the effect of escalating doses of d-fenfluramine (d-Fen) on the 5-hydroxytryptamine (5-HT)-depleting effect following subacute administration was investigated. Male Wistar rats (138-186g) were treated with d-Fen, either subacutely (5mg/kg i.p b.i.d for 4 days) or with escalating doses (0.5,1,1.5,2,3,4 & 5mg/kg b.i.d. i.p., 4 days at each dose). Control rats received saline (1ml/kg b.i.d. i.p.) and were either pair-fed (PF) or received food *ad libitum* (CONT). Rats were killed at intervals up to 30 days after the last dose of d-Fen. d-Fen and norfenfluramine (nor-Fen) levels in plasma and brain were determined by capillary GC. 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) levels were determined in brain by HPLC. In rats treated with escalating doses of d-Fen, d-Fen levels were greater in plasma (225%), hippocampus (Hipp; 266%) and hypothalamus (Hyp; 464%), and nor-Fen levels were lower in the Hyp (67%) and cortex (65%) compared to the subacute-treated rats on day 1 after drug withdrawal. 5-HT and 5-HIAA levels were reduced compared to PF and CONT in all tissues for up to 30 days after withdrawal from sub-acute d-Fen. Following escalating doses, 5-HT and 5-HIAA levels were reduced compared to CONT only on day 1 and only in the Cortex. 5-HT levels were also reduced in the Hipp of the PF group compared to CONT. These data suggest that escalating doses of d-Fen produced a desensitisation to the 5-HT depleting effect of a sub-acute challenge which cannot be explained by the small differences in drug levels.

772.10

INCREASED SECRETION OF CYTOKINES AND NEUROTOXINS BY CO-CULTURES OF HIV-1 INFECTED MACROPHAGES AND HUMAN FETAL ASTROCYTES K.A. Dzenko, R. J. White, P. Genis, H. Nottet, L. G. Epstein, H.E. Gendelman, and H.A. Gelbard* University of Rochester Medical Center, Rochester, NY and University of Nebraska Medical Center, Omaha, NE

HIV-1 infection of the developing central nervous system results in a primary encephalopathy. Few brain macrophages and microglia are productively infected with HIV-1, yet the neurological deficits seen in children with HIV-1 can be devastating. Genis et al. (J.E.M, 1992, 176:1703) demonstrated that only HIV-1-infected macrophages co-cultured with astrocytoma cell lines secrete markedly increased amounts of the cytokines IL-1β and TNFa as well as platelet activating factor (PAF) and arachidonic acid metabolites. This was not seen in HIV-1-infected or uninfected macrophages alone or in uninfected macrophages co-cultured with astrocytoma cells. We have investigated whether co-cultures of HIV-1-infected macrophages and primary human fetal astrocytes also secrete similar substances which may be neurotoxic to cultures of primary human fetal neurons. Co-cultures of human fetal astrocytes with HIV-1-infected macrophages secrete 3-10 times the amount of IL-1β relative to co-cultures with uninfected macrophages or to HIV-infected macrophages or uninfected macrophages alone (maximal IL-1β occurs at 36 hours of co-culture; range 110-2140 pg/ml; n=3); TNFa levels remained relatively low. Application of conditioned media (1:10 v/v) from co-cultures of HIV-1-infected macrophages and human fetal astrocytes destroy >90% of cultured human fetal neurons. Preliminary studies reveal that PAF (secreted in concentrations of 6-15 ng/ml in co-cultures of HIV-1-infected macrophages and astrocytoma cells) is toxic to human fetal neurons. Studies are in progress to determine whether PAF and other arachadonic acid metabolites are elevated in co-cultures of HIV-1-infected macrophages with human fetal astrocytes. These results may lead to new therapeutic intervention in the treatment of HIV-1 encephalopathy. (Supported by AmFAR grant #500258-12-PG and NINDS PO1 NS31492-01).

772.11

3-NITROPROPIONIC ACID REDUCES SUCCINIC DEHYDROGENASE ACTIVITY AND ATP LEVELS IN HIPPOCAMPAL SLICES. M.I. Sabri*, C.N. Allen, G.M. Pastine, S.E. MacMillan, P.S. Spencer. Center for Res. on Occup. & Environ. Toxicol., Oregon Health Sciences University, Portland, Oregon 97201.

3-Nitropropionic acid (3-NPA), a potent inhibitor of succinic dehydrogenase (SDH) activity, is a useful tool to probe the relationship between tissue energy state and neuronal integrity. We showed earlier that continuous treatment of rat hippocampal CA1 neurons with 3-NPA (1mM) induces a membrane hyperpolarization followed by a long lasting depolarization. The K^+ channel blocker glibenclamide attenuated the membrane hyperpolarization suggesting that 3-NPA-induced metabolic inhibition and ATP loss are responsible for activating ATP-sensitive K^+ channels (Riepe *et al.*, Brain Res. 586:61, 1992). To study the temporal relationship between the membrane potential and the energy metabolism we studied the effects of 3-NPA on SDH activity and ATP levels. Transverse hippocampal slices (400 μm) from adult Sprague Dawley rats were treated with 3-NPA (1 mM) in Krebs Ringer for 0, 20, 40, 90 and 120 min. to determine whether SDH activity and ATP levels coincide temporally with changes in membrane potential. SDH activity was rapidly reduced (approx. 80%) by 20 min, and this level was sustained throughout 3-NPA treatment. The reduction of ATP levels lagged behind the loss of SDH activity, was somewhat variable across trials, and considerable amounts of ATP (up to 50%) remained after prolonged 3-NPA treatment. In conclusion, the early small loss of ATP correlates temporally with membrane hyperpolarization, while the larger ATP loss correlates with irreversible membrane depolarization. [Supported in part by NS grant 19611].

772.12

EFFECT OF DIISOPROPYLPHOSPHOROFLUORIDATE (DFP) ON DORSAL AND VENTRAL SPINAL ROOTS IN NEONATAL RAT IN VITRO S.B. Deshpande* and S. Das Gupta, Dept. Physiol., Inst. Med. Sciences, Banaras Hindu Univ. Varanasi and Pharmacol. Toxicol. Division, Defence Research Development Establishment, Gwalior, India.

Depression of the spinal monosynaptic reflex (MSR) in neonatal rat spinal cord by DFP is known to be due to the modulation of cholinergic or non-cholinergic mechanisms (Das Gupta et al, Toxicol. Appl. Pharmacol. **95**:499, 1988). But the role of spinal root potentials in mediating the DFP-induced depression is not known. Therefore, the present study is performed to isolate the contribution of dorsal root (DR) or ventral root (VR) potentials in mediating the depression. Recording of either MSR or potentials from DR and VR was done in isolated rat spinal cord. DFP produced dose (1-1000 uM) dependent depression of MSR and maximal depression (75% of control) occurring at 1 mM. While DFP (1-10 uM) produced 20-25% increase in the area of DR or VR potential. Increasing the concentration of DFP above 10 uM decreased VR potentials while DR potentials remained at 25% increased level. Results in this study indicate that the depression of the MSR could be due to the nonspecific activation of several afferents (probably inhibitory neurons) resulting in decreased reflex activity (supported by grants from DRDE, Gwalior and ICMR, New Delhi).

772.13

Behavioral effects of a FGF receptor toxin in the rat hippocampus. S.A. Frautschy[1*], Waite, J.[2,3], T. Albright[1], J. Sheu[1], Winkler, J.[2,3], D. Martineau[1], D. Lappi[1], A-M Gonzalez and Thal, L.J.[2,3], [1]Whittier Inst., 9894 Genesee, La Jolla, Ca. 92037, [2]Dept. Neurosci., UCSD, [3]Dept. Neurology, VA., San Diego, 92161

Basic fibroblast growth factor (FGF)-Saporin (SAP) is a conjugate of a FGF and a ribosome inactivating plant toxin that is selective for cells with a high density of FGF receptors. Previously our laboratory has demonstrated that injection of this toxin into the hippocampus of the rat selectively destroys the neurons showing strong signals for basic FGF mRNA and basic FGF, the hippocampal CA3 pyramidal neurons and the lateral septal neurons. The unconjugated toxin was not toxic to these neurons. In order to determine the effect that this toxin had on spatial memory, working memory and passive avoidance, we performed the following tests using the Morris water maze. We stereotaxically injected 1 μl of artificial cerebrospinal fluid or 5.2 picomoles of FGF-SAP or FGF plus SAP in a 1 μl volume at a rate of 0.2/μl min after which we waited 5 min to prevent reflux (n=10). Injections were bilateral, both in the anterior and posterior hippocampus . Acquisition of the water maze task was impaired for both the FGF-SAP and uncoupled toxin groups compared with controls ($p<0.001$). The FGF-SAP group was significantly more impaired than the uncoupled toxin group in this test. In a working memory test conducted by moving the hidden platform daily and allowing animals 4 trials/day, the uncoupled toxin group performed as well as controls, but the FGF-SAP group was unable to learn the new locations. Single trial passive avoidance retention (96 h) was deficient only in the uncoupled toxin group. Training latencies for this test were not significantly different among groups. The different statistical results we find using passive avoidance and water maze testing, is probably due to different kinds of memory being affected by the different lesions. Therefore we are analyzing the lesions morphologically. We are also presently analyzing data of FGF or SAP treatment alone since the results suggest that either FGF or SAP is causing memory deficits in the acquisition test as well as the passive avoidance test. In summary the FGF-SAP toxin causes severe deficits in spatial memory and working memory, but not in passive avoidance.

772.14

THE EFFECT OF SYNTHETIC GLUCOCORTICOIDS ON BEHAVIOR AND BONE LEAD MOBILIZATION. P.W. Stewart, R.G. Burright, A. Yozawitz* and P.J. Donovick. Hutchings Psychiatric Center, Syracuse, NY 13210.

The use of synthetic glucocorticoids for medicinal purposes could be potentially dangerous in individuals with a history of childhood or occupational lead (Pb) exposure. High dose and/or long-term administration of glucocorticoids is known to promote osteoporosis in a significant number of people. Since over 90% of ingested Pb is ultimately stored in bone tissue, accelerated bone mass loss could lead to rapid remobilization of bone Pb to the bloodstream. This incremental increase in blood lead could be toxicologically significant, possibly correlating with further behavioral changes. To test this hypothesis, adult Binghamton Heterogeneous Stock (HET) mice were exposed to 16 weeks of .5% lead acetate or distilled water as the sole source of drinking fluid. After lead exposure was terminated, half of the mice in each group were treated with 9mg/kg prednisolone or vehicle for 8 weeks. This procedure has been shown to produce osteoporosis in laboratory animals. During the eighth week, all animals were tested for acquisition and extinction of a spatial task in the Morris water maze. Current data indicate that lead-exposed HETs extinguish more quickly than controls in this task. Blood Pb, bone Pb and bone density of all mice were determined immediately after behavioral testing.

772.15

A CYTOPROTECTIVE EFFECT OF NICOTINE ON HIPPOCAMPAL NEURONS. S.Kito*, J.Semba, #R.Miyoshi, M.Furutsu, A.Ando and L.Shimada. Division of Health Sciences, University of the Air, Chiba 261, #Department of Pharmacology, Tokyo Women's Medical College, Tokyo 162, Japan.

There have been several papers published in which nicotine is considered to have beneficial effects on impaired memory function. It has been also pointed out that glucocorticoid increases kainate-induced cytotoxicity on hippocampal neurons (Sapolsky et al. and Kito et al.)

In this paper how nicotine influences on the kainate-induced cytotoxicity accelerated by glucocorticoid, was studied.

Primary cultures of fetal hippocampal neurons for about 14 days were used for the experiment. After adding various concentrations (10^{-4}M - 10^{-9}M) of nicotine, cells were incubated for 24 hours. For the next 24 hours, cells were incubated with 10^{-5}M kainate and 10^{-4}M dexamethasone. On the following day, the medium was exchanged and Triton X-100 was added. Percentile survival of cells was then calculated by assaying intracellular LDH activity.

As the results, it was noticed that nicotine suppressed kainate-induced cytotoxicity potentiated by glucocorticoid. However, nicotine had no effect on kainate-induced cytotoxicity in the absence of dexamethasone.

772.16

EFFECT OF D-FENFLURAMINE ON TRYPTOPHAN HYDROXYLASE AND MITOCHONDRIAL BENZODIAZEPINE RECEPTORS BINDING IN RAT BRAIN T. Mennini, C. Bendotti, M.L. Presti, S. Baldessari, M.Fiori* and S. Garattini. Istituto di Ricerche Farmacologiche "M. Negri", Milano, Italy

In the rat d-Fenfluramine (dF) (10 mg/kg i.p. twice daily for 4 days) or 5,7-dihydroxytryptamine (5,7-DHT, 150 μg i.c.v.) give, 5 days after treatment, comparable decrease of 5-HT levels in innervated regions.While 5-HT concentration was significantly reduced in hippocampus and striatum up to one month after dF treatment, the levels of tryptophan hydroxylase (TPH) were reduced only in the hippocampus 5 days after injection. Unlike dF, i.c.v. 5,7-DHT induced a marked and long-lasting reduction of 5-HT and TPH in both brain regions. Thirty days after injection, 5,7-DHT but not dF markedly reduced the number of TPH labelled neurons in the dorsal raphe and raised the levels of TPH mRNA in spared neurons at all times examined. TPH mRNA levels were raised 5 and 15 days after dF treatment in the dorsal raphe and recovered 30 days after treatment. After i.c.v. 5,7-DHT there was an increase of 3H-PK11195 binding to mitochondrial benzodiazepine receptors (MBR) in the dorsal raphe and hippocampus, but not in striatum and cortex. However, when 5,7-DHT was injected in the medial forebrain bundle, no increase in MBR binding was measured in the hippocampus. After repeated dF treatment no significant changes in MBR binding was found in any brain region considered. These data suggest that i.c.v. 5,7-DHT but not dF damages 5-HT cell bodies,but leave unanswered the question of the mechanism of the long-lasting reduction of 5-HT levels caused by high repeated doses of dF.

772.17

DOWN REGULATION OF SEROTONIN UPTAKE CARRIERS AFTER CHRONIC D-FENFLURAMINE? M. Gobbi, M.L. Presti, L. Mancini, M.G. DeSimoni* and T. Mennini. Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy.

Decreased number of 5-HT uptake sites has been used as marker for the putative neurodegeneration of 5-HT nerve endings induced by high doses of d-fenfluramine (dF) and other substituted amphetamines. Alternatively, the long-lasting decrease could be due to down regulation of uptake sites in intact neurons without absolute loss of nerve endings. We investigated the effect of chronic high doses of dF in rats (10 mg/kg i.p., twice a day for 4 days). Five days after treatment a strong reduction (80%) of the Bmax of [3H]citalopram binding was seen in membranes from hippocampus or cerebral cortex, and a 74% decrease of the Vmax for [3H]5-HT uptake in cortical synaptosomes. In order to evaluate a possible down regulation of uptake sites we measured the dF-induced [3H]5-HT release from hippocampal synaptosomes, which is known to require functional 5-HT uptake carriers. We found that the releasing activity of dF is strongly decreased (51-81 %) in synaptosomes from chronic dF-treated rats as compared with vehicle-treated rats, while that induced by depolarization with 15 mM KCl was unchanged.The data obtained with depolarization indicate that after repeated treatment with high doses of dF the synaptosomes which take up 5HT have normal exocytotic machinery, including storage of 5HT into vescicles, independently from the absolute density of nerve endings. The results obtained with dF suggest a down regulation of 5HT uptake sites, although possible concomitant down regulation of intracellular sites important for dF effect cannot be excluded.

772.18

LONG-TERM EFFECTS OF SOMAN: CORRELATION BETWEEN IMPAIRED INCREMENTAL STEP DRL ACQUISITION AND BRAIN MORPHOLOGY. E. Grauer, Y. Kapon, L. Raveh, R. Sahar and T. Kadar*. Pharmacology, IIBR, Ness-Ziona, Israel.

Incremental step differential reinforcement of low rate (DRL) paradigm was used to detect behavioral deficiencies which were then correlated with alterations in brain morphology. Rats were injected with soman (40-42.5 µg/kg, iv). Surviving animals that displayed only immediate and short episodes of convulsions were included in the behavioral evaluation. Five weeks later, animals were trained on a CRF schedule, and were then shifted in succession to DRL5, DRL10, DRL20 and DRL30 schedules. Soman exposed animals showed significant impairment in DRL performance only at sessions immediately following a shift in schedule. The histological damage in these animals, 6 months post soman, was limited to the hippocampus and the fronto-parietal cortex (FPC) and correlated well with the specific behavioral impairment. Thus, soman exposure resulted in a long lasting impairment in the ability to adjust to changes in the environmental conditions, and this may be partially controlled by FPC. Additional animals with recurrent convulsions stopped their behavioral performance. Their brain pathology was extensive and included additional areas, e.g. piriform cortex, amygdala and thalamus. Thus, the damage seen in the more mildly affected animal was probably due to the direct neurotoxic effect of soman and can be distinguished from that caused by recurrent seizures.

NEURO-ONCOLOGY II

773.1

INDUCTION OF APOPTOSIS IN GLIOMA CELLS. S. Nakagawa, T. Shiraishi*, S. Kihara, S. Shimokawa, and K. Tabuchi. Dept. of Neurosurgery, Saga Medical School, 5 -1-1 Nabeshima, Saga 849, Japan.

The cause of eukaryotic cell death can be divided into two categories, such as incidental cell death and programmed cell death. Programmed cell death usually shows the morphology of apoptosis. Since apoptotic cells die without inflammatory reaction, induction of apoptosis seems to be useful for clinical treatment. Cultured human glioma cells (T98G) were treated with the various concentrations of agents, such as anti-Fas antibody, and methanol which are thought to induce apoptosis. Cell viability was scored daily by the trypan blue dye exclusion method. DNA which was extracted from cells treated for 48 hr showed bands with multiple of 180-200 base pairs. Electron micrograph showed typical apoptotic changes, such as condensation of chromatin, shrinkage of cell volume and apoptotic bodies. Our results clearly show that apotosis can be induced by treatment of anti-Fas antibody and methanol . We will discuss the biological significance of apoptosis in glioma-therapy.

773.2

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) EXPRESSED IN BRAIN TUMOR S. Shimokawa[1], M. Oh-uchida[2], K. Hori[2], K. Tabuchi[1] and A. Yoshino[3]*Dept. of Neurosurgery[1] & Biochemistry[2], Saga Medical School, Saga, Nihon Univ. Sch. of Med.[3] Tokyo, Japan.

The angiogenesis of tumors is thought to be induced by factors derived from tumor cells. The VEGF (Vascular endothelial growth factor) has a very strong effect for tumor angiogenesis. We examined the mRNA of VEGF in 54 samples (49 surgical specimens and 5 cultured glioma cells) by Northern blot analysis. Twelve (22%) out of 54 samples expressed VEGF mRNA. We observed 3 bands of mRNA (5.5,4.2,3.7Kb) in 5 samples, and smaller bands (1.2,1.0Kb) in 8 samples. These smaller bands have not been reported previously. These findings suggest that the smaller mRNAs may be transcripted by new initiation sites on the DNA including VEGF gene.

773.3

ROLE OF ATP-SENSITIVE K^+ CHANNELS IN HUMAN BRAIN TUMOR CELL GROWTH Y.S. Lee, M.M. Sayeed and R.D. Wurster*. Depts. of Neurological Surgery and Physiology, Loyola Univ. Med. Ctr., Maywood, IL, 60153.

The role of ATP-sensitive K^+ channels (K_{ATP}) in the growth of human nervous system tumor cells was evaluated. SK-N-MC human neuroblastoma and U-373 MG human astrocytoma cells were used as model tumor cells. The growth of these human tumor cells assessed using a hemocytometer, was inhibited by diazoxide, a known activator of K_{ATP}, in a dose-dependent manner. Glibenclamide, a potent inhibitor of K_{ATP}, by itself, did not significantly alter the growth of these tumor cells. However, co-incubation of this drug with diazoxide resulted in the inhibition of diazoxide-induced alteration of tumor cell growth. Furthermore, diazoxide significantly inhibited serum-induced intracellular Ca^{2+} mobilization measured by Fura-2 fluorescence technique. Glibenclamide also inhibited diazoxide-induced intracellular Ca^{2+} alteration. Taken together, the results suggest that in these human brain tumor cells K_{ATP} channels may exist and that the activity of this type of channels may regulate the growth of tumor cells through the modulation of agonist-induced intracellular Ca^{2+} mobilization.

773.4

PLATELET-DERIVED GROWTH FACTOR EXPRESSION AND MITOGENESIS IN MEDULLOBLASTOMA CELLS. L.A. Martell* and K.M. Muraszko. Section of Neurosurgery, The University of Michigan Medical Center, Ann Arbor, MI 48109.

Medulloblastomas, primitive neuroectodermal cerebellar tumors, are poorly differentiated and are among the most common central nervous system neoplasms of childhood. A growing body of evidence suggests that autocrine and paracrine secretion of growth factors may be involved in neoplastic transformation and brain tumor development. The autocrine activity of platelet-derived growth factor (PDGF) in medulloblastoma cell lines and surgical specimens was examined. PDGF B was expressed in 3 medulloblastoma cell lines (DAOY, D283MED, D341MED) and in 2/3 medulloblastoma surgical specimens by immunoblot analysis. PDGF-β receptors were expressed on D283 MED and D341MED cell lines, and on 1/3 medulloblastoma surgical specimens. In the D283MED cell line, PDGF stimulated DNA synthesis with an EC_{50} of approximately 0.1 nM. Maximal mitogenic effects were observed at 1 nM after 24 hours of incubation. Neutralizing PDGF antibody inhibited the mitogenic effect of PDGF by 68% and inhibited control DNA synthesis by 21%. The results suggest that PDGF may act in an autocrine manner to stimulate the growth of medulloblastoma cells. Thus, a PDGF-mediated autocrine loop may play a role in brain tumor oncogenesis and maintenance of the malignant phenotype in medulloblastomas.

773.5

MELATONIN INCREASES cfos mRNA IN MCF-7 HUMAN BREAST CANCER CELLS. K.M. Hull*, T.J. Maher, and K.L. Jorgenson. Massachusetts College of Pharmacy, Boston, MA 02115 and Interneuron Pharmaceuticals Inc., Lexington, MA 02173.

Melatonin has been demonstrated to increase estrogen receptor activity in MCF-7 cells, an estrogen receptor-positive, human breast cancer cell line. The fact that this effect is reversed by pretreatment with cycloheximide suggests that the activity of melatonin may be mediated via regulation of gene transcription. To test this hypothesis, MCF-7 cells were treated with melatonin (10^{-9}M) for 30 min, 1hr, or 2hr. The mRNA was isolated using a poly-dT cellulose column, separated via horizontal gel electrophoresis, transferred and UV-crosslinked to a charged nylon membrane. The membrane was probed separately with ^{32}P-cDNA oligonucleotides specific for either cfos or estrogen receptor mRNA. Laser densitometry of the autoradiographs revealed that cfos mRNA transcription increased to maximal levels (2-fold greater than vehicle control) 30 min following melatonin treatment. Subsequent time points demonstrated a progressive decrease in cfos mRNA expression. In contrast, melatonin treatment failed to alter the transcription of estrogen receptor mRNA at any of the time points tested. These data are the first to demonstrate the ability of melatonin to increase cfos mRNA expression in this cell line.

773.6

MICROGLIA IN A RAT GLIOMA AND THE ROLE OF TRANSFORMING GROWTH FACTOR-ß. W.J. Streit*, M.L. Supler, and R. Kiefer. Depts. of Neuroscience and Neurological Surgery, Univ. of Florida, Gainesville, FL 32610, and Dept. of Neurology, Univ. of Würzburg, Germany.

Previous studies have shown that experimental gliomas in rats, induced through intracerebral inoculation of RG-2 cells, are characterized by a widespread microglial cell infiltrate. Microglia within the glioma appear to be maximally activated, since they occur as full-blown brain macrophages expressing high levels of major histocompatibility antigens. In view of the high intensity of microglial activation observed *in vivo* and the known tumor cytotoxic activity of microglia-derived brain macrophages *in vitro*, one would expect them to be engaged in antitumor activity *in situ* within the rat glioma. However, we found no evidence for cytotoxic action within RG-2 gliomas, and therefore explored the possibility that the glioma produces substances with known immunosuppressive activity which might prevent microglia from exerting their antitumor function. Using Northern blotting we showed RG-2 gliomas to contain large amounts of mRNA encoding for transforming growth factor-ß (TGF-ß) in tissue samples taken from the tumor mass as well as from peritumoral tissue. *In situ* hybridization histochemistry was confirmative and revealed TGF-ß mRNA to be present in tumor cells and possibly in activated glial cells, but not in normal CNS tissue. Since TGF-ß has been shown to inhibit microglial cytotoxicity *in vitro*, we propose that the production of TGF-ß by rat glioma cells may be a strategy for evading immunological attack by endogenous microglial cells.

773.7

ANTIPROLIFERATIVE EFFECT OF THE GLUCOCORTICOID/ PROGESTERONE ANTAGONIST RU486 ON HUMAN NEUROBLASTOMA CELLS (SK-N-SH). L.A. Casulari, R.Maggi, F. Pimpinelli and F.Piva. M.Motta* *Department of Endocrinology, University of Milano, 20133 Milano, Italy*

RU486[17ß-hydroxy-11ß-(4-dimethylamino-phenyl-1)-17-(prop-1-ynyl) estra-4, 9-dien-3-one], a receptor antagonist of glucocorticoids and progesterone, exerts antiproliferative effects on lymphocytes and meningioma cells even in absence of glucocorticoids or progesterone. Experiments have been performed in the authors laboratory in order to analyze the effect of RU486 on the proliferation of the human neuroblastoma cell line SK-N-SH.

The results obtained show that a 24 h treatment "in vitro" with RU486 induced a dose-dependent inhibition (IC_{50} 5-6 µM; maximal inhibition 53%) of 3H-thymidine incorporation in SK-N-SH cells that was not accompanied by a decrease of the cell number. A dose-dependent inhibition of SK-N-SH cell number was evident after 3, 6 and 9 days of treatment (up to 40% inhibition). However SK-N-SH cells maintained their viability and competence to grow after removal of RU486. The inhibitory effect exerted by RU486 was not reversed by the treatment of the cells with the glucocorticoid agonist dexamethasone or with progesterone. However 10 µM progesterone brought about a strong inhibition (80%) of 3H-thymidine incorporation in SK-N-SH which was not influenced by RU486. These results seem to indicate that: a) RU-486 may exert "in vitro" a cytostatic effect on SK-N-SH neuroblastoma cells; b) this effect is not reversed by dexamethasone or progesterone; c) the antiproliferative action of RU486 does not seem to be mediated through the classical steroid receptors. *(Supported by CNR through the Projects BTBS # 92.0127PF70, ACRO # 92.02218PF39, Aging # 92.00356PF40 and by MURST).*

773.8

KILLING EXPERIMENTAL BRAIN TUMORS BY IN VIVO GENE TRANSFER OF HERPES-SIMPLEX I-THYIMIDINE KINASE AND SYSTEMIC GANCICLOVIR David Barba,† Penelope Coates,* Joseph Hardin,† Fred H. Gage.° Department of Neuroscience° and Division of Neurosurgery,† University of California at San Diego, La Jolla Ca 92093-0627, Cell Biol. and Anatomy*. TTUHSC, Lubbock TX, 79430.

The transfer of genes into target cell populations is being developed for the treatment of a variety of human diseases. In this report we investigated the killing of experimental 9L brain tumors in Fischer rats by implants of producer cells of HSV-TK retroviral vectors and systemic GCV treatments.

Treated tumors were significantly smaller than untreated controls after 17 days ($p<0.01$). In survival experiments, 20-25% of treated animals compared to 0 % of untreated animals survived 90 days. Histologic examination demonstrated regional tumor-selective killing in treated animals with 90 day survivors demonstrating no residual tumors. At ninety days behavioral testing showed that treated animals were no different than normal controls. Data suggests that tumor killing occurs despite incomplete HSV-TK gene transfer and is aided by transfer of the killing effect of HSV-TK/ GCV between confluent cells.

While incompletely understood this technique has potential applications in the investigation and treatment of cancer and neurodegenerative disorders.

773.9

ULTRASTRUCTURAL ALTERATIONS IN 36B10 GLIOMA FOLLOWING IRRADIATION. P.D. Sawin, T.C. Ryken, S.C. Robertson*, V.C. Traynelis Division of Neurosurgery, University of Iowa, Iowa City, IA 52242.

The effects of radiation on cultured glioma were studied. Cultures of rat 36B10 glioma were grown to subconfluence in F12:DMEM (1:1) supplemented with 10% fetal calf serum in six well Costar culture plates. Baseline photographs were obtained with a Nikon phase contrast microscope. Six identical plates were exposed to gamma radiation doses ranging from 0 to 50 Gray. At 48 hours, cells were photographed and selected samples were fixed in 2.5% glutaraldehyde and 0.1 M sodium cacodylate for transmission electron microscopy.

Marked toxicity was observed at doses of radiation higher than 5 Gray with retraction of cell processes and cell detachment. Approximately 50% of the cells exposed to 1 Gray of irradiation remained attached. Transmission electron microscopy of 36B10 glioma cells treated with 1 Gray of irradiation revealed both nuclear and cytoplasmic alterations when compared with control cultures. The nuclear membrane assumed an irregular appearance with margination of the chromatin. Disruption of the mitochondrial lamellar structure was observed as well as partial dissolution of the smooth endoplasmic reticulum. The radiation-induced toxicity in 36B10 glioma *in vitro* is most marked at doses greater than 5 Gray. The observed ultrastructural changes observed suggest that in 36B10 glioma, irradiation induces both cytoplasmic and nuclear alterations resulting in organelle injury, membrane retraction, process retraction, and cell detachment.

773.10

PERIPHERAL BENZODIAZEPINE RECEPTORS IN HUMAN GLIOMAS: EFFECT OF CHEMO AND/OR RADIOTHERAPY. I. Linfante, M.J. Fulham, R.H. Bobo, B. Guthrie, R. Boldry* and C. Ferrarese. Neuroimaging Branch /NINDS/NIH, Bethesda, MD 20892.

In brain tumors, glucose metabolism correlates directly with the degree of malignancy, in addition, gliomas display increased peripheral benzodiazepine receptors (PBR). In 9 untreated and 8 chemo and/or radiotherapy treated patients we investigated the relationship between PBR density (B_{max}) and glucose utilization rate (GUR) in different grades of cerebral gliomas. GUR was measured by Positron Emission Tomography with [^{18}F]2-fluorodeoxyglucose before the surgery and PBR B_{max}, was assessed by [^{3}H]PK-11195 in-vitro binding in the surgical specimens. PBR B_{max} and GUR showed a direct correlation in untreated tumors ($r^2 = 0.84$, $p=0.0005$), moreover PBR B_{max} appeared to be related with the degree of malignancy. In the treated patients there was no correlation between PBR and GUR ($r^2 = 0.13$, $p=0.37$). Further studies are required to investigate the absence of correlation between PBR B_{max} and GUR in treated patients with gliomas. The data provides the theoretical framework for the use of PBR ligands in imaging of pre-operative assessment of brain tumors.

773.11

PHARMACOKINETICS AND BRAIN TUMOR UPTAKE OF D,L-NAM - A HIGH AFFINITY ANTICANCER AMINO ACID. Y. Kohmo, N. H. Greig, and Q. R. Smith*. Laboratory of Neurosciences, NIA, NIH, Bethesda, MD 20892.

The success of brain tumor chemotherapy has been limited by the lack of good anticancer drugs that are readily taken up into tumor and brain tissue. This limitation has lead to the search for new, selective agents that more readily cross the blood-brain barrier (BBB). In previous studies, we identified a nitrogen mustard amino acid, D,L-NAM, that exhibits high affinity (K_m 0.2 μM) facilitated transport into brain via the large neutral amino acid carrier of the BBB (Takada et al., Cancer Res. 52: 2191-96, 1992). In the present study, we extend our work to examine the in vivo brain pharmacokinetics of D,L-NAM and to compare the selectivity of NAM accumulation in tumor and brain tissue. D,L-[^{3}H]NAM (4 μCi) was administered to rats i.v., and plasma and tissue samples were collected from 5 min to 4 hr thereafter. Samples were processed for drug concentration by HPLC. The results demonstrated that [^{3}H]NAM and its dechlorinated breakdown products gained ready access to brain with a half-time for equilibration of ~10 min and with a brain volume of distribution of >0.7 ml/g. Plasma half-time was ~60 min. Uptake into intracerebral Walker-256 carcinosarcoma tumor exceeded that into brain by 2.2 ± 0.1 fold (n=4). The results show that NAM exhibits good uptake into brain and brain tumor following intravenous administration.

773.12

MORPHOLOGICAL AND ULTRASTRUCTURAL ALTERATIONS IN CULTURED MALIGNANT GLIOMA TREATED WITH *CIS*-PARINARIC ACID. T.C. Ryken, V.C. Traynelis* Division of Neurosurgery, University of Iowa, Iowa City, IA 52242.

cis-Parinaric acid (16:3) is a plant-derived conjugated polyunsaturated fatty acid with toxic effects on cultured malignant glioma. Cytotoxic effects in cultured 36B10 rat glioma are observed at concentrations as low as 4 μM while cultured fetal rat astrocytes tolerate doses in excess of 40 μM with minimal toxicity.

To evaluate the morphological and ultrastructural alterations induced by *cis*-parinaric acid, triplicate cultures of 36B10 malignant glioma were incubated in F12:DMEM (1:1) media supplemented with 5% fetal calf serum with and without the addition of *cis*-parinaric acid (8 μM) for 24 hours. Phase contrast microscopy demonstrated cytoplasmic retraction with cell detachment and process retraction. Evaluation of cell surface morphology by scanning electron microscopy demonstrated marked loss of cell surface activity, loss of microvilli, involution of the cell processes, and frequent cell wall dissolution suggestive of extensive membrane disruption. Transmission electron microscopy revealed near total destruction of the mitochondria in the glioma cells treated with *cis*-parinaric acid. Marked distortion of the Golgi apparatus and involution of the nuclear membrane were also consistently observed.

The investigation of *cis*-parinaric acid induced cytotoxicity provides a model for the study of peroxidative damage in malignant glioma. The selective effects of conjugated fatty acids on malignant cell lines may result in chemotherapeutic agents which act by preferentially enhancing lipid peroxidation in neoplastic cells.

773.13

THE EFFECT OF BCNU AND GLUCOCORTICOID ON THE OXIDATIVE METABOLIC RESPONSE OF C6 GLIOMA CELLS. H.C. Liu*, Y.-F. Chang, T.-Y. Liu, C.-C. Hsieh, and C.-W. Chi. Neurological Institute and Department of Medical Research, Veterans General Hospital-Taipei, Taiwan, Republic of China.

BCNU is often used in combination with glucocorticoid to treat glioma. Whether BCNU or glucocorticoid has any effect on the oxidative metabolism of glioma is not clear. This study was to examine the effect of BCNU and/or glucocorticoid on the growth and oxidative metabolic responses of C6 glioma cells. Our results indicated no growth inhibition of C6 cells after a 24-hour continuous exposure to BCNU (95 ug/ml), hydrocortisone (1 uM) or both. Significant growth inhibition was found after C6 cells were exposed continuously to BCNU or BCNU + hydrocortisone for 48 hours. A continuous exposure of C6 cells to hydrocortisone only reduced the growth rate slightly. We examined the effect of hydrocortisone and/or BCNU on the intracellular oxidative metabolism using flow cytometry. Our results indicated that C6 cells produced low levels of reactive oxygen intermediates in response to 12-o-tetradecanoyl phorbol-13-acetate as compared to peripheral mononuclear cells. Hydrocortisone alone had little effect on the production of reactive oxygen intermediates in C6 cells, while BCNU and a combination of glucocorticoid + BCNU treatment for 48 hours increased the production.

773.14

CEREBROSPINAL FLUID INJECTION OF THALLIUM-201 FOR IMAGING INTRAVENTRICULAR DISSEMINATION OF BRAIN TUMORS. J.A. Rubertone*, N. Gaffin, J. Emrich, and L.W. Brady. Depts. of Anatomy and Radiation Oncology and Nuclear Medicine. Hahnemann Univ. Sch. of Med., Philadelphia, PA 19102

Intravenous injection of Thallium-201 (Tl-201) is an important diagnostic tool for imaging brain tumors. Since intrathecal injection of Tl-201 results in high resolution images of normal brain (Rubertone, et al., J. Nucl. Med. 1993; 34:99-103), studies were performed to test the usefulness of this technique for imaging intraventricular brain tumor. The caudoputamen nuclei of 10 male rats were stereotaxically inoculated with 15 uL of a C6 glioma cell suspension. Injection angles were calculated to allow needle tracts to pass through the lateral ventricle (LV). Two weeks post-implantation, rats received Tl-201 injections (90-200 uCi) in the contralateral LV. Three hours post-injection, unconscious rats were perfused. Brains were removed, cut in frozen section and processed for autoradiography (ARG). Comparisons of ARGs with H&E stained sections reveal that the inoculation technique employed allows for bilateral intraventricular dissemination of tumor. ARG's provide high resolution images of islands of Tl-201 labeled tumor cells far removed from implantation sites. These data suggest that intrathecal injection of Tl-201 may be an important new technique for imaging intraventricular brain tumor.

773.15

THE ASSOCIATION BETWEEN ANTI-GM1 ANTIBODY AND POEMS SYNDROME. M. H. FRIEDBERG*, K. L. FURIE AND M. J. GLANTZ. Department of Neurosciences, Brown University School of Medicine, Providence, R.I. 02912

POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein band, and skin changes) is an acronym for a paraneoplastic syndrome associated with osteosclerotic myeloma. We describe a 36-year-old man who presented with the characteristic features of POEMS and was found to have elevated anti-GM1 antibody titers. Initial ELISA studies revealed an asialo GM1 antigen titre of 1:12800. After treatment with IVIG the titre fell to 1:6400, with accompanying clinical improvement. When the clinical course subsequently declined, the Asialo GM1 titre had climbed to 1:12800. Melphalan administration resulted in subsequent improvement in symptomatology and a fall in Asialo GM1 titers to 1:1600. Thus antibody levels could repeatedly be decreased by IVIG or immmunosuppressive chemotherapy, and variation in antibody titre consistently reflected changes in clinical condition. The mechanism of the multi-organ system involvement is not understood. This case represents the first reported association between anti-GM1 antibody and POEMS. The fact that the clinical course correlated with the antibody titers supports a causal relationship between the nervous system component of this syndrome and GM1 auto-antibodies.

KEY WORD INDEX

The *Abstracts* Volume 19 Key Word Index is printed on the following pages. This subject index uses a permutation process to create an index entry for every key word in the abstract title. Key words are placed at the beginning of the center column of the index and the program numbers in the right column. Text reading left and right of the key word is retained for understanding in context. A slash (/) shows the end and the beginning of the author's title. Space limitations do not permit the full abstract title to be printed. Words with limited search value are not listed as key words. The BioSciences Information Service Subject Index is used by many scientific organizations and has become the standard in computerized scientific indexes.