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**ANNUAL REPORT
OF THE
ADDICTION RESEARCH CENTER
NATIONAL INSTITUTE ON DRUG ABUSE**

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**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse and Mental Health Administration**



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**Annual Report of the
Addiction Research Center
National Institute on Drug Abuse
January 1, 1990 - December 31, 1990
Roy W. Pickens, Ph.D., Director**

In 1990, scientists at the Addiction Research Center (ARC) made major contributions across a broad range of drug abuse issues. These contributions significantly increased our understanding of the causes, consequences, and treatments of drug abuse. They included further progress in characterizing the dopamine transporter, which has been shown to be strongly associated with the reinforcing properties of cocaine; further studies of the *sigma* receptor and its role in drug abuse; clarification of the sites in the brain at which hallucinogens act; progress toward developing possible medications for treating cocaine overdoses; studies of genetic factors associated with opiate and cocaine abuse which may eventually be important in the development of prevention and treatment programs; studies of the safety of carbamazepine, a drug which may be useful in the treatment of cocaine abuse; studies of the mechanisms involved in the cardiovascular effects of cocaine; clinical studies of nalmefene and buprenorphine, two drugs which may be useful in the treatment of opiate addiction; and a clinical study of carbamazepine for the treatment of cocaine abusers. These and other studies are described in this Annual Report.

In addition to the strides made in the ARC's science program mentioned above and described in detail in the following pages, a number of management initiatives were undertaken in 1990 to improve the oversight of the science program and to build a foundation for a stronger program in the future. In September, 1990, the ARC held the first of what will become annual Laboratory Reviews. These reviews are designed to provide the Director of the ARC with a formal presentation of the work of individual laboratories over the past year. A major effort was initiated in 1990 to provide for future expansion of several of the ARC's programs by obtaining new space. Approximately 12,000 square feet of remodeled space has been obtained in the "G Building," a building adjoining the ARC's building on the east side. This building will be used to expand our clinical ward from 18 to 32 beds, to provide space for an expanded PET program, and to expand our out-patient treatment research program from 40 to 80 slots. The out-patient treatment program will be operated under contract to provide basic drug abuse treatment services, allowing ARC staff to focus on innovative treatment research studies. The creation of this out-patient facility will also allow the ARC to expand its present Etiology program by providing it with the space now being used for treatment out-patient studies. The ARC has also obtained approximately 9,000 square feet of new space in the Triad Building, a building located about a quarter of a mile from the ARC building. This space will be used primarily to expand our animal research program which is facing severe space shortages in our current building.

Training is an integral part of the ARC's research program. Training programs at the ARC range from formal post-doctoral research fellowships to special summer training programs for high school science teachers. In 1990 the ARC provided training to 29 staff fellows, 7 visiting scientists, 17 visiting fellows, 2 IPAs and 1 IRTA. Training was provided to scientists from Japan, China, Hungary, Israel, Spain, the United Kingdom, Belgium, Denmark, Columbia, Italy, Poland, Argentina, India and Australia, as well as to scientists from the United States.

The Minority Recruitment and Training Program (MRTP) was established in 1990. The general goal is to increase the participation of minorities in research and training across the broad spectrum of activities at the ARC. Specifically, this involves increasing the number of minority persons who are trained for careers in drug abuse research, increasing the participation of minority persons in the design and execution of ARC research, increasing the sophistication of ARC scientists in the design of research relevant to minority concerns, and to enhance the access of minority researchers to ARC physical and human resources. Progress was made in each of these areas by efforts which included the following: visits by ARC staff to cluster groups of Historically Black Colleges and Universities throughout the

country to establish collaborative working relationships and obtain advice; development of contracts with minority professionals to assist in the establishment of training opportunities for minority persons at the Addiction Research Center; collaborative efforts with Historically Black Colleges and Universities in the Baltimore/Washington area in the development of conferences and training programs for undergraduate students; recruitment of minority scientists who are assisting in development of research via our guest worker and guest speaker programs, and consultantships.

In 1990, the Student Fellowship Program was supported primarily by a grant from Marion Merrell Dow Inc. for the fifth consecutive year. A total of 17 students, representing 11 colleges or universities, participated in the summer program and were placed in 12 laboratories throughout the ARC. On the basis of their interests, students were assigned to work directly with an ARC scientist on a specific research project. Additionally, students were encouraged to attend seminars, journal clubs, and clinical rounds to enhance their knowledge of drug abuse and to broaden their educational experience at the ARC.

Neuroscience Branch

Michael J. Kuhar, Ph.D. - Chief

Introduction

The Neuroscience Branch carries out interdisciplinary research to elucidate the mechanisms of action and the effects of abused drugs on biological systems. A major goal is to develop new knowledge which can be used in the development of new treatment and prevention strategies and new medications for drug abusers. Research areas include drug and neurotransmitter receptors, brain imaging, molecular biology, and the neuroanatomy and neurochemistry of reinforcement.

The Neuroscience Branch is composed of four laboratories: The Molecular Pharmacology Laboratory directed by Dr. Michael J. Kuhar; the Neuropharmacology Laboratory by Dr. Edythe London; and the Molecular Neurobiology Laboratory by Dr. George Uhl. The Neurobiology Laboratory was formerly directed by Dr. Errol De Souza, who left the ARC this past year. A search committee is currently evaluating applications to fill this position.

The Branch has been productive in a variety of areas. New chemical probes for the cocaine receptor/dopamine transporter have been characterized in *in vitro* and *in vivo* binding studies with the ultimate goal of characterizing the transporter and in carrying out brain imaging studies. PET scan studies of human volunteers have demonstrated a fundamental role of the amygdala in cocaine induced euphoria. A new, useful approach to study amphetamine uptake into nerve terminals has been developed. Receptor genes have been studied: a novel GABA receptor cDNA has been cloned and linkage between the human dopamine D₂ receptor gene and substance use was excluded.

The research of the Neuroscience Branch has received national and international recognition and attention. Dr. Michael Kuhar received the A. Ross McIntyre Award, which is given by the University of Nebraska Medical Center for an outstanding research achievement. He was also invited to give the first Ivan Davidson Memorial Lecture at the Bowman Gray School of Medicine. Dr. George Uhl received the NIDA Director's Award for outstanding achievement in establishing molecular biological and clinical programs. Dr. Edythe London received numerous invitations to present findings at national and international meetings. Dr. Errol De Souza received the Jordi Foch-Pi Award from the American Society for Neurochemistry for work carried out at the ARC. Dr. Arthur Weissman, a staff fellow in the Neurobiology laboratory, was awarded the ARC Staff Fellow Research Award.

1. Molecular Pharmacology Laboratory - Michael J. Kuhar, Ph.D., Chief

Overview

The focus of the Molecular Pharmacology Laboratory is the mesolimbic dopaminergic system and its relationship to drugs of abuse. Because of the strong evidence that mesolimbic dopaminergic neurons may be a final common pathway for some drugs of abuse, and because of the strong evidence that the psychostimulants, particularly cocaine, have receptors at the dopaminergic nerve terminal, we are currently focusing on elements of the dopaminergic synapse. A particular focus is the dopamine transporter, the "receptor" for cocaine. Current studies of the transporter include: a detailed structure-activity investigation using nearly a hundred analogues of cocaine and mazindol; efforts to purify and characterize the transporter protein; development of new ligands for both binding studies and PET and SPECT imaging; and behavioral testing of new cocaine analogues.

Summary of Ongoing Research:

A. The Cocaine Receptor.

Because of the identification of the dopamine transporter as the cocaine receptor related to drug self-administration, many studies have been focused on the dopamine transporter. A highly detailed structure-activity study of the binding of cocaine analogues to the dopamine transporter is being undertaken. At this point, approximately 60 cocaine analogues have been screened in binding assays. Several compounds that are an order of magnitude more potent than any other known cocaine analogue have been identified. In addition, several irreversible binding probes have been synthesized and characterized. The carbohydrate moiety of the dopamine transporter has been characterized extensively using enzymes that remove specific sugars from glycoproteins. It has been shown that the carbohydrate moiety is rich in sialic acids. Efforts are also underway to purify the dopamine transporter.

B. Drug Receptors, Neurotransmitters and Addiction.

This is a multifaceted project aimed at examining a variety of drugs and neurotransmitters that are associated with addiction. In one of our studies, we examined the binding of PCP to striatal cocaine receptors. We found that PCP has a low affinity for cocaine receptors and therefore would interact with cocaine receptors only at high concentrations. Thus, the bulk of the psychotropic effects of PCP are unlikely to be due to interaction with cocaine receptors. We also characterized the binding of opiate receptors with a new ligand, carfentanil, and identified a new ligand, spectramide, for D₂ dopamine receptors. Several studies are underway examining the effects of drug administration on dopamine receptors in the brain.

C. Measuring Drug Receptors In Vivo

Several new in vivo labeling ligands for the dopamine transporter have been identified. Perhaps the most promising is radiolabeled WIN 35,428. This ligand binds to cocaine receptors in vivo more efficiently than any other known compound. This finding allows us to study the occupancy of cocaine receptors in vivo by a variety of compounds. For example, in preliminary studies we recently showed that mazindol enters the brain and occupies cocaine receptors much more slowly than cocaine itself. These in vivo labeling studies will justify a study of cocaine receptors in living humans by PET and SPECT scanning in the near future.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00112-04 MPL

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Drug Receptors, Neurotransmitters and Addiction

Principal Investigators: Cooperating Units

P.I.	M.J. Kuhar	Chief, Neuroscience Branch
Others:	Cone, E.	Chief, Chemistry Laboratory, Clinical Pharmacology Branch
	Boja, J.W.	Staff Fellow, ARC

Cooperating Unit: None

Lab/Branch: Laboratory of Molecular Pharmacology,
Neuroscience Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1 **Professional:** 3/4 **Other:** 1/4

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

This project focuses on various drugs of abuse and the receptors with which they interact. We completed a study examining the binding of PCP and related compounds at the cocaine receptor. The relative potencies of these compounds were such that some of the behavioral effects of PCP might be related to its action at the cocaine receptor; in other words, the affinity of PCP at the cocaine binding site was interesting but considerably less than its affinity at its own receptor. (K_i of 1.59 mM vs. a K_i of about 0.12 mM). Thus, at high blood levels, PCP could interact with the cocaine receptor but it would most likely occupy the PCP site at the NMDA receptor at much lower concentrations.

Another study examined the movement of opiate receptors within neurons. Receptors are synthesized by the usual protein synthetic machinery of cells. They are then transported to sites and inserted into the membrane. We examined the transport of opiate receptors in rat vagus and in dorsal roots of spinal nerves. We found that the opiate receptors were transported in these neurofibers by fast transport and this agrees with many studies of other receptors. The binding sites in the axons had properties similar to those for receptors observed in brain tissue: the binding sites had appropriate pharmacology, were GTP sensitive as well as showed effects of sodium.

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Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Drug Receptors In Vivo

Principal Investigators: Cooperating Units

P.I.	M.J. Kuhar	Chief, Neuroscience Branch
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	Wagner, H.N.	Division of Nuclear Medicine, JHU
	Scheffel, U.	Division of Nuclear Medicine, JHU
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	Cline, E.	PRAT Fellow, Neuroscience Branch
	Pogun S.	Division of Nuclear Medicine, JHU
	Shaya, E.	Division of Nuclear Medicine, JHU

Cooperating Unit: Division of Nuclear Medicine,
Johns Hopkins University School of Medicine

Lab/Branch: Laboratory of Molecular Pharmacology,
Neuroscience Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 3 Professional: 2 1/4 Other: 3/4

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Considerable progress has been made in the area of imaging cocaine receptors in living animals. Our first efforts involved utilizing a known antidepressant drug, nomifensine. A detailed study of the in vivo binding characteristics of this compound revealed that it localized to dopamine transporters quite effectively but with a low specific to non-specific binding ratio. Because of this, we set out to develop more efficient binding ligands.

Studies from our laboratory previously showed that cocaine analogs, WIN-35,065-2 and WIN-35,428 were better ligands for the dopamine transporter in that higher specific to non-specific binding ratios were obtained in vivo. More recently, we utilized WIN-35,428 in a more extensive study which conclusively showed that this compound localized to cocaine receptors/dopamine transporters in rat striatum. We are in the process of utilizing this compound in its positron emitting form to carry out PET scanning studies of dopamine transporters in vivo.

One important use of in vivo labelling techniques is to examine the rate of occupancy of receptors in vivo by various drugs. Because of the availability of our in vivo labeling model using WIN-35,428, we were able to examine the relative rate of occupancy of cocaine receptor by mazindol, GBR-12,909 and

cocaine. We clearly showed that cocaine enters the brain and occupies cocaine receptors much more rapidly than mazindol or GBR-12,909. It is known that abuse liability is greater for drugs that enter the brain and occupy receptors rapidly. Thus, this model will be useful in quantitatively assessing how rapidly drugs enter the brain and occupy receptors; this will be helpful in contributing quantitative knowledge of this factor for abuse liability assessment.

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NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00108-04 MPL****Period Covered:** January 1, 1990 to December 31, 1990**Title of Project:** The Cocaine Receptor**Principal Investigators: Cooperating Units**

P.I.	M.J. Kuhar	Chief, Neuroscience Branch
Others:	Boja, J.W.	Staff Fellow, ARC
	Lew, R.	Visiting Fellow, ARC
	Simantov, R.	Visiting Fellow, ARC
	Carroll, I.	Research Triangle Institute
	Vaughan, R.	Visiting Fellow, ARC

Cooperating Unit: RTI**Lab/Branch:** Laboratory of Molecular Pharmacology,
Neuroscience Branch**Section:** None**Institute and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 6 **Professional:** 5 **Other:** 1**Check Appropriate Boxes:**

<input type="checkbox"/> Human Subjects	<input type="checkbox"/> Human Tissues	<input checked="" type="checkbox"/> Neither
<input type="checkbox"/> Minors		
<input type="checkbox"/> Interviews		

Summary of Work

In order to carry out a detailed study of the cocaine receptor, we have synthesized and tested a large number of cocaine analogs in collaboration with Dr. Ivy Carroll at RTI. For example, we found that analogs of cocaine that are also analogs of WIN 35,428 are potent in ligand binding studies as well as in dopamine transport studies in rat striatal tissue. These analogs are the most potent cocaine analogs known, some of them being 80 to 100 times more potent than cocaine itself. We have also synthesized ³H-WIN 35,065-2 and carried out binding studies because it is a potent cocaine compound that has been studied by a variety of laboratories.

These compounds also contribute substantially to structure-activity relationship information. We have shown that halogen substituents on the phenyl ring at the C3 carbon can increase potency. These studies have implications for understanding the nature of the cocaine receptor in the binding region of the molecule.

We have also utilized irreversible binding ligands at the cocaine receptor/dopamine transporter to study the carbohydrate moiety of the protein molecule. Our results indicate that the carbohydrate is rich in sialic acid residues and is probably N-linked to the protein.

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ABSTRACTS

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Carroll, F.I., J.W. Boja, A. Philip, A.H. Lewin, and M.J. Kuhar. Structure-Activity Relationships of Ring and Side-group Substitutions of the Cocaine Molecule. FASEB Journal **4**(3), 343, 1990.

Boja, J.W., A. Lewin, F.I. Carroll and M.J. Kuhar. Irreversible Binding to the Cocaine Receptor by Meta- and Para-isothiocyanato- benzoyllecgonine Methyl Ester. FASEB Journal **4**(3), 344, 1990.

Vaughan, R.A., R. Simantov, R. Lew, E. Webster and M.J. Kuhar. A Rapid Binding Assay for Soluble Dopamine Transporters. Soc. Neurosci. **16** (1), 745, 1990.

Lew, R., J.W. Boja, R. Simantov, F.I. Carroll, A. Lewin and M.J. Kuhar. New Photaffinity Probes for the Cocaine Receptor. Soc. Neurosci. **16** (1), 746, 1990.

Boja, J.W., T. Kopajtic, F.I. Carroll, A. Lewin and M.J. Kuhar. High Affinity Inhibition of the Cocaine Binding Site by Novel Cocaine Analogs. Soc. Neurosci. **16** (1), 746, 1990.

2. **Neuropharmacology Laboratory -- Edythe D. London, Ph.D., Chief**

Overview

The Neuropharmacology Laboratory investigates biological systems that mediate effects of abused drugs. Studies focus on molecular mechanisms, involving neurotransmitter systems. Techniques used include receptor binding, purification and identification of endogenous neuroactive substances, electrophysiology, and brain imaging. The information obtained may help design new treatments, including medications for substance abuse.

Summary of Ongoing Research:

A. Brain Imaging

These studies aim to elucidate brain mechanisms that underlie the etiology and sequelae of drug abuse. Euphorogenic treatments with morphine or cocaine reduced the regional cerebral metabolic rate for glucose (rCMRglc) in humans, particularly in cortical areas. These are the first and only large-scale studies with street-equivalent doses of euphoriant drugs. Cerebral ventriculomegaly was associated with insensitivity to the euphorogenic and cardiac stimulant properties of cocaine. The studies are being continued to relate mood to rCMRglc. Volunteers without drug abuse histories are being studied to determine if substance abusers have abnormal brain metabolism or electrical activity. A new study is examining effects of nicotine, with respect to tolerance and metabolic correlates of euphoria. Other protocols have been initiated to examine opioid and cocaine withdrawal, and potential therapeutic interventions. Methods to improve quantitation of PET measurements are in development.

Studies in rodents have focused on nicotine, psychomotor stimulants, and GP120 (HIV envelope glycoprotein). Chronic nicotine treatment produced tolerance to nicotine's effects on rCMRglc. Psychomotor stimulants, including cocaine and methylenedioxymethamphetamine (MDMA) stimulated rCMRglc in the extrapyramidal motor system and reduced rCMRglc in the lateral habenula. Findings with MDMA were consistent with stimulant and hallucinatory actions. Genetic differences in responsivity to cocaine were observed. As drug abusers are at risk for HIV infection, we examined the effect of GP120 on rCMRglc. GP120 reduced brain metabolism, reminiscent of decrements observed in AIDS patients with dementia. Studies in mice were performed to develop new ligands for imaging receptors with PET. The results demonstrated the feasibility of using radiolabeled nicotine and haloperidol as *in vivo* ligands.

B. Physiological Effects of Opioids

This project centers on neural systems that contribute to opioid effects. Interactions with Ca²⁺ antagonists were tested. In human volunteers, verapamil antagonized morphine-induced respiratory depression and tended to block euphoria. Interactions between nifedipine and U50488H on activities of L- and N-type Ca²⁺ channels in cultured dorsal root ganglion cells suggested additive effects at L and N channels. In the isolated spinal cord, nifedipine inhibited long latency C-fiber reflexes, but did not affect monosynaptic reflexes. Kappa and δ agonists had similar effects. Such studies may lead to safer and more effective opioid treatments.

Studies of the opioid abstinence syndrome involve intact rats, isolated neonatal rat spinal cords, and co-cultures of dorsal root ganglion and spinal dorsal horn neurons. Cerebral metabolic studies in rats showed that clonidine attenuates hypermetabolism during morphine withdrawal. We identified limbic and hypothalamic areas, not previously implicated in these phenomena.

Isomers of ketocyclazocine were tested for their ability to produce κ and σ effects in the dog. The inactivity of d- vs. l-ketocyclazocine did not reflect pharmacokinetics, and the actions of l-

ketocyclazocine typically were κ -like, lacking phencyclidine- or σ -like activity. We demonstrated that BW942C is a peptidic partial agonist at κ opioid receptors. Naltrexone-induced salivation in rats was established as a model for involvement of various opioid receptors in behavioral conditioning. l-Ketocyclazocine mainly acted as a κ drug whereas no pharmacological actions of d-ketocyclazocine were seen. We are investigating the mechanism by which DADLE, a δ opioid receptor ligand, prolongs organ survival time in an autoperfusion multi-organ preparation.

C. Ligand-Gated Ion Channels

This project is directed at elucidating modulatory mechanisms that govern the function of the superfamily of ligand-gated ion channels. The family includes the N-methyl-D-aspartate (NMDA), the nicotinic, and the gamma-aminobutyric acid (GABA) receptors.

The NMDA receptor has been a focus of study because of the interaction of phencyclidine (PCP) with sites inside the open state of the cationic channel formed by this receptor. We have studied new dimensions of NMDA receptor function, by identifying and characterizing polyamine binding sites on the NMDA receptor complex, and by discovering a mechanism of NMDA receptor regulation by redox phenomena. Some reductants (ascorbic acid, hydroquinone) inhibit ligand binding and receptor function, and protect cultured cortical cells from neurotoxicity due to excitatory amino acids. Others (dithiothreitol, mercaptoethanol), which break cystine disulfide bonds, potentiate NMDA action. Polyamine receptors offer promise of providing a template for the design of new therapeutic agents directed at the function of the NMDA receptor.

To understand the molecular basis of nicotine addiction, we study endogenous mechanisms regulating the function of nicotinic cholinergic receptors (nAChRs). We characterized interactions of noncompetitive inhibitors of nAChRs in rat brain, and used [3 H]mecamylamine as a new radioligand probe for the cationic channel of nAChRs. Nucleotides, in particularly ATP, were modulators of binding both at acetylcholine recognition sites and at sites thought to be located within the channel, suggesting a mechanism for modulation of nAChR function.

We investigated the actions of substances which might influence GABA_A receptors, which are primary targets for the actions of benzodiazepines. By using [3 H]pregnenolone sulfate and [3 H]dehydroepiandrosterone sulfate, modulatory sites on the GABA_A receptor complex were identified and characterized. Electrophysiological studies demonstrated that DHEAS is a noncompetitive inhibitor of the GABA_A receptor.

D. Sigma (σ) Receptor

The purpose of this project is to discover the biological roles of σ receptors. Structure-activity studies identified the most selective σ ligand (PRE-084) reported to date. Neuronal σ receptors were found throughout the animal kingdom. In cerebral metabolic studies, σ drugs elicited responses in σ receptor dense areas. Sigma receptors are selectively lost in certain areas of schizophrenic brains. A low-affinity receptor, closely related to tonic K⁺ channels was identified. The report was the first of a receptor affecting such a channel. The possible relationship between high- and low-affinity σ receptors is being investigated. Sigma receptors displayed a unique subcellular distribution. Solubilized receptors from rat brain and liver retain all pharmacological characteristics of membrane-bound receptors, including high affinity for progesterone. Purification of σ receptors is underway.

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Su, T.-P., Wu, X.-Z., Spivak, C.E., London, E.D. and Bell, J.A.: Binding studies on intact NCB-20 cells suggest σ receptor multiplicity: σ_1 and σ_2 . In: NMDA Related Agents: Biochemistry, Pharmacology and Behavior. Proceedings from a satellite symposium of the 17th Congress of Collegium Internationale Neuro-Psychopharmacologicum, Nagoya, Japan, Sept. 16-17, 1990, NPP Books, Inc., Ann Arbor, MI, T. Nabeshima, T. Kameyama, and E.F. Domino, eds.

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ABSTRACTS

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- Wong, D.F., Gibson, R., London, E.D., Burns, H.D., Shaya, E., Dannals, R.F., Ravert, H.T., Wilson, A.A. and Wagner Jr., H.N.: In vivo studies of σ receptors with radiolabeled haloperidol. Soc. Neurosci. Abstr. 16:1140, 1990.
- Zaczek, R., Culp, S., McCann, D.J. and De Souza, E.D.: Sequestration of ^3H -amphetamine into rat brain synaptosomes. Trans. Am. Soc. Neurochem. 21:248, 1990.
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- London, E.D.: Sigma receptor deficits in schizophrenia: Postmortem studies suggest a potential for PET diagnosis. Am. College of Neuro-Psychopharmacology Annual Meeting, San Juan, PR, Dec. 9-14, 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00200-05 NPL****Period Covered:** January 1, 1990 to December 31, 1990**Title of Project:**

CEREBRAL EFFECTS OF ABUSED DRUGS: BRAIN IMAGING IN HUMANS AND LABORATORY ANIMALS

Principal Investigator:

E.D. London (Chief, Neuropharmacology Lab, NPL, ARC)

Others from NPL, ARC: Kimes, A.S. (Biologist), Phillips, R.L. (Sr. Staff Fellow)

Stapleton, J.M. (Staff Fellow), Morgan, M.J. (Visiting Fellow), Yung, C.-K. (Visiting Fellow)

Cooperating Units:

ARC: Herming, R. (Visiting Scientist, Psychology of Vulnerability and Cognitive Studies Laboratory, VCS)

The Johns Hopkins Medical Institutions: Wong, D.F., Links, J., Dannals, R.F., Grayson, R., Wagner, H.N., Jr.

Lab/Branch: Neuropharmacology Laboratory/Neuroscience Branch

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 5.60 **Professional:** 4.10 **Other:** 1.5**Check Appropriate Boxes:** Human Subjects Human Tissues Neither Minors Interviews**Summary of Work:**

Human positron emission tomographic (PET) scanning, using the [¹⁸F]fluoro-deoxyglucose (FDG) method in placebo-controlled crossover studies, showed that euphorogenic doses of morphine or cocaine decrease rCMRglc, especially in cortical regions. The findings suggest that drugs of abuse produce euphoria by a mechanism which involves a reduction of rCMRglc. This hypothesis is being tested by examining the effects of other abused drugs (nicotine, buprenorphine). Future PET studies with FDG will be used to obtain an objective measure of the opioid abstinence syndrome in human subjects, in order to test the effects of potential medications.

Effects of nicotine and psychomotor stimulants on rCMRglc were studied by the deoxyglucose (DG) method in rats. Whereas nicotine stimulated rCMRglc in a pattern reflecting the distribution of nicotinic receptors, chronic nicotine produced tolerance, seen as a reduced response in some areas. In Fischer-344 rats, cocaine increased rCMRglc in motor areas and reduced rCMRglc in the lateral habenula. Lewis rats were more sensitive to the effects than Fischer-344 rats, and showed reductions in rCMRglc of the cortex, suggesting that genetic differences may influence susceptibility to cocaine abuse. Studies in gallamine-treated rats demonstrated that effects of psychomotor stimulant drugs on rCMRglc in motor systems are not secondary to limb movement.

The DG method also was used to identify brain areas important to opioid analgesia and the opioid abstinence syndrome. Although the formalin pain model was not associated with significant differences in rCMRglc as compared with control, morphine produced a dose-dependent reduction of rCMRglc in thalamic nuclei as well as in other areas implicated in nociception. The DG method was used to show that hypermetabolism in the brain, precipitated by administration of naloxone to opioid-dependent rats, is reversed by doses of clonidine which attenuate the opioid abstinence syndrome. Thus, efficacy of therapeutic interventions may be monitored by in vivo brain imaging in humans, using PET.

PUBLICATIONS

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London, E.D., Wilkerson, G.W., Ori, C. and Kimes, A.S.: Central action of psychomotor stimulants on glucose utilization in extrapyramidal motor areas of the rat brain. Brain Res. 512:155-158, 1990.

Henningfield, J.E., London, E.D. and Benowitz, N.L.: Arterio-venous differences in plasma concentrations of nicotine after cigarette smoking. JAMA 263:2049-2050, 1990.

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Cohen, S.R., Kimes, A.S. and London, E.D.: Morphine decreases cerebral glucose utilization in limbic and forebrain regions while pain has no effect. Neuropharmacology, in press.

Cascella, N.G., Pearlson, G., Wong, D.F., Broussolle, E.P.M., Nagoshi, C., Margolin, R.A. and London, E.D.: Effects of substance abuse on ventricular and sulcal measures assessed by computed tomography. British J. Psychiatry, in press.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project:

PHYSIOLOGICAL EFFECTS OF OPIOIDS

Principal Investigator:

E.D. London (Chief, Neuropharmacology Lab, NPL, ARC)

Others from NPL, ARC: Su, T.-P. (Pharmacologist), Bell, J.A. (Pharmacologist),

Vaupel, D.B. (Pharmacologist), Wu, X.-Z. (Visiting Associate),

Cooperating Units:

ARC: Goldberg, S. (Chief, Preclinical Pharmacology Branch), Katz, J. (Chief, Psychobiology Lab),

Cone, E. (Chief, Chemistry & Drug Metabolism Lab.)

Lab/Branch: Neuropharmacology Laboratory/Neuroscience Branch

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2.10 Professional: 2.10 Other: 0.00

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

Summary of Work:

We initiated studies on the interactions of verapamil (V), a Ca²⁺ channel antagonist, with morphine (M) in human volunteers. Preliminary findings suggest the following conclusions: 1. V reduces euphorogenic effects of M; 2. V reduces M-induced respiratory depression; and 3. V does not affect opioid analgesia.

Using the isolated spinal cord, nifedipine, another Ca²⁺ channel blocker, and opioids block long latency - fiber reflexes, but have no effect on short latency monosynaptic reflexes. In contrast, in dorsal root ganglion cell cultures, opioids block N-type Ca²⁺ channels and nifedipine blocks L-type channels. Thus, Ca²⁺ channel antagonists and opioids both interfere with synaptic transmission, but they appear to act at different Ca²⁺ channels within the neuronal membrane.

Comparisons of LAAM, norLAAM and dinorLAAM with morphine and methadone in the dog are being analyzed using a new parallel line bioassay program. NorLAAM is the most potent with respect to acute effects and in suppressing morphine withdrawal. In addition, LAAM and both metabolites produce acute physical dependence.

Binding studies suggest that opioid receptors may be involved in behavioral conditioning. Rats trained under an fixed-ratio schedule became supersensitive to the rate-suppressing effects of naltrexone after weekly injections of naltrexone. Both kappa (κ) and delta (δ), but not mu (μ) receptors were altered in certain brain areas suggesting that conditioning may involve changes in κ and δ opioid receptors.

In a multiple organ perfusion system, hibernation induction trigger (HIT) and DADLE, a synthetic δ opioid peptide, prolonged organ survival time. Mechanisms of actions of HIT and DADLE in this preservation model are under investigation.

The pharmacology of the pentapeptide BW942C was examined in human and animal urination studies, isolated tissue preparations and binding studies. Results of dose-response analysis, antagonism studies and tolerance-cross tolerance paradigms suggest that BW942C is the first identified partial κ agonist that is also a full μ agonist.

PUBLICATIONS

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Schindler, C.W., Wu, X.-Z., Su, T.-P., Goldberg, S.R. and Katz, J.L.: Enhanced sensitivity to the behavioral effects of naltrexone in rats: A conditioning phenomenon associated with opioid receptor changes. J. Pharmacol. Exp. Ther. 252:8-14, 1990.

Su, T.-P., Chien, S.F. and Oeltgen, P.R.: Hibernation Induction Trigger (HIT) extends preservation time in an autoperfusion multiorgan preparation. Clin. Pharmacol. Ther. 47:140, 1990.

Bell, J.A.: Naloxone-induced facilitation of C-fiber reflexes is reduced by chronic morphine. Eur. J. Pharmacol. 168:101-105, 1990.

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Period Covered: January 1, 1990 to December 31, 1990

Title of Project: LIGAND-GATED ION CHANNELS

Principal Investigator:

E.D. London (Chief, Neuropharmacology Lab, NPL, ARC)

Others From NPL, ARC: Mantione, C.R. (Sr. Staff Fellow.), Majewska, M.D. (Sr. Staff Fellow), Spivak, C.E. (Pharmacologist)

Cooperating Units:

Lab/Branch: Neuropharmacology Laboratory/Neuroscience Branch

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 5.20 Professional: 4.62 Other: .40

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

Summary of Work:

This project focuses on the receptor superfamily of ligand-gated ion channels, including the N-methyl-D-aspartate receptor (NMDA-R), the nicotinic cholinergic receptor (nAChR), and the GABA_A receptor (GABA-R).

NMDA-R is of interest because phencyclidine binds to sites inside the open state of the ionic channel formed by the receptor. This receptor has been linked to neurodegeneration in various conditions, including ischemia, epilepsy, and Huntington's disease. Our studies show that NMDA-R is regulated by tissue redox phenomena, as some reducing agents (e.g., ascorbic acid, hydroquinone) produce inactivation, whereas others (dithiothreitol) facilitate receptor activation. Furthermore, we found that ascorbic acid protects cultured cortical cells from the NMDA- and glutamate-induced toxicity. Using [³H]spermidine, we have identified and characterized polyamine receptors, which also appear to modulate activity of NMDA-R. Our assay system may provide a template for the design of therapeutic agents to alter the function of the NMDA-R.

[³H]Mecamylamine was used as a new radioligand probe for the cationic channels of nAChRs. We discovered that the binding of [³H]mecamylamine and [³H]chlorpromazine is markedly increased by some purinergic nucleotides (e.g., ATP), suggesting that they may be important modulators of nAChR. Preliminary studies have shown that polyamines negatively modulate the binding of [³H]mecamylamine but not [³H]methylcarbamylcholine (a ligand for the acetylcholine recognition site of nAChRs) in brain. Since both receptors are ligand-gated cationic channels, it seems possible that polyamines generally are regulators of such receptors.

Pregnenolone sulfate (PS) and dehydroepiandrosterone sulfate (DHEAS) are modulators of GABA-R. We examined binding of [³H]PS in the rat brain, noting that this steroid seems to interact at the interface

of the receptor with associated phospholipids. We identified and characterized specific binding sites for [³H]DHEAS, and demonstrated, by biochemical and electrophysiological methods, that DHEAS is a noncompetitive negative modulator of the GABA_A receptor complex.

PUBLICATIONS

Mantione, C.R., Demirgoren, S. and London, E.D.: Specific binding of [³H]spermidine to membranes of rat brain. Eur. J. Pharmacol. **180**:393-394, 1990.

Majewska, M.D., Demirgoren, S., Spivak, C.E. and London, E.D.: The neurosteroid dehydroepiandrosterone sulfate is an allosteric antagonist of the GABA_A receptor. Brain Res. **526**:143-146, 1990.

Majewska, M.D.: Steroid regulation of GABA receptor: ligand binding, chloride transport, behavior. In: Steroids and Brain Activity (Ciba Foundn. Symp. No. 153), (G. Bock and J. Marsh, eds.) Wiley, Chichester, 1990. PP. 83-106.

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Majewska, M.D.: Neurosteroids, metabolism and function. Neuroscience Facts **1**:2, 1990.

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Majewska, M.D. and Bell, J.A.: Ascorbic acid protects neurons from injury induced by glutamate and NMDA. Neuroreport **1**:194-196, 1990.

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Spivak, C.E., Waters, J.A. and Aronstam, R.S.: (+)-Octahydro-2-methyl-trans-5(1H)-isoquinolone methiodide: A probe to test the steric limits of agonists active at the nicotinic acetylcholine receptor. J. Mol. Graphics, in press.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00206-06 NPL****Period Covered:** January 1, 1990 to December 31, 1990**Title of Project:** SIGMA RECEPTORS**Principal Investigator:**

Su, T.-P. (Pharmacologist)

Others from NPL, ARC: London, E.D. (Chief, Neuropharmacology Laboratory), Spivak, C.E. (Pharmacologist), Bell, J.A. (Pharmacologist), Wu, X.-Z. (Visiting Associate), McCann, D. (Staff Fellow), Kimes, A.S. (Biologist)

Cooperating Units:**Lab/Branch:** Neuropharmacology Laboratory/Neuroscience Branch

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2.53 **Professional:** 2.43 **Other:** 0.10

Check Appropriate Boxes:

 Human Subjects Human Tissues Neither Minors Interviews**Summary of Work:**

This project examines molecular, electrophysiological, and in vivo interactions of ligands for sigma (σ) receptors. A unifying hypothesis for binding of σ ligands, including steroids, "atypical" antipsychotics, such as BMY-14802 and remoxipride, and the most selective σ ligand, PRE-084, was formulated using conformational fitting and electrostatic potential calculations. All σ ligands have a pharmacophore with three sites of interaction; the distances between the sites are identical for the ligands. Surface maps of electrostatic charges also are similar for all σ ligands tested.

Solubilized σ receptors were labeled with [³H]progesterone, providing the first direct demonstration of steroid binding to the receptors. Solubilized σ receptors also are modulated by certain anticonvulsant drugs. A preliminary estimation of the molecular weight of solubilized σ receptors was obtained using molecular sizing chromatography.

A low affinity σ receptor that modulates the closing of a tonic potassium channel was demonstrated in the NCB-20 cells. The low affinity receptor may play an important physiological and pharmacological role in locomotion regulation.

Studies of postmortem brains from schizophrenic patients demonstrated selective losses of σ receptors in the temporal cortex and dentate nucleus of the cerebellum, suggesting a role of the σ receptor in psychosis, and underscoring the importance of imaging the σ receptor in vivo. Studies in mice indicated that radiolabeled d-N-allylnormetazocine and haloperidol show potential to be developed as in vivo ligands. Studies of the binding of [¹²⁵I]p-iodophenyl amantylguanidine (PIPAG), a potential SPECT ligand, to guinea pig brain showed high affinity (0.6 nM) and a pharmacological profile and neuroanatomical distribution typical of the classical σ receptor.

Future work includes molecular modeling studies on other σ ligands, further chemical and pharmacological studies of PRE-084, purification of σ receptors, and biochemical studies on the mechanism of modulation of the low affinity σ receptor on the tonic potassium channel.

PUBLICATIONS

Vu, T.H., Weissman, A.D. and London, E.D.: Pharmacological characteristics and distributions of σ and phencyclidine binding sites in the animal kingdom. J. Neurochem. 54:598-604, 1990.

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Weissman, E.D., Broussolle, E.P. and London, E.D.: In vivo binding of [³H]d-N-allylnormetazocine and [³H]haloperidol to sigma receptors in the mouse brain. J. Chem. Neuroanatomy 3:347-354, 1990.

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Su, T.-P., Shuklar, K. and Gund, T.: Steroid binding at σ receptors: CNS and immunological implications. In: Steroids and Neuronal Activity (Ciba Foundn. Symp. No. 153), (D.J. Chadwick, K. Widdows, eds.) Wiley, Chichester, 1990.

Weissman, A.D., Cassanova, M.F., Kleinman, J.F., London, E.D. and De Souza, E.B.: Selective reduction of cerebral cortical sigma, but not PCP binding sites in schizophrenia. Biol. Psych., in press.

Su, T.-P., Wu, X.-Z., Spivak, C.E., London, E.D. and Bell, J.A.: Binding studies on intact NCB-20 cells suggest σ receptor multiplicity: σ_1 and σ_2 . In: NMDA Related Agents: Biochemistry, Pharmacology and Behavior. Proceedings from a satellite symposium of the 17th Congress of Collegium Internationale Neuro-Psychopharmacologicum, Nagoya, Japan, Sept. 16-17, 1990, NPP Books, Inc., Ann Arbor, MI, T. Nabeshima, T. Kameyama, and E.F. Domino, eds.

Wu, X.-Z., Bell, J.A., Spivak, C.W., London, E.D. and Su, T.-P.: Electrophysiological and binding studies on intact NCB-20 cells suggest presence of a low affinity sigma receptor. J. Pharmacol. Exp. Ther., in press.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: HIV INFECTION AND DRUG ABUSE

Principal Investigators:

Kimes, A.S. (Biologist, Neuropharmacology Laboratory)

Other: London, E.D. (Chief, Neuropharmacology Laboratory)

Cooperating Units:

USAMRICD, Aberdeen Proving Ground, MD, Smith, W.J. (Research Chemist, Biochemical Pharmacology Branch),

Intramural Research Program, NIAAA, Bethesda, MD, Tabakoff, B. (Director),

Szabo, J. (Visiting Fellow)

Lab/Branch: Neuropharmacology Laboratory/Neuroscience Branch

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.15 Professional: 0.15 Other: 0.00

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

Summary of Work:

Human immunodeficiency virus (HIV) infection in the central nervous system is characterized by dementia and deficits in motor functions. Cerebral metabolic effects of gp120 (a HIV viral envelope glycoprotein), which binds to brain membranes and T-lymphocytes, were studied in rats. Intracerebroventricular injection of gp120 reduced the regional cerebral metabolic rate for glucose in the lateral habenula and the suprachiasmatic nucleus, and produced an overall decrease in glucose metabolism. As reduced glucose metabolism is observed using positron emission tomography in humans presenting with HIV-associated dementia, the findings suggest that gp120 can alter neuronal function and contribute to HIV-related dementia.

As intravenous drug abusers show an abnormally high incidence of HIV infection, animal studies were performed to determine if chronic exposure to abused substances alters immune function. Mice receiving chronic opioid treatment had fewer circulating T-lymphocytes (helpers and suppressor/cytotoxic) than concurrent controls. The effect was dose-dependent, was not blocked by treatment with the opioid antagonist naltrexone, and could be observed within 24 h of initiation of treatment. Oxymorphone caused a similar effect. Morphine treatment did not affect mitogen-stimulated lymphocyte proliferation. This work suggests that morphine compromises immunocompetency and that the use of opioids by intravenous drug abusers may increase the incidence of infection subsequent to exposure to bacterial and viral agents.

PUBLICATIONS

Kimes, A.S., London, E.D., Szabo, G., Raymon, L. and Tabakoff, B.: Reduction of cerebral glucose utilization by the HIV envelope glycoprotein gp-120. Exp. Neurol., in press.

3. **Neurobiology Laboratory - Errol B. De Souza, Ph.D., Chief,**

Overview

The Laboratory of Neurobiology conducts research on the neurobiological underpinnings of drug abuse and addiction. At present, the Laboratory has three major areas of research which include 1) the study of the neuroendocrine aspects of addiction, with a focus on stress, hypothalamic peptides and drugs of abuse, 2) the study of the pharmacological and neurotoxic effects of drugs of abuse, and 3) the study of the brain-neuroendocrine-immune axis and its related peptides, hormones, lymphokines and monokines. The Laboratory utilizes a multifaceted approach which includes biochemical, cellular, pharmacological, neuroendocrine and neuroanatomical techniques to investigate the problems outlined above.

During the past year Dr. Errol B. De Souza has taken a position in industry and has left the ARC. At this point in time, a review of the Laboratory is being conducted and a search is made for a new Laboratory Chief. Within the next year, it is expected that plans will be made for the utilization of the resources in this laboratory.

Summary of Ongoing Research

Research has been conducted in a variety of areas related to drug abuse. One area has been corticotropin releasing factor (CRF) which is a stress-related neurotransmitter in the central nervous system. Relapse to addiction often is associated with stress and molecular mechanisms of stress have been explored in this context. The main focus of this program has been the CRF receptor and a number of studies have been carried out on this receptor.

Another area of research involves the role of neurotransmitters and their receptors in human neuropsychiatric disorders and neurodegenerative diseases. For example, changes in sigma and PCP receptors have been examined in the brains from human populations.

The designer drugs MDA and MDMA have potent, long-lasting neurotoxic effects in brain. These have been explored in rodent models of toxicity. Both biochemical and neurohistological changes have been identified.

Additional projects include an examination of neurochemical, neuroendocrine, and neurotoxic effects of other drugs. Also, interactions of the brain-endocrine-immune axis have been examined. In particular, receptors for interleukin-1 have been examined.

Publications

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Weissman, A.D., Casanova, M.F., Kleinman, J.E., London, E.D. and De Souza, E.B. Selective reduction in cerebral cortical sigma, but not PCP binding sites in schizophrenia. Biological Psychiatry 29:41-54, 1991.

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Goeders, N.E., Bienvendu, O.J. and De Souza, E.B. Chronic cocaine administration alters corticotropin-releasing factor receptors in the rat brain. Brain Research (in press).

Blake, M.J., Appel, N.M., Joseph, J.A., Stagg, C.A., Anson, M., De Souza, E.B. and Roth, G.S. Muscarinic acetylcholine receptor subtype mRNA expression and ligand binding in the aged rat brain. Neurobiol. of Aging (in press).

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Battaglia, G., Sharkey, J., Kuhar, M.J. and De Souza, E.B. Neuroanatomic specificity and time course of alterations in rat brain serotonergic pathways induced by MNDA (3,4-methylenedioxyamphetamine): assessment using quantitative autoradiography. Synapse (in press)

Cunningham, E.T., Jr., Wada, E., Carter, D.B., Tracey, D.E., Battey, J.F. and De Souza, E.B. Localization of interleukin-1 receptor messenger RNA in murine hippocampus. Endocrinology (in press)

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Appel, N.M., Mitchell, Wm.M., Garlick, R.K., Glennon, R.A., Titeler, M. and De Souza, E.B. Autoradiographic characterization of ¹²⁵I-labeled 2,5-dimethoxy-4-iodophenylisopropylamine (DOI): A phenylisopropylamine derivative labeling both 5HT₂ and 5HT_{1C} receptors. FASEB J., 4:A328, 1990.

Wolfe, S.A., Jr., Aguayo, L.G. and De Souza, E.B. Sigma receptors in rat pineal gland: Electrophysiology and autoradiographic localization. FASEB J., 4:A329, 1990.

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Takao, T., Tracey, D.E., Mitchell, Wm.M. and De Souza, E.B. Interleukin-1 receptors in mouse brain: Characterization and autoradiographic localization. Soc. for Neurosci. 16:1213, 1990.

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De Souza, E.B. and Weissman, A.D. Neurotoxicity of phencyclidine and related drugs: Introduction to the problem and human autopsy data. American College of Neuropsychopharmacology, San Juan, Puerto Rico, p. 82, 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00302-03 NBL

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Neurotoxic Effects of MDA and MDMA (Ecstasy)

Principal Investigators: Cooperating Units

P.I. E.B. De Souza Chief, Neurobiology Laboratory

Others: R. Zaczek Staff Fellow, ARC
N.M. Appel Staff Fellow, ARC
A. Weissman Staff Fellow, ARC
S.Y. Yeh Scientist, ARC
T. Insel Scientist, LCS, NIMH

Cooperating Unit: Laboratory of Clinical Science, NIMH

Lab/Branch: Laboratory of Neurobiology, Neuroscience Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 3.00 **Professional:** 2.2 **Other:** 0.8

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Substantial progress has been made in examining the mechanism of action and the effects of amphetamine as well as amphetamine analogs. We have found that ³H-amphetamine is sequestered by synaptosomal fractions from brain. The neurotoxic effects of MDMA on brain serotonin neurons has been explored further by both biochemical techniques as well as autoradiographical techniques. Overall, these studies elucidate the mechanism of action of amphetamine as well as further explain the neurotoxic effects of drugs like MDMA.

This project will not be continued in 1991.

PUBLICATIONS

Zaczek, R., Culp, S.G. and De Souza, E.B. Intrasyntosomal sequestration of [³H]-amphetamine and [³H]-methylenedioxy-amphetamine: Characterization suggests the presence of a factor responsible for maintaining sequestration. J. Neurochem. 54:195-204, 1990.

Zaczek, R., Culp, S., Goldberg, H., McCann, D.J. and De Souza, E.B. Interactions of [³H]-amphetamine with rat brain synaptosomes: Part I. Saturable sequestration. J. Pharmacol. Exp. Ther. (in press).

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De Souza, E.B., Battaglia, G. and Insel, T.R. Neurotoxic effects of MDMA on brain serotonin neurons: Evidence from neurochemical and radioligand binding studies. Annals New York Acad. Sci. (The Neuropharmacology of Serotonin), Vol. 600:682-698, 1990.

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Kuhar, M.J. and De Souza, E.B. Receptor autoradiography as an aid in explaining drug action. In: Imaging the Functional Neuroanatomy of Drug Action (E.D. London, ed.), The Telford Press, Caldwell, N.J. (in press).

Zaczek, R., Culp, S., McCann, D. and De Souza, E.B. Sequestration of ³H-amphetamine into rat brain synaptosomes. American Society of Neurochemistry Meeting, Abstr. #324, 1990

Zaczek, R., Culp, S. and De Souza, E.B. High-affinity active transport of [³H]-d-amphetamine into rat striatal synaptosomes. Soc. for Neurosci., 16:303, 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00303-03 NBL

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: CRF in Addictive, Neuropsychiatric and Neurodegenerative disorders

Principal Investigators: Cooperating Units

P.I. E.B. De Souza Chief, Neurobiology Laboratory

Others: D.E. Grigoriadis Postdoctoral Fellow, ARC
D. Price Professor, JHU
N. Goeders Assoc. Professor, LSU

Cooperating Unit: Neuropathology Laboratory, JHU
Department of Pharmacology, Louisiana State
University Medical Center

Lab/Branch: Laboratory of Neurobiology, Neuroscience Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 3.0 **Professional:** 2.0 **Other:** 1.0

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

The role of CRF in neurodegenerative diseases such as Alzheimer's disease has been examined. Changes in CRF and its receptor have been described. The role of CRF in neuropsychiatric disorders has been speculated upon as well as directly examined in patients with generalized anxiety disorder.

This project will not be continued in 1991.

PUBLICATIONS

McLeod, D.R., Hoehn-Saric, R., Zimmerli, W.D., De Souza, E.B., and Oliver, L.K. Treatment effects of Alprozolam and Imipramine: Physiological versus subjective changes in patients with generalized anxiety disorder. Biological Psychiatry 28:849-861, 1990.

De Souza, E.B., Bissette, G., Whitehouse, P.J., Price, D.L., Vale, W.W. and Nemeroff, C.B. Role of corticotropin-releasing factor (CRF) in neurodegenerative diseases. In: Corticotropin- Releasing Factor: Basic and Clinical Studies of a Neuropeptide, (E.B. De Souza and C.B. Nemeroff, eds.), CRC Press, Boca Raton, FL., pp. 335-349, 1990.

De Souza, E.B. Role of corticotropin-releasing factor in neuropsychiatric disorders and neurodegenerative diseases. Annual Reports in Medicinal Chemistry, Vol. 25 (Topics in Biology):215-224, 1990.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: CRF as a Stress Neurotransmitter in the Brain-Endocrine-Immune Axis

Principal Investigators: Cooperating Units

P.I. E.B. De Souza Chief, Neurobiology Laboratory

Others: D.E. Grigoriadis Postdoctoral Fellow, ARC
E. Webster Staff Fellow, ARC

Cooperating Unit: None

Lab/Branch: Laboratory of Neurobiology, Neuroscience Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 3.5 Professional: 2.8 Other: 0.7

Check Appropriate Boxes:

- ___ Human Subjects ___ Human Tissues X Neither
___ Minors
___ Interviews

Summary of Work

A variety of studies on CRF receptors in the brain-endocrine-immune axis have been carried out. CRF receptors have been identified in the mouse spleen; the cells bearing these receptors appear to be macrophages. Also, age-related decreases in CRF receptors have been identified in the brain and anterior pituitary gland of the rat. These major findings have been summarized in several publications.

This project will not be continued in 1991.

PUBLICATIONS

Webster, E.L., Tracey, D.E., Jutila, M.A., Wolfe, S.A. Jr. and De Souza, E.B. Corticotropin-releasing factor (CRF) receptors in mouse spleen: Identification of receptor bearing cells as resident macrophages. Endocrinology 127:440-452, 1990.

Heroux, J.A., Grigoriadis, D.E. and De Souza, E.B. Age-related decreases in corticotropin-releasing factor receptors in the brain and anterior pituitary gland of the rat. Brain Research 542:155-158, 1991.

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De Souza, E.B., Grigoriadis, D.E. and Webster, E.L. Role of brain, pituitary and spleen corticotropin-releasing factor (CRF) receptors in the stress response. In: The Stress of Life, Revisited (Methods and Achievements in Experiment Pathology) (G. Jasmin and M. Cantin, eds.), S. Karger, Switzerland (in press).

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De Souza, E.B. Role of corticotropin-releasing factor (CRF) and its receptors in coordinating the endocrine, autonomic and behavioral responses to stress. European Winter Conference on Brain Research, Les Arcs 2000, France.

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Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Neurotoxicity of Selected Drugs to Monoamine Neurons in Brain

Principal Investigators: Cooperating Units

P.I. E.B. De Souza Chief, Neurobiology Laboratory

Others: R. Zaczek Staff Fellow, ARC
 N.M. Appel Staff Fellow, ARC
 J.C. Contrera Pharmacologist, FDA

Cooperating Unit: Food and Drug Administration, Rockville, MD

Lab/Branch: Laboratory of Neurobiology, Neuroscience Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2.0 **Professional:** 1.5 **Other:** 0.5

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

The effects of selected drugs on monoamine neurons in brain has been examined. Fenfluramine, in high doses, has been found to decrease monoamine uptake sites in rat brain suggesting a neurotoxic effect at these high doses. The pharmacokinetics, and regional specificity as well as the time course of these effects have been examined. Also, DSP-4 has been shown to have different effects on norepinephrine uptake in the cerebral cortex versus the hypothalamus. These studies provide evidence for a heterogeneity of norepinephrine sites.

This project will not be continued in 1991.

PUBLICATIONS

Appel, N.M., Mitchell, Wm.M., Contrera, J.F. and De Souza, E.B. Effects of high-dose fenfluramine treatment on monoamine uptake sites in rat brain: Assessment using quantitative autoradiography. Synapse 6:33-44, 1990.

Zaczek, R., Battaglia, G., Culp, S., Appel, N.M., Contrera, J.F. and De Souza, E.B. Effects of repeated fenfluramine administration on indices of monoamine function in rat brain: Pharmacokinetics, dose response, regional specificity and time course data. J. Pharmacol. Exp. Ther. 253:104-112, 1990.

Zaczek, R., Fritschy, J-M., Culp, S., De Souza, E.B. and Grzanna, R. Differential effects of DSP-4 on norepinephrine uptake into synaptosomes from cerebral cortex and hypothalamus: Evidence for heterogeneity of the norepinephrine uptake sites. Brain Research 522:308-314, 1990.

Appel, N.M., Owens, M.J., Culp, S., Zaczek, R., Contrera, J.F., Bissette, G., Nemeroff, C.F. and De Souza, E.B. Role of brain corticotropin-releasing factor in the weight-reducing effects of chronic fenfluramine treatment in rats. Endocrinology (in press).

Appel, N.M., Zaczek, R., Mitchell, Wm.M. and De Souza, E.B. Immunohistochemical and autoradiographic investigations of high-dose fenfluramine treatment on monoamine neurons in rat brain. In: Proceedings of Int. Symp. on Serotonin: From Cell Biology to Pharmacology and Therapeutics, (P. Paoletti, P.M. Vanhoutte, N. Brunello and F.M. Maggi, eds.) Kluwer Academic Publishers, Boston pp. 625-629, 1990.

Appel, N.M., Zaczek, R., Owens, M., Culp, S., Nemeroff, C.B. and DeSouza, E.B. Relationships between brain serotonin (5HT) and corticotropin-releasing hormone (CRH) in the anti-obesity effects of fenfluramine. 1990 Winter Neuropeptide Conference, Breckenridge, Colorado, 1990.

De Souza, E.B. Role of corticotropin-releasing factor (CRF) in the development of obesity syndromes and in the effects of antiobesity drugs. Winter Neuropeptide Conference, Breckenridge, Colorado, 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00311-02 NBL

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Sigma and PCP Receptors in Neuropsychiatric Disorders

Principal Investigators: Cooperating Units

P.I.	E.B. De Souza	Chief, Neurobiology Laboratory
Others:	A.D. Weissman	Staff Fellow, ARC
	E.D. London	Chief, Neuropharmacology Lab, ARC
	M. Casanova	Scientist, NIMH
	J. Kleinman	Deputy Chief, Clin Brain Disorders Branch, NIMH

Cooperating Unit: Neuropharmacology Laboratory, ARC, NIDA
Clinical Brain Disorders Branch,
St. Elizabeth's Hospital, NIMH

Lab/Branch: Laboratory of Neurobiology, Neuroscience Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.5 **Professional:** 1.3 **Other:** 0.2

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

An interesting finding has been that sigma binding sites but not PCP binding sites are reduced in the cerebral cortex in schizophrenia. However, neither of these receptors are altered in brains thought to be derived from PCP abusers. Chronic administration of D-pentazocine does not alter brain sigma or dopamine receptors. These results suggest that there is a connection between sigma receptors and schizophrenia or, possibly between sigma receptors and the treatment of schizophrenia by psychoactive drugs.

This project will not be continued in 1991.

PUBLICATIONS

Weissman, A.D., Casanova, M.F., Kleinman, J.E., London, E.D. and De Souza, E.B. Selective reduction in cerebral cortical sigma, but not PCP binding sites in schizophrenia. Biological Psychiatry 29:41-54, 1991.

Weissman, A.D., Casanova, M.F., Kleinman, J.E., London, E.D. and De Souza, E.B. PCP and sigma receptors in brain are not altered after repeated exposure to PCP in man. Neuropsychopharmacology 4:95-102, 1991.

Weissman, A.D. and De Souza, E.B. Brain sigma and dopamine receptors are not modulated by chronic d-pentazocine administration in rats. Eur. J. Pharmacol. (in press).

Weissman, A.D. and De Souza, E.B. Postmortem investigations of sigma and PCP receptors in psychosis. In: Excerpta Medica International Congress Series (5th World Congress of Biological Psychiatry, Florence) 1991.

Weissman, A.D. and De Souza, E.B. Brain sigma and dopamine receptors are not modulated by chronic d-pentazocine administration in rats. Soc. for Neurosci. 16:1305, 1990.

De Souza, E.B. and Weissman, A.D. Neurotoxicity of phencyclidine and related drugs: Introduction to the problem and human autopsy data. American College of Neuropsychopharmacology, San Juan, Puerto Rico, p. 82, 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00307-03 NBL

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Effects of Cocaine on Monoamines and their Metabolites in Rat Brain

Principal Investigators: Cooperating Units

P.I. S.Y. Yeh Pharmacologist, ARC

Others: E.B. De Souza Chief, Neurobiology Lab, ARC

Cooperating Unit: None

Lab/Branch: Laboratory of Neurobiology, Neuroscience Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.5 **Professional:** 0.5 **Other:** 0.5

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

A controversy regarding cocaine effects is whether or not chronic cocaine causes a degeneration of monoaminergic neurons in brain. Currently, there are some papers in the literature suggesting that such a neurotoxic effect occurs but many investigators have failed to replicate these findings. In a detailed study, we were unable to obtain any evidence for a neurochemical neurotoxicity due to repeated cocaine administration. These results support the notion that chronic cocaine does not cause a degeneration of monoamine containing neurons although many other neurotoxic effects may be possible.

PUBLICATIONS

Yeh, S.Y. and De Souza, E.B. Lack of neurochemical evidence for neurotoxic effects of repeated cocaine administration in rats on brain monoamine neurons. Drug and Alcohol Dependence 27:51-61, 1991.

Yeh, S.Y. & De Souza, E.B. Lack of neurochemical evidence fro neurotoxic effects of repeated cocaine administration in rats on brain monoamine neurons. 19th meeting, Neuroscience Abstract, 1098 (1989).

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Role of Sigma Receptors in Endocrine Organs and Immune Tissue

Principal Investigators: Cooperating Units

P.I. E.B. De Souza Chief, Neurobiology Laboratory

Others: S.E. Wolfe, Jr. Staff Fellow, ARC

Cooperating Unit: None

Lab/Branch: Laboratory of Neurobiology, Neuroscience Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.8 **Professional:** 1.0 **Other:** 0.8

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Because sigma receptors are widely distributed in the body and because a number of drugs have effects at sigma receptors, the localization and effects of sigma receptors in the rat pineal gland were examined. The localization was examined by autoradiographic methods and the effects of the drugs were explored with electrophysiological techniques.

This project will not be continued in 1991.

PUBLICATIONS

Wolfe, S.A. Jr. and De Souza, E.B. Sigma receptors in the brain-endocrine-immune axis. In: Sigma, PCP and NMDA Receptor Systems (E.B. De Souza, E.D. London and D.H. Clouet, eds.), NIDA Research Monographs (in press).

Wolfe, S.A. Jr., Aguayo, L.G. and De Souza, E.B. Sigma receptors in rat pineal gland: Electrophysiology and autoradiographic localization. FASEB J. 4:A329, 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00309-03 NBL

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Interleukin-1 in the Brain-Endocrine-Immune Axis

Principal Investigators:

P.I. E.B. De Souza Chief, Neurobiology Laboratory

Others: T. Takao Visiting Fellow, ARC
E. Webster Staff Fellow, ARC
D.E. Tracey Visiting Scientist, Upjohn Co.

Cooperating Unit: The Upjohn Co., Kalamazoo, MI

Lab/Branch: Laboratory of Neurobiology, Neuroscience Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2.0 **Professional:** 1.5 **Other:** 0.5

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Interleukin-1 receptors were identified in the mouse testis as well as in the mouse brain. In the brain, the receptors were characterized by binding techniques and localized by autoradiographic techniques. Similar studies were carried out in the mouse kidney. Also, an interesting interaction between CRF receptors and Interleukin receptors were found in ATT-20 tumor cells where treatment with CRF resulted in an upregulation of IL-1 receptors.

This project will not be continued in 1991.

PUBLICATIONS

Takao, T., Mitchell, Wm.M., Tracey, D.E. and De Souza, E.B. Identification of interleukin-1 receptors in mouse testis. Endocrinology 127:251-258, 1990.

Takao, T., Tracey, D.E., Mitchell, Wm.M. and De Souza, E.B. Interleukin-1 receptors in mouse brain: characterization and neuronal localization. Endocrinology 127:3070-3078, 1990.

Takao, T., Mitchell, Wm.M. and De Souza, E.B. Interleukin-1 receptors in mouse kidney: identification, localization and modulation by lipopolysaccharide treatment. Endocrinology (in press).

Cunningham, E.T. Jr., Wada, E., Carter, D.B., Tracey, D.E., Battey, J.F. and De Souza, E.B. Localization of interleukin-1 receptor messenger RNA in murine hippocampus. Endocrinology (in press).

De Souza, E.B., Takao, T. and Tracey, D.E. Interleukin-1 receptors in the brain-endocrine-immune axis. Proceedings of the 17th C.I.N.P. Congress, Clinical Pharmacology, 1990.

Webster, E.L., Tracey, D.E. and De Souza, E.B. Corticotropin-releasing factor (CRF) treatment upregulates interleukin-1 (IL-1) receptors in AtT-20 pituitary tumor cells. The Endocrine Society, 72nd Annual Meeting, Abstr. #379, 1990.

Takao, T., Mitchell, Wm.M., Tracey, D.E. and De Souza, E.B. Identification of Interleukin-1 receptors in mouse testis. The Endocrine Society, 72nd Annual Meeting, Abstr. #420, 1990.

De Souza, E.B., Takao, T. and Tracey, D.E. Interleukin-1 receptors in mouse brain. 2nd International Congress of Neuroendocrinology. Neuroendocrinology Vol. 52(S1):76, 1990.

Wada, E., Cunningham, E.T. Jr., Mitchell, Wm.M., Carter, D.B., Tracey, D.E., Battey, J.F. and De Souza, E.B. Identification of interleukin-1 receptor mRNA in murine hippocampus. Soc. for Neurosci., 16:1213, 1990.

Takao, T., Tracey, D.E., Mitchell, Wm.M. and De Souza, E.B. Interleukin-1 receptors in mouse brain: Characterization and autoradiographic localization. Soc. for Neurosci. 16:1213, 1990.

De Souza, E.B., Takao, T. and Tracey, D.E. Interleukin-1 receptors in the brain-endocrine-immune axis. American College of Neuropsychopharmacology, San Juan, Puerto Rico, p. 66, 1990.

4. Molecular Neurobiology Laboratory - George R. Uhl, M.D., Ph.D., Chief

Overview

Drugs impact the nervous system through interactions with the products of specific genes, some characterized and others unknown. The Laboratory of Molecular Neurobiology, formed within the Neuroscience Branch in 1989, studies the structure and regulation of genes involved in the actions of abused drugs. The laboratory studies how drugs and neural function change gene regulation in the brain, the structures of the genes encoding drug and neurotransmitter receptors, and genetic differences in drug-abusing populations. Insights derived from these studies are applied in human clinical studies.

A principal working hypothesis motivating this work is that the mechanisms regulating genes of neurotransmission can reflect, or store, information about prior brain exposure to drugs or other stimuli. The laboratory thus studies specific patterns of brain regulation of genes for neurotransmitters impacted by abused drugs within specific neural populations in the brain. Genes for neurotransmitters that are modulated by abused substances such as preproenkephalin, genes for transcription factors that could be involved in this modulation, and genes expressed in key neurons of central brain pathways for reinforcement reward are studied in normal and transgenic animals. Knowledge of these regulated mechanisms guides the formulation of strategies for directly influencing gene expression in neurons, and clinical studies identifying whether such mechanisms can be discerned and manipulated in man.

A second major hypothesis is that better understanding of the detailed molecular structures of the receptor molecules for abused drugs, improved ability to develop anti-abuse medications working at these receptors, and ability to study gene abnormalities in drug-abusing populations will come through cloning receptor genes. The laboratory uses homology and expression strategies to elucidate the structures of receptor cDNAs and genes.

Summary of Ongoing Research

A. Receptor and Receptor-Modulating cDNAs

Identifying genes encoding the cell surface receptors for abused drugs is an important step in the molecular biology of drug abuse. Since these rare membrane proteins are difficult to purify through conventional means, the laboratory has utilized and developed DNA homology and expression cloning approaches for gene identification and characterization

Ligand-Gated Channels: GABA Rho and Others

Polymerase-chain reaction homology approaches utilize the similarity between receptor families to identify cDNAs with receptor-like properties. A novel benzodiazepine/ barbiturate/GABA receptor subunit cloned in collaborative studies including this laboratory displays interesting properties on expression that correspond to those previously described of the "GABA C" receptor. The robust electrophysiological responses of this receptor, expressed as a single subunit, make it an ideal backbone on which to superimpose the pharmacological and physiological properties conferred by domains of other GABA A receptor subunits. These approaches could allow more precise molecular definition of the poorly-understood sites for barbiturate and benzodiazepine drug actions.

PCR approaches have also defined other novel receptor subtypes that may lie in the inhibitory amino acid receptor family, and in the excitatory amino acid receptor family that includes the phencyclidine receptor.

G-Linked Receptor Expression and Modulation: Xenopus Oocytes and COS Cells

Cholecystokin (CCK) is a dopamine cotransmitter intimately involved with VTA circuits key to central mechanisms of reward and reinforcement. Subfractionation of libraries by sib selection has allowed isolation of a cDNA whose expression can lead to CCK responses when injected into oocytes by collaborators. The nature of these responses is consistent with a CCK-A receptor. The clone that confers these pharmacologically- and physiologically-appropriate responses has been sequenced, and its expression in brain noted in Northern analyses. The cDNA predicts an open reading frame that has a unique sequence, is not of the seven transmembrane class, but may be a modifier of the expression of an endogenous Xenopus CCK receptor gene regulator by antisense mechanisms.

The laboratory has defined strategies for expression of the cocaine receptor and the endothelin receptor in the Xenopus system, and has utilized COS cell transient expression in conjunction with ligand binding to allow exploration of the function of other unknown receptor-like cDNA clones.

Approaches to Transporter Cloning: Cocaine Receptor/Dopamine Transporter cDNA Sought by Oocyte Expression, PCR, LARS

The laboratory has taken three distinct approaches to cloning the cocaine receptor/dopamine transporter. Expression in Xenopus oocytes allows detection of uptake of radiolabeled dopamine in oocytes injected with mRNA prepared from tissue rich in dopaminergic cell bodies. The pharmacological and physiological specificity of transport is good, but the assay's sensitivity is variable. In a second approach, a newly-developed technique for ligand autoradiographic receptor screening is utilized. This technique was validated using beta adrenergic receptor expression, which documented that cDNA enrichments of 300-fold could be achieved in a single round of screening. These workers have tested a number of cocaine receptor radioligands for activity in this system, and have used an iodinated cocaine analog to screen libraries for expression of this receptor. In a third approach, the laboratory has used the transmembrane sequences that appear to be conserved between the GABA and norepinephrine transporters to clone PCR products and cDNAs belonging to the 12-transmembrane domain family of sodium-dependent transporters.

B. Neuronal Expression of Genes for Neurotransmitters Related to Drug Abuse

Understanding the ways in which neurons regulate their expression of the neurotransmitter genes that are related to drug abuse can help to elucidate neurochemical mechanisms for drug action, including mechanisms of tolerance and dependence. The laboratory has defined changes in the neuronal expression of several genes potentially related to drug action, and identified specific transcription factor pathways well positioned to play key roles in proenkephalin regulation *in vivo*. Transgenic animals that have been developed and characterized in the laboratory support a role for specific regulatory elements in tissue-specific expression, and in some but not in other examples of trans-synaptic gene regulation. Modified oligonucleotides that could help to experimentally regulate gene expression have been synthesized, and display remarkable abilities to enter and persist in brain neurons in largely-undegraded form that could act to regulate gene expression in a directed fashion.

Neuronal Expression of Neurotransmitter Genes in Central Brain Pathways of Reinforcement/Reward

Specific neuronal pathways in the brain are selectively and importantly implicated in the reinforcing and rewarding properties of a number of abused drugs, especially cocaine. The laboratory has examined key ventral tegmental area neurons of this circuitry, and found a substantial diversity of gene expression among the different subnuclei of neurons implicated in these processes. These studies complement ongoing clinical studies of drug effects in patients with lesions in VTA neurons.

PUBLICATIONS

Jayaraman, A., Nishimori, T., Dobnar, P. and Uhl, G. Cholecystokinin and neurotensin mRNAs are differentially expressed in subnuclei of the ventral tegmental area. J. Comp. Neuro. 296: 291-302, 1990.

Ratray, M., Lautar, S.L. and Uhl, G.R. Ligand autoradiographic receptor screening: receptor cDNA expression in replicas of transfected COS cells. Mol. Br. Res. 7(3): 249-259, 1990.

Uhl, G.R. Parkinson's disease: neurotransmitter and neurotoxin receptors and their genes. Eur. J. Neurol. 30(1): 21-30, 1990.

Uhl G. Neurotensin receptors. In: A. Bjorklund, T. Hokfelt, M. Kuhar (Eds.): Handbook of Chemical Neuroanatomy, Vol. IX. Elsevier, New York, 1990, pp. 443-453.

Price, D.L., Whitehouse, P.J., Struble, R.G., Hedreen, J.C. and Uhl, G.R. Transmitter systems in selected types of dementia. In: P. Riederer, N. Kopp and J. Pearson (Eds): An Introduction to Neurotransmission in Health and Disease. Oxford University Press, New York, 1990, pp. 349-357.

Uhl, G.R. Principles of assessing neurotransmitter receptors in disease. In: J. James Frost and Henry N. Wagner, Jr. (Eds.): Quantitative Imaging: Neuroreceptors, Neuroreceptors, Neurotransmitters, and Enzymes. Raven Press, Ltd., New York, 1990, pp. 9-18.

Uhl, G.R.. Messenger mRNA localization with the microscope: in situ hybridization using radiolabeled probes. In: Yamamura, Enna and Kuhar (Eds.): Methods in Neurotransmitter Receptor Analysis. Raven Press, New York, 1990, pp. 219-244.

Uhl, G.R. and Nishimori, T. Neuropeptide gene expression and neural activity: assessing a working hypothesis in nucleus caudalis and dorsal horn neurons expressing preproenkephalin and prodynorphin. Cell, and Mol. Neurobiology. 10(6): 73-98, 1990.

Nishimori, T., Buzzi, M.G., Chudler, E.H., Poletti, C.E., Moskowitz, M.A. and Uhl, G.R. Preproenkephalin upregulation in nucleus caudalis: high and low intensity afferent stimulation differentially modulate early and late responses. J. Comp. Neurol. 302: 1002-1018, 1990.

Articles in Press

Uhl, G.R., O'Hara, B., Shimada, S., Zacek, R., DiGiorgianni, J. and Nishimori, T. Dopamine transporter: expression in *Xenopus* oocytes. Mol. Br. Res., In press.

Uhl, G.R., Jayaraman, A., Nishimori, T., Shimada, S., Ratray, M. and O'Hara, B. Neuropharmacologic techniques in the molecular biology of schizophrenia. In: SC Schultz and CA Tamminga (Eds.): Schizophrenia Research, Advances in Neuropsychiatry and Psychopharmacology, Vol. I. Raven Press, Ltd., New York, In press.

Uhl, G.R., Appleby, D.A. and Nishimori T.N. Regulated expression of transcription factor and neurotransmitter genes in neural populations: studies using in situ hybridization with radiolabelled oligonucleotides probes. In: A. Calas and D. Eugene (Eds.): Recent Advances in Neurocytochemical Methods. Springer-Verlag, Berlin-Heidelberg, In Press.

Schaeffer, J.S., Lin, C-L, Kitayama S. and Uhl, G.R. Ligand autoradiographic receptor screening II: expression of receptor cDNA in transfected COS cells grown on polyester disks and its recovery. Mol. Brain Res., In press.

Shimada, S., Spivak, C. and Uhl, G. Endothelin receptor: A profoundly desensitizing receptor expressed in *Xenopus* oocytes. Eur. J. of Pharmacology, In press.

Cutting, G.R., Lu, L., O'Hara, B.F., Kasch, L.M., Montrose-Rafizadeh, C., Donovan, D.M., Shimada, S., Antonarakis, S.E., Guggino, W.B., Uhl, G.R. and Kazazian, H.H. Cloning of the γ -aminobutyric acid (GABA) ρ_1 cDNA: a GABA receptor subunit highly expressed in the retina. Proc. Natl. Acad. Sci., In press.

O'Hara, B.F., Smith, S.S., Persico, A., Wang, K., Cutting, G.R., Newlin, D.B., Gorelick, D.A. and Uhl, G.R. Dopamine D2 receptor alleles in substance abusers: confounding effect of race. JAMA, In press.

Uhl, G.R., Walther, D., Nishimori, T., Buzzi, G. and Moskowitz, M. Jun B, cJun, Jun D and cFOS mRNAs in nucleus caudalis neurons: Rapid selective enhancement by afferent stimulation. Mol. Brain Res., In press.

Stopa, E.G., Uhl, G.R., Mobtaker, H., Winnepenny, R., Hoefler, H., King, J.C., Bird, E.D. and Wolfe, H. Somatostatin-gene expression in human brains: in situ hybridization studies in postmortem tissue. V. Arch. Path., In press

Uhl, G.R., Appleby, D., Nishimori, T., Buzzi, M.G. and Moskowitz, M.A. Synaptic regulation of the enkephalin gene and transcription factors in vivo: possible roles in drug abuse. NIDA Research Monograph, Problems of Drug Dependence, 1990, Proceedings of the 52nd Annual Scientific Meeting, Committee on Problems of Drug Dependence, Inc., In press.

Uhl, G.R. Identifying and localizing gene expression important for the actions of abused drugs. In: Imaging the Functional Neuroanatomy of Drug Action, Telford Press, In press.

Abstracts

Jayaraman, A. and Uhl, G.R. Cholecystokinin (CCK) mRNA: Prominent expression in the rostral nigral neurons. Movement Disorders 5(1): 48, 1990.

Uhl, G.R., Shimada, S., O'Hara, B., DiGiorgianni, J., and Nishimori, T. Dopamine transporter mRNA and cDNA: Strategy for expression cloning a selective neurotoxin concentrator. Movement Disorders 5(1): 89, 1990.

Nishimori, T., Buzzi, G., Moskowitz, M.A., Ross, C., Snyder, S.H. and Uhl, G.R. Enkephalin convertase gene expression in rat nucleus caudalis neurons. Neurobiology of Nociception Abstract, 1990.

Uhl, G.R., Newlin, D.B., Pretorius, M.B., Park, J.S., Darwin, W.D. and Cone, E. Antagonist-withdrawal up-regulation of endogenous opiate antinociceptive systems. CPDD Annual Scientific Abstract, 1990.

Uhl, G.R., Buzzi, M.G., Appleby, D., Moskowitz, M.A. and Nishimori, T. Transcription factors binding to the preproenkephalin promoter: expression in neurons of normal and stimulated nucleus caudalis. Society for Neuroscience Abstracts 16(2): 1275, 1990.

Donovan, D.M., Cutting, G.R., O'Hara, B.F., Shimada, S.S. and Uhl, G.R. Receptor families: cDNAs identified by PCR & DNA homologies. Society for Neuroscience Abstracts 16(2) 1018, 1990.

O'Hara, B.F., DiGiorgianni, J.M., Shimada, S., Landau, E.M., Uhl, G.R. and Meiri, H. NT and CCK receptor cDNAs: enrichment by oocyte expression and cDNA library sib selection. Society for Neuroscience Abstracts 16(1): 82, 1990.

Shimada, S. and Uhl, G.R. Endothelin receptors: expression in *Xenopus* oocytes. Society for Neuroscience Abstracts 16(1): 686, 1990.

Uhl, G.R., Appleby, D. and Nishimori, T. Can we deduce mechanisms for neurotransmitter gene regulation in situ? The enkephalin promoter "cassette" and trans-synaptic transcription factor u-regulation. Third Research Symposium of the Center for Studies in Reproduction, Molecular and Cellular Advances in Endocrinology, Univ. Of Maryland School of Medicine, Oct. 1-2, 1990.

Uhl, G.R. Parkinson's disease: neurotransmitter and neurotoxin receptors and their genes. Parkinson/Alzheimer Digest 5: 20-21, 1990.

Abstracts in Press

Uhl, G.R., O'Hara, B.F., Smith, S.S., Persico, A., Newlin, D.B. and Gorelick. D2 receptor alleles in drug abusers: confounding effects of race. CPDD Annual Scientific Meeting, In press.

Uhl, G.R., Appleby, D., Buzzi, M.G. and Moskowitz, M. Dorsal horn proenkephalin regulation by primary afferents: co-regulation of specific transcription factor genes. Neurology, In press.

Jayaraman, A. and Uhl, G. Specific subpopulation of substantia nigra pars compacta neurons express the CCK gene. Neurology, In press.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project:

Receptor cDNA Expression Cloning Using Ligand Autoradiographic Screening

Principal Investigators: Cooperating Units

Uhl, G.R., Chief Laboratory of Molecular Neurobiology, ARC.

Others: Rattray, M.A.N., Foreign Fellow, MPL, ARC; Lautar, S., Research Lab Manager, MPL, ARC;

Lin, Glen, Research Technician (guest worker) Dept. of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205.

Lab/Branch:

Laboratory of Molecular Neurobiology, Neuroscience Branch

Section:

Gene Neuroscience Unit.

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2 **Professional:** 1 **Other:** 1

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

Summary of Work:

Understanding the receptor molecules that recognize abused drugs and the neurotransmitters impacted by drugs is an important step in determining the molecular mechanisms underlying drug abuse. Little is known about many of these molecules, because they have proven very difficult to purify through conventional approaches. The laboratory has continued to work to establish a method for directly cloning these molecules based on their ligand binding properties, and to exploit this approach.

Over the past year, these workers have made substantial progress toward this end. Previously, a cloned beta adrenergic receptor cDNA was used to document and optimize expression of the beta adrenergic receptor binding site in COS cells. In studies completed during this year, improved DNA recovery techniques and electroporation have resulted in recoveries of the plasmid present in very small number of cells with a reasonable frequency. This results in documented enrichments of up to 300-fold in a single step. The workers have progressed in adapting the method for use with the cocaine and PCP receptors. Goals for the current year include using this technique to attempt receptor cloning based on both cDNA recovery and subfractionating libraries and adaptation of the polymerase chain reaction to aid in recovery of the very small numbers of plasmids present. This approach continues to provide promise for allowing direct cloning of genes key to the action of several classes of abused substances.

PUBLICATIONS

Ratray, M., Lautar, S.L. and Uhl, G.R. Ligand autoradiographic receptor screening: receptor cDNA expression in replicas of transfected COS cells. Mol. Br. Res. 7(3): 249-259, 1990.

Schaeffer, J.S., Lin, C-L, Kitayama, S. and Uhl, G.R. Ligand autoradiographic receptor screening II: Expression of receptor cDNA in transfected COS cells grown on polyester disks and its recovery. Mol. Brain Res., In press.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project:

Receptor cDNA Expression Cloning Using Xenopus Oocyte Expression

Principal Investigators: Cooperating Units

Uhl, G.R., Chief Laboratory of Molecular Neurobiology, ARC

Others: Shimada, S., Visiting Scientist, LMN, ARC , O'Hara, B., Staff Fellow, LMN, ARC and DiGiorgianni, J., Technician (guest worker), Johns Hopkins University, Dept. of Neuroscience, Johns Hopkins School of Medicine; Spivak C., Pharmacologist , NPL, ARC, Drs. Suzanne Zukin and Michael Bennett, Albert Einstein College of Medicine, Dr. Emmanuel Landau, Mt. Sinai School of Medicine, New York.

Neuropharmacology Laboratory, ARC.

Lab/Branch:

Laboratory of Molecular Neurobiology, Neuroscience Branch

Section:

Gene Neuroscience Unit.

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.5 **Professional:** 1 **Other:** 0.5

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

Summary of Work:

Expression cloning is an attractive approach to identifying the genes and cDNAs encoding receptors for abused substances and for the neurotransmitters implicated in drug abuse (see above). The ability of the Xenopus oocyte to appropriately translate, post-translationally modify, and appropriately insert several receptors into its membrane has led us to establish this system as a screening tool for these cDNAs and receptors.

Progress in this project has included: 1) Obtaining electrophysiologic signals for neurotensin, cholecystokinin, and kainic acid from oocytes injected with these synthetic mRNA transcripts, 2) Cloning of a single cDNA that induces CCK-A responses in oocytes that are pharmacologically-appropriate, but likely due to upregulation of the endogenous CCK receptor gene by the injected transcript. This cDNA "CCK-UP" is expressed in several brain regions, and may provide important insights into the upregulation mechanisms important for one of the chief dopamine cotransmitters in the brain, 3) Characterizing interesting properties of the GABA-Rho1 receptor expressed in this system, including bicuculing-insensitivity. This approach thus enhances abilities to clone interestingc DNAs

through "sib selection" techniques, and improves abilities to characterize the properties of expressed cDNAs.

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NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00116-03 MNL****Period Covered:** January 1, 1990 to December 31, 1990**Title of Project:**

Genes Related to Drug Abuse I: Regulation of Opioid Peptide Genes.

Principal Investigators: Cooperating Units

Uhl, G.R. Others: Appleby, D., LMN, Research Technician, ARC/NIDA, DiGiorgianni, J., Technician (guest worker); Moskowitz, M., Associate Professor of Neurology & Neurosurgery*.

*Departments of Neurology, Neurosurgery, Massachusetts General Hospital, Harvard Medical School and Department of Neuroscience, Johns Hopkins University School of Medicine.

Lab/Branch:

Molecular Neurobiology Laboratory, Neuroscience Branch

Section:

Gene Neuroscience Unit

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2.0 **Professional:** 1 **Other:** 1**Check Appropriate Boxes:** Human Subjects Human Tissues Neither Minors Interviews**Summary of Work:**

Drugs alter the expression of many important genes in the brain. These changes in gene expression are likely to contribute to long-term drug effects, such as tolerance and dependence. Continuing studies of the genes encoding endogenous morphine-like peptides suggest that drug-induced gene regulation depends on the circuits connecting to the neuron and the duration of drug exposure.

During the past year, the laboratory has monitored cellular levels of neuropeptide mRNAs and of the transcription factor genes that may alter expression of these mRNAs to assess gene regulation related to functional activity in these neurons. In studies completed during this year, transsynaptic regulation of preproenkephalin expression in pain-modulating neurons of the nucleus caudalis of the spinal tract of the trigeminal was described in detail, and the AP-1 and CREB family transcription factors that could participate in this regulation were identified. Transgenic mice possessing a specific portion of the preproenkephalin promoter were produced, and their responsiveness to only certain trans-synaptic activators of preproenkephalin expression noted. Interesting effects of expressed minigene constructs on male fertility and testicular function were found. Finally, approaches to directly modifying these transcription factor pathways in brain with intraparenchymal injection of modified oligonucleotides were validated. These approaches allow understanding of mechanisms important for attempts to therapeutically manipulate drug influences on gene expression. Preliminary results from a human study using opiate antagonists to change the expression of these opioid peptide genes provide evidence for the

efficacy of such targeted therapies.

PUBLICATIONS

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Uhl, G.R., Appleby, D., Nishimori, T., Buzzi, M.G. and Moskowitz, M.A. Synaptic regulation of the enkephalin gene and transcription factors in vivo: possible roles in drug abuse. NIDA Research Monograph, Problems of Drug Dependence, 1990, Proceedings of the 52nd Annual Scientific Meeting, Committee on Problems of Drug Dependence, In press.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00117-02 MNL

Period Covered: January 1, 1990 to December 31, 1990

Title of Project:

Genes Related to Drug Abuse II: Central Brain Pathways of Reinforcement/Reward.

Principal Investigators: Cooperating Units

Uhl, G.R. Others: Appleby, D., Research Technician, LMN, ARC NIDA, Rao, J., Dept. of Neurology, Louisiana State University, New Orleans, LA.

Lab/Branch:

Molecular Neurobiology Laboratory, Neuroscience Branch

Section:

Gene Neuroscience Unit

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2 **Professional:** 1 **Other:** 1

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work:

Neurons in the ventral tegmental area are major constituents of central brain pathways of drug reinforcement. Despite this potential central role in the actions of many abused drugs, however, the detailed expression of important neurotransmission genes in these neurons has not been elucidated. The expression of the genes encoding two of the dopamine-cotransmitter peptides, cholecystinin and neurotensin, have thus been mapped to neurons in this area during this year. In these studies, a surprising region-to-region variation in the expression of neurotensin and CCK genes in these neuronal subdivisions has been found. Such detailed studies are necessary before defining activities of cocaine and other abused drugs on this expression. These approaches thus allow detailed examination of the ways in which drugs and other physiologic processes influence gene regulatory mechanisms that could serve as a store for some of the information about prior drug use that may accompany tolerance and dependence.

The potential function of these neurons in human drug-induced reinforcement/reward is being studied as well. Parkinson's disease patients, whose brains lose VTA neurons, are assessed after administration of methylphenidate. Blunting of drug effects on mood in these patients would support a central role for these neurons in reinforcement/reward in man.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00314-01 MNL

Period Covered: January 1, 1990 to December 31, 1990

Title of Project:

D₂ Receptor Gene Allelic Association with Substance Use

Principal Investigators: Cooperating Units

Uhl, G.R., Chief Laboratory of Molecular Neurobiology, ARC

Others: O'Hara, B., Staff Fellow, Laboratory of Molecular Neurobiology, ARC; Farmer, S., Laboratory Technician, Laboratory of Molecular Neurobiology, ARC; Persico, A., Visiting Fellow, Laboratory of Molecular Neurobiology, ARC; Cooperating Units: Smith, S., Staff Fellow, Etiology Branch, ARC; Newlin, D., Acting Branch Chief, Etiology Branch, ARC; Gorelick, D., Chief, Treatment Branch, ARC.

Lab/Branch:

Laboratory of Molecular Neurobiology, Neuroscience Branch

Section:

Gene Neuroscience Branch

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2.5 **Professional:** 1.5 **Other:** 1

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work:

Recent observations that the dopamine D₂ receptor gene Taq I RFLP may be associated with alcoholism have motivated attempts to test whether or not this genotype is associated with an increased incidence of drug abuse. Over the past year, these workers have made substantial progress toward an initial test of the possible allelic association between the A1 allele and self-reported drug use. DNAs from approximately 160 individuals from the Addiction Research Center, Francis Scott Key Medical Center, and Johns Hopkins School of Medicine Genetics clinic have been analyzed. A cDNA subclone that improves the assay has been constructed. A racial association with the A1 allele has been identified, and self-reported use of a number of different drugs have been assessed for possible linkage with the A1 allele. Goals for the current year include: Assaying whether individuals with different genotypes have different responses to methylphenidate, following up on any drug-allele associations, and considering the role of the Laboratory of Molecular Neurobiology in larger-scale genetic linkage studies.

PUBLICATIONS

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Dopamine D₂ receptor alleles in substance abuses: confounding effect of race. JAMA (Submitted).

Preclinical Pharmacology Branch

Steven R. Goldberg, Ph.D., Chief

Introduction

The Preclinical Pharmacology Branch conducts research in experimental animals on the behavioral modes of action of drugs of abuse both in producing reinforcing, punishing and discriminative stimuli and in altering established behavior controlled by non-drug events such as food or electric shock. It also studies the role of genetics in determining the effects of drugs of abuse. The overall goal of the Branch is to understand how drugs of abuse affect whole animals, with an eventual goal being the discovery of effective treatment regimens. Studies cover a wide range of topics, including the pharmacology of opioids, psychomotor stimulants, and benzodiazepine dependence, alterations in the acquisition and retention of classically conditioned behavioral and physiological responses by drugs of abuse, consequences of repeated drug administration, and environmental and genetic determinants of drug-seeking and drug-taking behavior. Drugs are also evaluated to characterize physiological and toxic actions which accompany acute and prolonged administration, delineate the mechanisms responsible for these effects and establish methods for preventing or reversing the effects.

Research is carried out in both nonhuman primates (rhesus and squirrel monkeys) and non-primates. New drugs are evaluated for abuse potential by comparison of reinforcing, aversive and discriminative stimulus effects, and by comparison of effects of prototypic drugs of abuse on neurophysiologic systems. Emphasis is placed on the use of pharmacological, environmental and genetic interventions to alter the effects of drugs of abuse. These aims are intended to further the overall goals of the Addiction Research Center by providing a background of information to be used in developing rational clinical procedures for the prevention and treatment of drug abuse.

The Preclinical Pharmacology Branch consists of two laboratories, a Behavioral Pharmacology and Genetics Laboratory and a Psychobiology Laboratory. The two laboratories are subdivided into functional and collaborative units with emphasis on behavioral pharmacology, drug self-administration, physiological psychology, pharmacogenetics, behavioral and biochemical genetics, medications development and neuropsychopharmacology and toxicity.

1. Behavioral Pharmacology and Genetics Laboratory - Steven R. Goldberg, Ph.D., Chief

Overview

The Behavioral Pharmacology and Genetics Laboratory is responsible for research in experimental animals on environmental, historical and pharmacological determinants of the reinforcing and other behavioral effects of drugs of abuse and on their physiological effects including toxicity. Drugs of abuse from different pharmacological classes, including psychomotor stimulants, opioids, barbiturates and benzodiazepines are investigated to develop an understanding of how drug-seeking becomes strong and persistent over time and how it might be weakened by pharmacologic or behavioral means. Laboratory objectives are pursued using a variety of experimental procedures, including (1) assessing the reinforcing effects of drugs of abuse using intravenous self-administration procedures, (2) quantifying their behavioral effects using schedules of food presentation or electric shock delivery or postponement as baselines, (3) determining their effects as discriminative stimuli using two-lever and three-lever choice situations, and (4) determining the physiological effects of drugs of abuse, including cardiovascular toxicity and lethality.

The Behavioral Pharmacology and Genetics Laboratory also conducts behavioral, pharmacological and

biochemical studies using genetically-defined animal models to investigate genetic factors underlying individual differences in response to the acute and chronic administration of drugs of abuse. The overall goal is to develop and apply behavioral pharmacogenetic approaches to assess and differentiate genetic and environmental factors underlying individual differences in response to drugs. Additional efforts are aimed at identifying, at the biochemical level, gene products which are involved in the acute, reinforcing and toxic effects of drugs of abuse, as well as the biochemical mechanisms underlying changes associated with the long-term administration of these drugs. In general, we are characterizing genetic factors associated with drug abuse and integrating this information with the results from the studies characterizing the environmental and behavioral factors associated with drug abuse.

Summary of Ongoing Research

A. Control of Behavior By Drug Injection

Drugs serve as positive reinforcers to maintain and strengthen behavior leading to their administration and can control behavior through their ability to function as discriminative stimuli. In many situations, drugs of abuse probably function through multiple mechanisms to persistently sustain long sequences of drug seeking behavior that are very resistant to extinction. Schedule-controlled performances provide a meaningful way to analyze these long sequences of drug-seeking behavior in the same way as operant behavior maintained by other events such as food or shock. Using a variety of self-administration procedures, ongoing experiments are being conducted to evaluate behavior maintained by drugs and the ability of pharmacological treatments, such as antagonist administration or the development of dependence, to modify drug self-administration behavior and/or food-maintained behavior.

One series of experiments involved the attempts at pharmacological modification of cocaine self-administration. In cardiovascular studies in squirrel monkeys (see project summary) we found that treatment with calcium channel blockers such as nimodipine will reverse or prevent cardiovascular changes produced by cocaine. However, pre-session treatments with calcium channel antagonists that were sufficient to reverse the effects of cocaine were without effect on cocaine-maintained behavior. In another series of experiments, the effects of administration of serotonergic drugs on the rate of responding by squirrel monkeys self-administering cocaine or responding for food pellets under fixed-ratio schedules of reinforcement are being conducted. In these studies, the effects of acute pretreatments of several 5HT₂ antagonists will be evaluated in squirrel monkeys responding for cocaine. The direct effect of these pretreatments to disrupt ongoing food-maintained behavior will be assessed in the same subjects.

Nicotine dependence is thought to be a major obstacle to smoking cessation in man. Sertraline, a serotonergic uptake inhibitor that is effective as an antidepressant, is being evaluated for its usefulness as a potential treatment to facilitate smoking cessation. An ongoing project in the laboratory was designed to assess sertraline's effects in an animal model of nicotine dependence, nicotine self-injecting monkeys. Monkeys were initially trained to self-administer 10 to 30 •g/kg, i.v. cocaine under a fixed ratio 30, time-out 5 minute schedule of reinforcement. When the pattern of responding for cocaine was stable, a dose of nicotine (30 •g/kg, i.v.) that has been previously shown to maintain maximal rates of self-injection was substituted for cocaine. A dose-response curve for nicotine (0, 10, 30, 56, 100 •g/kg, i.v.) was then generated by substituting a series of nicotine doses for a period of 3 days. The second phase of the study involves evaluating the effects of sertraline pretreatments on self-administration behavior maintained by 30 •g/kg nicotine. A series of sertraline doses or vehicle (0, 3, 6, 12 mg/kg) will be administered by gavage prior to administration of each of three doses of nicotine or vehicle (0, 10, 30, 100 •g/kg, i.v.). As a control for non-specific effects of sertraline, nicotine or sertraline-nicotine combinations on food-reinforced responding, the effects of these drugs are being evaluated in squirrel monkeys. These monkeys are trained under the same fixed-ratio 30, time-out 5 minute schedule of reinforcement used in the nicotine self-injection study, except that food pellets are delivered instead of drug injections. A

nicotine dose response curve was generated by administering nicotine doses (0.1, 0.3 and 1.0 mg/kg, i.m.) prior to the session. As above, these doses of nicotine and vehicle will be evaluated in combination with sertraline.

In addition to differences in pharmacological efficacy of drugs to control or modify behavior, it is clear that behavioral and environmental factors play an important role in the the control that even highly efficacious drugs exert on behavior. The focus of experiments in the newly established rhesus self-administration lab are to study the pharmacological, behavioral, and environmental variables involved in initiating and maintaining drug self-administration. Certain drugs, such as cocaine and other psychomotor stimulants generally function effectively as reinforcers under a variety of conditions. Other drugs such as benzodiazepines, some opioids and caffeine, however, have been studied only under relatively limited conditions, and generally maintain low levels of responding. The ability of these compounds to maintain self-injection behavior can be modified by a number of environmental and behavioral factors, such as stimuli associated with their administration, schedules of reinforcement, access conditions, concurrent availability of other drug and non-drug reinforcers (i.e., food), behavioral history and pharmacological manipulations such as antagonist administration or the development of tolerance/dependence.

Parallel comparative studies in squirrel monkeys and humans in which subjects are given the opportunity to self-administer comparable doses of cocaine, morphine, nicotine and other drugs under similar behavioral schedules and experimental conditions provide a means to assess the generality of biological variables influencing drug self-administration. These studies allow an opportunity to evaluate the role of environmental variables and the role of conditioning in human drug taking behavior and whether those roles differ from the roles of those variables in animal models of drug taking. We have previously shown that second-order schedules of drug self-administration, where drug is injected only at the end of each daily session, can support a large amount of behavior in both humans and squirrel monkeys. In addition, in the human studies we have shown that with these schedules, low doses of morphine can support self-administration even though the subjects report no subjective effects of these drug doses. This result indicates that subjective report of a drug effect may not be an important factor in the positive reinforcing effects of drugs of abuse. To further substantiate these findings, we are currently repeating these experiments. In addition, we are also testing subjects who administer low morphine doses with the opioid antagonist naltrexone to determine whether any physiological sign of precipitated withdrawal can be observed. Subjective reports will also be taken during the withdrawal test to determine whether withdrawal may also occur independent of subjective report, or whether there is a closer match between the subjective reports and withdrawal than between self-administration and subjective reports.

B. Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals

General information on the behavioral pharmacology of a drug in a pertinent species is necessary to evaluate quantitatively how the drug functions as a reinforcer or a punisher as well as to establish a profile of behavioral effects. Schedules of food presentation with both fixed-interval and fixed-ratio components have been used most frequently in this type of study since they generate a wide range of rates and patterns of responding within a session and provide stable, long-term baselines for chronic studies in individual animals. The present project involves the assessment of both the acute and chronic effects of a variety of drugs on schedule-controlled behavior.

We have recently shown that while the calcium channel antagonists are effective in antagonizing the cardiovascular effects of cocaine, they do not significantly modify the direct behavioral effects of cocaine. This includes both the rate-increasing and rate decreasing effects of cocaine. We have also completed a long-term study designed to determine whether tolerance to either the rate-increasing or rate-decreasing effects of cocaine could be observed using a second-order schedule where the animals were allowed as long a period of time as needed to complete the schedule requirements. Under these

conditions, we did not observe any tolerance development to the effects of cocaine.

We have previously shown that the opioid antagonist naltrexone produces clear behavioral sensitivity when its effects are determined on schedule-controlled behavior in rats. This phenomenon appears to be related to conditioning process, as it is long-lasting and undergoes extinction. These results indicate that opioid antagonist enhanced sensitivity may be an important factor in compliance in opioid abuse treatment with naltrexone. We have recently shown that this enhanced sensitivity is pharmacologically specific, with cross-sensitivity occurring only to pure opioid antagonists. Further, we have also demonstrated that enhanced sensitivity occurs to salivation produced by high doses of naltrexone. This result is important as it allows us to study the phenomenon of enhanced sensitivity independently of schedule-controlled behavior. We have therefore studied receptor binding in these animals that show enhanced sensitivity with the salivation measure. In collaboration with Dr. Su in the Neuroscience branch we have shown that specific changes occur in opioid receptor binding. In addition, as opioid antagonist also interacts with GABA, we have been studying GABA binding. To date, those results have been inconclusive.

Behaviorally active drugs can also serve as discriminative stimuli to guide behavioral choice. Ongoing drug discrimination projects in the laboratory using cocaine, opioids, caffeine and benzodiazepines agonists have helped to define and characterize the spectrum of behavioral effects produced by the drug, to compare a range of other compounds to characterize the relative potency and efficacy to produce drug-like effects, and to evaluate the drug's mechanisms of action at the receptor level. For example, we are currently studying the discriminative stimulus properties of the mu agonist morphine and the kappa agonist ethylketocyclazocine. In particular, we are interested to see if calcium channel antagonists, which can block some of the physiological effects of opioids, might also antagonize the discriminative stimulus properties of these drugs. Similar studies are also underway in human subjects under the direction of Dr. Vaupel from the Neuroscience Branch. In addition, we are also studying the effects of deprenyl, a monoamine oxidase inhibitor, to study the role of these processes in the discriminative stimulus properties of psychomotor stimulants.

Since most human drug taking behavior involves chronic long-term use of an illicit drug or non-medical abuse of a prescribed medication, the consequences of chronic administration of drugs on schedule-controlled behavior and the discriminative functions of drugs are being evaluated. Although the development of tolerance and dependence appears to be related to pharmacological factors, such as chronic dose, period of exposure, conditions of administration (continuous vs. intermittent), tolerance can also be modified by environmental factors, such as the requirements of the task, presentation of conditioned stimuli, and the relationship between the task and the drug exposure. Manipulation of these environmental factors can result in the attenuation or elimination of tolerance even though high doses of drugs are being administered chronically.

Behavioral factors have been shown to strongly influence the effects of chronic drug administration, often resulting in differential tolerance development. It is clear that tolerance can develop to the behavioral effects of benzodiazepines as a result of pharmacological exposure, but several studies have suggested that behavioral experience may only augment the rate of tolerance development. Recently, however, the demonstration of differential or contingent tolerance has been shown to be dependent upon the dose of the chronic drug, and the degree of training. Specifically, these studies have shown that the practice of a task under the influence of a drug using a PRE/POST injection strategy underlies the development of tolerance to the sedative effects of midazolam on food maintained behavior and to the effects of chlordiazepoxide on self-stimulation behavior. Ongoing studies in the lab have been designed to (1) assess the contributions of behavioral variables to the development of tolerance to the rate-decreasing effects of chlordiazepoxide (CDP) (i.e., contingent tolerance) and (2) determine the contributions of behavioral tolerance to CDP on sensitivity to acute administration of non-benzodiazepine compounds.

C. Cardiovascular Changes Induced by Cocaine.

Several studies in the Behavioral Pharmacology and Genetics Laboratory are directed toward determining the effects of abused drugs on cardiovascular function. These studies are directed both at basic mechanisms and at potential treatment agents. We have found, for instance, that adrenergic mechanisms play an important role in the cardiovascular effects of cocaine. In studies in squirrel monkeys we have shown the alpha-1 adrenergic mechanisms are important to cocaine's pressor effect, while both beta-1 and beta-2 adrenergic mechanisms are important to cocaine's tachycardiac effect. In particular, the alpha-1 antagonist prazosin was particularly effective in antagonizing cocaine's effects on cardiovascular function in squirrel monkeys. In parallel studies in rats, we have shown that prazosin can also antagonize the lethal effects of cocaine. Together, these results suggest that prazosin may be a particularly useful agent in the treatment of cocaine related medical emergencies. These studies have also shown that, contrary to previous finding, beta adrenergic antagonists should not be used in treatment. In rats, the beta antagonist propranolol will exacerbate cocaine-induced lethality. In squirrel monkeys, while propranolol will antagonize the tachycardiac effect of cocaine, it will potentiate the cocaine's pressor effect. Thus, beta antagonists should be avoided in treatment.

An important aspect of this last year's research effort has been the development of effective techniques for studying cardiovascular function in conscious, freely-moving rats. These studies using conscious rats indicate that cocaine increases blood pressure and heart rate similar to its effects in squirrel monkeys. Further, a single injection of cocaine produces rapid sensitization to the pressor effects of its subsequent injections administered at 24 hr intervals. The cardiovascular effects of cocaine in rats are completely antagonized by noncompetitive or mixed type autonomic ganglionic blockers, while these effects are partially antagonized by the competitive ganglionic blockers. Cocaine also potentiates the peripheral cardiovascular effects of norepinephrine and inhibits the effects of tyramine, however, these effects occur at doses that are 10 times larger than those doses of cocaine alone required to produce cardiovascular effects. Thus, these results provide substantial evidence that the cardiovascular effects of cocaine in conscious rats are mainly centrally mediated. In agreement with this finding, we have recently shown that cocaine methiodide, a quaternary derivative of cocaine which should not cross the blood brain barrier does not affect cardiovascular function in conscious squirrel monkeys. Cocaine methiodide does potentiate the effects of exogenously administered norepinephrine, suggesting that it does have actions in the periphery. In anesthetized animals, some effects of cocaine methiodide are observed, although they are small and transient. Thus, our recent results from both rats and squirrel monkeys confirm that there is an important central component to the cardiovascular effects of cocaine.

Recent studies in squirrel monkeys have also been directed toward comparing the effects of methamphetamine to cocaine on cardiovascular function. While the effects of methamphetamine appear to be mediated through the same noradrenergic processes as cocaine, an important aspect of methamphetamine's cardiovascular effects are also mediated through dopaminergic processes. This result suggests that cocaine and methamphetamine may act through different systems to affect cardiovascular function.

D. Genetic Factors in Response to Chronic Drug Treatment

In spite of the widespread recognition that there are strong individual differences in liability for drug abuse, relatively few studies designed to elucidate genetic factors associated with chronic drug use have been conducted. We are conducting a series of studies designed to evaluate pharmacogenetic differences in response to the chronic administration of drugs of abuse (cocaine and opioids) among genetically defined strains of mice and rats. The use of a pharmacogenetic approach not only facilitates the understanding of individual differences in response to chronic drug administration, it also provides a tool for understanding the biochemical mechanisms underlying these responses. We have investigated changes in susceptibility to cocaine-induced seizures following the long-term administration of cocaine

among inbred mouse strains. These studies revealed that genetic factors mediate not only acute sensitivity to the convulsant properties of cocaine but also changes in seizure susceptibility known to occur upon repeated administration of cocaine. The repeated administration of cocaine resulted in the development of either sensitization or tolerance to the convulsant effects of cocaine depending on the genetic background of the individual being examined. Having identified genotypes that are qualitatively different in their response to chronic cocaine, we are now using these animal models to address questions relating to the mechanisms underlying the effects of chronic cocaine.

Cocaine exerts its effects through a number of biochemical systems. The convulsant and epileptogenic properties of cocaine are thought to be related, at least in part, to its local anesthetic effects. In a series of follow-up studies, we found that genetic factors also mediate sensitivity to the convulsant properties of the pure local anesthetic, lidocaine, and that there are genetic differences in response to the repeated administration of lidocaine, that is, depending on the genotype being examined chronic lidocaine produced either an increased or a decreased sensitivity to cocaine-induced seizures. Furthermore, the chronic administration of subconvulsant doses of cocaine results in the development of cross-sensitization or cross-tolerance to the convulsant effects of lidocaine, again with the ultimate outcome being dependent upon the genetic background of the genotype being examined. Thus, the local anesthetic properties of cocaine may account for some of the individual differences in the effects of chronic cocaine administration.

We have recently expanded our initial chronic cocaine studies to evaluate the ability of carbamazepine to modulate the convulsant and epileptogenic effects of cocaine. The primary site of action of carbamazepine is at voltage dependent sodium channels. These ion channels are known to be the site of action for local anesthetics such as cocaine and lidocaine. In that carbamazepine has been suggested as having some clinical use for the treatment of cocaine addiction, these studies are providing not only more information on the mechanisms underlying cocaine's effects, but also preclinical data on possible toxic side effects associated with the use of carbamazepine as a treatment for chronic cocaine use. Our results, to date, indicate that chronic, dietary carbamazepine attenuates, but does not completely inhibit, the cocaine-kindling process in a genotype-specific manner. Chronic carbamazepine also lowers the threshold for acute cocaine-induced seizures in some, but not all of the genotypes examined. This effect last for at least 3 days after the cessation of carbamazepine treatment, suggesting that some long-lasting biochemical change may have occurred. A finding of relevance to our earlier studies showing that chronic cocaine or lidocaine treatment resulted in sensitization or tolerance depending on the genotype being examined is the observation that chronic carbamazepine affected the development of tolerance, but not sensitization to the convulsant properties of cocaine. These studies have also shown that the regimen of administration of these drugs may have important implications in that a chronic period of carbamazepine administration is required for the attenuation of cocaine kindling and cocaine-induced seizures. These studies also revealed that the concurrent administration of carbamazepine and cocaine has genotype-specific lethal effects. Interestingly, the same data set suggests that while in one genotype the combination of the two drugs is lethal, in another mouse strain carbamazepine may serve attenuate the anorectic effects of cocaine. The mouse strains identified in the studies discussed above will serve as useful animal models for elucidating the mechanisms underlying some of the effects of chronic cocaine and/or carbamazepine.

We have begun to examine changes in ion channel function and binding parameters associated with chronic drug administration. Preliminary results suggest that cocaine kindling may be associated with a decrease in the ability of the inhibitory neurotransmitter, GABA, to stimulate the uptake of chloride ions into neurons. In addition to continuing to examine these changes in GABAergic function, we have been developing techniques for assessment of other ligand- and voltage-gated ion channels, notably voltage-dependent sodium channels. While it is generally recognized that cocaine has major effects on these sodium channels, very few investigations have addressed the involvement of sodium channels in cocaine's actions. It is anticipated that these techniques will be useful for understanding the convulsant and epileptogenic properties of cocaine and should facilitate a greater understanding of the biochemical mechanisms underlying the effects of cocaine and the interactions between cocaine and carbamazepine.

Our studies are also being expanded to include assessment of biochemical changes resulting from the chronic administration of opioids and opioid antagonists. To date, we have identified an inbred mouse strain that differs from other strains we have examined in the number of neuronal mu opioid receptors and are correlating this difference with apparent differences in behavioral responses to opioid treatment. Similar biochemical assays are currently being conducted on brain tissue from rats chronically treated with an opioid antagonist.

E. Pharmacogenetics: Acute Response to Drug Administration

The behavioral genetics model investigates individual differences in behavior as a composite of unique individual biology in context of its historical and present environment. To this end, behavior genetics analysis of individual differences in response to drugs of abuse such as alcohol and nicotine have proven useful in establishing heritable factors in acute response to ethanol and in determining traits with common genetic backgrounds. The ability to determine what physiological effects of ethanol are inherited independently has led to important molecular genetic discoveries and may lead to possible pharmacological interventions in the treatment of alcoholism. In addition to the work done with ethanol, previous studies investigating acute behavioral responses to opioids have demonstrated genotype to be an important factor.

The use of inbred strain panels to estimate genetic correlations across ethanol-related phenotypes has proven useful in establishing heritable factors in acute response to ethanol and in determining traits with common genetic backgrounds. In addition to the work done with ethanol, previous studies investigating acute behavioral responses to opioids have demonstrated genotype to be an important factor. Initial studies in our laboratory suggest that the genetic rank order sensitivity among a number of opioid-related phenotypes such as analgesia, activity, hypothermia, muscle rigidity and receptor density do not consistently covary across genotype. Although opioid-related responses have been shown to have a heritable component, relatively few phenotypes have been investigated in a manner designed to determine estimates of phenotypic covariation. Determination of phenotypes with common or independent mechanisms is important for the development of compounds with therapeutic value independent of addiction liability and unwanted side-effects in addition a possible treatment for opioid addiction. The purpose of these studies is to determine the acute sensitivity of inbred strains and selected mouse lines for opioid-induced hypothermia, straub tail, analgesia and locomotion. The degree of physiological and behavioral covariance across genotype may indicate which genetic components are inherited in susceptibility to opioid-induced toxicities. In addition, these data would contribute significantly to ongoing investigations of genetic differences in opioid-reinforced behavior.

In collaboration with Dr. Uhl of the Neuroscience Branch we are also evaluating behaviorally the acute response to opioids in transgenic mice which are over-expressing the endogenous opioid enkephalin. To date, the level of expression in brain has been insufficient to produce any significant behavioral changes. Additional mice have been recently bred which should have higher level of expression and biochemical assessments of genetic differences in opioid receptor binding parameters.

The use of pharmacogenetic methods is also useful in elucidating the biochemical mechanisms associated with drug responses. We are currently assessing the influence of ligand affinity for and receptor density of opiate and serotonergic receptor subtypes on opiate-induced analgesia, hypothermia and locomotion. We have also used pharmacogenetic correlations to give us some information concerning the biochemical mechanisms mediating toxic responses to acute injections of cocaine. Using pharmacogenetic methods, we have shown clear genetic differences in sensitivity to cocaine-induced seizures and lethality across a variety of genetic strains of mice. Further, using a Classical Mendelian Analysis, we have data suggesting that a single gene associated with serotonergic 5HT2 receptors appears to mediate sensitivity to seizures. Using a different research strategy, pharmacological correlations, we have shown that the

binding of cocaine and related compounds to serotonin transporters appears to have a primary influence on seizures, while dopamine transporters has the greatest influence on lethal responses to cocaine. Drug binding to muscarinic and sigma receptors appears to attenuate both toxic responses. Related to these receptor binding studies, since polyamines appear to modulate transport systems for ions and neurotransmitters, and since cocaine produces its seizurgenic and lethal effects primarily via binding to serotonin and dopamine transporters, we intend to determine the effects of polyamines on cocaine-induced seizures and lethality.

We are currently assessing the potential efficacy of several pharmacotherapeutic strategies on cocaine-induced toxicity, including sigma related drugs and antidepressants. We have observed a stereospecific effect of the sigma compound SKF10047 on cocaine-induced seizures. Since stereospecific effects of sigma compounds on behavioral phenomena have rarely been shown, we intend to assess the effects of several sigma ligands on measures of cocaine toxicity. It is hoped that the results may suggest antagonist and agonist properties of several sigma-related compounds. In addition, since cocaine produces its seizurgenic and lethal effects primarily via binding to serotonin and dopamine transporters, and since many antidepressant might be used clinically by potential cocaine users, we intend to determine the effects of various antidepressants on cocaine-induced toxicity.

Finally, we have begun a project for the determination of the seizurgenic or lethal effects of cocethylene and several cocaine metabolites and congeners. Several such compounds have been shown in the blood or urine of cocaine-related emergency room cases. This project will assess whether these compounds might produce toxic effects by the same receptor mechanisms by which cocaine produces these effects. Thus, both biochemical and behavioral assessments of the potencies of these compounds will be performed. The results will be compared to our models of cocaine-induced seizures and lethality.

F. Pharmacogenetic Factors in Drug Reinforced Behavior

Previous studies in our laboratory have provided evidence to indicate an important genetic component in the acquisition of operant ethanol-reinforced behavior. Current research activities are aimed at determining the role of genotype in operant opioid-reinforced behavior; these studies include investigating the genetic and environmental components important not only in the acquisition but the maintenance and extinction of drug-reinforced behavior as well. The goal of our opioid drug self-administration project is to utilize recombinant inbred strains to investigate the role of opioid receptor subtypes and co-segregating opioid-related phenotypes in opioid self-administration. Opioid related phenotypes such as analgesia, hypothermia, activation, withdrawal and opioid-reinforced behavior, will be investigated in the parental strains C57BL/6 and BALB/C mice along with the CxBk subline. The CxBk mice are known to be deficient in mu-opioid binding sites and to be less sensitive than the C57BL strain to the analgesic and locomotor stimulatory effects of opioids. These data along with the use of several other CxB sublines will allow for the generation of phenotypic strain distribution patterns for in vitro and in vivo correlates of opioid reinforced behavior. Importantly, the use of the CxBk subline allows for the direct testing of known genetically inherited biochemical differences in the predisposition to opioid addiction. Thus far, several important findings have been made using this approach. Mu receptor populations may not account for individual variability in the acquisition of opioid-reinforced behavior following extensive training procedures. Inbred strains that varied significantly in mu receptor populations did not differ in the acquisition of etonitazene self-administration. Importantly, variation in mu receptor population may contribute to the extent to which an individual may self-administer opioids or the degree to which the behavior is maintained in the absence of drug availability. Individual variability may put some individuals at risk for acute opioid-induced toxicities during opioid self-administration. For example, C57BL/6 and CxBb mice do not differ in the respiratory depressant effects of etonitazene, yet drug intake to C57BL/6 mice is approximately four times the amount of CxBh mice during self-administration sessions. Collaborative efforts within the lab and in the Neuroscience Branch have begun to determine which underlying biochemical substrates may account for individual differences

seen in the propensity to exhibit opioid-reinforced behavior.

In addition to investigating the genetic factors in acute sensitivity to opioids, current studies are also accessing the extent to which genetic factors affect conditioned place preference (CPP). The CPP paradigm measures the ability of a drug to engender conditioned reinforcement to previously neutral stimuli. The purpose of these studies are two-fold. First, these studies will determine if similar genetic differences are found in the ability of a drug to engender CPP compared to the propensity to exhibit operant self-administration. Similar genetic correlations across inbred strains would support common mechanism(s) responsible for maintaining operant self-administration and CPP. In addition, these studies are important for determining the reliability of the CPP paradigm to predict drug-reinforced behavior. Second, the genetic rank order for the ability of opioids to establish CPP will be correlated with the acute response to other opioid-related phenotypes in order to determine the degree of genetic covariation.

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NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00001-06 BPL****Period Covered:** January 1, 1990 to December 31, 1990**Title of Project:** Control of Behavior by Drug Injection**Principal Investigators:**

P.I.:	S.R. Goldberg	Chief	BPGL, NIDA, ARC
Others:	C.W. Schindler	Research Psychologist	BPGL, NIDA, ARC
	J.A. Prada	Research Psychologist	BPGL, NIDA, ARC
	C.A. Sannerud	Staff Fellow	BPGL, NIDA, ARC
	J.-W. Zheng	Visiting Associate	BPGL, NIDA, ARC
	S. Yasar	Visiting Fellow	BPGL, NIDA, ARC

Cooperating Units: None**Lab/Branch:** Behavioral Pharmacology and Genetics Laboratory
Preclinical Pharmacology Branch**Section:** None**Institute and Location:**Addiction Research Center, National Institute on Drug Abuse,
Baltimore, MD 21224**Total Man Years:** 2.50 **Professional:** 2.00 **Other:** 0.50**Check Appropriate Boxes:**

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work:

Using self-administration procedures, several different types of experiments are being conducted. The abuse liability of drugs are being assessed by comparing the rates and patterns of responding maintained by various drugs, including cocaine, nicotine and other psychomotor stimulants, benzodiazepines and other sedative/anxiolytics, morphine and other opioids. These studies will compare responding maintained under fixed-ratio, fixed-interval schedules and complex second-order schedules. The ability of pharmacological treatments and the development of tolerance/dependence to modify drug self-administration behavior and/or food maintained behavior is also being assessed. In addition to differences in pharmacological efficacy of drugs, it is clear that behavioral and environmental factors can modify the control that even highly efficacious drugs exert on behavior. The focus of experiments in the rhesus self-administration lab are to study the pharmacological, behavioral, and environmental variables involved in initiating and maintaining drug self-administration. Certain drugs, such as cocaine and other psychomotor stimulants generally function effectively as reinforcers under a variety of conditions. Other drugs such as benzodiazepines, some opioids, and caffeine, however, have been studied only under relatively limited conditions, and generally maintain low levels of responding. Parallel comparative studies in squirrel monkeys and humans in which subjects are given the opportunity to self-administer comparable doses of cocaine, morphine, nicotine and other drugs under similar behavioral schedules and

experimental conditions provide a means to assess the generality of biological variables influencing drug self-administration. We have previously shown under a second-order schedule of drug self-administration, low doses of morphine can support self-administration in humans even though the subjects report no subjective effects of these drug doses. This result indicates that subjective reports of a drug effect may not be an important factor in the positive reinforcing effects of drugs of abuse. To further substantiate these findings, we are currently repeating these experiments. In addition, we are also testing subjects who administer low morphine doses with the opioid antagonist naltrexone to determine whether any physiological signs of precipitated withdrawal can be observed. Subjective reports will also be taken during the withdrawal test to determine whether withdrawal may also occur independent of subjective report, or whether there is a closer match between the subjective reports and withdrawal than between self-administration and subjective reports.

Publications

Goldberg, S. R., Schindler, C. W., & Lamb, R. J. (1990) Second-order schedules and the analysis of human drug-seeking behavior. *Drug Development Research*, 20, 217-229.

Griffiths, R.R., Lamb, R.J., Sannerud, C.A., Ator, N.A. and Brady, J.V. (1990) Self-injection of barbiturates, benzodiazepines and other sedative-anxiolytics in baboons. *Psychopharmacology*, in press.

Katz, J.L. and Goldberg, S.R. Second-order schedules of drug injection: Implications for understanding reinforcing effects of abused drugs. In: *Advances in Substance Abuse, Behavioral and Biological Research Vol. 4.*, N.K. Mello, Ed., Jessica Kingsley Publishers, Ltd., London, UK, in press.

Lamb, R. J., Preston, K. L., Henningfield, J. E., Schindler, C. W., Meisch, R. L., Davis, F., Katz, J. L., & Goldberg, S. R. (1990) The reinforcing and subjective effects of morphine in post-addicts: A dose-response study, in press.

Mansbach, R.S., Sannerud, C.A., Griffiths, R.R., Balster, R.L., Harris, L.S. Intravenous self-administration of 4-methylaminorex in primates. *Drug and Alcohol Dependence*. 26:137-144, 1990.

Sannerud, C.A., Ator, N.A., and Griffiths, R.R. (1990). Methocarbamol: evaluation of reinforcing and discriminative stimulus effects. *Behavioural Pharmacology*, in press.

Spear, D.J., Muntaner, C., Goldberg, S.R. and Katz, J.L. Methohexital and cocaine self-administration under fixed-ratio and second-order schedules. *Pharmacology Biochemistry and Behavior*, in press.

Swedberg, M.D.B., Henningfield, J.E. and Goldberg, S.R. Nicotine dependency: animal studies. In: *Nicotine Psychopharmacology: Molecular, Cellular and Behavioral Aspects*, S. Wonnacott, (Ed.), M.A.H. Russell and I.P. Stolerman, Oxford University Press, Oxford, pp. 38-76, 1990.

Abstracts

Ator, N.A., Sannerud, C.A., and Griffiths, R.R. (1990) Abuse liability of benzodiazepine (BZ) receptor ligands. Proceeding from the 5th World Congress of Biological Psychiatry, Florence, Italy (in press).

Griffiths, R.R., Sannerud, C.A., Lamb, R.J., Ator, N.A., and Brady, J.V. (1990). Self-injection of barbiturates, benzodiazepines, and other sedative-anxiolytics in baboons. In: *Problems of Drug Dependence 1990*. Harris, L.S. (ed). NIDA Research Monograph No. 105. Washington, D.C.:U.S. Government Printing Office, 329.

Sannerud, C.A., Kaminski, B.J. and Griffiths, R.R. (1990) Lack of self-injection behavior maintained by N-N-dimethylamphetamine in baboons. *The FASEB Journal*, in press.

Schindler, C. W., Tella, S. R., Prada, J. A., & Goldberg, S. R. (1990) Failure of calcium channel entry blockers to antagonize the behavioral effects of cocaine in squirrel monkeys. The FASEB Journal, 4, A745.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals

Principal Investigators:

P.I.	S.R. Goldberg	Chief	BPGL, NIDA, ARC
Others:	J.A. Prada	Research Psychologist	BPGL, NIDA, ARC
	C.W. Schindler	Research Psychologist	BPGL, NIDA, ARC
	C.A. Sannerud	Staff Fellow	BPGL, NIDA, ARC
	R.J. Marley	Staff Fellow	BPGL, NIDA, ARC
	J.-W. Zheng	Visiting Associate	BPGL, NIDA, ARC
	S. Yasar	Visiting Fellow	BPGL, NIDA, ARC

Cooperating Units: None

Lab/Branch: Behavioral Pharmacology and Genetics Laboratory
Preclinical Pharmacology Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse,
Baltimore, MD 21224

Total Man Years: 4.46 Professional: 2.76 Other: 1.70

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work:

General information on the behavioral pharmacology of a drug in a pertinent species is necessary to evaluate quantitatively how the drug functions as a reinforcer or a punisher as well as to establish a profile of behavioral effects. Schedules of food presentation with both fixed-interval and fixed-ratio components have been used most frequently used in this type of study since they generate a wide range of rates and patterns of responding within a session and provide stable, long-term baselines for chronic studies in individual animals. The present project involves the assessment of both the acute and chronic effects of a variety of drugs on schedule-controlled behavior. We have recently shown while the calcium channel antagonists are effective in antagonizing the cardiovascular effects of cocaine, they do not significantly modify the direct behavioral effects of cocaine. This includes both the rate-increasing and rate-decreasing effects of cocaine. We have also completed a long-term study designed to determine whether tolerance to either the rate-increasing or rate-decreasing effects of cocaine could be observed using a second-order schedule where the animals were allowed as long a period of time as needed to complete the schedule requirements. Under these conditions, we did not observe any tolerance development to the effects of cocaine. We have also recently shown that the enhanced sensitivity which

occurs to opioid antagonists is pharmacologically specific, with cross-sensitivity occurring only to pure opioid antagonists. Further, we have demonstrated that this enhanced sensitivity occurs to salivation produced by high doses of naltrexone. This result is important as it allows us to study the phenomenon of enhanced sensitivity independently of schedule-controlled behavior. In collaboration with Dr. Su in the Neuroscience branch we have shown that specific changes occur in opioid receptor binding following opioid antagonist treatment. In addition to their direct effects on behavior, drugs of abuse can also function as discriminative stimuli. Most of these studies are being performed in rats and we are studying the discriminative stimulus effects of cocaine and other psychomotor stimulants, opioids and the benzodiazepines. These studies are designed to characterize the relative potency and efficacy of test drugs to produce drug-like effects, and to evaluate the drug's mechanism of action at the receptor level. For example, we are currently conducting experiments to determine if calcium channel antagonists, which can block some of the physiological effects of opioids, might also antagonize the discriminative stimulus properties of these drugs. Similar studies are also underway in human subjects under the direction of Dr. Vaupel from the Neuroscience Branch.

Publications

Griffiths, R.R., Evans, S.M., Heishman, S.J., Preston, K.L., Sannerud, C.A., Wolf, B.A., and Woodson, P.P. Low-dose caffeine discrimination in humans. Journal of Pharmacology and Experimental Therapeutics, 252:970-978, 1990.

Griffiths, R.R., Evans, S.M., Heishman, S.J., Preston, K.L., Sannerud, C.A., Wolf, B.A., and Woodson, P.P. Low-dose caffeine withdrawal. Journal of Pharmacology and Experimental Therapeutics, 25:1123-1132, 1990.

Sannerud, C.A., Ator, N.A., and Griffiths, R.R. (1990) Comparison of the discriminative stimulus effects of midazolam after intracranial and peripheral administration in the rat. Life Sciences (in press)

Sannerud, C.A., Allen M., Cook, J.M., and Griffiths, R.R. (1990) Behavioral effects of benzodiazepine ligands in non-dependent, diazepam dependent and diazepam withdrawn baboons. European Journal of Pharmacology (in press).

Schindler, C. W., Wu, X.-Z., Su, T.-S., Goldberg, S. R., & Katz, J. L. (1990) Enhanced sensitivity to behavioral effects of naltrexone in rats. Journal of Pharmacology and Experimental Therapeutics, 252, 8-14.

Schindler, C. W., & Harvey, J. A. (1990) The use of classical conditioning procedures in behavioral pharmacology. Drug Development Research, 20, 169-187.

Schindler, C. W., White, M. F., & Goldberg, S. R. (1990) Effects of morphine, ethylketocyclazocine, *N*-allylnormetazocine and naloxone on locomotor activity in the rabbit. Psychopharmacology, 101, 172-177.

Thomas, D. A., Weiss, S. J., & Schindler, C. W. (1990) The effects of chlordiazepoxide and Ro 15-1788 on preference for punished and unpunished response alternatives in rats. Psychopharmacology, 102, 333-338.

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Witkin, J. M., Schindler, C. W., Tella, S. R., & Goldberg, S. R. (1990) Interaction of haloperidol and SCH 23390 with cocaine and dopamine receptor subtype-selective agonists on schedule-controlled behavior of squirrel monkeys. Psychopharmacology, in press.

Young, A.M., Sannerud, C.A., Steigerwald, E.S., Doty, M.D., Lipinski, W.J., and Tetrick, L.E. Tolerance to morphine stimulus control: Role of morphine maintenance dose. Psychopharmacology, 102:59-67, 1990.

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Sannerud, C.A., Ator, N.A., Fischette, C.T., and Griffiths, R.R. (1990). Behavioral effects of tandospirone in male baboons. Society for Neurosciences Abstracts 16, 1322.

Sannerud, C.A. and Griffiths, R.R. (1990) Behavioral effects of chronic abecarnil administration in baboons. In: Problems of Drug Dependence 1990. Harris, L.S. (ed). NIDA Research Monograph No. 105. Washington, D.C.:U.S. Government Printing Office, 328, in press

Sannerud, C.A. and Griffiths, R.R. (1990) Assessment of benzodiazepine physical dependence in baboons. Pharmacology, Biochemistry and Behavior (in press).

Sannerud, C.A., Alastra, A.J.G., and Harger, P.L.(1990) Contingent tolerance to chlordiazepoxide in rats. Pharmacology, Biochemistry and Behavior, (in press).

Schindler, C. W., Tella, S. R., Prada, J. A., & Goldberg, S. R. (1990) Failure of calcium channel entry blockers to antagonize the behavioral effects of cocaine in squirrel monkeys. The FASEB Journal, 4, A745.

Schindler, C. W., Goldberg, S. R., & Katz, J. L. (1990) Pharmacological specificity of enhanced sensitivity to naltrexone in rats. Pharmacology Biochemistry and Behavior, 36, 438.

Schindler, C. W., Wu, X.-Z., Su, T.-P., Thorndike, E. B., Goldberg, S. R., & Katz, J. L. (1990) Enhanced sensitivity to naltrexone in rats: Effects on salivation and opioid receptor binding. Society for Neuroscience Abstracts, 16, 1192.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00009-04 BPL****Period Covered:** January 1, 1990 to December 31, 1990**Title of Project:** Cardiovascular Changes Induced by Cocaine**Principal Investigators:**

P.I.:	C.W. Schindler	Research Psychologist	BPGL, NIDA, ARC
Others:	S.R. Goldberg	Chief	BPGL, NIDA, ARC
	S.R. Tella	Guest Worker	BPGL, NIDA, ARC
	G.R. Korupolu	Visiting Fellow	BPGL, NIDA, ARC
	J.-W. Zheng	Visiting Associate	BPGL, NIDA, ARC

Cooperating Units: None**Lab/Branch:** Behavioral Pharmacology and Genetics Laboratory
Preclinical Pharmacology Branch**Section:** None**Institute and Location:**Addiction Research Center, National Institute on Drug Abuse,
Baltimore, MD 21224**Total Man Years:** 2.86 **Professional:** 2.86 **Other:** 0**Check Appropriate Boxes:**

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work:

The effects of cocaine and other psychomotor stimulants on a number of physiological parameters are being studied in conscious squirrel monkeys and rats. Recent studies in squirrel monkeys have indicated that alpha-1 adrenergic mechanisms are importantly involved in the pressor effects of both cocaine and methamphetamine, while both beta-1 and beta-2 adrenergic mechanisms are important for the tachycardiac effect of both drugs. Based on these studies, the alpha-1 antagonist prazosin would appear to be an ideal drug for the treatment of cardiovascular complications due to psychomotor stimulant abuse. Unlike with cocaine, dopaminergic mechanisms have been shown to be importantly involved in the cardiovascular effects of methamphetamine. In addition, recent studies have also indicated that, contrary to our previous findings, central mechanisms do appear to be significantly involved in the cardiovascular effects of cocaine in squirrel monkeys. The studies using conscious rats indicate that cocaine increases blood pressure and heart rate similar to its effects in squirrel monkeys. Further, a single injection of cocaine produces rapid sensitization to the pressor effects of its subsequent injections administered at 24 hr intervals. The cardiovascular effects of cocaine in rats are completely antagonized by noncompetitive or mixed type autonomic ganglionic blockers, while these effects are partially antagonized by the competitive ganglionic blockers. Cocaine also potentiates the peripheral cardiovascular effects of norepinephrine and inhibits the effects of tyramine, however, these effects occur at doses that are 10

times larger than those doses of cocaine alone required to produce cardiovascular effects. Thus, these results provide substantial evidence that the cardiovascular effects of cocaine in conscious rats are mainly centrally mediated. Acute lethality studies indicate that various adrenergic agents modify acute cocaine intoxication. As with the cardiovascular effects in squirrel monkeys, prazosin was particularly effective against cocaine lethality.

Publications

Schindler, C. W., Tella, S. R., Witkin, J. M., & Goldberg, S. R. (1990) Effects of cocaine alone and in combination with haloperidol and SCH 23390 on cardiovascular function in squirrel monkeys. Life Sciences, in press.

Tella, S. R., Schindler, C. W., & Goldberg, S. R. (1990) The role of central and autonomic neural mechanisms in the cardiovascular effects of cocaine in conscious squirrel monkeys. Journal of Pharmacology and Experimental Therapeutics, 252, 491-499.

Tella, S. R., Schindler, C. W., & Goldberg, S. R. (1990) Rapid sensitization to the cardiovascular effects of cocaine in rats. European Journal of Pharmacology, in press.

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Trouve, R., Nahas, G.G., Manger, W.M., Vinyard, C. and Goldberg, S.R. Interactions of nimodipine and cocaine on endogenous catecholamines in the squirrel monkey. Proc. Soc. Exp. Biol. & Med., 193, 171-175, 1990.

Witkin, J.M., Johnson, R.E., Jaffe, J.H., Goldberg, S.R., Grayson, N.A., Rice, K.C. and Katz, J.L. The partial opioid agonist, buprenorphine, protects against lethal effects of cocaine. Drug and Alcohol Dependence, in press.

Abstracts

Goldberg, S. R., Tella, S. R., & Schindler, C. W. (1990) Antagonism of cocaine-induced pressor response but not acute lethality by calcium channel entry blockers in rats. The FASEB Journal, 4, A744.

Goldberg, S. R., Tella, S. R., & Schindler, C. W. (1990) Adrenergic mechanisms in the cardiovascular effects of cocaine in squirrel monkeys. The FASEB Journal, in press.

Korupolu, G. R., Tella, S. R., Schindler, C. W., & Goldberg, S. R. (1990) Modification of cocaine-induced cardiovascular effects, convulsions and lethality by adrenoceptor blocking agents in rats. The FASEB Journal, in press.

Schindler, C. W., Tella, S. R., Katz, J. L., & Goldberg, S. R. (1990) Effects of cocaine and cocaine methiodide on cardiovascular function in squirrel monkeys. The FASEB Journal, in press.

Tella, S. R., Schindler, C. W., & Goldberg, S. R. (1990) Antagonism of cocaine-induced cardiovascular changes by calcium channel entry blockers in conscious squirrel monkeys. The FASEB Journal, 4, A744.

Tella, S. R., Schindler, C. W., & Goldberg, S. R. (1990) A single intravenous bolus injection of cocaine enhances the pressor effects of subsequent injection in conscious rats. Circulation, 82, III-147.

Tella, S. R., Schindler, C. W., Korupolu, G. R., & Goldberg, S. R. (1990) Variable degree of antagonism of cardiovascular effects of cocaine by ganglionic blockers in conscious rats. The FASEB Journal, in press

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00012-02-BPL****Period Covered:** January 1, 1990 to December 31, 1990**Title of Project:** Genetic Factors in Response to Chronic Drug Treatment**Principal Investigators:**

P.I.:	R.J. Marley	Staff Fellow	BPGL, NIDA, ARC
Others:	S.R. Goldberg	Chief	BPGL, NIDA, ARC
	N.L. Goodman	Research Pharmacologist	BPGL, NIDA, ARC

Cooperating Units: None**Lab/Branch:** Behavioral Pharmacology and Genetics Laboratory
Preclinical Pharmacology Branch**Section:** None**Institute and Location:**Addiction Research Center, National Institute on Drug Abuse,
Baltimore, MD 21224**Total Man Years:** 1.36 **Professional:** 0.76 **Other:** 0.60**Check Appropriate Boxes:**

<input type="checkbox"/> Human Subjects	<input type="checkbox"/> Human Tissues	<input checked="" type="checkbox"/> Neither
<input type="checkbox"/> Minors		
<input type="checkbox"/> Interviews		

Summary of Work:

The purpose of this project is to use a pharmacogenetic approach to evaluate individual differences in response to chronic administration of drugs of abuse or drugs proposed for the treatment of drug abuse. Genetic differences in response to the convulsant and epileptogenic effects of cocaine have been demonstrated by examining the development of increased susceptibility to the seizure inducing properties of cocaine following repeated administration of the drug (pharmacological kindling). Genetically distinct strains of mice that differ quantitatively and qualitatively in their response to chronic cocaine have been identified and are being employed to study the mechanisms underlying the effects of long-term cocaine use and to assess possible treatments for cocaine toxicity. We have demonstrated that individual differences in response to the epileptogenic effects of cocaine are associated with its local anesthetic properties. Evaluation of the ability of carbamazepine to modulate the convulsant and epileptogenic effects of cocaine have shown that chronic carbamazepine attenuates the development of increased sensitivity to cocaine-induced seizures in a genotype-specific manner. In addition to genetic difference, the regimen of carbamazepine administration appears to be important in determining its ability to attenuate cocaine's effects. These studies also revealed that chronic carbamazepine administration, in conjunction with chronic cocaine treatment, has lethal consequences in certain genotypes. Assessment of the biochemical mechanisms underlying the changes observed following chronic cocaine treatment are presently being conducted. Preliminary results suggest that cocaine kindling is associated with a downregulation of GABAergic function. Genetic differences in response to pharmacological kindling

with a benzodiazepine inverse agonist have also been demonstrated and are being compared with the differences observed for cocaine kindling. Assessments of biochemical changes associated with chronic opiate treatment are also being conducted.

Publications

Gallager, D.W., R.J. Marley and T. D. Hernandez. Biochemical and electrophysiological mechanisms underlying benzodiazepine tolerance and dependence. in The Biological Basis of Drug Tolerance and Dependence, ed. by J. Pratt, Academic Press, in press, 1990.

Marley, R.J., C. Heninger, T.D. Hernandez and D.W. Gallager. Chronic administration of FG 7142 via continuous i.c.v. infusion increases GABAergic function. Neuropharmacology, in press, 1990.

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Wehner, J.M., B.J. Martin, R.J. Marley and J.I. Ponder. Behavioral studies of GABAergic responses in LS and SS mice: Are ethanol sensitivity and responses to GABAergic agents regulated by common mechanisms? In Initial Sensitivity to Ethanol, ed. by R. A. Deitrick and A. A. Pawlowski, NIAAA Res. Monograph 20, pp. 345 - 380, 1990.

Abstracts

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Goldberg, S.R. & R. J. Marley. A pharmacogenetic approach towards an understanding of drug abuse. Abstracts of the British Association for Psychopharmacology. 1990.

Marley, R.J., J.M. Witkin, & S.R. Goldberg. A pharmacogenetic evaluation of the cocaine-kindling process. Society for Neuroscience Abstracts, #1133, 1990.

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Witkin, J.M., S.R. Goldberg & R.J. Marley. Lack of a genetic correlation between the convulsant and epileptogenic effects of cocaine and lidocaine. Abstracts of Comm. Prob. Drug Dep. 52nd Ann. Sci. Mtg., 1990.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Pharmacogenetics: Acute Responses to Drug Administration

Principal Investigators:

P.I.:	G.I. Elmer	Staff Fellow	BPGL, NIDA, ARC
Others:	S.R. Goldberg	Chief	BPGL, NIDA, ARC
	M.C. Ritz	Senior Staff Fellow	BPGL, NIDA, ARC
	R.J. Marley	Staff Fellow	BPGL, NIDA, ARC
	C.W. Schindler	Research Psychologist	BPGL, NIDA, ARC

Cooperating Units: None

Lab/Branch: Behavioral Pharmacology and Genetics Laboratory
Preclinical Pharmacology Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse,
Baltimore, MD 21224

Total Man Years: 2.66 **Professional:** 1.96 **Other:** 0.70

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work:

The use of inbred strains to estimate genetic correlations across drug-related phenotypes is useful in establishing heritable factors in acute response to drugs and in determining traits with common genetic mechanisms. Determination of phenotypes with a common or independent mechanisms is important for determining drug mechanisms of action, setting criterion for selective breeding, developing predictive models of self-administration, and in the determination of individual genotypes at risk for the acute toxic effects. The purpose of these studies is to determine sensitivity of inbred strains for opiate-induced analgesia, stimulation, sensitization, respiratory depression, hypothermia and straub tail. The degree of covariance across genotype may indicate which genetic components influence susceptibility to opiate-induced toxicities and to genetic differences in opiate-reinforced behavior. We are also currently assessing the influence of serotonergic receptor subtypes on opiate-induced analgesia, hypothermia and locomotion. Recent findings include 1) A strong correlation between opiate receptor concentration, analgesic sensitivity and drug-intake, 2) Opioid self-administration behavior does not correlate with the stimulant effects of opioids and 3) Demonstration that the amount of opioid that maintains drug-reinforced behavior and that which produces significant respiratory depression varies greatly as a function of genotype. In collaboration with Dr. Uhl of the Neuroscience Branch we are also evaluating behaviorally the acute response to opioids in transgenic mice which are over expressing the endogenous

opioid enkephalin. To date, the level of expression in brain has been insufficient to produce any significant behavioral changes. We have also used pharmacogenetic and pharmacological correlations to elucidate the biochemical mechanisms mediating toxic responses to cocaine. Using pharmacogenetic methods, we have shown genetic differences in sensitivity to cocaine-induced seizures and lethality. We also have data suggesting that a single gene associated with serotonergic 5HT₂ receptors appears to mediate sensitivity to seizures. We have shown that the binding of cocaine and related compounds to serotonin transporters appears to have a primary influence on seizures, while dopamine transporters has the greatest influence on lethal responses to cocaine. Drug binding to muscarinic and sigma receptors appears to attenuate both toxic responses. We are currently assessing the potential efficacy of several pharmacotherapeutic strategies on cocaine-induced toxicity, including sigma related drugs and antidepressants.

Publications

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George, F.R., Ritz, M.C. and Meisch, R.A. Ethanol produces similar fixed-ratio rate-depressant effects in ALKO AA and ANA rats. Advances in Alcohol and Substance Abuse, 9, 31-42, 1990.

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Kuhar, M.J., Ritz, M.C. and Boja, J.W. The dopamine hypothesis of the reinforcing properties of cocaine. Trends in Neuroscience, in press, 1990.

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Ritz, M.C., Cone, E.J. and Kuhar, M.J. Cocaine inhibition of ligand binding at dopamine, norepinephrine and serotonin transporters: A structure-activity study. Life Sciences, 46, 635-645, 1990.

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Ritz, M.C. and George, F.R. Cocaine-induced seizures: Mediation by specific CNS receptors (presented at the 1989 annual ACNP meeting). Neuropsychopharmacology, 1990.

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Ritz, M.C. and George, F.R. Cocaine toxicity: Distinct neurotransmitter systems are associated with seizures and death. Society for Neuroscience Abstracts, #242.8, 16, 581, 1990.

Ritz, M.C. and George, F.R. Antidepressant drugs appear to enhance cocaine-induced toxicity (presented at the 1990 annual ACNP meeting). Neuropsychopharmacology, in press, 1990.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Pharmacogenetic Factors in Drug Reinforced Behavior

Principal Investigators:

P.I.: G.I. Elmer Staff Fellow BPGL, NIDA, ARC

Others: S.R. Goldberg Chief BPGL, NIDA, ARC

Cooperating Units: None

Lab/Branch: Behavioral Pharmacology and Genetics Laboratory
Preclinical Pharmacology Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse,
Baltimore, MD 21224

Total Man Years: 1.16 Professional: 0.66 Other: 0.50

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work:

The objectives of the proposed research are to identify and study factors that control drug reinforced behavior using genetically divergent mouse and rat populations. The methodology and principles of operant conditioning and pharmacogenetic analysis will be used. The studies will be limited to conditions in which the drug is taken orally and functions as a positive reinforcer. The focus will be on the variables that control drug reinforced behavior, especially genetic variables, but also including pharmacological variables and environmental variables, e.g., drug concentration and fixed ratio size. The proposed studies are important because (1) drug intake will be examined under conditions in which it is taken orally and functions as a reinforcer; (2) they will explore genetic and environmental factors and their interactions which contribute to drug self-administration; and (3) the use of genetically defined animals will provide information concerning the degree to which genetic factors regulate drug-seeking behavior. These studies complement ongoing investigations into the genetic factors affecting the acute response to drugs of abuse and will contribute the determination of traits with common or independent genetic backgrounds. In addition these studies are important in the development of predictive models of self-administration behavior and the determination of individual genotypes at risk for the acute toxic effects of the drug. Recent findings included 1) Developing oral cocaine self-administration procedures, 2) Defining genetic differences in reinforcement from opiates; and 3) Determining common and independent genetic factors in the acute, toxic and reinforcing effects of opiates.

Publications

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2. Psychobiology Laboratory - Jonathan L. Katz, Ph.D., Chief

Overview

A major portion of the research efforts of the Psychobiology Laboratory are directed at examining the pharmacology of cocaine and the neurotransmitter systems that are involved in the effects of cocaine. In addition, there are continuing projects on benzodiazepines and amphetamines. One goal is to develop a better understanding of pharmacological mechanisms involved in the behavioral effects of cocaine as well as the toxicity that occurs at high doses. Another focus is the development of new pharmacological approaches to the treatment of cocaine abuse. Studies of cocaine mechanisms have examined the behavioral effects of compounds acting on specific components of the dopamine system. Studies within each of these areas have obvious implications for studies within the other areas.

Summary of Ongoing Research

A. Basic Mechanisms of cocaine effects

The primary findings and implications for the current year and future directions are: (1) Both D1 and D2 receptor systems appear to be involved in many of the behavioral effects of cocaine, though neither agonist actions at these receptors alone fully reproduces cocaine effects. Non-dopaminergic effects may be important components of the pharmacological profile cocaine. (2) The lethal effects of cocaine administration appear to principally involve peripheral rather than central nervous system mechanisms. The specific pathophysiological processes involved however, remain to be determined. (3) An influence of cholinergic systems on the behavioral effects of cocaine has been suggested. Certain muscarinic antagonists can mimic some aspects of the behavioral pharmacology of cocaine. Efforts are now being directed toward defining the pharmacological nature of the stimulant effects of these drugs. (4) Differences in the involvement of postsynaptic dopamine receptors in the effects of various stimulants have been established. The differential modulation of these stimulants by GABAergic agents is under investigation. (5) D1 receptors appear to be preferentially involved in the lethal effects of cocaine. Detailed documentation of the role of dopamine receptor subtypes in cocaine toxicity is a continuing experimental effort. (6) Agonist activity at mu-opioid receptors confers stereospecific protection against cocaine lethality. (7) Modulation of excitatory amino acid neurotransmission can profoundly alter the convulsive effects of cocaine. Ongoing efforts are directed at elucidating the responsible components of this system. (8) Tolerance that develops to the behavioral effects of cocaine does not confer cross tolerance to all dopamine uptake inhibitors.

In collaboration with the Neuroendocrinology Laboratory and the Neuroscience Branch studies have been conducted to test whether chronic administration of cocaine, or its withdrawal, produces changes in neuroendocrine or receptor binding parameters in the rat. To date we have found that repeated injections of cocaine causes a hyperprolactinemia, and increases neurotensin binding in the prefrontal cortex. Preliminary results also indicate that binding to the dopamine transporter is decreased in the nucleus accumbens after chronic cocaine administration. These results may relate to cocaine dependence, tolerance or sensitization.

B. Drug Development

These studies are designed to provide preclinical information for the development of medications to be used in the treatment of drug abuse. The primary focus of this work is to determine pharmacological means for modulating behavioral and toxic actions of abused compounds, and to evaluate new chemical entities (synthesized in-house and from outside sources) for safety and efficacy in the design of potential rational treatment strategies.

The primary findings and implications for the current year and future directions are: (1) Buprenorphine protects against the lethal effects of cocaine providing drug-interaction safety information for future studies of efficacy in cocaine abuse treatment. (2) Two classes of compounds which block the N-methyl-D-aspartate receptor protect against the high-dose convulsant effects of cocaine that are insensitive to standard anticonvulsants. These studies suggest a novel avenue for developing new treatments for seizures induced by cocaine overdose. (3) A novel class of compounds which are capable of blocking the stimulant effects of cocaine has been identified. Ongoing studies will determine whether other effects of cocaine related to its abuse and toxicity can be similarly altered. (4) A syndrome of hypersensitivity to dopaminergic stimulation after withdrawal from high doses of cocaine has been identified. This phenomenon is being further studied to determine if it can serve as a model of cocaine dependence for evaluating treatment agents. (5) Compounds proposed by NIDA as potential treatments for cocaine abuse have been examined in preclinical screens for safety and efficacy; these studies are in progress.

C. Behavioral pharmacology of dopamine systems

Several of our previous findings suggested that dopamine antagonists, acting selectively at either D1 or D2 receptors, did not robustly antagonize several behavioral effects of cocaine. In response to these findings we have examined the interactions of specific D1 and D2 agonists and antagonists. These studies indicate that: (1) the D2 antagonist, sulpiride, is an effective antagonist of some behavioral effects of the D2 agonist, quinpirole in primates; (2) the D2 antagonist, haloperidol was not an effective antagonist of the D2 agonist, quinpirole, in rats; (3) the D1 antagonist, SCH 23390, is not effective as an antagonist of the D1 agonist, SKF 38393 in either rats or primates. We are therefore, pursuing some further studies of the interactions of these drugs using several behavioral endpoints. These studies will also pursue a number of different compounds as agonists and antagonists of D1 and D2 receptors in order to more fully characterize the behavioral pharmacology of these drugs and the contribution of D1 dopamine receptor systems to the pharmacology of cocaine.

We have initiated several studies of the effects of cocaine analogs in collaboration with the Neuroscience Branch. One of these studies has examined a drug that binds irreversibly to the cocaine binding site. This compound, para-isothiocyanato- benzyloecgonine methyl ester (para-isococaine), has been administered into the nucleus accumbens in rats. Following this treatment, cocaine which normally produces a large stimulation in locomotor activity, was inactive. In contrast, apomorphine, a direct receptor agonist, retained activity. These studies are being followed in order to more fully characterize this effect. Obviously, these results may have important consequences in a pharmacological analysis of mechanisms of cocaine effects.

Several antidepressants that block the uptake of dopamine do not appear to be widely abused. In addition, several of these compounds have been studied in displacement studies and have not fully displaced cocaine from its binding sites. This residual cocaine binding may represent binding to another site that may be responsible for the reinforcing effects of cocaine and may differentiate cocaine and non-abused dopamine uptake blockers. In order to examine this possibility, the discriminative effects of cocaine and other dopamine uptake blockers will be compared.

Several studies are currently being planned on the neuroanatomical substrates of the psychomotor stimulant effects of cocaine. Intracerebral injections will be used to investigate the pharmacological nature of neuroanatomical sites related to the actions of cocaine.

Acetylcholine and GABA are found in high concentrations in the nucleus accumbens. These studies will investigate the interconnections of these systems with dopaminergic neurons by injecting cholinergic or GABAergic agonists and antagonists into mesolimbic sites, and testing their effects on locomotor activity. This behavior appears to be a good model for psychomotor stimulant action. Important findings obtained with locomotor stimulation will be advanced to studies of cocaine self-administration. These

studies will provide leads for pharmacological modulations of other transmitter systems that may control the behavioral effects of cocaine.

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Witkin, J. M. and Tortella, F. C. Blockade of the convulsant effects of cocaine by MK- 801 in a diazepam-insensitive mouse model. Society for Neuroscience Abstracts **16**: 305, 1990.

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Sharpe, L. G., Pilotte, N. S., Mitchell, W. M., De Souza, E. B. and Dax, E. M. Withdrawal from chronic cocaine decreased dopamine transporter sites in the rat nucleus accumbens (NAc). Abstract presented at Soc. Neurosci. Nov. 1990.

Pilotte, N. S., Sharpe, L. G. and Dax E. M. Chronic cocaine modifies growth hormone release after 5-hydroxytryptophan in male rats. Abstract presented at Soc. Neurosci. Nov. 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00103-01 PBL****Period Covered:** January 1, 1990 to December 31, 1990**Title of Project:** Basic Mechanisms of cocaine effects.**Principal Investigators:**

Co-PI:	J.L. Katz	Chief	PBL, NIDA, ARC
Co-PI:	J.M. Witkin	Research Psychologist	PBL, NIDA, ARC
Others:	L. Sharpe	Research Psychologist	PBL, NIDA, ARC
	P. Terry	Visting Fellow	PBL, NIDA, ARC
	E. Tirelli	Visiting Fellow	PBL, NIDA, ARC

Cooperating Units: None**Lab/Branch:** Psychobiology Laboratory, Preclinical Pharmacology Branch**Section:** None**Institute and Location:**Addiction Research Center, National Institute on Drug Abuse
Baltimore, Maryland 21224**Total Man Years:** 2.9 **Professional:** 1.9 **Other:** 1.0**Check Appropriate Boxes:**

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work:

Studies of the basic mechanisms of the effects of cocaine have utilized several behavioral procedures. The stimulant effects of cocaine are assessed in studies of locomotor activity in rodents, as well as studies of learned operant behavior. In addition, the subjective effects of cocaine are examined in studies of the discriminative stimulus effects, and reinforcing effects of cocaine. Additional studies are conducted assessing cocaine overdose toxicity in which the lethal and convulsive effects of cocaine are assessed.

Initial studies have investigated the roles of dopamine receptor subtypes in the effects of cocaine. These studies have indicated that both D1 and D2 receptor systems appear to be involved in the discriminative effects of cocaine, however, agonist actions at only one of these receptors does not appear to be sufficient to fully reproduce the subjective effects of cocaine. Results of these studies are forming the basis for further studies that will examine the effects of several of these dopaminergic agents on cocaine self-administration. Previous studies from this laboratory have indicated that the toxic effects of cocaine may be primarily mediated by actions at D1 dopamine receptors. Recent further studies have indicated that these toxic effects of cocaine appear to principally involve peripheral rather than central nervous system mechanisms. The toxic effects of cocaine may be influenced by actions mediated by several other neurotransmitter systems besides the dopamine system. Studies have indicated that agonist actions at mu-opioid receptors can protect against the lethal effects of cocaine. This action may be the basis for the potential therapeutic effects of buprenorphine as a cocaine abuse treatment. In addition, the convulsive

effects of cocaine can be attenuated by the administration of excitatory amino acid antagonists, as well as modulators of these systems.

Other studies have investigated the behavioral and physiological effects of repeated administration of cocaine. The tolerance that develops to the effects of cocaine on learned operant behavior is relatively minor compared to that occurring with other drugs of abuse. It appears that learning plays a significant role in the development of tolerance to cocaine. Along with that tolerance there can be physiological changes. Repeated injections of cocaine can produce a hyper-prolactinemia, and increases neurotensin binding in the prefrontal cortex (where neurotensin is co-localized with dopamine). Preliminary results also indicate that binding to the dopamine transporter is decreased in the nucleus accumbens.

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Witkin, J. M. and Goldberg, S. R. Effects of cocaine on locomotor activity and schedule-controlled behaviors of inbred rat strains. Pharmacology Biochemistry and Behavior 37: 339-342, 1990.

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Katz, J.L., Griffiths, J.W. and Witkin, J.M. Lack of cross tolerance to dopamine agonists in cocaine-tolerant rats. Psychopharmacology, 101: S28, 1990. Paper presented to the Third Biennial Meeting of the European Behavioural Pharmacology Society, 1990.

Schindler, C.W., Tella, S.R., Katz, J.L. and Goldberg, S.R. Effects of cocaine and cocaine methiodide on cardiovascular function in squirrel monkeys. FASEB Journal, [In Press].

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Katz, J. L., Griffiths, J. W. and Witkin, J. M. Lack of cross tolerance to dopamine agonists in cocaine-tolerant rats. Psychopharmacology 101: (Suppl) S28, 1990.

Katz, J. L., Nichols, D. E. and Witkin, J. M. Effects of dopamine receptor-selective drugs in rats trained to discriminate cocaine from saline. Society for Neuroscience Abstracts 16: 253, 1990.

Marley, R. J., Witkin, J. M. and Goldberg, S. R. A pharmacogenetic evaluation of the cocaine kindling process. Society for Neuroscience Abstracts 16: 305, 1990.

Pilotte, N. S., Mitchell, W. M., Sharpe, L. G., De Souza, E. B. and Dax, E. M. Chronic cocaine administration and withdrawal from cocaine modify central neurotensin receptors in rats. Abstract presented at CPDD, June, 1990.

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Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Drug Development

Principal Investigators:

Co-PI:	J.M. Witkin	Research Psychologist	PBL, NIDA, ARC
Co-PI:	J.L. Katz	Chief	PBL, NIDA, ARC
Others:	E. Tirelli	Visiting Fellow	PBL, NIDA, ARC

Cooperating Units: None

Lab/Branch: Psychobiology Laboratory, Preclinical Pharmacology Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse
Baltimore, Maryland 21224

Total Man Years: 1.9 **Professional:** .9 **Other:** 1.0

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work:

These studies are designed to provide preclinical information for the development of medications to be used in the treatment of drug abuse. This work utilizes leads developed in studies of the basic mechanisms of the effects of cocaine in order to further develop pharmacological means for modulating behavioral and toxic actions of cocaine. New chemical entities (synthesized in-house and from outside sources) for safety and efficacy in the design of potential rational treatment strategies.

The primary findings and implications for the current year and future directions are: (1) Buprenorphine protects against the lethal effects of cocaine. The mechanism by which this effect occurs appears to be mu-receptor mediated. The effect was stereospecific, and did not occur in a strain of mice that was mu-receptor deficient. Other mu agonists were equally efficacious with potencies that varied according to their relative affinities for the mu receptor.

Drugs that competitively or non-competitively block the N-methyl-D-aspartate receptor were found to protect against the high-dose convulsant effects of cocaine. This protection was afforded at doses of cocaine that produced effects that could not be antagonized by standard anticonvulsants. These studies suggest a novel avenue for developing new treatments for seizures induced by cocaine overdose. Work on other modulators of this receptor and its associated mechanisms are in progress.

Other studies are being conducted in order to develop a model for assessing cocaine withdrawal

phenomena. A syndrome of hypersensitivity to dopaminergic stimulation after withdrawal from high doses of cocaine has been characterized. If this phenomenon proves to be a valid model of cocaine dependence it will be utilized for evaluating potential cocaine-withdrawal treatment agents.

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NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00105-01 PBL****Period Covered:** January 1, 1990 to December 31, 1990**Title of Project:** Behavioral pharmacology of dopamine systems**Principal Investigators:**

Co-PI:	J.L. Katz	Chief	PBL, NIDA, ARC
Co-PI:	J.M. Witkin	Research Psychologist	PBL, NIDA, ARC
Others:	L. Sharpe	Research Psychologist	PBL, NIDA, ARC
	P. Terry	Visting Fellow	PBL, NIDA, ARC
	E. Tirelli	Visting Fellow	PBL, NIDA, ARC

Cooperating Units: None**Lab/Branch:** Psychobiology Laboratory, Preclinical Pharmacology Branch**Section:** None**Institute and Location:**

Addiction Research Center, National Institute on Drug Abuse
Baltimore, Maryland 21224

Total Man Years: 2.9 **Professional:** 1.9 **Other:** 1.0**Check Appropriate Boxes:**

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work:

These studies are directed at a better understanding of the behavioral effects of drugs acting on dopamine neurotransmission. Several previous studies had results indicating that selective D1 or D2 dopamine agonists and antagonists were not functioning as they would be expected based on their *in vitro* pharmacology. Subsequent studies have been directed at quantitative assessments of behavioral effects of agonist-antagonist interactions. These studies have utilized several different behavioral endpoints, including grossly observable behavior, locomotor activity, consummatory behavior, learned operant behavior, and drug discrimination. In addition, a series of studies is examining the behavioral effects of drugs that are thought to bind irreversibly to the dopamine transporter. These studies will provide answers to several basic questions regarding the functioning of this site as well as provide information that may be of use in the development of drugs to treat cocaine abuse. Finally, studies are being conducted that address the interactions of the dopamine system with cholinergic and GABAergic systems.

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Clinical Pharmacology Branch

Jack E. Henningfield, Ph.D., Chief

Introduction

The Clinical Pharmacology Branch conducts studies of the effects of drugs in human volunteers to provide the basic information necessary to understand, treat, and prevent drug abuse and dependence. The Branch is comprised of three laboratories: Biology of Dependence and Abuse Potential Assessment, Jack E. Henningfield, Ph.D., Chief; Chemistry and Drug Metabolism, Edward J. Cone, Ph.D., Chief; and Neuroendocrinology/ Immunology Laboratory, Jack E. Henningfield, Ph.D., Acting Chief.

The Clinical Pharmacology Branch emerged from the initial program of basic human research which began in the 1930's at the Addiction Research Center in Lexington, Kentucky. It was evident then that the reconciliation of clinical reports with scientific theories of drug addiction could best be accomplished through the careful observation of human volunteers in a controlled research setting. Drugs were administered and withdrawn, and the consequences documented, while minimizing risks to the volunteers. Factors likely to be relevant to the course and/or treatment of drug dependence were also evaluated, e.g., medications. This program of research constituted the clinical pharmacology program of the ARC and today is represented by the Clinical Pharmacology Branch along with the Etiology and Treatment Branches.

The Clinical Pharmacology Branch is well suited to investigate the biological basis of drug abuse and dependence by conducting studies that involve observations during the administration and withdrawal of pharmacologic agents in human volunteers. There is no administrative obstacle to the laboratories working collaboratively to investigate phenomena ranging from metabolism of an administered drug, to the modulation of its effects by the neuroendocrine system, to effects of drug deprivation on performance and subjective response. The diverse range of expertise and technological support required by such a program is available in three laboratories of the branch.

Much of the present research effort of the Branch represents collaborations among its laboratories as well as with other Branches of the ARC. Such multidisciplinary collaborations represent one of the unique strengths of scientific exploration at the ARC. The Clinical Pharmacology Branch has also continued in its historically important mission of providing a training ground for the development of researchers and clinicians. This training mission is administratively stimulated by our efforts to maintain a balance of tenured to non-tenured scientists in which approximately one third of the scientists leave the branch every two to three years.

Senior scientists of the Branch are regularly invited to provide lectures and training courses, review grants, and provide consultative advice on scientific issues to other Federal agencies and to both national and international organizations. Dr. Jack E. Henningfield serves as an advisor to the US Surgeon General, Centers for Disease Control, Food and Drug Administration and other agencies on issues pertaining to nicotine dependence. Dr. Henningfield collaborates with national and international organizations on issues pertaining to the assessment of the abuse liability of chemicals and development of drugs. Dr. Edward J. Cone has received national and international recognition for his work on the detection of drugs of abuse in biological fluids. His advice is widely sought by federal agencies such as the Department of Defense and private industry. He was invited to present his findings on the detection of drugs in hair to the second International Congress of Therapeutic Drug Monitoring and Toxicology in Barcelona, Spain and to numerous scientific groups in the United States. Dr. Cone also serves as a consultant to the National Laboratory Certification Program. Dr. Stephen J. Heishman serves as a lecturer and consultant to the Federal Aviation Administration in their drug testing program. Dr. Wallace B. Pickworth is a widely recognized author and consultant on the development and evaluation of pupilometric devices for possible use in onsite assessment of drug exposure.

1. Biology of Dependence and Abuse Potential Assessment Laboratory
- Jack E. Henningfield, Ph.D., Chief

The Biology of Dependence and Abuse Potential Assessment Laboratory (BDL) assesses the biological basis of drug dependence using quantitative experimental procedures of the behavioral and pharmacological disciplines; and assesses the abuse liability and physical dependence potential of selected compounds. These aims are intended to serve the overall mission of the ARC in providing a better foundation for understanding drug dependence and for developing rational approaches for preventing and treating drug dependence.

The BDL evolved out of a tradition of research whose goal was to characterize drug-induced changes in behavior and physiologic function; specifically, phenomena such as drug seeking, tolerance, and physical dependence. The understanding of these phenomena and their interrelations provides much of the pharmacologic and behavioral basis for evolving theories of drug dependence. A practical product of this research was the development of standardized procedures to assess the potential of drugs to produce dependence, i.e., abuse liability and physical dependence potential tests. Early research by Himmelsbach, Frazier, Isbell, Martin, and others, produced fundamental observations upon which much of current theory about the understanding and treatment of drug dependence is based. Specific areas of exploration included the following:

- a. the relationship between drug administration and development of tolerance, physical dependence and changes in mood and behavior;
- b. the use of drug substitution and antagonist administration procedures to study the biologic basis of drug dependence and to treat addicted people;
- c. the phenomena whereby drug administration could lead to the alleviation of dysphoric mood states or the production of euphoric mood states by the presentation of certain drugs; and
- d. patterns of drug seeking in the presence and absence of pharmacologic pretreatment.

In the course of conduct of these and other basis studies, new strategies of assessment emerged. The methods included the use of observer ratings, pupilometry and cardiovascular assessment, and electroencephalogram (EEG) to provide objective markers of drug administration, as well as the development of new instruments for assessing the effects of drugs on mood, feeling, and behavior. Data obtained using such methods and instruments proved not only to be useful in exploration of the basic phenomena underlying drug dependence, but also led to objective methods of abuse liability assessment. The ability to both quantitatively and qualitatively characterize the clinical pharmacology of substances was also fundamental in the development of more selective, safer, and more efficacious agents for the alleviation of human disease and suffering.

Most studies of the BDL are multidisciplinary in nature and involve collaborations with one or more other laboratories of the ARC. With such multidisciplinary efforts it is possible to quantitate the subjective physiologic, behavioral, electrophysiologic, cognitive, pharmacodynamic, pharmacokinetic, reinforcing, aversive, and other effects of drugs, as well as to assess the biologic generality of phenomena by comparative animal-human research.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00037-01 BDL

January 1, 1990 to December 31, 1990

Title of Project: Physiologic, cognitive and subject effects of commonly abused drugs

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: W.B. Pickworth Pharmacologist, BDL, ARC,NIDA

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Subjects with histories of polydrug abuse are studied on the Residential Research Unit to assess the effects of several classes of abused drugs on cognitive, subjective and physiologic measures. The main purpose of the study is to parametrically compare the sensitivity of various testing instruments across several classes of drugs, doses and time. The results are theoretical important because they will evaluate the sensitivities of methods used in the drug abuse field. The study is of practical importance because it evaluates the utility of dynamic pupillography as a drug detection screeen. The subject testing has been completed (n=9). Preliminary results suggest that pupillometry may identify recent ingestion of opiates, marijuana and pentobarbital. The results are submitted for presentation at the 1991 CPDD meeting.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00028-02 BDL

January 1, 1990 to December 31, 1990

Title of Project: Assessment of Mazindol for Abuse Liability

Principal Investigators: Cooperating Units

P.I.: J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: W.B. Pickworth Pharmacologist, BDL, ARC,NIDA
M.J. Kuhar Chief, Neuroscience Branch

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Subjects with histories of stimulant abuse are studied on the Residential Research Unit to determine the abuse liability of mazindol (an anorectant with some psychomotor stimulant properties) to methylphenidate (a prototypic psychomotor stimulant with a known potential for abuse). This study was performed because mazindol has been used in binding studies aimed at isolating the cocaine receptor. The results of these studies indicated that mazindol has high affinity binding at cocaine-sensitive dopamine receptor sites. Mazindol is a theoretically interesting drug since its apparent mechanism of action (blocks reuptake of norepinephrine and dopamine) suggests that it would have abuse potential. However, one previous study and limited clinical experience, suggest that it is seldom abused. Therefore additional characterization of the clinical pharmacology of mazindol could be of importance in analytic efforts as well as drug development. This study is conducted in collaboration with the Neuroscience Branch. Subject testing has been completed. Mazindol and methylphenidate increased heart rate and diastolic blood pressure and decreased hunger. Mazindol decreased vigor and increased measures of fatigue and tired and elevated scores on the PCAG and LSD scales of the ARCI. Methylphenidate did not cause the sedative-like effects seen after mazindol. Subjects reported disliking for each drug. These data indicate that at doses three times the therapeutic level mazindol poses little abuse potential. On the other hand its dysphoric effects call to question the acceptability of mazindol for the treatment of cocaine dependence. The data were presented at the 1990 CPDD meeting and a manuscript has been prepared for submission to Pharmacol Biochem and Behavior.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00029-02 BDL

January 1, 1990 to December 31, 1990

Title of Project: Interaction Between Ethanol and Prostaglandin Synthetase Inhibitors**Principal Investigators: Cooperating Units****P.I.** J.E. Henningfield Chief, Clinical Pharmacology Branch**Others:** W.B. Pickworth Pharmacologist, BDL, ARC,NIDA
F.R. George Staff Fellow**Lab/Branch:** Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch**Section:** None**Institute and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: **Professional:** **Other:****Check Appropriate Boxes:** **Human Subjects** **Human Tissues** **Neither**
 Minors
 Interviews**Summary of Work**

Subjects with histories of moderate alcohol use are studied on the Residential Research Unit to assess the effects of ethanol following pretreatment with neither acetaminophen (325, 650, 1300 and 1950 mg) or placebo. Acetaminophen is a prostaglandin synthetase inhibitor that has been shown to reduce several behavioral and physiologic effects of alcohol in animal studies, alcohol appears to act in part by increasing prostaglandin levels. This drug interaction study makes use of our standard procedures for assessing abuse potential and performance to evaluate the possibility of such antagonistic effects in human subjects. This study is conducted in collaboration with the Preclinical Branch. Subject testing has been completed. Preliminary analyses indicate that alcohol at this dosage (0.625 gm/kg, taken over 90 mins) caused subjective effects (drunk, feel drug, sober, etc) but did not reliably change physiologic or performance measures. Pretreatment with acetaminophen did not influence the subjective effects. The results are submitted for publication.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00033-02 BDL

January 1, 1990 to December 31, 1990

Title of Project: Nicotine Patch: Effects on Smoking Subjective and Physiologic Functions

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: W.B. Pickworth Pharmacologist, BDL, ARC,NIDA

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

A recently developed nicotine patch will be studied in residential research volunteers. The effect of three patches containing 0, 30 and 60 mg will be evaluated on ad lib smoking, subjective effects and physiologic measures. The patch will be tested in subjects with and without histories of drug abuse. The study is of practical importance in the development of a new therapy for smoking cessation. The subject testing phase (n=10) of the experiment has been completed. The results suggest that nicotine patch reduced spontaneous smoking in a dose-related fashion. The patch did not cause subject liking and was judged to have little abuse potential. The results will be presented at the 1991 CPDD meeting.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00038-01 BDL**

January 1, 1990 to December 31, 1990

Title of Project: Transcranial Electrostimulation Therapy (TCET) During Smoking Cessation**Principal Investigators: Cooperating Units****P.I.** W.B. Pickworth Pharmacologist, BDL, ARC,NIDA**Others:** J.E. Henningfield Chief, Clinical Pharmacology Branch**Lab/Branch:** Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch**Section:** None**Institute and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.8 **Professional:** 1.3 **Other:** .5

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Subjects with histories of cigarette smoking wishing to stop are recruited for this treatment study. Subjects are randomly assigned to a treatment group (n=50) which receives small impercatible electric current (30 microamps pulsed for 60 min.) for 1 hr on 5 consecutive days. The sham treated (n=50) group are connected to the device but no current is delivered. Dependent variables include: cigarettes smoked, CO, urinary cotinine, Hatsukami withdrawal score, nicotine craving, mood changes and physiologic data (HR, BP). The study has been approved by the IRB and subject recruitment and treatment has started.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00039-01 BDL

January 1, 1990 to December 31, 1990

Title of Project: Physiologic and Performance Effects of Ethanol and Pentobarbital and Interactions with Indomethacin

Principal Investigators: Cooperating Units

P.I. W.B. Pickworth Pharmacologist, BDL, ARC, NIDA

Others: J.E. Henningfield Chief, Clinical Pharmacology Branch

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: .8 **Professional:** .5 **Other:** .3

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Subjects of either sex with histories of alcohol and sedative abuse are studied on the Residential Research Unit to assess the effects of indomethacin pretreatment on the performance, physiologic and subjective effects of sedative drugs. Animal research suggests that inhibitors of prostaglandin synthesis reduce the effects of ethanol but these results have not been confirmed in humans. The protocol has been approved by the IRB and subject recruitment and testing has started.

January 1, 1990 to December 31, 1990

Title of Project: Archival Data Base Project

Principal Investigators: Cooperating Units

P.I. C.A. Haertzen Research Psychologist, BDL, ARC, NIDA

Others:

J.E. Henningfield	Chief, Clinical Pharmacology Branch
W.R. Lange	Medical Director, ARC, NIDA
J.H. Jaffe	NIDA
W.E. Weddington	Former Staff Fellow
L. Covi	Visiting Scientist
S. Tiffany	Visiting Scientist

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institute and Location

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Data combined into an Admission Data Base consisting of tests obtained on recruitment (Addiction Severity Index, SCL-90 Symptom Check List, Shipley IQ) and tests obtained on admission (Diagnostic Interview Schedule, Buss-Durkee Hostility, Minnesota Multiphasic Personality Inventory, and Alcohol Related Behavioral Questionnaire) continued to be relevant. Thus, behavioral hostility, as revealed by a simulation of the effects of alcohol was related to a diagnosis of alcohol dependence over and above prediction afforded by hostility ascribed to a drug free status (see Walter et al., 1990).

Archival data from the Addiction Research Center Inventory collected in Lexington, Kentucky on prisoner heroin addicts for a no-drug condition was analyzed for seasonal effects. Could heroin addicts who are frequently depressed show the seasonal pattern typically found for those with seasonal affective disorders? Seasonal effects were found, but a summer pattern was found characterized by increased sedative-hypnotic effects (tiredness, etc, as measured by the PCAG scale)(see Haertzen, 1991). To pursue the question further, the SCL-90 tests obtained on recruitment at the Addiction Research Center in Baltimore were analyzed for seasonal effects. Again a significant summer effect was found. Depression was enhanced. In addition, sleep impairment, as indicated by the items in the Additional Scale, was elevated. Psychopathology, as measured at the time of recruitment, may be affected by environmental influences or greater behavioral variability in sleeping patterns coincident with summer.

A significant elevation was also found for SCL-90 Aggression. As a follow-up on this finding researchers at the Patuxent prison searched their data base for adverse behavior reports for the year 1990. They found an increased incidence in adverse behavior in the summer months, especially June.

A data base for a questionnaire on cocaine craving designed by Dr. Tiffany was set-up and analyzed. In keeping with the results of treatment oriented studies by Drs. Weddington and Covi, a depressive mood was correlated with cocaine craving.

Publications:

Haertzen, C.A. and Hickey, J.E.: Addiction Research Center Inventory (ARCI): Measurement of Euphoria and Other Drug Effects. In Bozarth, M.A. (Ed.) Methods of Assessing the Reinforcing Properties of Abused Drugs. New York, NY, Springer-Verlag, 1987, pp. 489-524.

Lange, W.R., Haertzen, C.A., Hickey, J.E., Snyder, F.R., Dax, E.M., and Jaffe, J.H.: Nitrite inhalants: Patterns of abuse in Baltimore and Washington, D.C. Am J Drug Alcohol Abuse 14:29-39, 1988.

Rose, M.R., Brown, B.S., and Haertzen, C.A.: Comparison of the characteristics and functioning of cocaine treatment and cocaine research subjects. Am J Drug Alcohol Abuse 15:251-260, 1989.

Fishbein, D.H., Herning, R.I., Pickworth, W.B., Haertzen, C.A., Hickey, J.E., and Jaffe, J.H.: EEG and Brainstem auditory evoked response potentials in adult male drug abusers with self-reported histories of aggressive behavior. Biological Psychiatry 595-611, 1989.

Muntaner, C., Nagoshi, C., Jaffe, J.H., Walter, D., Haertzen, C., Fishbein, D.H.: Correlates of self-reported early childhood aggression in subjects volunteering for drug studies. Am J Drug Alcohol Abuse 15:383-402, 1989.

Weddington, W.W., Brown, B.S., Haertzen, C.A., Cone, E.J., Dax, E.M., Herning, R.I., Michaelson, B.S.: Changes in mood, craving, and sleep during acute abstinence reported by male cocaine addicts: A controlled, residential study. Archives of General Psychiatry. In press.

Haertzen, C.A., Hickey, J.E., Rose, M.R. and Jaffe, J.H.: The relationship between a diagnosis of antisocial personality and hostility: Development of an Antisocial Hostility Scale. J Clin Psychol 46:679-686, 1990.

Walter, D., Nagoshi, C., Muntaner, C. & Haertzen, C.A. The prediction of drug dependence from expectancy for hostility while intoxicated. International J of Addictions, 25:1151-1168, 1990.

Weddington, W.W., Brown, B.S., Haertzen, C.A., Hess, J.M., Mahaffey, J.R., Kolar, A.F. & Jaffe, J.H. Comparison of amantadine and desipramine combined with psychotherapy for treatment of cocaine dependence. American Journal Drug Alcohol Abuse 17:137-152, 1991.

Haertzen, C.A. Geophysical variables and behavior: LXV. Seasonal changes in mood in opioid addicts on the Addiction Research Center Inventory. Psychological Reports 68:360-362 1991.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00040-01 BDL**

January 1, 1990 to December 31, 1990

Title of Project: Opioid Agonist and Antagonist Sensivity in Opiate-Experienced Individuals**Principal Investigators: Cooperating Units****P.I.** J.E. Henningfield Chief, Clinical Pharmacology Branch**Others:** S.J. Heishman Research Psychologist, BDL, NIDA/ARC
C. Cohen Visiting Scientists, BDL, NIDA/ARC**Lab/Branch:** Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch**Section:** None**Institute and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:**Check Appropriate Boxes:** **Human Subjects** **Human Tissues** **Neither** **Minors** **Interviews****Summary of Work**

Several recent studies have investigated the phenomenon of acute opioid physical dependence or antagonist sensitivity in humans. These studies have shown that a mild withdrawal syndrome can be precipitated by the opioid antagonist, naloxone, administered 45 minutes to 24 hours after a single dose of morphine. These findings are particularly interesting given that the opioid abstinence syndrome has traditionally been thought to develop only after prolonged exposure to opiates. However, these studies have only used non-dependent opiate-experienced subjects. It is not known whether or to what extent an opiate history contributes to the development of acute dependence. If differences in agonist and/or antagonist sensitivity are found between opiate-experienced and opiate-naive individuals, it could reflect residual tolerance or dependence in opiate-experienced individuals due to their chronic opioid exposure. Another interesting possibility is that differences in sensitivity may reflect biological differences between opiate-experienced and opiate-naive individuals that predate initial drug use and thus confer some vulnerability or predisposition to use or abuse opiate drugs. This research will examine the following issues: a) differences in subjective and physiological sensitivity to opioid agonists between opioid-experienced and opioid naive subjects, b) differences in acute antagonist-precipitated withdrawal (antagonist sensitivity) between these groups, and c) whether any differences in antagonist sensitivity are related to dose of the antagonist.

Subject testing was begun in 1990 and is nearly completed. A preliminary report of data will be presented at the 1991 meeting of the Committee on Problems of Drug Dependence.

January 1, 1990 to December 31, 1990

Title of Project: Discriminative Stimulus Effects of Stimulant Drugs

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: S.J. Heishman Research Psychologist, BDL, NIDA/ARC
C. Cohen Visting Scientist, BDL, NIDA/ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

The supply of legally available amphetamines was reduced by about 80% following the 1970 Controlled Substances Act, which classified all amphetamine-type stimulants as Schedule II drugs. This void was filled by the production of "look-alike" drugs designed to mimic the stimulant effect of amphetamines. The main psychoactive agent in many of these preparations is caffeine or caffeine combined with one or more sympathomimetic amines, such as ephedrine and phenylpropanolamine (PPA). Individually, caffeine, ephedrine, and PPA are relatively safe drugs when taken in moderate or therapeutic doses. However, little is known about the behavioral pharmacology of their combined effects in "look-alike" stimulants, including their discriminative stimulus effects or potential for abuse when individuals exceed the therapeutic dosage regimen in an attempt to achieve amphetamine-like euphoria.

In a series of studies, we will investigate the subjective, physiological, and discriminative stimulus effects of a stimulant that is widely used on a daily basis (caffeine), some that are used clinically (mazindol, ephedrine, PPA), and some that have known or potential abuse liability (d-amphetamine, mazindol, caffeine/ephedrine/PPA combined "look-alike" stimulants). The knowledge gained from these studies will enable us to draw clearer distinctions among stimulants in terms of their behavioral and subjective effects. Additionally, these studies will provide seminal information concerning the behavioral pharmacology of "look-alike" stimulants, which pose a potential public health risk from a medical and an abuse liability standpoint. We plan to begin testing subjects in 1991.

January 1, 1990 to December 31, 1990

Title of Project: Effect of Reinforcement Contingencies on Human Task Performance

Principal Investigators: Cooperating Units

P.I.: J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: S.J. Heishman Research Psychologist, BDL, NIDA/ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section:

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: **Professional:** **Other:**

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Although various psychomotor and cognitive tasks are widely utilized in studies assessing the effects of psychoactive drugs on performance, no study, to our knowledge, has systematically examined the effect of varying contingencies of reinforcement on human performance. In this context, a reinforcement contingency can be defined as an experimental condition in which some monetary rewards is paid upon completion of a particular behavior. In most studies, subjects perform tasks with no particular consequence for accurate performance or are paid some arbitrary amount for correct responding. This lack of attention to the effects of reinforcement contingencies on performance is somewhat surprising given the extensive animal literature reporting dramatic effects of manipulating reinforcement conditions on schedule-controlled behavior.

Manipulating reinforcement contingencies on performance is an objective, measureable means of varying what is commonly referred to as motivation. Obviously, a person's level of motivation can be an important factor in determining the quality and quantity of their performance. The lack of standardizing a person's motivational level by holding constant contingencies of reinforcement can result in behavior that is subject to uncontrolled variation. A series of studies will examine the effects of manipulating reinforcement contingencies on human performance by differentially reinforcing task speed versus task accuracy. Subject testing began in 1990, and four separate experiments have been completed (N=21). Results indicate that, in general, subjects' behavior has not readily come under the control of the reinforcement contingencies. Further studies will be designed to determine what contingency conditions reliably control task performance.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00034-02 BDL

January 1, 1990 to December 31, 1990

Title of Project: Opioid Self-Administration in Humans

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: S.J. Heishman Research Psychologist, BDL, NIDA/ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section:

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

The effect of withdrawal states on drug reinforcement and drug self-administration has received little systematic attention from drug abuse researchers. This is a critical omission because it is generally assumed that humans will seek drugs to alleviate unpleasant or relapsing withdrawal symptoms, thus maintaining their state of physical dependence or relapsing after a period of abstinence. This research will examine the following issues: (a) the pattern of self-administration when only low doses of opiates are available, (b) the effect of opioid antagonist-precipitated withdrawal on opiate self-administration, and (c) the relationship between self-administration behavior and subjective drug effects. This research should be useful in the development of better methods to predict abuse liability of drugs, because it combines the two primary strategies of abuse liability assessment, self-administration and subjective effects testing, in a single study. In addition to addressing these important pharmacological-behavioral interactions, this research may ultimately result in more effective treatment methods for drug abuse. Pilot testing of residential subjects with a history of opioid abuse has been completed, and the main study should begin in 1991.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00026-02 BDL**

January 1, 1990 to December 31, 1990

Title of Project: Assessment of Opioid Agonists and Antagonists**Principal Investigators: Cooperating Units****P.I.:** J.E. Henningfield Chief, Clinical Pharmacology Branch**Others:** S.J. Heishman Research Psychologist, BDL, NIDA/ARC
E.J. Cone Chief, Chemistry & Drug Metabolism Laboratory
R.E. Johnson Former Chief, Research Support Branch
P.J. Fudala Former Deputy Chief, RSB, NIDA, ARC**Lab/Branch:** Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch**Section:****Institute and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:**Check Appropriate Boxes:** **Human Subjects** **Human Tissues** **Neither**
 Minors
 Interviews**Summary of Work**

Subjects with histories of opioid abuse were studied on the Residential Research Unit to investigate the effects of nalmefene, a new investigational opioid antagonist with relatively few agonist effects. This research should be useful in determining the possible utility of this long-acting (several days) opioid antagonist for the treatment of opioid dependent persons. This research is being conducted in collaboration with the Chemistry and Drug Metabolism Laboratory and the Research Support Branch. Two studies were planned, the first will assess the abuse liability of nalmefene and the second will determine the efficacy of nalmefene to block the subjective and physiological effects of morphine. The first study has been completed. Results indicated that nalmefene did not produce typical opiate-like abuse liability, but that side effects, such as feelings of agitation and irritability, muscle tension, headache, and insomnia may limit its use as possible treatment for opioid dependence. The second study was recently completed, and the data are currently being analyzed. A preliminary report will be presented at the 1991 meeting of the Committee on Problems of Drug Dependence.

Abstracts:

Fudala, P.J., Johnson, R.E., Heishman, S.J., Cone, E.J. and Henningfield, J.E. A dose run-up and safety evaluation of nalmefene in human volunteers. In L.S. Harris (Ed.), Problems of Drug Dependence 1989. NIDA Research Monograph 95 (pp. 451-452). Washington, DC: US Government Printing Office, 1990.

Fudala, P.J., Johnson, R.E., Heishman, S.J. and Henningfield, J.E. Evaluation of the abuse liability of nalmefene. Clinical Pharmacology and Therapeutics, 49: 167, 1991.

Publications:

Fudala, P.J., Heishman, S.J., Henningfield, J.E. and Johnson, R.E. Human pharmacology and abuse potential of nalmefene. Clinical Pharmacology and Therapeutics, 49: 300-306, 1991.

January 1, 1990 to December 31, 1990

Title of Project: Psychotropic Properties of Stimulants and Sedatives: Discriminative Properties

Principal Investigators: Cooperating Units

P.I.: J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: S.J. Heishman Research Psychologist, BDL, NIDA/ARC
R.J. Lamb Former Staff Fellow
W.R. Lange Medical Director, ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section:

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

In these studies the psychotropic effects of the prototypical stimulant, d-amphetamine, were compared to those of another stimulant and to the effects of a sedative and an opioid. These comparisons were conducted in subjects with histories of stimulant and either opioid or sedative abuse, and were carried out using two different types of procedures simultaneously. The first procedure was a drug discrimination task. In the drug discrimination procedure subjects were trained to respond on one lever following administration of the training dose of d-amphetamine and on another lever in the absence of d-amphetamine. Correct responding was reinforced by money. The second procedure was a traditional abuse liability assessment procedure that utilized physiologic and self-report measures.

To date two studies have been conducted. In the first the effects of amphetamine and hydromorphone were compared. In the second the effects of amphetamine, methylphenidate, and diazepam were compared. In both studies amphetamine dose-relatedly occasioned d-amphetamine appropriate responding. Methylphenidate, also, dose-relatedly occasioned d-amphetamine appropriate responding. In contrast neither diazepam nor hydromorphone occasioned d-amphetamine appropriate responding. The subjective effects of d-amphetamine and methylphenidate were similar and covaried with their discriminative effects, while the subjective effects of diazepam were clearly different. In contrast, the only self-report measure that distinguished hydromorphone from d-amphetamine were drug identifications. Thus these studies show that drug discrimination procedures can be drug-class specific in humans, and that while these discriminative effects can covary with the subjective effects of the drug, the discriminative effects of amphetamine under these conditions appear to be controlled in a manner most similar to the identification of a drug.

Abstracts:

Lamb, R.J. and Henningfield, J.E. (1990) Human d-amphetamine drug discrimination: Testing with d-amphetamine and hydromorphone. In: L.S. Harris (Ed.) Problems of Drug Dependence 1989, NIDA Research Monograph 95 (pp. 423-424). Washington, DC: US Government Printing Office.

Heishman, S.J., Lange, W.R. and Henningfield, J.E. (1990) Discriminative stimulus effects of d-amphetamine, methylphenidate and diazepam in humans. Pharmacology Biochemistry and Behavior, 32: 1090.

Heishman, S.J., Lamb, R.J. and Henningfield, J.E. (1990) Discriminative stimulus effects of drugs in humans. Stimulants and sedatives. Pharmacology Biochemistry and Behavior, 36: 428.

Publications:

Heishman, S.J. and Henningfield, J.E. (1991) Discriminative stimulus effects of d-amphetamine, methylphenidate and diazepam in humans. Psychopharmacology, in press.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00031-02 BDL**

January 1, 1990 to December 31, 1990

Title of Project: Effects of Nicotine in Nonsmokers**Principal Investigators: Cooperating Units****P.I.** J.E. Henningfield Chief, Clinical Pharmacology Branch**Others:** S.J. Heishman Research Psychologist, BDL, NIDA/ARC
F.R. Snyder Statistician, NOVA**Lab/Branch:** Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch**Section:** None**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.10 **Professional:** 0.30 **Other:** 0.8**Check Appropriate Boxes:** **Human Subjects** **Human Tissues** **Neither**
 Minors
 Interviews**Summary of Work**

Nonsmokers are exposed to nicotine given in the form of nicotine polacrilex gum; preliminary testing suggests that this formulation is of low abuse liability and is safe if given according to prescribed procedures. Two important experimental questions are addressed in this study. One concerns the further evaluation of the effects of nicotine polacrilex gum in nonsmokers to determine the possible effects of nicotine on cognitive performance in the absence of pre-existing nicotine dependence. Nicotine enhances performance in deprived smokers; however, it remains to be determined if nicotine dependence is a precondition for this effect. The second question is of general importance to the understanding of the development of drug dependence. Using a model of daily repeated voluntary cumulative dosing, the course of possible development of tolerance to the subjective, behavioral and physiologic actions of nicotine will be determined. Such data cannot be readily obtained with other drugs of abuse, and probably not with forms of nicotine known to be of high abuse liability (e.g., cigarettes), but may be safely collected following the procedures used in this study. Subject testing is completed (n=12) and data are currently being analyzed. Preliminary results indicate that nicotine did not enhance task performance and that tolerance to the effects of nicotine developed for some, but not all, measures. A preliminary report of the data was presented at the 1990 meeting of the Committee on Problems of Drug Dependence and a more complete report will be made at the 1991 meeting of the American Psychological Association.

Abstracts:

Heishman, S.J., Snyder, F.R. and Henningfield, J.E. Effect of repeated nicotine administration in nonsmokers. In: Problems of Drug Dependence 1990, NIDA Research Monograph, in press.

Heishman, S.J., Richards, L.M. and Henningfield, J.E. Effect of nicotine on cognitive and psychomotor performance in nonsmokers. Pharmacology Biochemistry & Behavior, in press.

January 1, 1990 to December 31, 1990

Title of Project: Lobeline and Nicotine: Subjective, Physiologic and Kinetic Effects

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: S.M. Evans Staff Fellow, BDL, NIDA/ARC
W.B. Pickworth Pharmacologist, BDL, NIDA/ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laborator
Clinical Pharmacology Branch

Section: None

Institute and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Lobeline is used in a variety of over-the-counter aids for smoking cessation but it has never been documented in scientific studies to be efficacious as an aid to cessation. Experimental data, however, suggests that it may be more effective in alternate formulations and/or presented at higher dose levels. Despite the wide spread use of lobeline there are little data on its kinetics or specific dose-related effects on human subjective and physiologic responses, and on its effects on cigarette smoking. The major purpose of the present study was to determine the safety of lobeline given intravenously over a period of 5 minutes in doses up to 8 mg. The present study also compared the effects of pretreatment of intravenously administered lobeline, placebo and nicotine on physiologic effects, subjective effects and kinetics. In addition, the effects of these drugs on cigarette smoking behavior was also evaluated. We have recently completed this study and are currently writing up the report. Four subjects completed the full dose-range of lobeline and nicotine with no adverse effects on either cardiovascular measures (ECG, blood pressure, heart rate) or other subjective effects. These results suggest that lobeline is safe even when given as a 5 min intravenous injection up to doses of 8 mg. Inspection of the subjective effects data suggest that doses administered were not producing any effects similar to standard drugs of abuse. Preliminary results also indicate that the doses of lobeline and nicotine administered using the injection procedure in the present study did not show any decreases on cigarette smoking behavior. At this time, plasma samples have yet to be analyzed so there are no kinetic data.

January 1, 1990 to December 31, 1990

Title of Project: Arterial Kinetics of Smoked Cocaine

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: S.M. Evans Staff Fellow, ARC
E.J. Cone Chief, CDM Laboratory

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Currently, smoked cocaine or "crack" is thought to have greater addictive effects than other routes of cocaine administration, including intravenous administration. Surprisingly, despite the fact that smoked cocaine represents one of the most serious medical and social challenges to our society today there are no data from humans on the levels of cocaine that actually reach the arterial blood stream enroute to the brain.

The purpose of this study is to directly compare the effects of smoked cocaine to those of intravenously administered cocaine primarily on the kinetics of cocaine in both arterial and venous blood. Standard cardiovascular measures and subjective effects will be evaluated concurrently with the arterial and venous blood draws. Subjects will have current histories of using cocaine by both routes of administration. Subjects will be exposed to 3 doses of smoked cocaine or "crack" and 3 doses of intravenous cocaine.

To date we have obtained the IND to administer smoked cocaine. We have also met several times with the anesthesiologists to review the protocol and technical details with the study nurses. We are planning to recruit our first subject mid-May.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00047-01 BDL

January 1, 1990 to December 31, 1990

Title of Project: Outpatient Drug Discrimination

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: S.M. Evans Staff Fellow, BDL, NIDA/ARC
C.E. Johanson Collaborator, USUHS

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

The purpose of this study was to determine if normal volunteers could be trained to discriminate therapeutic doses of antihistamines (e.g., tripelemnamine and diphenhydramine) from placebo and to evaluate the dose-relationship and pharmacological specificity of the discrimination. This protocol is currently under review by the IRB.

January 1, 1990 to December 31, 1990

Title of Project: Triazolam Self-Administration: Effects of Yohimbine Pretreatment

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: J.R. Roache Former Staff Fellow, BDL, NIDA, ARC
R.A. Meisch Former Staff Fellow, BDL, NIDA, ARC
S.A. Klein Former Staff Fellow, BDL, NIDA, ARC
J.H. Jaffe Former Director, NIDA, ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.70 **Professional:** 2.00 **Other:** 5.00

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

The purpose of this study was to examine the effects of yohimbine pretreatment on the self-administration of triazolam in subjects with histories of sedative abuse. Two issues of relevance to the behavioral pharmacology of drug abuse are being addressed: the first involved the development of procedures to measure sedative/anxiolytic drug self-administration; and, the second was to examine the effects of yohimbine pretreatment on triazolam self-administration. It is of basic theoretical, as well as clinical, interest to define methods to detect the effects of one drug on the self-administration of another drug. In addition, yohimbine has been shown to produce neuroendocrine changes and subjective mood states in humans which resemble anxiety. Thus, this study could provide important information related to hypotheses of drug abuse which involve psychiatric vulnerability factors.

Data collection has been completed and a manuscript has been submitted for publication.

January 1, 1990 to December 31, 1990

Title of Project: Effects of Drugs on Cigarette Smoking and Responses to Nicotine

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: R. Nemeth-Coslett Former Staff Fellow, BDL, NIDA, ARC
F.C. Davis Nurse, FSK
A.H. Sampson Nurse, FSK

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.23 **Professional:** 0.03 **Other:** 0.20*

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Initial studies were conducted in the physical facilities of the Behavioral Pharmacology Research Unit at Johns Hopkins University medical School in collaboration with Dr. R.R. Griffith which provided some research support. For example, multiple measures of cigarette smoking, subjective effect, and physiologic effect were collected during ad libitum smoking sessions in normal volunteers following administration of mecamylamine, naloxone, or marijuana.

Presently, basic measures of cigarette smoking are being collected from all subjects on the Clinical Research Unit and data analyses have begun. This database-type of study appears to be providing the opportunity to quantitate the effects of a wide range of variables on cigarette smoking (i.e., atropine administration, cocaine withdrawal, buprenorphine administration, and passive tobacco smoke exposure).

Publications

Nemeth-Coslett, R. and Griffiths, R.R.: Naloxone does not affect cigarette smoking. Psychopharmacology, 89:261-264, 1986.

Nemeth-Coslett, R., Henningfield, J.E., O'Keeffe, M.K. and Griffiths, R.R.: Effects of mecamylamine on human cigarette smoking and subjective ratings. Psychopharmacology, 88:420-425, 1986.

Nemeth-Coslett, R., Henningfield, J.E., O'Keeffe, M.K. and Griffiths, R.R.: Effects of marijuana on human cigarette smoking and physiologic changes and subjective responses. Pharmacol Biochem Behav 25:659-665, 1986.

Nemeth-Coslett, R., Henningfield, J.E., O'Keeffe, M.K. and Griffiths, R.R.: Nicotine gum: Dose-related effects on cigarette smoking and subjective ratings. Psychopharmacology 92:424-430, 1987.

Rose, J.E., Sampson, A., Levin, E.D. and Henningfield, J.E.: Mecamylamine increases nicotine preference and attenuates nicotine discrimination. Pharmacol Biochem Behav. In press.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00010-06 BDL**

January 1, 1990 to December 31, 1990

Title of Project: Behavioral and Pharmacologic Factors in Nicotine Replacement for Tobacco Dependence**Principal Investigators: Cooperating Units****P.I.** J.E. Henningfield Chief, Clinical Pharmacology Branch**Others:** W.B. Pickworth Pharmacologist, BDL, NIDA, ARC
C. Cohen Visiting Scientist, BDL, NIDA, ARC
Eric Simmons Coppin State College
Alex Radzius Research Assistant, BDL, NIDA, ARC**Lab/Branch:** Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section:

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.50 **Professional:** 0.15 **Other:** 0.35**Check Appropriate Boxes:** **Human Subjects** **Human Tissues** **Neither**
 Minors
 Interviews**Summary of Work**

Nicotine polacrilex (chewing gum) has been under investigation as a replacement for tobacco-delivered nicotine and also as a convenient drug administration modality which provides a model of more general interest for drug dependence researchers. For example, nicotine gum was employed in our initial studies to examine the capabilities of this Laboratory's recently established performance and electrophysiologic assessment approaches for evaluating drug effects. The course of research conducted using this preparation has been determined by the priorities of the ARC and the Chief of the Biology of Dependence Laboratory. These studies have included the following: (1) Effects of nicotine gum replacement on cigarette smoking and tobacco smoke exposure; (2) Pharmacodynamic effects of nicotine gum compared to other routes of nicotine administration; (3) Abuse liability of nicotine gum; (4) Dose-related effects on subjective, behavioral, and physiologic variables, including studies of the factors which may affect the functional dose, such as chewing and swallowing rates; (5) Effects of nicotine gum administration on learning and performance in non-smokers; and (6) Role of oral pH in nicotine absorption.

Publications

Nemeth-Coslett, R., Benowitz, N.L., Robinson, N. and Henningfield, J.E.: Nicotine Gum: Chew rate, subjective effects and plasma nicotine. Pharmacol Biochem Behav 29:747-751, 1988.

Pickworth, W.B., Herning, R.I. and Henningfield, J.E.: Electroencephalographic effects of nicotine gum in humans. Pharmacol Biochem Behav 25:879-882, 1986.

Jasinski, D.R. and Henningfield, J.E.: Conceptual Basis of Replacement Therapies for Chemical Dependence. In Pomerleau, O.F., Pomerleau, C.S., Fagerstrom, K.O., Henningfield, J.E. and Hughes, J.R. (Eds.): Nicotine Replacement: A Critical Evaluation. New York, NY, Alan R. Liss, 1988, pp. 13-34.

Waranch, H.R., Henningfield, J.E. and Edmunds, M.: Letter to the editor: Elimination of nicotine gum use following successful replacement therapy for cigarette smoking. Lancet January 2-9:49-50, 1988.

Snyder, F.R. and Henningfield, J.E.: Effects of acute nicotine deprivation and administration: Assessment on computerized performance tasks. Psychopharmacology. In press.

Pickworth, W.B., Herning, R.I. and Henningfield, J.E.: Mecamylamine reduces some EEG effects of nicotine chewing gum in humans. Pharmacol Biochem Behav 30:149-153, 1988.

Pomerleau, O.F., Pomerleau, C.S., Fagerstrom, K.O., Henningfield, J.E. and Hughes, J.R.: (Eds.): Nicotine Replacement: A Critical Evaluation. New York, NY, Alan R. Liss, 1988.

Jarvik, M.E. and Henningfield, J.E. Pharmacological adjuncts for the treatment of nicotine dependence. In: J.D. Slade and C.T. Orleans (eds.) Nicotine Addiction: Principles and Management. Oxford University Press, in press.

Cone, E.J. and Henningfield, J.E. Premier 'smokeless cigarettes' can be used to deliver crack. Journal of the American Medical Association 261(1):41, 1989.

Rose, J.E., Sampson, A., Levin, E.D. and Henningfield, J.E. Mecamylamine increases nicotine preference and attenuates nicotine discrimination. Pharmacology Biochemistry and Behavior 32(4):933-938, 1989.

Henningfield, J.E. and Woodson, P.P. Dose-related actions of nicotine on behavior and physiology: Review and implications for replacement therapy for nicotine dependence. Journal of Substance Abuse 1:301-317, 1989.

Henningfield, J.E., London, E.D. and Benowitz, N.L. Arterial-venous differences in plasma concentrations of nicotine after cigarette smoking. Journal of the American Medical Association 263:2049-2050, 1990.

Boren, J.J., Stitzer, M.L. and Henningfield, J.E. Preference among research cigarettes with varying nicotine yields. Pharmacology Biochemistry and Behavior 36:191-193, 1990.

Henningfield, J.E., Radzius, A., Cooper, T.M. and Clayton, R.R. Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. Journal of the American Medical Association, 264:1560-1564, 1990.

Henningfield, J.E., Radzius, A., Cooper, T.M. and Clayton, R.R. Oral pH: A factor in the treatment of nicotine addiction. Journal of the American Dental Association, under review.

January 1, 1990 to December 31, 1990

Title of Project: Opioid Self-Administration: Humans Compared to Animals

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: R.J. Lamb UMDNJ
S.R. Goldberg Chief, Preclinical Branch
J.L. Katz Chief, Psychobiology Laboratory, ARC
C.W. Schindler Staff Fellow, NIDA, ARC
R.A. Meisch Visiting Scientist, U of Tex, Houston

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.15 **Professional:** 0.10 **Other:** 0.05

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Studies with animals have shown that stimuli associated with drug delivery can come to function as variables that partially control drug-seeking behavior and the likelihood of resumption (i.e., relapse) to such behavior, even in the absence of the drug. Analogous research strategies are being used to assess the generality of these findings to human subjects. In addition, these procedures provide data on the degree of correspondence between self-reported drug effects and drug seeking behavior. The human studies have produced a number of interesting results. When the consequences of varying the dose of morphine available on self-administration, physiological effects, and self-reported effects were examined, it was found that low doses of morphine (3.75 mg) maintained rates of responding above placebo and constricted pupillary diameter, but did not reliably alter the self-reports of the subjects, indicating a dissociation between the subjective effects of morphine and morphine's reinforcing properties. Another study evaluated the role of a stimuli paired with drug administration on the maintenance of responding. Initial results suggested that the stimuli were of less importance than in an analogous study with animals, as well as in somewhat similar study of cocaine self-administration by humans.

Publication

Lamb, R.J., Preston, K.L., Henningfield, J.E., Schindler, C.W., Meisch, R.A., Davis, F., Katz, J.L. and Goldberg, S.R.: The Reinforcing and Subjective Effects of Morphine in Post-Addicts: A Dose-response Study. J Pharm Exp Ther. Submitted.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00007-05 BDL**

January 1, 1990 to December 31, 1990

Title of Project: Effects of Commonly Used Drugs on Behavioral Performance in Normal Subjects**Principal Investigators: Cooperating Units****P.I.** J.E. Henningfield Chief, Clinical Pharmacology Branch**Others:** P.P. Woodson Former Staff Fellow, BDL, NIDA, ARC

J.D. Roache Former Staff Fellow, BDL, NIDA, ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch**Section:** None**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.45 Professional: 0.45 Other: 1.00**Check Appropriate Boxes:** **Human Subjects** **Human Tissues** **Neither**
 Minors
 Interviews**Summary of Work**

The possible adverse effects on performance of an antihistamine and alcohol were evaluated in non-residential subjects without histories of drug abuse, other than cigarette smoking. The study involved the use of strategies recommended by the Joint Triservices Working Group (Army Contract) to assess behavioral (i.e., cognitive) performance. Measures included the standard Army Performance Assessment Battery (PAB), prototypic portions of the Unified Triservices Battery (UTC PAB), critical flicker fusion, and mood, as well as cardiovascular and other basis physiologic variables.

Preliminary analysis of data from the first study suggest that alcohol and chlorpheniramine produced dose-related effects on several self-report measures and mixed effects on performance across measures. These initial results suggest that the PAB is less sensitive compared to the Digit Symbol Substitution Task with respect to the level of performance disruption by alcohol or chlorpheniramine.

Subsequently, a new protocol compared a non-centrally acting antihistamine (terfenadine) to a centrally acting one (diphenhydramine) as well as to the benzodiazepine, triazolam. Data collected has been completed and the results are presently being analyzed to prepare a report for publication. This was the final study in the series of those conducted in collaboration with the Joint Triservices Working Group (Army Contract).

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00030-02 BDL

January 1, 1990 to December 31, 1990

Title of Project: Passive Tobacco Smoke: Nicotine Absorption, Subjective Effects and Performance

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: P.P. Woodson Former Staff Fellow
J.D. Roache Former Staff Fellow

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.35 **Professional:** 0.15 **Other:** 0.20

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Volunteers were tested to determine the effects of exposure to ambient tobacco smoke, generated by a cigarette smoking machine, on standard measures of subjective and physiologic effect as well as on performance. It was hoped that the use of the performance battery included in this study would provide a quantitative assay by which to determine if various ambient levels of tobacco smoke can produce dose-dependent effects on performance and physiology which are comparable to those observed with cigarette smoking. Initial research demonstrated the safety and reliability of the procedures for inducing passive tobacco smoke exposure. Data collection has been completed and a report for publication is in preparation.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00004-05 BDL

January 1, 1990 to December 31, 1990

Title of Project: Comparative Self-Administration (Monkeys and Human): Nicotine and Cocaine

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: R.J. Lamb Former Staff Fellow
S.R. Goldberg Chief, Preclinical Branch
C.W. Schindler Staff Fellow, Preclinical Branch

Lab/Branch: Biology of Dependence and abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: Professional: Other:

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

This was a collaborative project with the BPL in which the human research was conducted on the Residential Research Unit and parallel animal studies were conducted in the BPL. The use of the self-administration (SA) study paradigm permitted an assessment of the relative contribution of environmental and pharmacologic factors to the self-administration of drugs. Parallel comparative studies in squirrel monkeys and humans in which subjects are given the opportunity to self-administer comparable doses of cocaine and nicotine under similar behavioral schedules and experimental conditions also provide a means to assess the generality of biological variables influencing drug SA. This research has shown that responding is maintained in human subjects. The stimuli that are associated with injections of cocaine develop conditioned reinforcing effects in the humans in a manner similar to the manner in which these effects develop in squirrel monkeys. These studies have also demonstrated that a research strategy employing drug SA in human subjects can yield all of the important information of single-dose studies, and also, provide information on the direct reinforcing effects of the compound which may be compared to the large base of animal drug SA. Data collection has been completed and need only to undergo final analyses before publication.

Publications

Goldberg, S.R. and Henningfield, J.E.: Reinforcing effect of nicotine in humans and experimental animals responding under intermittent schedules of i.v. drug injection. Pharmacol Biochem Behav 30:227-234, 1988.

Henningfield, J.E., Nemeth-Coslett, R., Katz, J.L. and Goldberg, S.R. Intravenous cocaine self-administration by human volunteers: Second-order schedules of reinforcement. In: Harris, L.S. (ed.): NIDA Research Monograph 76, Washington, D.C.: U.S. Government Printing Office, 1987, pp. 266-273.

Henningfield, J.E. and Goldberg, S.R. Pharmacological determinants of tobacco self-administration by humans. Pharmacol Biochem Behav 30:221-226, 1988.

January 1, 1990 to December 31, 1990

Title of Project: Acquisition of Dependence to Cigarettes and Smokeless Tobacco

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: E.J. Cone Chief, CDM, NIDA, ARC
A. Radzius Research Assistant, BDL, NIDA, ARC
K.O. Fagerstrom Sweden

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: Pharmacia Leo therapeutics AB, Helsingborg, Sweden

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.50 **Professional:** 0.25 **Other:** 0.25

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Questionnaires were given to populations of experienced cigarette and/or smokeless tobacco users (785 responses), and to a population which included persons who had never used tobacco (496 responses). The purpose of the questionnaires was to determine changes in the amount of tobacco products consumed as a function of time and to assess the level of nicotine dependence, as measured by the Fagerstrom Tolerance Questionnaire (FTQ). Findings that have emerged from initial analysis of the first population include the following: (1) Smokeless Tobacco use begins about one year earlier than cigarette use (15.5 vs 16.3); (2) Males begin smoking about one year earlier than females; (3) Tobacco consumption increased over time (i.e., dose graduation); (4) The dose escalation was negatively accelerated with no difference between sexes; (5) Age of starting smoking is negatively correlated with the age of quitting and also with predicted FTQ scores after the same number of years of smoking; (6) Four of 8 questions on FTQ scale are correlated with total FTQ score. Analyses in progress are: (1) Analysis of brands smoked; (2) Prediction of dependence based on the amount of tobacco product consumed at some early point in history; and, (3) Analysis of the data from the 496 response population. These data need only to undergo final analyses before publication.

Publications

Henningfield, J.E., Clayton, R. and Pollin, W. The involvement of tobacco in alcoholism and illicit drug use. British Journal of Addiction 85:279-292, 1990.

Henningfield, J.E., Cohen, C. and Giovino, G.A. Can genetic constitution affect the 'objective' diagnosis of nicotine dependence? American Journal of Public Health, 80:1040-1041, 1990.

Brigham, J., Henningfield, J.E. and Stitzer, M.L. Smoking relapse: A review. International Journal of the Addictions, in press.

Henningfield, J.E., Cohen, C. and Slade, J.D. Is nicotine more addictive than cocaine? British Journal of Addictions, in press.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00014-03 BDL**

January 1, 1990 to December 31, 1990

Title of Project: Cholinergic Agonists and Antagonists**Principal Investigators:** Cooperating Units**P.I.:** J.E. Henningfield Chief, Clinical Pharmacology Branch**Others:** R.I. Heming Staff Fellow, Etiology Branch
W.B. Pickworth Pharmacologist, BDL, NIDA, ARC**Lab/Branch:** Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch**Section:** Etiology Branch**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.70 **Professional:** 0.20 **Other:** 0.50**Check Appropriate Boxes:** **Human Subjects** **Human Tissues** **Neither**
 Minors
 Interviews**Summary of Work**

Ten male volunteers without histories of drug abuse, except for cigarette smoking, were tested to assess the possible adverse performance effects of a cholinomimetic and a cholinergic antagonist, each given alone and in combination. A dose run-up procedure was employed in which physostigmine was administered i.v. in an ascending dose series (0.25, 0.5, 1.0, 1.5, and 2.0 mg) first alone, then following pretreatment with 5.0 or 10.0 mg of methscopolamine, a peripherally active antagonist. Methscopolamine was given to assess the degree to which peripheral blockade reduced physiological effects and/or performance impairment. The Army Performance Assessment Battery (PAB), including components of the Triservices PAB, was used to evaluate behavioral performance. Preliminary analyses are ongoing.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00012-07 BDL

January 1, 1990 to December 31, 1990

Title of Project: Factors Influencing Behavioral and Physiologic Response to Opioids (Mu Project)

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: E.J. Cone Chief, CDM, NIDA, ARC
S.T. Higgins Univ. of Vermont
K. L. Preston BPRU, JHU
J.H. Jaffe Former Director, NIDA, ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: Biology of Vulnerability, Chemistry and Drug Metabolism Laboratory

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.90 **Professional:** 0.40 **Other:** 0.50

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Following from the observations that post-addicts and non-opioid users are differentially sensitive to opioids, and perhaps even respond qualitatively differently, and the possibility that such differences either predispose certain persons to opioid abuse and/or contribute to relapse, this study was conducted to experimentally examine such population differences in response to mu and kappa opioids. Prominent measures included discrimination thresholds of behavioral effects, physiologic responses, and neuroendocrine response. Post-addict and opioid-naive subjects were intended to be separately tested for comparison. Initial phase testing involving post-addict volunteers was completed, however, changes in priorities resulted in the termination of the protocol before opioid-naive subjects were tested. The final report has been submitted for publication.

Publication:

Higgins, S.T., Preston, K.L., Cone, E.J., Henningfield, J.E. and Jaffe, J.H. Behavioral, Physiological, and Hormonal Effects of a Naloxone Challenge Following Acute Morphine Pretreatment in Humans. In Harris, L.S. (Ed.), NIDA Research Monograph 76. Washington, D.C., U.S. Government Printing Office, 1987, pp. 266-273. Manuscript submitted.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00005-05 BDL

January 1, 1990 to December 31, 1990

Title of Project: Abuse Liability of Smokeless Tobacco Products

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: A. RADIUS Research Assistant, BDL, NIDA, ARC

E.J. Cone Chief, CDM, NIDA, ARC

N.L. Benowitz Collaborator, Univ. of California

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: Chemistry and Drug metabolism Laboratory
Division of Clinical Pharmacology and Experimental Therapeutics
University of California, San Francisco

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.37 **Professional:** 0.07 **Other:** 0.30

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

In two studies, tobacco users were tested with a commercially available smokeless tobacco product (i.e., pouches of snuff), and with a smokeless cigarette through which air is sucked to inhale vaporized nicotine. Standardized methods of abuse liability assessment were used.

The smokeless tobacco study consisted of two phases. The first evaluated the effects of dose and the possibility that rate of expectoration would alter nicotine extraction and effects. Dose-related changes were found in the magnitude and duration of action of measures such as reduction in urge to smoke and strength of effects observed. The second phase evaluated the relationship of the effects observed to plasma levels of nicotine; these were found to be closely related to the dose administered, thus confirming the reliability of this system of nicotine delivery. The study was smokeless cigarettes indicated similar dose-related effects as those found with the commercial tobacco products; nicotine levels were negligible, suggesting the possibility that this route of nicotine administration may produce effects mediated by its peripheral stimulus properties which resemble those of smoking cigarettes. Testing has been completed.

Publications

Henningfield, J.E. How tobacco produces drug dependence. In: J.K. Ockene (ed.), The Proceedings of the World Congress on the Pharmacologic Treatment of Tobacco Dependence. Cambridge, MA: Institute for the Study of Smoking Behavior and Policy, pp. 19-31, 1986.

Cullen, J.W., Blot, W., Henningfield, J.E., Boyd, g., Mecklenberg, R. and Massey, M.M. Health consequences of using smokeless tobacco: Summary of the Advisory Committee's Report to the Surgeon General. Public Health Reports 101:355-373, 1986.

Connolly, G.N., Winn, D.M., Hecht, S.S., Henningfield, J.E., Walker, B. and Hoffman, D. The re-emergence of smokeless tobacco. N Eng Med 314:1020-1027, 1986.

Glover, E.D., Schroeder, K.L., Henningfield, J.E., Severson, H.H. and Christen, A.G. An interpretative review of smokeless tobacco research in the United States: Part I. Journal of Drug Education 18(4):285-310, 1988.

Glover, E.D., Schroeder, K.L., Henningfield, J.E., Severson, H.H. and Christen, A.G. An interpretative review of smokeless tobacco research in the United States: Part II. Journal of Drug Education 19(1):1-19, 1989.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00032-02 BDL

January 1, 1990 to December 31, 1990

Title of Project: Dopaminergic lesions and subjective effects of methylphenidate

Principal Investigators: Cooperating Units

P.I. G.R. Uhl Visiting Scientist, MNL, NIDA, ARC

Others: M.J. Kuhar Chief, NB, NIDA, ARC
J.E. Henningfield Chief, CPB, NIDA, ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.30 **Professional:** 0.10 **Other:** 0.20

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

The purpose of this research study is to examine whether the effect of the drug "Methylephenidate" that has been used in the therapy of Parkinson's disease is different in patients with Parkinson's disease compared with individuals without this disease. The study will test whether differences in feeling that these drugs can induce in normal individuals may or may not be present in patients with Parkinson's disease. Preliminary testing was initiated in 1989, the final phase of this study is now underway.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00035-02 BDL

January 1, 1990 to December 31, 1990

Title of Project: Why do substance abusers seek help? What are their worries about that help?

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: R.E. Johnson Former Chief, RSB, NIDA, ARC
D. Brooke Visiting Scientist, RSB, NIDA, ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.20 **Professional:** 0.10 **Other:** 0.10

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

A survey of ARC research subjects was conducted to investigate the reasons that people seek treatment, and what their worries about that treatment are. The intent of this protocol is to obtain answers to these questions which will enable us to make it easier for people to seek help. Subjects were asked to fill out two questionnaires and a cover sheet on their past experience of seeking help. A preliminary manuscript has been developed and will be submitted for publication.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00011-05 BDL

January 1, 1990 to December 31, 1990

Title of Project: Physiologic Dependence to Tobacco: Cigarette Withdrawal and Nicotine Substitution

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: R. Nemeth-Coslett Former Staff Fellow, BDL, NIDA, ARC
R. Herning Staff Fellow, EB, NIDA, ARC
W.B. Pickworth Pharmacologist, BDL, NIDA, ARC
W.R. Lange Medical Director, NIDA, ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: .80 **Professional:** .55 **Other:** .25

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Heavy tobacco users, otherwise without drug abuse histories, were studied on the Residential Research Unit. In the withdrawal study, subjects were assessed for nicotine and cotinine, general cardiovascular functioning, passive EEG and evoked cortical potential, and caloric intake, during 10 days of cigarette deprivation and when smoking resumed. In the substitution phase of the study, subjects were tested during alternating cycles of 4 days smoking and 3 days abstinence. In this phase, subjects were similarly assessed as described above, but on days in which they were not permitted to smoke, they were given pieces of gum to chew 12 times per day at one hour intervals: the gum contained either 0, 2 or 4 mg of nicotine. We found that an orderly withdrawal emerged. It included impaired performance, which did not recover within the ten days of abstinence, but did recover when cigarette smoking resumed. Nicotine gum reversed major signs of tobacco withdrawal, confirming that the withdrawal was nicotine specific. This effect was dose-related, e.g., 4 mg gum restored performance to baseline levels, whereas 2 mg gum only partially restored performance. Placebo gum use was accompanied by withdrawal. Together, these results confirm that nicotine replacement can be a viable mode of alleviation of the tobacco withdrawal syndrome, but is of little benefit in reducing desire to smoke (which appears to be pharmacologically related to abstinence but appears readily elicited by environmental stimuli).

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00008-04 BDL

January 1, 1990 to December 31, 1990

Title of Project: Behavioral Performance and Physiologic Effects of Drugs: Atropine and Diazepam

Principal Investigators: Cooperating Units

P.I. J.E. Henningfield Chief, Clinical Pharmacology Branch

Others: R.J. Lamb Former Staff Fellow, NIDA, ARC
S.T. Higgins Former Staff Fellow, NIDA, ARC
R.I. Herming Staff Fellow, EB, NIDA, ARC
W.B. Pickworth Pharmacologist, BDL, NIDA, ARC
F.R. Snyder Statistician
W.R. Lange Medical Director, NIDA, ARC

Lab/Branch: Biology of Dependence and Abuse Potential Assessment Laboratory
Clinical Pharmacology Branch

Section: Etiology Branch

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: .10 **Professional:** 5 **Other:** 5

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Studies were conducted to assess the effects of the drugs on performance at various tasks. An additional aspect of this research was to identify possible electrophysiological effects. Atropine and diazepam were found to produce dose-related effects on a variety of measures of subjective response as well as performance on the computerized Performance Assessment Battery (PAB).

These studies have been completed and data analyses are underway. Preliminary analysis of the results from the study on diazepam indicate that most measures were affected in an orderly time and dose-related manner. Most measures were surprisingly insensitive, however, and significant effects were often not seen until the administration of the highest dose of diazepam (40 mg). The Army developed measures did not appear to be more sensitive than traditional measures (e.g., DSST).

Publications:

Higgins, S.T., Woodward, B.M. and Henningfield, J.E. Effects of atropine on the repeated acquisition and performance of response sequences in humans. Journal of the Experimental Analysis of Behavior 51:5-15, 1989.

Higgins, S.T., Lamb, R.J. and Henningfield, J.E. Dose-related effects of atropine on behavioral and physiologic responses in humans. Pharmacology Biochemistry and Behavior 34(2):303-311, 1989.

2. Chemistry and Drug Metabolism Laboratory - Edward J. Cone, Ph.D.

The Laboratory of Chemistry and Drug Metabolism performs chemical, pharmacokinetic, metabolic and pharmacodynamic research with human subjects related to the chemistry of substance abuse. Presently, studies are underway to further delineate the pharmacokinetic and pharmacodynamic profile of marijuana, opiates and methamphetamine. The focus of these studies is the exploration of the relationship between drug levels in various body fluids to behavior, performance and physiological effects. An additional focus is the evaluation of the usefulness of unusual body fluids or tissues, e.g., saliva, nails and hair for drug detection. Our initial findings indicate that each body fluid or tissue provides a unique but slightly different historical record of drug exposure. It is important in the diagnosis, treatment and prevention of drug abuse that we have an understanding of the information provided by drug tests on various body fluids and the relationship of these tests to drug-induced effects. Also, the risk of unknowing drug exposure, e.g., "crack" smoke and methamphetamine smoke, is being evaluated. The laboratory performs basic research in the area of chemical methodology development; new methods must be developed as new drugs appear in the illicit drug market and as new and important metabolites are identified in metabolic studies. In related studies, the validity of commercial test methods presently used in employment drug testing are being evaluated for precision and accuracy with clinical specimens collected under highly controlled conditions.

Summary of Ongoing Research

Specific research projects which were actively pursued in 1990 are briefly summarized below. Only those studies for which personnel from this laboratory were the principal investigators are discussed.

A. The Pharmacokinetics and Pharmacodynamics of Opiate Analgesics.

The goals of this study include: 1) the evaluation of the usefulness of a heroin "marker" as a means of detecting heroin addicts in urine and saliva of subjects after heroin abuse; 2) determination of the relationship between plasma levels and saliva levels of active drug or metabolite and pharmacologic effects; 3) the use of saliva as a screening media for opiates; and 4) validity assessment studies of commercial drug assays for opiates.

B. Studies on the Validity of Drug Testing Methodology.

The goal of this study is to compare test results of commercial screening assays for drugs in urine with test results obtained by gas chromatography/mass spectrometry (GC/MS). Standard specimen sets utilized in these studies consist of clinical drug specimens collected under highly controlled conditions following drug administration and "spiked" standards at known concentration. A complete validity assessment of opiate assays was completed utilizing clinical drug specimens collected following heroin, morphine, codeine, hydromorphone, hydrocodone, buprenorphine, oxycodone and oxycodone administration.

C. Drug Assay Development Studies on Drugs of Abuse.

The aim of this ongoing project is to develop specific, sensitive and reliable assays for drugs of abuse in a variety of biological media. For example, test methodology was developed for the detection of opiates in hair. This assay was used to study the appearance of morphine and codeine in human facial hair after controlled dosing. This assay provided the first documented evidence of the time period required for an administered opiate to appear in hair. Work also continues on the refinement of an assay for the simultaneous assay of cocaine and metabolites in body fluids. Another assay is currently under development for the determination of buprenorphine in blood, saliva and urine. Buprenorphine is a promising new drug for the treatment of opiate and cocaine addiction. Other assays also are developed for support of ongoing pharmacokinetic and pharmacodynamic studies.

D. Buprenorphine Pharmacodynamics.

Buprenorphine is an opioid partial agonist which shows promise as a treatment agent for heroin and cocaine addiction. Although buprenorphine has limited bioavailability by the oral route of administration, it is effective by the sublingual route. Current studies are underway to determine its bioavailability by the sublingual and buccal route. Concurrent behavioral and physiological effects will be measured for correlation with blood levels. Urine will be tested for buprenorphine and metabolite content. The detection period for buprenorphine in urine and saliva will be determined. In addition, following chronic buprenorphine dosing, the blood levels of drug and metabolite will be determined in order to evaluate the importance of accumulation of drug and active metabolites.

E. Fast Action Dynamics of Marijuana Smoking.

The immediate effects of smoking marijuana on behavior and performance will be evaluated in this study. Behavioral and physiological measures will be collected before, during and after smoking. Blood and saliva samples will be collected concurrently and will be analyzed for tetrahydrocannabinol and metabolite content as well as selected hormones. The study is designed to evaluate the mechanistic and functional effects of smoking marijuana in human subjects. The study will have a unique focus on the early changes that occur in the physiology, behavior and the neuroendocrine system during the smoking of marijuana cigarettes.

F. Passive Inhalation of Drugs of Abuse.

When drugs of abuse are smoked, e.g., marijuana, cocaine, heroin, phencyclidine and methamphetamine, some of the volatile material is released into the atmosphere. Depending on the local environment, bystanders may be exposed to small doses of the drug and its pyrolyzed breakdown materials. Laboratory methods are being developed to experimentally simulate an atmosphere of drug smoke and means of withdrawing air samples for chemical analysis. These methods will be used to assess the potential hazards of passive inhalation of drugs of abuse.

G. Methamphetamine Pharmacodynamics.

Methamphetamine is a stimulant with effects similar to cocaine. Historically, it has a history of abuse both as a licit and illicit drug. Presently, there is concern that a new form of methamphetamine, "ice", may be abused in the same manner as the smokeable form of cocaine, i.e., "crack". Methods are under development to study the effects of this new form of methamphetamine. The pharmacokinetic profile, abuse liability and chemistry of "ice" will be evaluated.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00002-05 CDM

January 1, 1990 to December 31, 1990

Title of Project: Validity Studies of Commercial Drug Screening Assays

Principal Investigators: Cooperating Units

PI	E.J. Cone	Chief	CDM, ARC, NIDA
Others	D. Darwin	Chemist	ARC, NIDA
	S. Dickerson	Lab Tech	ARC, NIDA
	T. Maguire	Chemist	ARC, NIDA
	B. Holicky	Nurse	ARC, NIDA

Lab/Branch: Laboratory of Chemistry and Drug Metabolism
Clinical Pharmacology Branch

Section: Naval Screening Laboratory, Jacksonville, FL (J. Mitchell and B. Paul).

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 08 **Professional:** 01 **Others:** 0.7

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Commercial assays for the detection of drugs of abuse in urine change periodically and must be reevaluated for validity of detection. Studies are designed to test the validity of new assays on clinical specimens obtained from drug users under controlled conditions.

Healthy male volunteers with a history of chemical substance abuse participate in these studies. Informed consent is obtained and all procedures are approved by the hospital Institutional Review Board. Commercial assays for detection of drugs of abuse in urine are tested for validity with specimens collected under controlled dosing conditions. A variety of drugs of abuse are studied at various dose levels. The results of the assays are compared to GC/MS analyses.

These studies test the validity of commercial assays on clinical samples instead of "spiked" samples and provide unique and valuable information to the military and industry concerning their time course of detection, specificity and accuracy.

Publications:

Cone, E.J., Yousefnejad, D. and Dickerson, S.L., Validity testing of commercial urine cocaine metabolite assays. IV. Evaluation of the Emit^R d.a.u.TM Cocaine Metabolite Assay in a quantitative mode for detection of cocaine metabolite. J. Forensic Sci., **35**: 786-791, 1990.

Cone, E.J., Dickerson, S. Forensic Drug Testing for Opiates: IV. Analytical Sensitivity, Specificity and Accuracy of Commercial Urine Opiates Immunoassays. J. Anal. Toxicol., in press, 1991.

Cone, E.J., Darwin, W.D., Dickerson, S. Evaluation of the Abuscreen ONTRAK Assay for Cocaine (Metabolite), submitted, Clin. Chem.,

Cone, E.J. On-site Drug Testing: Expediency Versus Accuracy. Employment Testing, BWR:621-28.

Abstracts:

Dickerson, S.L. and Cone, E.J., Drug Assay Development XXII. Evaluation of the Abuscreen/Ontrak Assay for Qualitative Detection of Cocaine Metabolite in Human Urine. American Chemical Society, MARM, Madison, NJ, May 23-25, 1990.

Cone, E.J., Darwin W.D. and Dickerson, S.L. Validity Assessment of the Abuscreen ONTRAK Assay for Cocaine. Society of Forensic Toxicology, Sept. 11-15, 1990.

Cone, E.J., Darwin, W.D. and Dickerson, S. Detection of Buprenorphine in Human Biofluids utilizing Diagnostic Products Corporation's (DPC) Double Antibody Radioimmunoassay. The International Association of Forensic Toxicologists 27th International Meeting, Perth, Western Australia, Oct. 19-23, 1990.

Huestus, M.A., Cone, E.J., and Mitchell, J. Accuracy of Immunoassays for the Detection of Cocaine Metabolites in Urine at current and Proposed NIDA Cutoffs. American Academy of Forensic, Anaheim, CA, Feb. 18-23, 1991.

Cone, E.J. and Mitchell, J. Can the NIDA Cutoffs for Opiate Urine Screening and Confirmation be Lowered? American Academy of Forensic, Anaheim, CA, Feb.18-23, 1991.

Maguire, T., Darwin, W.D., and Cone, E.J. Drug Assay development XXIII. Simultaneous Assay for Cocaine (C), Norcocaine (NC0, Benzoylcegonine (BE) and Ecgonine Methyl Ester (EME) in Human Biofluids by GC/MS. American Chemical Society, MARM, Madison, NJ, May 23-25, 1990.

Darwin, W.D., Maguire, T.E. and Cone, E.J. Simultaneous Assay for Cocaine, Benzoylcegonine, Ecgonine Methyl Ester, Norcocaine and Cocaethylene in Human Biofluids. Society of Forensic Toxicology, Sept. 11-15, 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00003-05 CDM

January 1, 1990 to December 31, 1990

Title of Project: Detection of Drugs of Abuse in Human Saliva

Principal Investigators: Cooperating Units

PI	E.J. Cone	Chief	CDM, ARC, NIDA
Others	D. Darwin	Chemist	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA
	S. Dickerson	Lab Tech	ARC, NIDA
	T. Maguire	Chemist	ARC, NIDA
	B. Holicky	Nurse	ARC, NIDA

Lab/Branch: Chemistry and Drug Metabolism Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.4 **Professional:** 0.1 **Others:** 1.3

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

The presence of drugs of abuse in saliva of human subjects after drug administration was studied to determine the feasibility of drug testing with saliva.

Healthy male subjects with a history of chemical substance abuse volunteered for the studies. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. Following the administration of cocaine, marijuana or opiate, saliva and blood samples were collected periodically. Behavioral and physiological measures were made concurrently with collection of biofluids. Samples were analyzed by RIA and gas chromatography/mass spectrometry. Significant correlations of blood levels with saliva levels were found for cocaine and opiates. Investigations are continuing on marijuana.

These studies provide the scientific basis for development of new non-invasive tests for drug abuse.

Publications:

Darwin, W.D., Maguire, T., Cone, E.J., Carroll, F.I. Drug Assay Development XXVI. Simultaneous assay for cocaine (C), Cocaethylene (CE), Norcocaehtylene (NCE), Benzoylecgonine (BE), Ecgonine Methyl Ester (EME) and Norcocaine (NC) In human Biofluids by GC/MS. 25th ACS MARM, Newark, DL, May 21-23, 1991.

Cone, E.J., Dickerson, S.L., Darwin, W.D., Fudala, P. and Johnson, R.E., Elevated Drug Saliva Levels Suggest a "Depot-Like" Effect in Subjects Treated with Sublingual Buprenorphine. Committee on problems of Drug Dependence, Richmond, VA June 11-14, 1990.

Huestis, M.A., Heishman, S.J. and Cone, E.J. Plasma and Saliva THC Levels and Behavioral Effects following repeated Marijuana Exposure. Society of Forensic Toxicology, Sept. 11-15, 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00006-04 CDM**

January 1, 1990 to December 31, 1990

Title of Project: Pharmacokinetics and Pharmacodynamics of Opiate Analgesics**Principal Investigators: Cooperating Units**

PI	E.J. Cone	Chief	CDM, ARC, NIDA
Others	D. Darwin	Chemist	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA
	S. Dickerson	Lab Tech	ARC, NIDA
	B. Holicky	Nurse	ARC, NIDA

Lab/Branch: Laboratory of Chemistry and Drug Metabolism
Clinical Pharmacology Branch**Institution and Location:** Addiction Research Center, NIDA, Baltimore, MD 21224**Total Man Years:** 1.4 **Professional:** 0.3 **Others:** 1.1**Check Appropriate Boxes:**

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

The effects of single doses of intramuscularly administered opiates (heroin, morphine, hydromorphone, codeine, oxycodone, oxymorphone) and sublingual buprenorphine are being studied in male human volunteers in order to determine the relationship of blood and saliva levels to pharmacologic effects. Additionally, the study is being performed to determine if a metabolic marker for heroin abuse can be found in urine.

The subjects are healthy males with a history of heroin abuse. Informed consent is obtained and all procedures are approved by the hospital Institutional Review Board. A total of three test doses (placebo and two active doses) are administered in random order. Test measures are made for 24 hrs and biological fluids are collected for 7 days after each test. The biological fluids will be analyzed for drug and metabolites by chromatographic and immunoassay techniques.

The significance of this study lies in the potential value of saliva as a new test medium for detection of drugs of abuse and the characterization of the time course of excretion of metabolic markers for heroin and other opiates in urine and saliva.

Publications:

Pickworth, W.B., Welch, P., Henningfield, J.E. and Cone, E.J. Opiate-induced pupillary effects in humans. in press, 1990.

Vaupel, D.B., Cone, E.J., Johnson, R.E. and Su, T-S. Kappa Opioid Partial Agonist Activity of the Enkephalin-like Pentapeptide BW942C Based on Urination and in Vitro Studies in Humans and Animals. *J. Pharmacol. Exp. Ther.*, 252: 225-34, 1990.

Furman, W.R., Munster, A.M. and Cone E.J., Morphine Pharmacokinetics during Anesthesia and Surgery in Burn Patients. *J. Burn Care Rehabil.*, 11: 391-4, 1990.

Cone, E.J., Welch, P., Mitchell, J.M. and Paul, B.D. Forensic Drug Testing for Opiates: I. Detection of 6-Acetylmorphine in Urine as an Indicator of Recent Heroin Exposure; Drug and Assay Considerations and Detection Times. *J. Anal. Toxicol.*, 15: 1-7 1991.

Mitchell, J.M., Paul, B.D., Welch, P. and Cone E.J. Forensic Drug Testing for Opiates; Metabolism and Excretion Rates of Morphine in Humans after Morphine Administration. *J. Anal. Toxicol.*, in press, 1991.

Cone, E.J., Welch, P., Paul, B.D. and Mitchell, J.M. Forensic Drug Testing for Opiates. Urinary Excretion rates of Morphine and Codeine following Codeine Administration. *J. Anal. Toxicol.*, in press, 1991.

Abstracts:

Walsh, S.L., Preston K.L., Stitzer, M.L., Dickerson, S.L., Cone, E.J., Bigelow, G.E. The Behavioral and Pharmacokinetic Profile of High Dose Buprenorphine Administered Sublingually in Humans. Society for Neuroscience, New Orleans, LA, Nov. 10-15, 1991.

Cone, E.J., Welch, P., Paul, B. and Mitchell, J., Specificity of 6-Acetylmorphine in Urine as an Indicator of Heroin Use. AAFS, Cincinnati, OH, Feb. 19-24, 1990.

Mitchell, J., Paul, B., Welch, P. and Cone, E.J., Clinical Studies Indicate that Morphine is not Metabolized to Codeine in Human Subjects., AAFS, Cincinnati, OH, Feb., 19-24, 1990.

Fudala, P.J., Johnson, R.E., Heishman, S.J., Cone, E.J., and Henningfield, J.E., A Dose Run-up and Safety Evaluation of Nalmefene HCl in Human Volunteers. NIDA Research Monograph 95. Rockville: The Committee on Problems of Drug Dependence, Inc. 1990: 451-52.

furman, W.R., Cone, E.J., Bengson, Z.B., Stiff, J.L., and Munster, A.M., Morphine Pharmacokinetics During Anesthesia and Surgery in Burn Patients., American Burn Association. Las Vegas, Nevada, March 30, 1990.

Uhl, G.R., Newlin, D.B., Pretorius, M.B., Park, J.S., Darwin, W.D. and Cone, E.J., Antagonist-Withdrawal Up-Regulation of Endogenous Opiate Antinociceptive Systems. Committee on Problems of Drug Dependence, Richmond, VA. June 11-14, 1990.

Darwin, W.D. and Cone, E.J. Drug Assay Development. XXI. Solid Phase Extraction (SPE) of Buprenorphine from Human Biofluids. American Chemical Society, MARM, Madison, NJ, May 23-25, 1990.

Cone, E.J., Holicky, B., Pickworth, W. and Johnson, R.E. Pharmacologic and Behavioral Effects of High Doses of Intravenous Buprenorphine, Committee on Problems of Drug Dependence, Palm Beach, FL, June 16-20, 1991.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00007-03 CDM**

January 1, 1990 to December 31, 1990

Title of Project: Pharmacokinetics and Pharmacodynamics of Drugs of Abuse in Hair**Principal Investigators: Cooperating Units**

PI	E.J. Cone	Chief	CDM, ARC, NIDA
Others	B. Holicky	Nurse	ARC, NIDA
	S. Dickerson	Lab Tech	ARC, NIDA
	D. Darwin	Chemist	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA
	T. Maguire	Chemist	ARC, NIDA

Lab/Branch: Laboratory of Chemistry and Drug Metabolism
Clinical Pharmacology Branch**Section:** None**Institution and Location:** Addiction Research Center, NIDA, Baltimore, MD 21224**Total Man Years:** 0.8 **Professional:** 0.2 **Others:** 0.6**Check Appropriate Boxes:**

<input checked="" type="checkbox"/> Human Subjects	<input type="checkbox"/> Human Tissues	<input type="checkbox"/> Neither
<input type="checkbox"/> Minors		
<input type="checkbox"/> Interviews		

Summary of Work

Drug residues have been detected in human hair specimens by a variety of analytical techniques. These reports have generated substantial interest in using hair as a historical record of drug usage. Studies are designed to determine the presence and time course of drugs of abuse in human hair.

Healthy male volunteers with a history of chemical substance abuse will participate in the study. Informed consent will be obtained and all procedures will be approved by the hospital Institutional Review Board. Subjects will reside on the clinical ward of the ARC. Head and facial hair specimens will be obtained prior to and after administration of drugs of abuse. Blood, saliva and urine specimens also will be obtained. Analyses of tissue and biofluids for drug will be performed by radioimmunoassay and gas chromatography/mass spectrometry.

The studies will provide the scientific basis for determining the usefulness of hair as a "historical record" for substance abuse.

Publications:

Periodicals:

Cone, E.J. Testing human hair for drugs of abuse. I. Individual dose and time profiles of morphine and codeine in plasma, saliva, urine and beard compared to drug-induced effects on pupils and behavior. J. Anal. Toxicol. **14**: 1-7, 1990.

Cone, E.J., Yousefnejad, D., Darwin, W.D. and Maguire, T. testing Human Hair for Drugs of Abuse II. Identification of Unique Cocaine Metabolites in Hair of Drug Abusers and Evaluation of Decontamination Procedures. J. Anal. Toxicol., in press, 1991.

Chapter:

Cone, E.J. and Dickerson, S.L. Analysis of human facial hair for morphine and codeine; Excretion patterns after single doses. In Proceedings of the International Association of Forensic Toxicologists, 1989, in press, 1990.

Abstract:

Maguire, T., Darwin, W.D., and Cone, E.J. Drug Assay Development. XXVII. Simultaneous Assay for the detection of Cocaine and Opiates in Human Hair by GC/MS. 25th ACS MARM, Newark, DL, May 21-23, 1991.

January 1, 1990 to December 31, 1990

Title of Project: Pharmacokinetics and Pharmacodynamics of Methamphetamine

Principal Investigators: Cooperating Units

PI	E.J. Cone	Chief	CDM, ARC, NIDA
Others	B. Holicky	Nurse	ARC, NIDA
	D. Darwin	Chemist	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA
	T. Maguire	Chemist	ARC, NIDA

Lab/Branch: Laboratory of Chemistry and Drug Metabolism, Clinical Pharmacology Branch

Section: None

Institution and Location: Addiction Research Center, NIDA, Baltimore, MD 21224

Total Man Years: 0.5 **Professional:** 0.1 **Others:** 0.4

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Methamphetamine is an amphetamine-like stimulant with substantial abuse liability by the intravenous route. Recently, a new form of methamphetamine ("ice") has been reported to be abused via the smoking route.

This study will evaluate various chemical forms of methamphetamine in human volunteer subjects. Informed consent will be obtained and all procedures will be approved by the hospital Institutional Review Board. Methamphetamine will be administered by the smoking and intravenous routes. The pharmacokinetic profile will be determined by analysis of blood samples. The bioavailability and abuse liability of the smoked drug will be obtained by comparison to the intravenous route. Urine, saliva, and hair specimens will be collected for drug detection studies on methamphetamine.

These studies will evaluate for the first time, the abuse potential of smoked methamphetamine and will allow drug detection methods to be developed for this new form of methamphetamine.

January 1, 1990 to December 31, 1990

Title of Project: Fast Action Dynamics of Marijuana

Principal Investigators: Cooperating Units

PI	M.A. Huestis	Fellow	CDM, ARC, NIDA
Others	E.J. Cone	Chief	ARC, NIDA
	B. Holicky	Nurse	ARC, NIDA
	D. Darwin	Chemist	ARC, NIDA
	J. Henningfield	Chief	BDL, ARC, NIDA
	A. Sampson	Nurse	ARC, NIDA

Lab/Branch: Laboratory of Chemistry and Drug Metabolism
Clinical Pharmacology Branch

Section: None

Institution and Location: Addiction Research Center, NIDA, Baltimore, MD 21224

Total Man Years: 0.9 **Professional:** 0.6 **Others:** 0.3

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Although early changes which occur during the smoking of marijuana are more likely to be indicative of its mode of action, this phase of the use of marijuana has largely been ignored and very little is known regarding what happens to a human subject during the smoking process.

This study will detail the effects of smoking marijuana cigarettes on a variety of systems including physiologic effects, behavior and hormonal systems. In addition, blood and saliva levels will be determined during and after smoking. Blood and saliva levels will be compared to drug-induced effects and hormonal changes.

The results from this study will provide the most comprehensive assessment of marijuana's effects that occur both during and after smoking and should provide important insight to the mode of action of this widely abused drug.

Publications:

Heishman, S.J., Huestis, M.A., Henningfield, J.E. and Cone, E.J. Acute and Residual Effects of Marijuana: Profiles of Plasma THC Levels, Physiological, Subjective and Performance Measures. *Pharmacol. Biochem. Beh.*, 37: 561-65, 1990.

Huestis, M.A., Heishman, S.J. and Cone, E.J. Profile of Repeated Marijuana Exposure: Plasma and Saliva THC Levels, Performance, Physiological and Subjective Effects Following Smoking in a Controlled Clinical Setting. *The International Association of Forensic Toxicologists 27th International Meeting*, Perth, Western Australia, Oct. 19-23, 1990.

Huestis, M., Sampson, A., Holicky, B. and Cone, E.J. The Fast Action Pharmacodynamics of Marijuana Smoking, *Committee on Problems of Drug Dependence*, Palm Beach, FL, June 16-20, 1991.

January 1, 1990 to December 31, 1990

Title of Project: Methodological Assessment of the Risk of Passive Inhalation of Drugs of Abuse

Principal Investigators: Cooperating Units

PI	E.J. Cone	Chief	CDM, ARC, NIDA
Others	D. Yousefnejad	Chemist	ARC, NIDA
	T. Maguire	Chemist	ARC, NIDA

Lab/Branch: Laboratory of Chemistry and Drug Metabolism, Clinical Pharmacology Branch

Section: None

Institution and Location: Addiction Research Center, NIDA, Baltimore, MD 21224

Total Man Years: 0.7 **Professional:** 0.1 **Others:** 0.6

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

When drugs of abuse are smoked, volatile components and pyrolysis material escape into the atmosphere. Depending on the local environment, bystanders may be exposed to the drug by passive inhalation of the contaminated air.

Present studies are underway to develop means of heating drugs of abuse in a controlled environment and measuring air levels of drug in order to evaluate this potential hazard. Initially, free-base cocaine "crack" and methamphetamine "ice" will be evaluated for potential passive inhalation exposure.

Unknowing drug exposure could be dangerous to unsuspecting bystanders, particularly to small children. These studies will establish limits of exposure to volatile components of drugs under controlled conditions.

Publications:

Yousefnejad, D. and Cone, E.J. Drug assay development. XXIV. Determination of cocaine in air by capillary gas chromatography/mass spectrometry. American Chemical Society Meeting, 24th MARM, May 23-25, 1990.

Yousefnejad, D., Cone, E.J. Drug Assay Development. XXV. Determination of Cocaine in Room Air By GC/MS. 25th ACS MARM, Newark, DL, May 21-23, 1991.

Yousefnejad, D. and Cone, E.J. Drug Assay Development XXIV. Determination of Cocaine in Air by Capillary Gas Chromatography/Mass Spectrometry. American Chemical Society, MARM, Madison, NJ, May 23-25, 1990.

3. Neuroendocrinology/Immunology Laboratory - Jack E. Henningfield, Ph.D., Acting Chief

The Neuroendocrinology/Immunology laboratory investigates mechanisms by which substances of abuse, particularly cocaine and tetrahydrocannabinol, act to alter two of the body's homeostatic mechanisms; the endocrine and immune systems. This is important because neurosecretion is a marker of CNS function and may be altered markedly by substance abuse. Further, neurohormones interact with the immune system and may be important regulators of immune function. Examination of alterations in endocrine function simultaneously with immune function may help to explain the relative contributions of neuroendocrine and local regulation to alter immune function in substance abusers, and also mechanisms by which substances of abuse alter immune function. The more rapid progress to AIDS and death in substance abusers with HIV infection when compared with other groups of HIV infected individuals may, thus, be explained.

Neuroendocrine and immune function in substance abusers on the ARC research ward are being examined, thereby providing relevant clinical findings and developing animal models that mimic the clinical findings. Neurohormones are monitored as CNS markers in studying the physiological and pharmacological effects of substances of abuse on the hypothalamo-pituitary system in clinical and basic research settings. The neuroendocrine hormones are regulated by releasing factors and neurotransmitters released from the hypothalamus, steroid hormones and other feedback loops. Each of these may be perturbed by substances of abuse. Consideration of perturbators or regulators and subsequent measurement of the release neurohormones may be used to suggest mechanisms of drug actions on the hypothalamo-pituitary system. In animal models, the relevance of the hypothalamo-pituitary responses to CNS mechanisms is being explored.

The goals of the laboratory are:

- a. to investigate the disturbances of neuroendocrine secretion caused by substances of abuse.
- b. to continue research into basic mechanisms of neuroendocrine secretion, endocrine-mediated immune function and their relationship to substance use or abuse.
- c. to investigate the interactions between substances of abuse, neurohormones and altered immune function, and to address the hypothesis that substances of abuse act as immunodepressors and may be cofactors in the development of AIDS in HIV infected substance users.
- d. to determine the HIV antibody status of ARC volunteers, research subjects and addicts in the NIDA HIV-antibody prevalence study.
- e. to provide quantitation of drug concentrations in body fluids and tissue extracts.

Techniques employed by the NEI Laboratory

- a. radioimmunoassay of hormones and substances of abuse in human and rat body fluids and tissues.
- b. quantitation of hormones and neurotransmitters by HPLC.
- c. clinical tests of neuroendocrine secretion.
- d. in vivo and in vitro experimental techniques such as indwelling catheterization and portal vein cannulation; perfusion, reverse hemolytic plaque assay, in vivo microdialysis, lymphocyte function tests and receptor quantitation for studying neuroendocrine and immune function in animals.

Neurosecretion in Substance Abuse

Release of hormones from the hypothalamo-pituitary axis is a marker of CNS function. CNS function is being examined by studying neuroendocrine secretion particularly in volunteers who have used substances of abuse (cocaine and cannabinoids) over prolonged periods of time. Cocaine acts primarily through dopaminergic mechanisms and, used chronically, may result in either dopamine depletion or

hypersensitivity to dopamine-mediated responses. By examining neuroendocrine parameters in detail, the relative contribution of dopamine and other neuroendocrine regulators in the hypothalamo-pituitary axis may be elucidated. In volunteers who used cocaine heavily and who were abruptly withdrawn from the drug on the ARC ward, prolactin concentrations throughout the day and over 3 weeks following withdrawal were elevated compared with volunteers who did not use cocaine. (Dopamine is a tonic inhibitor of prolactin release.) Resting levels in hormones of the hypothalamo-pituitary-adrenal axis were not altered, suggesting chronic cocaine use has a greater and long lasting effect on dopaminergic hypothalamic neurons. In male volunteers who had a heavy use of cannabinoids, prolactin secretion was decreased compared with secretion in occasional users.

These detailed studies of endocrinological alterations at rest are being extended by examining neurosecretion under stimulated conditions to obtain further information on the relative contributions of particular neurotransmitters to the control of neuroendocrine secretion in chronic substance abuse. Evidence suggests that hypersensitivity of responses in both the dopaminergic and serotonergic systems occurs. This is being explored in detail. The gradual loss of the hypersensitivity created by substance use and observed during withdrawal may be important in relapse.

Using the rat, a model for chronic cocaine use has been established, passively administering smaller doses of cocaine than are usually used in such paradigms, and in multiple divided doses over 10 days. This regimen resulted in endocrinological findings similar to those observed in the male volunteers withdrawing from cocaine. Prolactin levels were measured prior to and following cocaine administration immediately following cocaine administration. Immediately following cocaine administration in the rats, prolactin was increasingly depressed until on day 10 it was below detectable levels but increased to hyperprolactinemic levels 24 hours after the last injection. To examine the relevance of alterations observed in the hypothalamo-pituitary system, the brains of these animals are being examined to establish whether alterations in neurotransmitters the tuberoinfundibular neurons reflect those in other brain regions. By reverse hemolytic plaque assay it has been established that cocaine has no direct action on pituitocytes, but release of prolactin from individual cells in response to dopamine is greater and occurs from more cells in the cocaine treatment rats suggesting hypersensitivity to dopamine. Future studies will concentrate on comparing CNS mechanisms with neurosecretory mechanisms in this model in response to various stimulators and depressors administered *in vivo* and on examination of the anatomy and mechanisms of alteration and their response to therapeutic agents and the study of withdrawal phenomena. The rat model will also enable examination of the effects of cocaine on other systems, particularly cardiac and immunological systems.

Although dopaminergic mechanisms may be most important in cocaine abuse, cocaine also affects serotonergic mechanisms. The serotonergic agonist, metachlorophenylpiperazine (mCPP) has been shown to release prolactin and cortisol which may be followed as *in vivo* markers of its CNS action. Studies of the acute effects of mCPP compared with those of fenfluramine, which has been more commonly studied, are complete. Studies examining the more chronic effects of mCPP are being carried out in humans and rats. Provocative tests suggest that serotonergic mechanisms in chronic cocaine users may be hypersensitive, in which case a chronic serotonergic agonist such as mCPP may be important in therapy. Therefore, in the future, the interactions of mCPP in cocaine treated animals or in humans withdrawing from cocaine are to be examined.

Mechanisms of Endocrine-Mediated Immune Function

Prolactin is an important immune-regulator. Because marked disturbances of prolactin secretion in substance users have been observed and a rat model for cocaine has demonstrated similar alterations in prolactin release, studies have commenced to examine the mechanisms of alterations of immunological function by substances of abuse. Growth hormone may have similar importance in immune-regulation and is similarly disturbed in cocaine abusers. The role of growth hormone in lymphocyte function will be investigated in new studies. These studies involve examining prolactin-sensitive ornithine decarboxylase

activity and other parameters of lymphocyte activity in animals chronically administered substances of abuse. The immunosuppressant properties of substances of abuse will be assessed in rats by observing the rat, and measuring neuroimmunomodulating parameters (including prolactin and growth hormone) and lymphocyte function.

Interactions Between Substance Abuse, the Endocrine and Immune System

The immunologic effects of substances of abuse have been and are being assessed on a clinical level in collaboration with Dr. William Adler's immunology group at the Gerontology Research Center. Amyl nitrite has been implicated as an etiological factor in the development of Kaposi's Sarcoma, the most common malignant complication of AIDS in homosexuals. In a study where amyl nitrite was administered to volunteers it was found that it depressed natural killer cell function during administration and that a rebound occurred in other parameters. This suggested an alternating, relative immunodepression/immunostimulation cycle could be induced by using the drug which, in turn, could promote opportunistic infections or compromise immuno-surveillance. Similar immunological techniques have been used to examine endocrine and immune function in tetrahydrocannabinol administration. Lastly, immune function during cocaine and nicotine administration is being assessed. These studies are unusual because they are conducted in a controlled environment and subjects are used as their own controls. At this stage, studies are carried out in HIV seronegative volunteers. Future studies will be made with HIV seropositive volunteers.

Publications

Ulrichsen, J., Partilla, J.S., and Dax, E.M. Long-term administration of m-chlorophenyl-piperazine (mCPP) to rats induces changes in serotonin receptor binding, dopamine levels and locomotor activity without altering prolactin and corticosterone secretion. Psychopharmacology. Submitted.

Buckenmeyer, P.J., Goldfarb, A.H., Partilla, J.S., Pineyro, M.A., and Dax, E.M. (1990) Endurance training, not acute exercise, differentially alters beta-receptors and cyclase in skeletal fiber types. Am Physiol 258 (1 Pt 1): E71-7.

Dax, E.M. (1990) Drug dependence in the differential diagnosis of allergic respiratory disease. Annal Allergy 64 (3): 261-3.

Dax, E.M., Adler, W.H., Nagel, J.E., Lange, W.R. and Jaffe, J.H. Inhalation of volatile nitrites induces changes in in vitro immune function. Clin. and Exp. Immunol. Submitted.

Dax, E.M., Partilla, J.S., Pineyro, M.A., and Gregerman, R.I. (1990) Altered glucagon- and catecholamine hormone-sensitive adenylyl cyclase responsiveness in rat liver membranes induced by manipulation of dietary fatty acid intake. Endocrinology 127 (5): 2236-2240.

Dax, E.M., Pilotte, N.S., Adler, W.H., Nagel, J.E., and Lange, W.R. (1989) The effects of 9-ene-tetrahydrocannabinol on hormone release and immune function. J Steroid Biochem, 34 (1-6): 263-270.

Dax, E.M., Pilotte, N.S., Adler, W.H., Nagel, J.E. and Lange, W.R. (1990) Short-term W⁹tetrahydrocannabinol (THC) does not affect neuroendocrine or immune parameters. NIDA Monograph. In Press.

Fudala, P.J., Jaffe, J.H., Dax, E.M., Johnson, R.E. (1990) Use of buprenorphine in the treatment of opioid addiction II: Physiological and behavioral effects of daily and alternate day administration and abrupt withdrawal. Clin Pharmacol Ther 47 (4): 525-34.

Lange, W.R., Ball, J.C., Dax, E.M. et al. A follow-up study of a parent HIV seropositivity among parenteral drug abusers in 1971-72. In press.

Lange, W.R., Dax, E.M., Kovacs, R., Kreider, S., and Frame, J. (1989) Are missionaries at risk of AIDS? Southern Medical Journal 82, 1075-1078.

Lange, W.R., Fudala, P.J., Dax, E.M., Johnson, R.E. (1990) Safety and side-effects of buprenorphine in the clinical management of heroin addiction. Drug Alcohol Depend 26 (1): 19-28.

Litow, R., Robinson, N., Herning, R., Jaffe, J.H. and Dax, E.M. Cognitive function and EEG changes with the inhalation of amyl-nitrite. Psychopharmacology. Submitted.

Pilotte, N.S., Mitchell, W.M., Sharpe, L.G., de Souza, E.B. and Dax, E.M. Chronic cocaine administration and withdrawal from cocaine modify central neurotensin receptors in rats. SYNAPSE. In Press.

Pilotte, N.S., Sharpe, L.G., and Dax, E.M. (1990) Multiple, but not acute, infusions of cocaine alter the release of prolactin in male rats. Brain Res 512: 107-112.

Ulrichsen, J., Partilla, J.S., and Dax, E.M. Long-term administration m-chlorophenyl-piperazine (mCPP) to rats induces changes in serotonin receptor binding, dopamine levels and locomotor activity without altering prolactin and corticosterone secretion. Psychopharmacology. Submitted.

Weddington, W.W., Brown, B.S., (1990) Haertzen, C.A., Cone, E.J., Dax, E.M., Heming, R.I., Michaelson, B.S. Changes in mood, craving, and sleep reported by male cocaine addicts during acute abstinence: A controlled, residential study. Arch Gen Psych 47 (9): 861-868.

ABSTRACTS

Pilote, N.S., Johnson, R.L., and Dax, E.M. (1990) Chronic cocaine in vivo modifies prolactin release after dopamine in vitro. Presented at 2nd International Congress of Neuroendocrinology, Bordeaux, France. Abst. #P4.93.

Pilote, N.S., Mitchell, W.M., Sharpe, L.G., de Souza, E.B., and Dax, E.M. (1990) Cocaine-induced reduction in neurotensin binding in midbrain is reversed during withdrawal from cocaine. Committee on Problems of Drug Dependence, Richmond, Virginia.

Newlin, D.B., Pretorius, M.B., Wong, C. and Dax, E.M. (1990) Acute marijuana smoking reduces vagal tone. Committee on Problems of Drug Dependence, Richmond, Virginia.

Fralich, J., Lange, R.W., and Dax, E.M. (1990) Prevalence trends of HIV infection among drug abusers in Baltimore, Maryland. Sixth International Conference on Aids, San Francisco, California.

Dax, E.M. and Pilote, N.S. (1990) Growth hormone (GH) release is altered in men who abruptly cease long-term cocaine. Presented at 2nd International Congress of Neuroendocrinology, Bordeaux, France. Abst. #P3.59.

Pilote, N.S., Sharpe, L.G. and Dax, E.M. (1990) Chronic cocaine modifies growth hormone release after 5-hydroxytryptophan in male rats. Presented at 20th Ann. Mtg. Soc. Neuroscience, St. Louis, Mo. Abst. #291.7.

Sharpe, L.G., Pilote, N.S., Mitchell, W.M., de Souza, E.B., and Dax, E.M. (1990) Withdrawal from chronic cocaine decreased dopamine transporter sites in the rat nucleus accumbens (NAC). Presented at 20th Ann. Mtg. Soc. Neuroscience, St. Louis, Mo., Abst. #111.18.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00004-04 NEI

January 1, 1990 to December 31, 1990

Title of Project: Inhalable Nitrites - Immune Function and Abuse Potential**Principal Investigators:**

PI:	E.M. Dax	Laboratory Chief	NEI,ARC,NIDA
Others:	J.H. Jaffe	NIDA	
	W.R. Lange	Medical Director	ARC, NIDA
	R. Herning	Laboratory Chief	CHP, ARC, NIDA
	R.M. Litow	Research Technologist	NEI, ARC, NIDA
	N. Robinson	Registered Nurse	NEI, ARC, NIDA
	W.H. Adler	Clin. Immunology Section	GRC, NIA
	J.A. Nagel	Clin. Immunology Section	GRC, NIA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch

Section: None**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years 1 **Professional:** 0.25 **Others:** 0.75**Check Appropriate Boxes:**

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

The intake and frequency of inhalation of volatile nitrites has been associated with the incidence of Kaposi's sarcoma in people suffering from AIDS. Animal and in vitro lymphocyte studies have shown that immune cell function can be altered by these agents. However, no study has related directly the effects of nitrites administered in vivo to disturbances of immune function in humans. Thus, a study has been conducted in healthy, HIV negative volunteers. An inhalation protocol in which the subject inhaled 3 doses of amyl nitrite for 3 days and 1 dose on the fourth day has been conducted. In an extended protocol a second group of volunteers were administered subsequent, single inhalations of nitrite 3-4 days apart, to a total of 13 inhalations over 3 weeks. A battery of immune function tests in the subjects' lymphocytes, was carried out on 2 occasions prior to the inhalation protocol, immediately following the last dose, and at 1, 4, and 7 days after the last dose. Results showed a decrease in natural killer cell activity, the lymphocyte function reputedly responsible for tumor cell scavenging. The single doses of nitrite administered at 3-4 day intervals continued to suppress this activity. Lymphocyte numbers and subsets were not altered during the inhalation protocols, but showed a non-specific rise on cessation of the drug. Discrepancies between mitogen stimulated [³H]thymidine incorporation, a measure of the activity potential of lymphocytes, and antibody production by the T lymphocyte-dependent, B-cells indicated a deficit in T-cell function during nitrite exposure.

The nitrites were demonstrated to have minimal abuse potential.

Publications

Litow, R., Robinson, N., Herning, R., Jaffe, J.H. and Dax, E.M. Cognitive function and EEG changes with the inhalation of amyl-nitrite. *Psychopharmacology*. Submitted.

Dax, E.M., Adler, W.H, Nagel, J.E., Lange, W.R. and Jaffe, J.H. Inhalation of volatile nitrites induces changes in in vitro immune function. *Clin. and Exp. Immunol.* Submitted.

January 1, 1990 to December 31, 1990

Title of Project: HIV Prevalence: In Depth Survey of Baltimore

Principal Investigators:

PI: E.M. Dax Laboratory Chief NEI, ARC, NIDA

Others: W.R. Lange Medical Director ARC, NIDA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.0 **Professional:** 0.25 **Others:** 0.75

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

The seroprevalence of HIV antibodies in surveyed intravenous substance users (IVSUs) who were either recently enrolled into treatment or were on a waiting list for enrollment was 29%. The rate among ARC research subjects with parenteral drug use histories has averaged 24%, and among area prostitutes with heavy drug use histories, 34%. In Baltimore, 94% of IVSUs had shared needles, and even though HIV seropositivity was not associated with a needle-sharing history, there was an association between the intensity of sharing and the probability of being seropositive. A much stronger association was observed between seropositivity and "shooting gallery" visitation, suggesting that this milieu of sharing, rather than other environments, is the real risk factor.

Very distinct ethnic group differences in HIV infection were observed, with Blacks being much more likely to be seropositive than Whites (odds ratio = 8.18, 95% CI 3.35-19.97). There was no significant difference in HIV infection between Blacks in Baltimore and in New York City. Shooting gallery visitation appears to be much more a phenomenon among Black IVSUs than it is in White (X² = 8.23, p<0.01). HIV infection has appreciably penetrated Baltimore's addict community. The overall seroprevalence rate in Baltimore in 1986 (29%) approximated that of New York in 1979 (27%) where the rate subsequently jumped to 58% in some areas by 1984 and has increased to 60% in 1987.

Hepatitis antigen and antibody status of these subjects has been assessed. There was no concordance of Hepatitis B infection and HIV infection. Other data concerning Hepatitis D is being analysed.

The second wave of this study is being initiated.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00006-04 NEI

January 1, 1990 to December 31, 1990

Title of Project: Cannabinoids and Their Effects on the Immune System and Cognitive Function

Principal Investigators:

PI:	E.M. Dax	Laboratory Chief	NEI, ARC, NIDA
Others:	W.R. Lange	Medical Director	ARC, NIDA
	N.S. Pilotte	Staff Fellow	NEI, ARC, NIDA
	R.M. Litow	Research Technologist	NEI, ARC, NIDA
	J.S. Partilla	Chemist	NEI, ARC, NIDA
	N. Robinson	Registered Nurse	NEI, ARC, NIDA
	J.R. Mahaffy	Registered Nurse	NEI, ARC, NIDA
	W.H. Adler	Clin. Immunology Section	GRC, NIA
	J.A. Nagel	Clin. Immunology Section	GRC, NIA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2 **Professional:** 0.5 **Others:** 1.5

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Delta-9-tetrahydrocannabinol (THC) has been hypothesized to influence immune function. However, this has not been investigated in a comprehensive fashion in humans. The purpose of this study is to measure and study the effects of THC on immune function. To investigate immune-endocrine correlations, hormone parameters defining the activity of the hypothalamo-pituitary-adrenal axis have been measured during THC administration. (The effects of THC on cognitive function will also be investigated.) Experienced THC users have been recruited for study. Immune function of lymphocytes in vitro has been investigated during orally administered and inhaled THC and during the washout phase.

Publications

Dax, E.M., Pilotte, N.S., Adler, W.H., Nagel, J.E., Lange, W.R. (1990) The effects of 9-ene-tetrahydrocannabinol on hormone release and immune function. *J. Steroid Biochem*, 34: 263-270.

Dax, E.M., Pilotte, N.S., Adler, W.H., Nagel, J.E. and Lange, W.R. (1990) Short-term Δ^9 tetrahydrocannabinol (THC) does not affect neuroendocrine or immune parameters. Committee on Problems of Drug Dependence, Richmond, Virginia.

Newlin, D.B., Pretorius, M.B., Wong, C. and Dax, E.M. (1990) Acute marijuana smoking reduces vagal tone. Committee on Problems of Drug Dependence, Richmond, Virginia.

Robinson, N., Lange, W.R., Dax, E.M. EKG alterations following Δ^9 tetrahydrocannabinol. (Submitted).

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00007-04 NEI

January 1, 1990 to December 31, 1990

Title of Project: Neuroendocrine Secretion During Cocaine Withdrawal**Principal Investigators:**

PI:	Elizabeth Dax, M.D. Ph.D.	Laboratory Chief	NEI, ARC, NIDA
Others:	W. Weddington, M.D.		TEI NIDA
	Nancy Pilotte, Ph.D.	Staff Fellow	NEI, ARC, NIDA
	Edrich Anderson, R.N.	Registered Nurse	NEI, ARC, NIDA
	Teri Gendron	Research Technologist	NEI, ARC, NIDA

Lab/Branch: Neuroendocrinology/Immunology Branch
Clinical Pharmacology Branch

Section: None**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 3 **Professional:** 1 **Others:** 2**Check Appropriate Boxes:**

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary Work

Cocaine withdrawal (and withdrawal from other drugs) is associated with CNS disturbances which are reflected in altered neurohormonal secretion, secondary to CNS neurotransmitter alterations. In men known to be cocaine abusers, the secretion of neurohormones has been examined during cocaine withdrawal. Prolactin secretion is under tonic inhibition by dopamine from the hypothalamus. The neurotransmitter most closely associated with cortisol release is serotonin. In the volunteers withdrawn from cocaine, prolactin levels were higher than in men who had not ever taken cocaine, and the diurnal rhythms in prolactin secretion were disturbed. The men were followed for up to 21 days with little change in the profiles of prolactin release. Cortisol levels and rhythms were similar to controls over this withdrawal period. These results suggest that chronic cocaine abuse results in dysfunction of dopamine mediated mechanisms of neurosecretion.

The alterations in the hypothalamo-pituitary-adrenal axis resulting from chronic cocaine abuse, is being further defined. This will enable study in volunteers whose serotonergic and dopaminergic functions are predictably manipulated, with tests that perturb the hypothalamic-pituitary-adrenal axis at a known level. Standard endocrine diagnostic tests (TRH, CRF stimulation and L-dopa suppression) in conjunction with drugs that perturb dopaminergic and serotonergic function have been carried out. The study will provide further information on dopaminergic control of hormonal secretion and its role in maintaining diurnal rhythms of hormones. It may provide an important means of assessing the efficacy of treatment protocols. Mechanisms of these changes is being investigated in a rat model of cocaine withdrawal.

Publications

Weddington, W.W., Brown, B.S., Haertzen, C.A., Cone, E.J., Dax, E.M., Herning, R.I., Michaelson, B.S. Changes in mood, craving, and sleep reported by male cocaine addicts during acute abstinence: A controlled, residential study. *Arch Gen Psych* 47 (9): 861-868.

Dax, E.M. and Pilote, N.S. Growth hormone (GH) release is altered in men who abruptly cease long-term cocaine. Presented at 2nd International Congress of Neuroendocrinology, Bordeaux, France, June, 1990, Abst. #P3.59.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00008-04 NEI

January 1, 1990 to December 31, 1990

Title of Project: The Effects of Cocaine on Hormone Secretion from the Anterior Pituitary

Principal Investigators:

PI:	E.M. Dax	Laboratory Chief	NEI, ARC, NIDA
	N.S. Pilotte	Staff Fellow	NEI, ARC, NIDA
Others:	L.G. Sharpe	Research Psychologist	BVL, ARC, NIDA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location: Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2 **Professional:** 1 **Others:** 1

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Although there is a large body of evidence linking cocaine use with central dopamine function, little is known about the direct or indirect effects of cocaine on the release of hormones from the anterior pituitary. The release of prolactin (PRL) is inhibited by dopamine originating from a discrete population of hypothalamic neurons. Thus, prolactin release is an indirect measure of dopamine release.

We have found that rats receiving daily i.v. infusions of cocaine are mildly hyperprolactinemic before the daily session of cocaine as early as 5-10 days after initiation of the treatment. Furthermore, PRL is decreased markedly at the end of the infusion period. This persistent effect appears to be related to the ability of cocaine to block the uptake of released dopamine and a possible decrease in the ability of the neuron to release more dopamine in the absence of cocaine. In contrast, dopamine plays little if any role in the normal release of growth hormone (GH) from the anterior pituitary. Thus, cocaine does not affect the peripheral concentrations of GH unless the release of this hormone is stimulated by serotonin. The ability of serotonin to release GH is diminished immediately after cocaine treatment, perhaps reflecting the loss of access to a readily-releasable pool of GH, a functional uncoupling of serotonin to its receptors on neurons that secrete growth hormone-releasing factor, or a desynchronization of the normal pulsatile circadian rhythm of the release of GH.

Publications

Pilote, N.S., Sharpe, L. G. and Dax, E.M. (1990) Multiple, but not acute, infusions of cocaine alter the release of prolactin in male rats. *Brain Res.* 512: 107-112.

Dax, E.M. and Pilote, N.S. Growth hormone (GH) release is altered in men who abruptly cease long-term cocaine. Presented at 2nd International Congress of Neuroendocrinology, Bordeaux, France, June, 1990, Abst. #P3.59.

Pilote, N.S., Sharpe, L.G. and Dax, E.M. Chronic cocaine modifies growth hormone release after 5-hydroxytryptophen in male rats. Presented at 20th Ann. Mtg. Soc. Neuroscience, St. Louis, Mo. Abst. #291.7

January 1, 1990 to December 31, 1990

Title of Project: Development of Monoclonal Antibodies to Drugs and Hormones

Principal Investigators:

PI:	E.M. Dax	Laboratory Chief	NEI, ARC, NIDA
Others:	C. Dersh	Chemist	NEI, ARC, NIDA
	R. Zaczek	Staff Fellow	ARC, NIDA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2 **Professional:** .25 **Others:** 1.75

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Usually antibodies to treatment drugs, substances of abuse or hormones are not commercially available unless there is wide market. Treatment drugs, such as buprenorphine, are unlikely to have antibodies developed until the efficacy of the drug is established. Therefore, this laboratory is developing antibodies to buprenorphine in order to establish a radioimmunoassay. Mice have been immunized with buprenorphine and demonstrate the presence of antibodies on initial tests. Spleen cells will be harvested and fused to myeloma cells to produce cell lines. Testing for production of antibodies in the cell line will be carried out and any clones producing highly specific and high affinity antibodies will be isolated. Buprenorphine antibodies will be used to establish a radioimmunoassay so that the drug may be quantitated in urine, plasma and tissue extracts. Other drugs that antibodies may be raised against include amphetamine and metamphetamine, cocaine and cocaine metabolites, and metachlorophenylpiperazine (mCPP). Antibodies are also presently being raised against vasopressin and rat prolactin, for which commercially available antibodies are limited.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00011-03 NEI

January 1, 1990 to December 31, 1990

Title of Project: Neuroendocrine Correlates of HIV Infection and the Development of ARC and AIDS

Principal Investigators:

PI: E.M. Dax Laboratory Chief NEI, ARC, NIDA
W.R. Lange Medical Director ARC, NIDA

Others: Lawrence Brown, M.D., M.P.H., Vice President for Research and Medical Affairs,
Addiction Research and Treatment Inc., Brooklyn, N.Y.

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1 **Professional:** 0.5 **Others:** 0.5

Check Appropriate Boxes:

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

The human immunodeficiency virus infects the central nervous system resulting in a wide range of neurological deficits. One problem in management of HIV-infected people is predicting the disease's prognosis and course. The control of the neuroendocrine system and many feed back loops both endocrine and immunological are a property of the CNS, particularly of the hypothalamus. Several studies have shown disruption of neuroendocrine function. In a large group of drug abusers the neuroendocrine/endocrine status will be correlated with HIV status, clinical history, drug history, and presence of opportunistic infections. To date, clinical data from 800 patients have been collected. Their HIV antibody status and hormonal measurements are being assessed.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00012-03 NEI

January 1, 1990 to December 31, 1990

Title of Project: HIV Sero-status in Missionaries From Africa, 1968-1983

Principal Investigators:

PI:	W.R. Lange	Medical Director	ARC, NIDA
	E.M. Dax	Laboratory Chief	NEI, ARC, NIDA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch

Section: None

Institution and Location:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1 **Professional:** 0.5 **Others:** 0.5

Check Appropriate Boxes:

<input type="checkbox"/> Human Subjects	<input checked="" type="checkbox"/> Human Tissues	<input type="checkbox"/> Neither
<input type="checkbox"/> Minors		
<input type="checkbox"/> Interviews		

Summary of Work

The origins and timing of HIV spread into the U.S. remain in question. One possibility is that alterations in the virus' genetic makeup led to its current pathogenic properties, but a similar virus may have been transported from Africa where HIV is endemic. We have screened approximately 6000 plasmas from missionaries travelling between Africa and the U.S. between 1968 and 1983. Although the group may be considered low risk for sexually transmitted diseases, they are a group with high casual contact with the African people. Approximately 200 plasmas were found to be positive on ELISA screening but none was found to have HIV specific proteins detected by Western Blot. Further analysis of the HIV proteins are being carried out. Selected plasmas are being screened for related virus, including HTLV1.

Publications

Lange, W.R., Dax, E.M., Kovacs, R., Kreider, S., and Frame, J. (1989) Are missionaries at risk of AIDS? *Southern Medical Journal* 82: 1075-1078.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00013-03 NEI

January 1, 1990 to December 31, 1990

Title of Project: Neuroendocrine Correlates of Aggressive/Impulsive Behavior**Principal Investigators:**

PI: E.M. Dax Laboratory Chief NEI, ARC, NIDA

Others: C.S. Contoreggi Staff Fellow NEI, ARC, NIDA
D. Fishbein Guest Scientist ARC, NIDA
J.H. Jaffe NIDA

Lab/Branch: Neuroendocrinology/Immunology Branch
Clinical Pharmacology Branch

Section: None**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 4.0 **Professional:** 1.5 **Others:** 2.5**Check Appropriate Boxes:**

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

When men grouped according to their aggressive/impulsive scores on standard psychological tests, are challenged with a serotonergic stimulator, such as fenfluramine, the neuroendocrine response is attenuated in the more aggressive, more impulsive men, suggestive of alterations in central serotonergic mechanisms. Further, results suggest that hostility ratings decrease with fenfluramine administration suggesting possible treatment rationales for the study. Aggression and impulsivity may be important personality characteristics in initiating and perpetuating addictive behavior. In order to investigate mechanisms of this behavior, establish neuroendocrine markers, suggest treatment possibilities and assess the efficacy of treatment paradigms, we are extending these studies with the more specific serotonergic agonist, metachlorophenylpiperazine (mCPP). We are examining whether mCPP administration gives similar results to fenfluramine. Subsequent studies will examine serotonergic as well as dopaminergic secretion in greater detail. Using neurohormones as markers of these responses, secretion will be examined in the presence of either a serotonergic or dopaminergic agonist (mCPP or bromocryptine, respectively). Neuroendocrine provocation tests will be used to further define alterations of function in the aggressive men.

Publications

Contoreggi, C.S., Fishbein, D.H., Jaffe, J.H. and Dax, E.M. Comparison of neuroendocrine effects of fenfluramine and metachlorophenylpiperazine in male volunteers. In preparation.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00014-02 NEI**

January 1, 1990 to December 31, 1990

Title of Project: The effects of cocaine on prolactin secretion from single cells of the anterior pituitary gland**Principal Investigators:**

PI:	N.S. Pilotte	Staff Fellow	NEI, ARC, NIDA
Others:	E.M. Dax	Laboratory Chief	NEI, ARC, NIDA
	R.L. Johnson	Biologist	NEI, ARC, NIDA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch**Section:** None**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1 **Professional:** .5 **Others:** .5**Check Appropriate Boxes:**

<input type="checkbox"/> Human Subjects	<input type="checkbox"/> Human Tissues	<input type="checkbox"/> Neither
<input type="checkbox"/> Minors		
<input type="checkbox"/> Interviews		

Summary of Work

In a recently completed study, we found that in rats that received programmed infusions of 1 mg/kg cocaine every 12 min for 2 hr over 10 days, the pre-infusion concentrations of prolactin (PRL) increased in a time-dependent manner whereas post-infusion levels of PRL were decreased by cocaine. Because dopamine (DA) and PRL are reciprocally related in male rats, these changes could involve modification of adenohipophysial dopamine D2 receptors. Dispersed anterior pituitary cells were obtained from rats treated chronically with cocaine or saline. The cells were used in a reverse hemolytic plaque assay that permitted direct visualization of PRL release from single lactotropes after different treatments in vitro. The cells were incubated with media, cocaine, thyrotropin releasing hormone (TRH), or dopamine (DA) in vitro. There were 4 major findings. 1) Basal PRL release was greater in rats treated with cocaine: more cells secreted PRL and the individual cells secreted more PRL. 2) Cocaine in vitro did not affect PRL release. 3) TRH stimulated PRL release similarly from lactotropes of cocaine- or saline-treated rats. 4) DA in vitro inhibited PRL release dose-dependently from both cocaine- and saline-treated rats when the concentration of DA met or exceeded that observed in hpothalamo-hipophysial portal blood. However, lactotropes from cocaine-treated rats were more sensitive to the inhibition by DA. Paradoxically, very low concentrations of DA (<10⁻⁹M) enhanced PRL release from cells from cocaine-treated rats. These data confirm the findings of others that DA-deprived lactotropes release more PRL when challenged with low concentrations of DA and suggest that one consequence of chronic use of cocaine is a diminished release of DA in the absence of cocaine.

Publications

Pilote, NS, Johnson, RL, Dax, EM. Chronic cocaine in vivo modifies prolactin release after dopamine in vitro. Presented at 2nd International Congress of Neuroendocrinology, Bordeaux, France, June 24-29, 1990, Abst. #P4.93.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00015-02 NEI**

January 1, 1990 to December 31, 1990

Title of Project: The effects of cocaine on dopamine release from hypothalamic neurons.**Principal Investigators:**

PI:	N.S. Pilotte	Staff Fellow	NEI, ARC, NIDA
Others:	L.G. Sharpe	Research Psychologist	BVL, ARC, NIDA
	I.M. Mefford	Special Expert	CP, NIMH
	E.M. Dax	Laboratory Chief	NEI, ARC, NIDA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch**Section:** None**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1 **Professional:** .75 **Others:** .25**Check Appropriate Boxes:**

<input type="checkbox"/> Human Subjects	<input type="checkbox"/> Human Tissues	<input type="checkbox"/> Neither
<input type="checkbox"/> Minors		
<input type="checkbox"/> Interviews		

Summary of Work

In a recently completed study, we found that in rats that received programmed infusions of 1 mg/kg cocaine every 12 min for 2 hr over 10 days, the pre-infusion concentrations of prolactin (PRL) increased in a time-dependent manner whereas post-infusion levels of PRL were decreased by cocaine. Because dopamine (DA) and PRL are reciprocally related in male rats, these changes could involve modification of the release of DA from hypothalamic tuberoinfundibular neurons. We are testing this hypothesis in rats treated as described above for 9 days with cocaine or saline. On the 10th day, the hypothalamo-hypophysial portal blood will be collected for 30 min before the initiation of passive infusions of cocaine or saline, during 60 min of intermittent infusion, and for 30 min following a challenge of amphetamine. Arterial blood will be collected concurrently. These aliquots will be assayed in Dr. Mefford's laboratory using microbore high performance liquid chromatography. If there are differences between cocaine- and saline-treated animals, another series will be performed with lidocaine as the infusate as a control for the local anesthetic effects of cocaine. This experiment will provide the first evidence of cocaine-induced modifications of functional DA release coupled to a physiological relevant event, the release of PRL, and can serve as a model of the action of cocaine on other central DA systems.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00016-02 NEI**

January 1, 1990 to December 31, 1990

Title of Project: Effects of cocaine and withdrawal from cocaine on central receptors for peptides, catecholamines, and catecholamine uptake markers.**Principal Investigators:**

PI:	N.S. Pilotte	Staff Fellow	NEI, ARC, NIDA
Others:	W.M. Mitchell	Lab Manager	NBL, ARC, NIDA
	L.G. Sharpe	Research Psychologist	BVL, ARC, NIDA
	E.B. de Souza	Laboratory Chief	NBL, ARC, NIDA
	E.M. Dax	Laboratory Chief	NEI, ARC, NIDA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch**Section:** None**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 3 **Professional:** 1.5 **Others:** 1.5**Check Appropriate Boxes:**

<input type="checkbox"/> Human Subjects	<input type="checkbox"/> Human Tissues	<input type="checkbox"/> Neither
<input type="checkbox"/> Minors		
<input type="checkbox"/> Interviews		

Summary of Work

Cocaine is thought to produce many of its effects through an interaction with dopaminergic neuronal systems. Cocaine's neurochemical effects may include modifications in the numbers of receptors or uptake sites for dopamine (DA) or other regulatory peptides colocalized with DA, such as neurotensin (NT). If such changes occur, it is not known if they are permanent. Thus, we treated rats with programmed infusions of isotonic saline or 1 mg/kg cocaine every 12 min for 2 hr over 10 days and killed them within 15 min of the last infusion. Other rats were treated identically, but were killed 10 days later. Brains were removed and immediately frozen. Ten micron sections were taken through areas known to contain DA perikarya or terminals and binding experiments were conducted on the slices to determine the loci and number of binding sites for NT, and desmethylimipramine-insensitive mazindol binding sites to mark the DA transporter. Additional sections were taken for analysis of binding of paroxetine, and corticotropin releasing hormone. Analysis for NT sites is complete at this time. We found that cocaine reduced NT binding sites in the ventral tegmental area, substantia nigra and pars lateralis and that these reductions were reversed 10 days later. In addition, NT binding in the prefrontal cortex of rats killed within 15 minutes of their final infusion of cocaine was twice that of saline-treated rats and these sites were increased by an additional 50% ten days after withdrawal of cocaine. In contrast, the binding of DA uptake sites was not changed at the end of the period of cocaine administration, but was reduced in the nucleus accumbens ten days after withdrawal of cocaine. The persistent up-and-down-regulation of these receptors may be intimately involved in the long-lasting behavioral and psychological effects associated

with the use of cocaine and abstinence from it.

Publications

Pilotte, N.S., Mitchell, W.M., Sharpe, L.G., de Souza, E.B. and Dax, E.M. Chronic cocaine administration and withdrawal from cocaine modify central neurotensin receptors in rats. *SYNAPSE*. In Press.

Sharpe, L.G., Pilotte, N.S., Mitchell, W.M., and de Souza, E.B. Withdrawal of repeated cocaine decreases autoradiographic labeling of dopamine transporter in rat nucleus accumbens. Submitted to *Eur J Pharmacol*.

Pilotte, N.S., Mitchell, W.M., Sharpe, L.G., de Souza, E.B., Dax, E.M. Cocaine-induced reduction in neurotensin binding in midbrain is reversed during withdrawal from cocaine. Presented at CPDD. June, 1990.

Sharpe, L.G., Pilotte, N.S., Mitchell, W.M., de Souza, E.B., and Dax, E.M. Withdrawal from chronic cocaine decreased dopamine transporter sites in the rat nucleus accumbens (NAC). Presented at 20th Ann. Mtg. Soc. Neuroscience, St. Louis, Mo., Abst. #111.18.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00017-02 NEI**

January 1, 1990 to December 31, 1990

Title of Project: Cardiac effects of I.V. cocaine administration as measured by radionucleotide scanning, echocardiography and holter monitoring.**Principal Investigators:**

PI:	E.M. Dax	Laboratory Chief	NEI, ARC, NIDA
	W.R. Lange	Medical Officer	ARC, NIDA
	N. Chandra	Cardiologist	FSKMC
Others:	C.S. Contoreggi	Assistant Medical Officer	ARC, NIDA
	J. Fralich	Physician's Assistant	ARC, NIDA
	F. Levin	Staff Fellow	ARC, NIDA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch**Section:** None**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2 **Professional:** 1.5 **Others:** .5**Check Appropriate Boxes:**

Human Subjects **Human Tissues** **Neither**
 Minors
 Interviews

Summary of Work

Cocaine use is associated with sudden death which is often due to cardiac complications. The mechanism of cocaine's effect on cardiac function is not understood. In healthy volunteers who use cocaine, cardiac function will be monitored in the absence and presence of cocaine by holter monitoring, echocardiography and radionucleotide (Thallium) scanning. In addition, physiological, neuroendocrinological and peripheral nervous system data will be obtained.

NOTICE OF INTRAMURAL RESEARCH PROJECT**Z01 DA 00018-02 NEI**

January 1, 1990 to December 31, 1990

Title of Project: The effect of chronically administered metachlorophenylpiperazine on rat brain receptors, neurotransmitters and neuroendocrine hormone secretion.**Principal Investigators:**

PI:	E.M. Dax	Laboratory Chief	NEI, ARC, NIDA
Others:	J. Ulrichsen	Foreign Fellow	NEI, ARC, NIDA
	J.S. Partilla	Research Chemist	NEI, ARC, NIDA

Lab/Branch: Neuroendocrinology/Immunology Laboratory
Clinical Pharmacology Branch**Section:** None**Institution and Location:**

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2 **Professional:** 1 **Others:** 1**Check Appropriate Boxes:**

<input checked="" type="checkbox"/> Human Subjects	<input type="checkbox"/> Human Tissues	<input type="checkbox"/> Neither
<input type="checkbox"/> Minors		
<input type="checkbox"/> Interviews		

Summary of Work

Metachlorophenylpiperazine (mCPP) is a serotonergic agonist/antagonist which may be useful in treatment of disorders such as depression and aggression which are associated with substance abuse. mCPP may have therapeutic value for cocaine abuse. Although neuroendocrine and other responses to acute treatment with mCPP have been studied, no studies of alterations with chronic administration have been made. We will conduct these studies in rats chronically treated with mCPP. Appropriate receptors and neurotransmitters along with neuroendocrine responses and behavioral parameters will be quantitated. The interaction of mCPP with cocaine effects will be investigated.

The effects of chronic mCPP on human neuroendocrine responsiveness will also be assessed. Subjects will be given the neuroendocrine challenges of TRH- and CRH - stimulation tests after chronic mCPP administration.

Etiology Branch

David B. Newlin, Ph.D., Acting Chief

Overview

The Etiology Branch is concerned with the causes of drug abuse. Research is conducted with human subjects in both clinical and laboratory settings. Dr. David Newlin is Acting Chief of the Etiology Branch, and a permanent Branch Chief currently is being recruited.

Vulnerability Laboratory - David. B. Newlin, Ph.D., Acting Chief

The main focus of the Vulnerability Laboratory concerns mechanisms of addiction, with special emphasis on populations who are at high risk for developing drug abuse. Broad sections of the population are exposed to illicit drugs, but only a small percentage develop serious drug problems. The central question is what constitutional and environmental factors promote the development of drug abuse, and what are the mechanisms by which initial drug use is translated into addiction.

High risk populations that are being studied include infants exposed to drugs in utero, individuals at genetic or familial risk, individuals at risk due to certain premorbid personality characteristics, individuals with genetic markers for alcoholism and/or drug abuse, and established drug abusers who are at risk for relapse.

Several different mechanisms of addiction are being studied that are thought to relate to the process by which at-risk individuals develop drug abuse. These mechanisms include attentional deficits in childhood and aggressive-impulsive characteristics in adolescents, electrocortical characteristics, Pavlovian drug conditioning mechanisms, enkephalinergic transcriptional processes, deviant responses to common drugs that may explain high risk status, individual differences in reward to abused drugs, access to drugs and alternative reinforcers, craving for drugs, and withdrawal phenomena.

Specific studies in the Vulnerability Laboratory span the range from infants to adulthood. We are initiating research on infants exposed to cocaine and other drugs in utero which we measure vagal tone, response to startle, electroencephalographic activity and developmental course, as well as mother-infant interactions. This research is expected to provide invaluable noninvasive physiological and behavioral data on outcome in infants exposed to drugs during pregnancy. Similar research is being conducted with 8 - 11 year old children who had been exposed to opiates in utero, compared to children whose mothers were exposed to opiates after pregnancy (during child-rearing) and mothers not exposed to drugs. This research should indicate long-term effects of in utero exposure and child-rearing effects of maternal exposure to drugs.

In the adolescent age range, we are studying responses to alcohol, methylphenidate, and mCPP in young men (aged 21-25) who are at high risk for developing drug abuse and alcoholism because of a family history of alcoholism or personal history of hyperactivity. This research involves a wide range of measures, including autonomic, EEG, neuroendocrine, and subjective report of intoxication and drug effects following drug challenge in these individuals. This work in progress is expected to delineate differences in acute and chronic drug-induced responses that may account for the increased risk status of these individuals.

Research with gene regulation of the endogenous opiate system has moved into a second phase of replication and extension of previous work. We found that chronic treatment with opiate antagonists lead to greater anti-nociceptive effects during the antagonist wash-out period. We are currently conducting follow-up research to replicate this effect and to determine whether this effect is pre- or post-synaptic.

Other research on mechanisms of addiction involve studying the acute effects of various abused and nonabused drugs on the cardiovascular system in order to elucidate parasympathetic effects of these drugs. This research is driven by our linkage hypothesis that proposes central linkage between dopaminergic reward mechanisms, psychomotor stimulant effects, and vagally-mediated heart rate increases to abused drugs. Following prediction, we have found that alcohol, morphine, cocaine, and smoked marijuana decrease vagal tone, in some cases dramatically. This is evidence that the supposed sympathomimetic effects of these drugs are largely due to parasympathetic rather than sympathetic mechanisms. We are currently extending this research to replicate the alcohol, opiate, and marijuana effects on vagal tone, and to study new drugs such as nicotine, barbiturates, d-amphetamine, methylphenidate, mCPP, and naloxone-precipitated withdrawal.

Our research with induced cocaine craving, in which we found that alcohol intoxication increased self-report of cocaine craving, is being extended to follow-up on the large and reliable individual differences in cocaine craving. We have found that high cocaine cravers have increased resting vagal tone, THM index, and activity, and lower heart rates than low cocaine cravers. This pattern is similar to findings in infants in which temperamental traits of "fussiness" have been related to similar cardiovascular and behavioral differences.

Previous research on cognitive and evoked potential correlates of cocaine withdrawal is being extended to include longer intervals following cocaine exposure and a more comprehensive cognitive and evoked potential battery of measures. This research is providing a very effective documentation of the temporal effects of cocaine withdrawal, as well as possible residual effects of cocaine or preexisting characteristics of cocaine abusers.

Publications

Herning, R.E., Glover, B.J., Weddington, W.W., Koeppl, B.S., and Jaffe, J.H. Cognitive decrements during cocaine abstinence were not related to depression. Biological Psychiatry. Submitted January, 1990, In revision.

Weddington, W.W., Brown, B.S., Haertzen, C.H., Cone, E.J., Dax, E.M., Herning, R.I., and Michaelson, B.S. Changes in mood, craving and sleep during acute abstinence reported by male cocaine addicts: A controlled residential study. Archives of General Psychiatry, 47: 861-868, 1990.

Litow, R.M., Herning, R.I., Robinson, N., Jaffe, J.H., and Dax, E.M. Cognitive function and EEG testing in volunteer men inhaling volatile nitrites. Submitted Psychopharmacology, June, 1990.

London, E.D., Cascella, N.G., Wong, D.F., Phillips, R.L., Dannels, R.F., Links, J.M., Herning, R., Grayson, R., Jaffe, J.H., and Wagner, H.N. Cocaine-induced reduction of glucose utilization in human brain: A study using Positron Emission Tomography and FDG. Archives of General Psychiatry, 47, 567-576, 1990.

Herning, R.I., Glover, B.J., Koeppl, B., Weddington, W., and Jaffe, J.H. Cognitive deficits in abstaining cocaine abusers. In: Residual Effects of Abused Drugs (J. Spenser and J. J. Boren, Eds.) National Institute on Drug Abuse Monograph Series, 101:167-178, 1990.

London, E.D., Broussolle, E.P.M., Links, J.M., Wong, D.F., Cascella, N.G., Dannels, R.F., Sono, M., Herning, R., Snyder, F.R., Rippetoe, L.R., Toung, T.J.K., Jaffe, J.H., Wagner, H.N. Morphine-induced metabolic changes in the brain: Studies with Positron Emission Tomography and FDG. Archives of General Psychiatry, 47, 73-81, 1990.

Herning, R.I., Glover, B.J. and Henningfield, J.E. Attention deficits during nicotine abstinence. Psychopharmacology, Submitted Jan., 1989.

Pickworth, W.B., Herning, R.I., Koeppl, B. and Henningfield, J.E. Atropine-induced changes in spontaneous electroencephalogram in human volunteers. Military Medicine, 155: 166-170, 1990.

Newlin, D.B., & Thomson, J.B. (1990). Alcohol challenge with sons of alcoholics: A critical review and analysis. Psychological Bulletin, 108, 383-402.

Newlin, D.B., Byrne, E.A., & Porges, S.W. (1990). Vagal mediation of the effect of alcohol on heart rate. Alcoholism: Clinical and Experimental Research, 14, 421-424.

Newlin, D.B., Pretorius, M.B. (1990). Sons of alcoholics report greater hangover symptoms than sons of nonalcoholics: A pilot study. Alcoholism: Clinical and Experimental Research, 14, 713-716

Newlin, D.B., & Pretorius, M.B. (1991). Prior exposures to the laboratory enhance the effect of alcohol. Journal of Studies on Alcohol, in press.

Newlin, D.B., & Thomson, J.B. (1991). Chronic tolerance and sensitization to alcohol in sons of alcoholics. Alcoholism: Clinical and Experimental Research, in press.

Newlin, D.B., & Pretorius, M.B. (1991). Nonassociative mechanisms in the development of preferences for alcoholic flavors: Differences between sons of alcoholics and sons of nonalcoholics. Addictive Behaviors, in press.

O'Hara, B.J., Smith, S.S., Persico, A., Wang, K., Cutting, G.R., Newlin, D.B., Gorelick, D.A., Uhl, G.R. (1991). Dopamine D2 receptor alleles in substance abusers: Confounding effect of race, submitted.

Published Abstracts

Pretorius, M.B., Wong, C.J., & Newlin, D.B. (1990). Cardiovascular components of the response to morphine. Committee on Problems of Drug Dependence.

Newlin, D.B., Pretorius, M.B., Wong, C.J., & Dax, E. (1990). Acute marijuana smoking reduces vagal tone. Committee on Problems of Drug Dependence.

Uhl, G., Newlin, D.B., Pretorius, M.B., Park, J., & Cone, E. (1990). Antagonist-withdrawal up-regulation of endogenous opiate antinociceptive systems. Committee on Problems of Drug Dependence.

Hickey, J.E., Suess, P.E., Spurgeon, L., Newlin, D.B., & Porges, S.W. (1991). Vagal tone and attention in 8 to 12 year old males exposed to opiates in utero: A preliminary report. Committee on Problems of Drug Dependence.

Newlin, D.B., Wong, C.J., Pretorius, M.B., & Muntaner, C. (1991). Alcohol ingestion increases self-report of cocaine-craving: Individual differences in craving. Alcoholism: Clinical and Experimental Research, 12, 365.

Pretorius, M.B., Newlin, D.B., Wong, C.J., & Better, W.E. (1991). Individual differences in cocaine-craving: Physiological and affective correlates. Committee on Problems of Drug Dependence.

Newlin, D.B., Pretorius, M.B., Wong, C.J., Stapleton, J.M., & London, E.D. (1991). Acute intravenous cocaine reduces cardiac vagal tone in cocaine abusers. Committee on Problems of Drug Dependence.

Dax, E.M., Newlin, D.B., Better, W.E., Wong, C.J., & Pretorius, M.B. (1991). Intravenous morphine produces initial heart rate increases and cardiac vagal tone decreases. Committee on Problems of Drug Dependence.

Uhl, G.R., O'Hara, B.J., Smith, S.S., Persico, A., Wang, K., Cutting, G.R., Newlin, D.B., & Gorelick, D.A. (1991). Dopamine D2 receptor alleles in substance abusers: Confounding effect of race. Committee on Problems of Drug Dependence.

Smith, S.S., Newlin, D.B., Uhl, G.R. (1991). Reliability and validity of the ARC Drug Use Survey. Committee on Problems of Drug Dependence.

Herning, R.I., Koepl, B., Pickworth, W., Johnson, R.E., Fudala, J.H., Khazan, N. EEG Characteristics of buprenorphine maintenance and withdrawal in former heroin dependent subjects. Submitted to Society for Neuroscience 1991

Herning, R.I., Glover, B.J., Koepl, B., Reddish, R., and London, E. Effects of Cocaine and Cocaine Withdrawal on the CNS: EEG, Evoked Potential and Performance. Fifth World Congress of Biological Psychiatry, Florence, Italy, June 9-14, 1991

Herning, R.I., Brigham, J., Stitzer, M.L., Glover, B.J., Pickworth, W.B. and Henningfield, J.E. The effects of nicotine on information processing: Mediating a deficit. Society for Psychophysiological Research, Boston, MA., Oct., 1990

Herning, R.I., Glover, B.J., Koepl, B., Reddish, R., Levin, F., Dax, E. Cognitive Deficits during cocaine abstinence persist. Committee on Problems of Drug Dependence, Richmond, June, 1990

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Individual Differences in Cocaine Craving: Physiological and Affective Correlates.

Principal Investigators: Cooperating Units

Newlin, D.B., Pretorius, M.B., Wong, C.J., & Better, W.E.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2 **Professional:** 1 **Other:** 1

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

We studied continuous self-report of cocaine-craving, autonomic measures (heart rate, cardiac vagal tone index, general motor activity, finger, and cheek temperature) and self-reported affect (POMS) in 20 male research volunteers with heavy cocaine abuse histories. All subjects were exposed to a cocaine videotape and audiotape in counter-balanced order with a control audio and videotape. The autonomic correlates of craving induced by the cocaine-stimuli were small and could be attributed to nonspecific psychophysiological responding while attending to an external stimulus. However, autonomic and affective correlates emerged when we correlated overall levels of cocaine-craving with pre-stimulus heart rate and self-reported affect. Replicating our preliminary study with a smaller number of residential volunteers, cocaine-craving was negatively correlated ($r = -.45, p < .05$) with resting (i.e., pre-stimulus) heart rates; craving was also negatively correlated ($r = -.44, p < .06$) with baseline forehead temperature. Cocaine-craving was positively correlated with both positive and negative affect on the POMS. These results indicated stable trait characteristics rather than reactions to the tapes. There were interesting parallels between the autonomic patterns of the higher cocaine-craving subjects and "fussy," irritable, dysregulated infants. Cocaine abusers who do not crave cocaine may have blunted affect. Cocaine-craving was much greater in this outpatient study than our otherwise similar residential study, suggesting that drug availability or anticipation may determine the intensity of cocaine-craving. Unlike the preliminary study, frequency (but not quantity) of cocaine use was positively correlated ($r = .70, p < .001$) with cocaine-craving. These results indicate that stable individual physiological correlates of cocaine-craving may be more robust than evoked responses to cocaine-stimuli in this paradigm.

Publications

Pretorius, M.B., Newlin, D.B., Wong, C.J., & Better, W.E. (1991). Individual differences in cocaine-craving: Physiological and affective correlates. *Committee on Problems of Drug Dependence*.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Alcohol Ingestion Increases Self-Report of Cocaine-Craving: Individual Differences in Craving

Principal Investigators: Cooperating Units

Newlin, D.B., Wong, C.J., Pretorius, M.B., & Muntaner, C.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 3 **Professional:** 1 **Other:** 2

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Cocaine abusers often report difficulty abstaining from cocaine while intoxicated with alcohol, and alcoholism and cocaine dependence have strong comorbidity. Therefore, we sought to determine whether alcohol intoxication would increase cocaine-craving induced by exposure to videotapes of an individual self-administering cocaine compared to a control tape of an individual painting. Subjects were 12 male residential volunteers with histories of both heavy alcohol and cocaine use. They drank water the first day, and a high (1.1 g/kg), moderate (0.64 g/kg), placebo (0.0 g/kg) dose of alcohol, or water on 4 separate (approx. alternate) days in pseudo-randomized order in double-blind fashion. Continuous self-report of desire for cocaine and autonomic measures were recorded before drinking, and during and after watching the stimulus tapes in the rising and falling BAC curves.

Although mean levels of cocaine-craving were not intense, subjects reported significantly more cocaine-craving after ingestion of alcohol; this effect was nonsignificantly greater in the rising BAC curve when BAC was highest. We then divided subjects into 7 who craved cocaine and 5 with minimal or no craving during the entire experiment; these two groups had equivalent cocaine and alcohol histories. High cocaine-cravers had trait characteristics of significantly lower resting heart rate, higher vagal tone index, and greater general motor activity on a stabilometer under their chairs both before and after drinking. Lower resting heart rates among high cocaine-cravers was replicated in a second (nonresidential) study with 20 cocaine abusers. The autonomic pattern for high cocaine-cravers parallels that of "fussy," irritable, dysregulated infants. The results suggest a role for alcohol intoxication in craving for cocaine. They also underscore the potential importance of individual differences in drug-craving among users with equivalent abuse histories.

Publications

Newlin, D.B., Wong, C.J., Pretorius, M.B., & Muntaner, C. (1991). Alcohol ingestion increases self-report of cocaine-craving: Individual differences in craving. Alcoholism: Clinical and Experimental Research, 12, 365.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Intravenous Morphine Produces Initial Heart Rate Increases and Cardiac Vagal Tone Decreases.

Principal Investigators: Cooperating Units

Newlin, D.B., Better, W.E., Wong, C.J., Pretorius, M.B., & Dax, E.M.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1 Professional: 0.25 Other: 0.75

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

We have found that many abused drugs increase heart rate (HR) and decrease cardiac vagal tone index (V). Traditional views of the limited effect of the opiates on the cardiovascular system would suggest that the opiates represent an exception to this observation. However, this may be due to recordings taken after compensatory mechanisms have stabilized cardiovascular parameters. Therefore, we recorded HR and V continuously before, and for 30 min after i.v. morphine (15 mg) injection to measure initial cardiovascular responses. V is a well-validated measure of vagal inhibition of the heart based on time series analysis of HR variability entrained with respiration (i.e., respiratory sinus arrhythmia). The subjects were 9 opiate abusers who were research volunteers living on a residential ward. Intravenous morphine produced immediate HR increases ($p < .01$) of +9 bpm, and V decreases ($p < .05$) of -1.4 log units. These responses gradually returned toward baseline during the 30 min after injection. These effects were in the same direction, but of larger magnitude than our previous results with i.m. morphine (20 mg). Therefore, morphine may not be an exception to the pattern of cardiovascular responding to various abused drugs when considering initial responses before compensatory mechanisms develop. Moreover, these results indicate that the HR response to morphine has a substantial parasympathetic component.

Publications

Dax, E.M., Newlin, D.B., Better, W.E., Wong, C.J., & Pretorius, M.B. Intravenous morphine produces initial heart rate increases and cardiac vagal tone decreases. Presented at Committee on Problems of Drug Dependence, Palm Beach, Florida, 1991.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Cardiovascular Responses to Naloxone-Precipitated Withdrawal: A Test of a Hypothesis Concerning Drugs of Abuse.

Principal Investigators: Cooperating Units

Newlin, D.B., Wong, C.J., Better, W.E., and Cheskin, L.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.25 **Professional:** 0.25 **Other:** 1

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

We have examined cardiovascular responses in humans to a wide range of abused drugs, including cocaine, marijuana, alcohol, nicotine, methylphenidate, morphine, dilaudid, and pentobarbital. All these drugs increase heart rate and decrease vagal tone, particularly cocaine and marijuana. Vagal tone measures parasympathetic influences on the heart noninvasively by quantifying respiratory sinus arrhythmia, or heart rate variability entrained with respiration. Withdrawal of vagal inhibition produces tachycardia (i.e., increased heart rate). We have proposed that stimulation of the mesolimbic dopamine reward system by these abused drugs produces parallel activation of locomotor activity (Wise & Bozarth, 1987) and vagally-mediated tachycardia. This raises the possibility that measuring parasympathetic withdrawal and its associated tachycardia may prove useful as a simple index of a drug's abuse liability. This would require that psychoactive drugs that are not abused do not also show the same pattern (i.e., decreased vagal tone and increased heart rate).

The purpose for this study was to determine whether the tachycardia sometimes produced by naloxone-precipitated withdrawal from opiates is mediated by decreased vagal tone. We hypothesized that this tachycardia is sympathetically rather than parasympathetically mediated because naloxone is not an abused drug.

We administered 0.4 mg intramuscular naloxone to 12 opiate users who were classified as opiate-dependent on the basis of clinical history and toxicology. All 12 subjects exhibited signs of naloxone-precipitated withdrawal, as indicated by elevated scores on the Opiate Withdrawal Scale. We recorded heart rate and vagal tone continuously before and for 30 min after the intramuscular injection of naloxone. The cardiovascular response peaked from 11 to 16 min after the injection. We preselected the 8 subjects with the greatest heart rate increases in order to provide the strongest possible test of the hypothesis concerning vagal tone (i.e., vagal tone would not be expected to decrease if heart rate did not increase). For these 8 subjects, heart rate increased significantly ($F(1,7)=20.3, p<$

005) approx. 7 to 8 beats/min, and vagal tone decreased slightly but nonsignificantly $F(1,7)=4.4$, n.s.). A lower frequency (approx. 0.10 Hz) rhythm in the heart rate variability spectrum increased nonsignificantly ($F(1,7)=3.0$, n.s.).

This pattern of cardiovascular results was very different from that of any abused drug that we have assessed (listed above). We interpreted this pattern to indicate that, as predicted, the tachycardia from naloxone-precipitated withdrawal was sympathetically as opposed to parasympathetically mediated.

Publications

Newlin, D.B., Wong, C.J., Better, W.E., & Cheskin, L.J. Cardiovascular Responses to Naloxone-Precipitated Withdrawal: An Exclusionary Test of a Hypothesis Concerning Drugs of Abuse. Paper presented at the Association for the Advancement of Behavior Therapy, 1991.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Acute Intravenous Cocaine Reduces Cardiac Vagal Tone in Cocaine Abusers.

Principal Investigators: Cooperating Units

Newlin, D.B., Pretorius, M.B., Wong, C.J., Stapleton, J.M., & London, E.D.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.5 **Professional:** 0.5 **Other:** 1

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Researchers have assumed that the pronounced tachycardia produced by cocaine is due to sympathetic autonomic mechanisms because cocaine blocks reuptake of catecholamines. We studied the acute effects of cocaine on parasympathetic mechanisms to determine if there was a significant vagal component to this tachycardia. We used a noninvasive measure of cardiac vagal tone. This measure, which has been well-validated in animals and human subjects, is based on time series analysis of successive R - R intervals. Vagal tone index quantifies heart rate variability in the same frequency band as respiration (i.e., respiratory sinus arrhythmia). We considered vagal blockade impractical to resolve this issue because it produces very large baseline shifts in heart rate. We administered cocaine (20 mg and 40 mg) and placebo (saline) intravenously on separate days in pseudo-randomized order in double-blind fashion to 10 male residential volunteers with histories of cocaine abuse. Cocaine produced dose-dependent increases in heart rate. The effect was precisely mirrored by robust decreases in vagal tone index, as well as decreases in a lower frequency heart rate rhythm associated with blood pressure homeostasis. Injection of saline (i.e., cocaine cues) produced an initial 14 bpm increase in heart rate that had no significant vagal component. Vagal tone index and the lower frequency rhythm decreased approximately 2 to 2.5 log units in response to 40 mg cocaine, with a trough 7 to 14 min after intravenous administration. Therefore, cocaine produced a pronounced decrease in heart rate variability. The results indicate that cocaine-induced tachycardia has a strong parasympathetic component. Further research is needed to determine whether the vagal and sympathetic effects of cocaine on the autonomic nervous system are additive or synergistic. The findings have implications for a better understanding of the cardiotoxicity of cocaine.

Publications

Newlin, D.B., Pretorius, M.B., Wong, C.J., Stapleton, J.M., & London, E.D. (1991). Acute intravenous cocaine reduces cardiac vagal tone in cocaine abusers. Paper presented at Committee on Problems of Drug Dependence, Palm Beach, Florida, 1991.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project:

The ARC Drug Expectancy Questionnaire: An Instrument for Assessing Expectancies Concerning Use of Cocaine, Heroin, Marijuana, Alcohol, and Nicotine.

Principal Investigators: Cooperating Units

Wong, C.J., Newlin, D.B., Better, W.E., & Pretorius, M.B.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.10 **Professional:** 0.10 **Other:** 1

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

In the alcohol literature, researchers have found that cognitive expectations about how alcohol will affect people are potent predictors of individual alcohol use. These expectations tend to be stronger predictors of drinking than other variables, such as demographics or familial history of alcoholism. People who expect, for example, that alcohol will make them happy, friendly, attractive, etc., drink more alcohol than people who expect that alcohol will make them clumsy, unattractive, and sleepy. These cognitive expectations can be measured in primary school children, and appear to be a product of both societal attitudes toward alcohol intoxication and individual experiences with the drug.

We developed the Addiction Research Center Drug Expectancy Questionnaire (ARCDEQ) to extend this research to drugs other than alcohol. We included tobacco as a comparison or control drug because we thought it unlikely to show the magnitude of subjective expectations associated with the other drugs. The ARCDEQ has 46 items for each of five drugs (i.e., alcohol, cocaine, heroin, marijuana, and tobacco). Thirty six of the items referred to expectations about acute effects of the drug, such as feeling "anxious" or feeling "bold." These items were balanced to include those on each end of continuums represented by "good" vs. "bad" effects, stimulant vs. depressant effects, enhancing vs. impairing effects, and prosocial vs. hostile effects. Ten items were also included for each drug to assess longterm expectations about how chronic use will affect them, such as "enjoy life more" or "get sick." Each item used a Likert scale with descriptive anchors of "unlikely" to "likely", with "neither" in the center of the scale.

We have administered this questionnaire in computerized form to 86 abstinent, light, and heavy drug users. To date, 75 men and 11 women have answered the ARCDEQ. Twenty subjects answered the questionnaire twice to assess test-retest reliability. For each drug, we divided subjects based on

whether they were naive, light, or heavy users of that particular drug, based on quantity-frequency items from the ARCDEQ itself, and the ARC Drug Use Survey, administered separately.

We will report on preliminary analyses of this data in which we eliminated some items and developed empirically-derived scales for data reduction and reporting. We consider expectations about abused drugs to be important for two reasons.

First, they suggest motives for excessive drug use and may predict who escalates from experimental to heavy use. Second, they have direct relevance for prevention and psychological treatment of drug abuse, namely, to develop interventions to change these expectancies.

Publications:

Wong, C.J., Newlin, D.B., Better, W.E., & Pretorius, M.B. The ARC Drug Expectancy Questionnaire: An Instrument for Assessing Expectancies Concerning Use of Cocaine, Heroin, Marijuana, Alcohol, and Nicotine.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Acute Effects of Various Abused Drugs on Heart Rate and Cardiac Vagal Tone: A Common Factors Approach.

Principal Investigators: Cooperating Units Newlin, D.B., Pretorius, M.B., Wong, C.J., Better, W.E., & Pickworth, W.B.

Lab/Branch: Etiology Branch

Section: Vulnerability Laboratory

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.5 **Professional:** 0.5 **Other:** 1

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Drug-induced cardiovascular responding appears to be a common factor among abused drugs that may be linked to psychomotor stimulant activation and increased mesolimbic dopamine levels. Therefore, the pattern of cardiovascular responses to abused drugs may reflect their reward value. We measured heart rate (HR) and vagal tone index (V) before, 60 and 120 min after double-blind administration of low and high dosages of smoked marijuana, or oral alcohol, hydromorphone, pentobarbital, and d-amphetamine. There were two triple-dummy (i.e., smoke, drink, and capsule) placebo sessions. The 12 sessions were in randomized order on approx. alternate days. The subjects were 9 male poly-drug abusers who were residential volunteers. V is a well-validated measure of parasympathetic inhibition of the heart that quantifies respiratory sinus arrhythmia using time series analysis, i.e., beat-to-beat variability in HR that is entrained with respiration. Marijuana, alcohol, and pentobarbital increased HR and decreased V relative to placebo in a dose-dependent manner; these results replicate our previous findings with marijuana and alcohol. D-amphetamine increased HR relative to placebo only at the low dose; it appeared to fail to increase HR at the high dose because of baroreceptor mechanisms associated with blood pressure increases. Hydromorphone had no effect on HR or V at 60 or 120 min after drug ingestion. We have shown that HR increases and V decreases occur immediately after opiate administration, and are well compensated by 60 or 120 min. These results suggest some commonality in the cardiovascular responses to various abused drugs, and may reflect the common excitatory aspects of these drugs. However, cardiovascular responses during the rising blood drug curves may better illustrate this pattern because they occur before compensatory mechanisms develop.

Publications

Newlin, D.B., Pretorius, M.B., Wong, C.J., Better, W.E., & Pickworth, W.B. Paper presented at the Committee on Problems of Drug Dependence, Palm Beach, Florida, June, 1991.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Antagonist-Withdrawal Up-Regulation of Endogenous Opiate

Principal Investigators: Cooperating Units Uhl, G., Newlin, D.B., & Pretorius, M.B.

Lab/Branch: Etiology Branch

Section: Vulnerability Laboratory

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.5 **Professional:** 0.5 **Other:** 1

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Changes in expression of the principle opioid peptide gene, preproenkephalin, follow stimulation or inhibition of inputs to antagonist drugs. The duration of proenkephalin gene up- or down-regulation can outlast the duration of the stimulus, suggesting that regulated gene expression could provide one substrate for storing information about previous stimulus or drug exposure. This would have direct implications for possible mechanisms of opiate tolerance and withdrawal. We have thus sought evidence for functional up-regulation of enkephalinergic gene regulation systems in humans. The subjects were 19 males with no reported histories of opiate abuse. Pain self-report to a 5 min ice-water immersion and cold-stress-induced analgesia were tested before 8 days of antagonist treatment, 2 days after the last dose of antagonist (when excretion of antagonist metabolites was finished) or placebo, and finally 30 min after an acute oral dose of naloxone. Self-report of pain to the initial stages of the ice-water immersion were significantly reduced in subjects 2 days after opiate antagonist treatment. Initial results of the study provide evidence for increased function in endogenous opioid systems after antagonist washout. Current studies aim to separate pre- and post-synaptic components to this effect.

We studied 30 normal males in a second study that was a replication and extension of the first. The procedure was similar, with the addition of an oral hydromorphone challenge at the end to: 1) quantify the degree of analgesia to a mu-type opiate and 2) rule out post-synaptic changes as an explanation of the earlier results.

Publications

Uhl, G.R., Newlin, D.B., Pretorius, M.B., Park, J., & Cone, E. (1990). Antagonist-withdrawal up-regulation of endogenous opiate antinociceptive systems. Paper presented at Committee on Problems of Drug Dependence, Palm Beach, Florida, 1991.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Vagal Tone and Attention in 8 to 12-year-old Males Exposed to Opiates in Utero: A Preliminary Report.

Principal Investigators: Cooperating Units Hickey, J.E., Suess, P.E., Spurgeon, L., Newlin, D.B., & Porges, S.W.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.5 **Professional:** 0.5 **Other:** 1

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

Summary of Work

We assessed vagal tone changes during an attention demanding CPT task in 12 boys (mean age 9 yrs, 5 mos) exposed prenatally to opiates and 12 (mean age 9 yrs, 10 mos) male controls. Mothers of opiate-exposed and control boys were primarily single and of lower income. Groups did not differ significantly on mother's education, income, or marital status. Racial composition of the groups also did not differ (opiate-exposed: 8 black, 4 white, controls 7 black, 5 white). Vagal tone was measured pre- and post-baseline and during the 3 tasks of the Gordon Diagnostic System. Vagal tone is a heart rate variability measure that quantifies parasympathetic inhibition of the heart. Results indicated that opiate-exposed boys failed to suppress vagal tone compared to control boys when distractors were added to a vigilance task ($p < .05$). In normal children and adults, vagal tone is suppressed during tasks requiring sustained attention. These preliminary results indicate that normal physiological responses to increased attentional demand may be impaired in opiate-exposed boys in this age range. These physiological response patterns were not associated with prenatal alcohol, nicotine, or marijuana exposure in these samples. The design of this study does not distinguish among genetic, teratogenic, or child-rearing practice effects. Further research is needed to replicate and extend these findings as a possible risk factor for subsequent drug abuse in children exposed prenatally to opiates.

Publications

Hickey, J.E., Suess, P.E., Spurgeon, L., Newlin, D.B., & Porges, S.W. Vagal tone and attention in 8 to 12 year old males exposed to opiates in utero: A preliminary report. Paper presented at Committee on Problems of Drug Dependence, Palm Beach, Florida, 1991.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Cognitive Neurophysiologic Signs of Cocaine Abstinence

Principal Investigators: Cooperating Units Herning, R.I.,

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 1.60 **Professional:** .40 **Other:** 1.20

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Cognitive impairments and sleep disruption have been reported in patients withdrawing from cocaine. The nature of these disorders have yet to be documented in clinical laboratory studies. The present study evaluates cognitive information processing in subjects on a clinical ward withdrawing from cocaine with a battery of tasks (auditory rare event monitoring, two continuous performance tasks, four Sternburg memory tests). Sleep quality and duration is monitored by a subjective questionnaire. Fourteen subjects including controls have been tested in this study over a 6 to 8 week withdrawal period. Stimulus evaluation and memory deficits were observed in the cocaine addicts.

Clarification of the nature of the cognitive deficits and of sleep loss will lead to more effective treatment strategies for cocaine withdrawal.

Publications

Herning, R.E., Glover, B.J., Weddington, W.W., Koepl, B.S., and Jaffe, J.H. Cognitive decrements during cocaine abstinence were not related to depression. Biological Psychiatry. Submitted January, 1990, in revision.

Weddington, W.W., Brown, B.S., Haertzen, C.H., Cone, E.J., Dax, E.M., Herning, R.I., and Michaelson, B.S. Changes in mood, craving and sleep during acute abstinence reported by male cocaine addicts: A controlled residential study. Archives of General Psychiatry, 47: 861-868, 1990.

Herning, R.I., Glover, B.J., Koepl, B., Reddish, R., Levin, F., Dax, E. Cognitive deficits during cocaine abstinence persist. Paper presented at Committee on Problems of Drug Dependence, Palm Beach, Florida, June, 1991.

Herning, R.I., Glover, B.J., Koepl, B., Weddington, W., and Jaffe, J.H. Cognitive deficits in abstaining cocaine abusers. In: Residual Effects of Abused Drugs (J. Spenser and J.J. Boren, Eds.) National Institute on Drug Abuse Monograph Series, 101: 167-178, 1990.

Herning, R.I., Glover, B.J., Koepl, B., Reddish, R., and London, E. Effects of Cocaine and Cocaine Withdrawal on the CNS: EEG, Evoked Potential and Performance. Fifth World Congress of Biological Psychiatry, Florence, Italy, June 9-14, 1991.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Mapping the Effects of Cocaine by EEG

Principal Investigators: Cooperating Units Heming, R.I., London, E., & Stapleton, J.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: .40 **Professional:** .20 **Other:** .20

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

The effects of cocaine on scalp EEG and FDG PET scans are being compared to determine the brain areas involved in the cocaine-induced euphoria. In previous studies, cocaine increased EEG beta power. The distribution of cortical areas responsible for the EEG beta increase and the time course of the beta increase have not as yet been determined. The present study was designed to answer these two questions.

The complimentary nature of the EEG and PET data will delineate the anatomical and electrophysiologic mechanisms involved in cocaine induced euphoria.

Twenty subjects were tested using EEG measures with placebo, 20mg and 40mg of cocaine in double blind order in previous years and seven additional subjects were tested during the current year. EEG beta increased in dose dependent manner starting immediately after the injection and continuing for twenty minutes. The increase in EEG beta was maximal in frontal cortical areas. The relationship between the increase in beta and subjective state is currently being investigated.

Publications

London, E.D., Cascella, N.G., Wong, D.F., Phillips, R.L., Dannels, R.F., Links, J.M., Heming, R.I., Grayson, R., Jaffe, J.H., and Wagner, H.N. Cocaine-induced reduction of glucose utilization in human brain: A study using Positron Emission Tomography and FDG. Archives of General Psychiatry, 47, 567-576, 1990.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Acute Abstinence from Tobacco: Electrophysiological and Cognitive Signs

Principal Investigators: Cooperating Units Herning, R.I., Henningfield, J., & Pickworth, W.B.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: .025 **Professional:** .025 **Other:** 0.0

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

The laboratory's efforts were directed toward the quantification of the cognitive and performance deficits during nicotine withdrawal and the treatment of these deficits with nicotine chewing gum. The EEG, cognitive, and cognitive process was monitored during a ten-day period of tobacco withdrawal in heavy smokers. Some of the changes persisted over the entire ten-day deprivation period. These measures included EEG alpha frequency, theta power, performance on selected cognitive tasks (especially a rapid arithmetic task) and a cognitive event related potential measure (N100 amplitude). Stimulus evaluation time, as measured by P300 latency, and the depth of stimulus evaluation battery were affected early during the tobacco deprivation period, but returned to smoking levels later during the deprivation period. Thus, the cognitive deficits are clearly apparent during abstinence from tobacco and contribute to relapse during treatment. The deficits during withdrawal have at least two different components - one affecting stimulus evaluation which dissipates after 5 to 7 days of abstinence and one affecting attention accompanied by lower arousal which persists ten days or longer. During the year this data was analyzed and two papers were submitted for publication.

Publications

Herning, R.I., Glover, B.J., and Henningfield, J.E. Attention deficits during nicotine abstinence. Psychopharmacology, Submitted January, 1989.

Herning, R.I., Brigham, J., Stitzer, M.L., Glover, B.J., Pickworth, W.B., and Henningfield, J.E. The effects of nicotine on information processing: Mediating a deficit. Society for Psychophysiological Research, Boston, Massachusetts, October, 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 02001-05 VL

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Mapping the Effects of Opioid Agonists by EEG

Principal Investigators: Cooperating Units Heming, R.I., London, E.D., Stapleton, J., & Philips, R.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: .025 **Professional:** .025 **Other:** 0

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Effects of morphine on the scalp EEG and FDG PET scans are being compared to determine the brain areas invoked in euphoria. Etiology collected in past years and is now analyzing the EEG data from 20 scalp locations from post addicts receiving placebo, 15 and 30 mg injections of morphine. These subjects subsequently received FDG PET scans while receiving placebo and 30 mg of morphine. The PET scans are performed by our collaborators. The EEG data by itself provides insight into time course of electrophysiologic effects of a mu agonist in humans and the cortical distribution of mu effects. PET techniques do not by themselves provide information about the time course of the mu effects. In the preliminary analysis, twelve subjects had increased EEG delta and the theta power beginning 15 minutes and persisting until 45 minutes after the intramuscular injection. Changes in artifact detection were being investigated so that the relationship between these EEG changes and subjective effects of morphine can be investigated.

Publications

London, E.D., Broussolle, E.P.M., Links, J.M., Wong, D.F., Cascella, N.G., Dannels, R.F., Sono, M., Herning, R., Snyder, F.R., Rippetoe, L.R., Toung, T.J.K., Jaffe, J.H., Wagner, H.N. Morphine-induced metabolic changes in the brain: Studies with Positron Emission Tomography and FDG. Archives of General Psychiatry, 47, 73-81, 1990.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 03101-05 VL

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Effects of Atropine on Cognitive Information Processing

Principal Investigators: Cooperating Units Herning, R.I.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: .025 **Professional:** .025 **Other:** 0

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

Summary of Work

An extensive battery of sensory and cognitive electrophysiological tasks is used to assess sensory, cognitive and performance deficits produced by atropine. The tasks include eyes open and eyes closed EEG, brainstem auditory evoked response, pattern reversal visual evoked response, the auditory rare event monitoring task, auditory continuous performance task and Sternberg auditory memory task (both immediate and delayed). Each of four doses of atropine (0, 2, 4 and 6 mg/70 kg) is investigated on two occasions. Eight subjects have been tested on these procedures.

The purpose of the study is to better understand the effects of cholinergic agents on cognition and performance; in particular, where in the information processing sequence atropine exerts its effects. The EEG and evoked response data have been reported in military and scientific journals. Atrophine at doses 4 mg or greater increase EEG slowing and reduces cognitive evoked potentials and performance. The EEG results were published and evoked potential analysis began over the last year.

Publications

Pickworth, W.B., Herning, R.I., Koepl, B. and Henningfield, J.E. Atropine-induced changes in spontaneous electroencephalogram in human volunteers. Military Medicine, 155: 166-170, 1990.

Period Covered: January 1, 1990 to December 31, 1990

Title of Project: Neurocognitive Status of Young Boys Exposed to Opiates in Utero

Principal Investigators: Cooperating Units Heming, R.I., Spencer, J., and Guo, X.

Lab/Branch: Etiology Branch

Section:

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: .70 **Professional:** .70 **Other** 0-

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

The study seeks to determine whether boys 8 to 12 who were exposed to opiates in utero, have any neurocognitive deficits as compared to similar aged control boys. Two control groups were employed in this study. Both groups were not exposed to opiates in utero. The boys in one group lived with an opiate using mother and the boys in the other group did not. The boys exposed in utero to opiates have increased intentional tremor and appear to have alterations in event related potentials. The study is ongoing and about 30 boys have been tested.

Treatment Branch

David Gorelick, M.D., Ph.D., Chief

Overview

The Treatment Branch conducts research on the efficacy and safety of existing and developing pharmacologic and psychosocial treatments for drug abuse, including the influence of treatment on the biomedical consequences of drug abuse. Current research focuses on cocaine and opiate abuse. Research is carried out on both the ARC residential unit and the outpatient clinic. The Branch also collaborates, as appropriate, with other clinical facilities in the Baltimore area. The Treatment Branch is organized into the Pharmacotherapy Laboratory (David A. Gorelick, M.D., Ph.D., Chief), Clinical Trials Laboratory (Paul Fudala, Acting Chief), and Drug Abuse Treatment Evaluation Unit (John Ball, Ph.D., Chief).

The Branch studies new treatments with a view toward developing effective strategies for use by the clinical treatment community. Potential therapeutic medications are chosen for study on several grounds: 1) their existing clinical use, even in the absence of controlled scientific data, 2) theoretical deduction from the known neuropharmacology of drugs of abuse, or 3) leads from other ARC or NIDA researchers. Detailed diagnostic and biopsychosocial characterization of subjects is done to identify predictors of treatment compliance and response, develop optimum matching of patients to treatment, and determine the extent to which biomedical and psychosocial consequences of drug abuse are affected by treatment. These objectives are pursued using a variety of research techniques, including (1) single-blind and double-blind, placebo-controlled designs with pharmacologic interventions; (2) experimental designs employing random assignment to control or comparison groups; (3) obtaining and quantifying observational data to clarify behaviors significant to the conduct of drug abuse treatment. Whenever possible, long-term follow-up is obtained on subjects after active treatment has ended, in order to assess the persistence of treatment effects.

Multidisciplinary studies are frequently conducted in collaboration with other laboratories of the ARC, including the Chemistry and Drug Metabolism and Neuroendocrinology Laboratories (Clinical Pharmacology Branch), Vulnerability Laboratory (Etiology Branch), and Molecular Neurobiology Laboratory (Neuroscience Branch). In addition, several clinical drug abuse programs of the Maryland Substance Abuse Administration, University of Maryland School of Medicine, and Department of Veterans Affairs have indicated a willingness to collaborate with the Branch.

Long-term goals of the Branch will continue to be the exploration of scientific issues significant to the treatment process and the examination of interventions that have promise for improved treatment. Specific areas of interest include the role of neurotransmitter receptor ligands and anti-convulsants as potential therapeutic medications for drug abuse, the impact of HIV infection on drug abuse treatment, and concurrent psychiatric diagnoses in drug abusers. Many of these efforts are in cooperation with NIDA's Medication Development Division and AIDS program.

1. Pharmacotherapy Laboratory - David Gorelick, M.D., Ph.D., Chief

Overview

The goal of the Pharmacotherapy Laboratory is the development of new pharmacologic treatments for drug abuse. Potential treatment medications are evaluated in a controlled residential environment using a variety of interdisciplinary experimental paradigms (e.g., drug self-administration) that allow study of clinically relevant mechanisms of action (both pharmacological and psychological), potential to produce

toxicity and/or adverse interactions with drugs of abuse, and the pharmacokinetics of the medication. Various behavioral, psychological, physiologic, and pharmacokinetic parameters are measured, including those performed in collaboration with other ARC laboratories, such as electrophysiological assessments and PET scanning.

Summary of Current Research

A. Effects of carbamazepine on cocaine self-administration

The anti-convulsant medication carbamazepine has attracted much attention as a potential treatment for cocaine addiction, but there is little systematic data from controlled human studies on either its efficacy or the safety of its interactions with cocaine. This double-blind, double-dummy, placebo-controlled residential study evaluates the effect of targeted carbamazepine plasma levels on cocaine self-administration, self-reported cocaine craving, and conditioned responses to cocaine-associated stimuli in 18 cocaine addicts. This study also evaluates the influence of carbamazepine on the subjective and cardiovascular effects of cocaine, and the pharmacokinetics of carbamazepine in cocaine addicts.

B. Comparison of detoxification treatments for opiate addiction

The purpose of this ongoing inpatient study is to compare the efficacy of buprenorphine to the alpha-2-adrenergic agonist clonidine for the rapid detoxification of heroin addicts. A major focus of this study will be to determine whether a successful opiate detoxification can be accomplished by administering buprenorphine for no longer than 72 hours, since federal regulations allow for the use of an opiate for up to 72 hours for opiate-dependence treatment without special licensing requirements of the practitioner.

C. HIV infection, high-risk behaviors, and drug abuse

HIV infection is associated with intravenous drug use and high-risk behavior such as needle sharing, but relatively little is known about these variables in non-intravenous drug abusers or how these variables are influenced by drug abuse treatment. This study will evaluate the influence of drug of abuse and route of administration on HIV antibody status and high-risk behaviors, as well as the latter's influence on treatment compliance and outcome. These issues will be addressed both retrospectively, by analyzing data already collected on ARC subjects, and prospectively, by administering questionnaires or structured interviews to patients entering drug abuse treatment research protocols.

D. Esterase activity in human cocaine abusers

Plasma and RBC esterases are the chief metabolizing enzymes for cocaine in humans. Studies with other substrates indicate that these enzymes are under genetic control and show population variability, but there are no human studies of their effects on cocaine metabolism or cocaine abuse. This study, in collaboration with Dr. Raymond Woosley, Georgetown University, will measure plasma and RBC esterase activity in cocaine abusers and determine the influence of this metabolic parameter on response to cocaine and treatment outcome.

E. Dopamine D2 receptor allelic linkage in substance abuse

Recent research reports have suggested a possible association between a particular dopamine D2 receptor allele and alcoholism. The Treatment Branch is collaborating with the Molecular Neurobiology Laboratory in recruiting and diagnosing subjects for a study of the association between dopamine D2 receptor allele and heavy peak lifetime use of a variety of drugs, including alcohol, cocaine, opiates, and nicotine. Possible confounding factors, such as racial background of subjects and possible drug use in control subjects, are also being addressed.

PUBLICATIONS

Ball, John C. "Opening the "Black Box" of Drug Abuse Treatment - Measurement and Evaluation of the Treatment Domain," Committee on Problems of Drug Dependence, Inc. (Abstracts), Fifty-Second Annual Scientific Meeting, June 10- 14, 1990.

Ball, John C. "The Status of Methadone Maintenance Treatment in the United States," Australian Methadone Conference. Keynote Speaker (Sydney, Australia). July 9-10, 1990.

Ball, John C. "Evaluating Methadone Maintenance Programs," Keynote Speaker Midwest Regional Methadone Conference, Milwaukee, Wisconsin, September 17-18, 1990.

Ball, J.C. "A Comprehensive Evaluation of Methadone Maintenance Programs in New York City, Philadelphia and Baltimore," *Advances in Alcohol & Substance Abuse* (Guest Issue), (In press).

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Title of Project: Effects of Carbamazepine on Cocaine Self-Administration

Principal Investigators: David A. Gorelick, M.D., Ph.D., Linda Weinhold, Ph.D., Frances Rudnick Levin, M.D., Jack Henningfield, Ph.D., Ed Cone, Ph.D., David Newlin, Ph.D., Ronald Herning, Ph.D., W.R.Lange, M.D.

Cooperating Units: Chemistry and Drug Metabolism Lab, Vulnerability Lab, Office of Medical Affairs.

Lab/Branch: Pharmacotherapy Lab/Treatment Branch

Section: NONE

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 4.0 Professional: 1.0 Other: 3.0

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

This double-blind, double dummy, placebo-controlled (diphenhydramine-25 mg BID) residential study assesses the psychological, physiological, cardiovascular, cognitive, electroencephalographic, and pharmacokinetic effects of the carbamazepine-cocaine interaction in cocaine-abusing subjects not currently dependent on other drugs.

Eighteen subjects are randomly assigned to 4 parallel groups: (1) low plasma carbamazepine levels (1-3 mg/L), (2) placebo short-stay (6 weeks); (3) middle plasma carbamazepine levels (4-7 mg/L); and (4) placebo long-stay (9 weeks). Subjects can self-administer cocaine-25 mg IV (or blank) or receive a monetary reward up to thrice daily 3 days each week by making a stimulus-controlled operant response. On self-administration days, subjects undergo 24-hour ambulatory monitoring of cardiovascular function, and answer computer administered questions on their subjective state. Subjects' response to cocaine-associated stimuli and their EEG and cognitive function are assessed periodically. Thus, the influence of carbamazepine on cocaine reinforcement and cocaine-induced psychological and physiological effects can be assessed. Blood, saliva, and hair samples are collected periodically to assess cocaine and carbamazepine pharmacokinetics.

This is the largest, most detailed study to date investigating the clinical pharmacology of the carbamazepine-cocaine interaction.

Title of Project: Comparison of Detoxification Treatment for Opiate Addiction

Principal Investigators: Lawrence J. Cheskin, M.D., Paul Fudala, Ph.D.

Cooperating Units: Neuropharmacology Lab, Vulnerability Lab

Lab/Branch: Pharmacotherapy Lab/Treatment Branch

Section: NONE

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD
21224

Total Man Years: 1.2

Professional: .2

Other: 1.0

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

This study is a double-blind, double-dummy comparison of buprenorphine (1-4 mg sl daily), a partial opiate agonist, vs. clonidine (0.2 - 0.9 mg po daily), an alpha-2 adrenergic agonist, in the treatment of acute opiate withdrawal. Sixteen patients are randomly assigned to receive one of the 2 medications for 3 days, followed by 14 days of inactive placebo. Patients are also stratified by degree of opiate dependence, as measured by a cutoff opiate withdrawal score following naloxone challenge (0.4 mg im).

Outcome measures include both physiological and psychological signs and symptoms of opiate withdrawal. In addition, optional subprotocols involve measuring vagal and sympathetic tone as reflected in variations in cardiac interbeat interval (in collaboration with the ARC Vulnerability Lab), and cerebral metabolism using positron emission tomography (PET) with 2-F-DG (in collaboration with ARC Neuropharmacology Lab and Hopkins PET Center).

To date, 12 patients have completed the study, which is the first direct, controlled clinical comparison of buprenorphine with a standard treatment for acute opiate withdrawal.

NOTICE OF INTRAMURAL RESEARCH

Z01 DA 00101-01 PTL

Title of Project: HIV Infection, High-Risk Behaviors, and Drug Abuse Treatment

Principal Investigators: David A. Gorelick, M.D., Ph.D., Ivan D. Montoya, M.D., MPH., W.R. Lange, M.D., Judy Hess, M.A., Weddington, M.D.

Cooperating Units: Office of Clinical Director

Lab/Branch: Pharmacotherapy Lab/Treatment Branch

Section:NONE

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD
21224

Total Man Years: 0.50 Professional: 0.25 Other: 0.25

Check Appropriate Boxes:

Human Subjects ___ Human Tissues ___ Neither
___ Minors
 Interviews

Summary of Work

This two-phase project evaluates the relationship between sociodemographic, psychosocial, cognitive, and drug use variables and HIV infection in drug abusers, and the influence of HIV infection on drug abuse treatment compliance and outcome. The first phase involves retrospective analysis of data already collected on ARC subjects, using two analytic approaches: 1) case-control comparisons of subjects HIV antibody positive or negative who are matched on appropriate variables and 2) multivariate analyses using the entire sample of subjects to determine variables associated with HIV infection and treatment compliance and outcome. The second phase prospectively collects data on HIV infection high-risk behaviors and attitudes using self-report questionnaires and structured interviews. Data is collected from ARC treatment research subjects at treatment entry and again at follow-up in order to evaluate possible changes due to drug abuse treatment or drug abstinence.

Initial analysis of retrospective case-control data from 22 HIV-antibody positive, physically asymptomatic cocaine addicts and 22 matched HIV seronegative cocaine addicts indicated that seropositive subjects were significantly more likely to be HIV cocaine users. Otherwise, there were no significant differences between the two groups in sociodemographic, psychosocial, cognitive, or treatment compliance variables.

Publications:

Weddington, WW, Haertzen CA, Hess JM, Brown BS: Psychological reactions and retention in treatment according to HIV-serostatus: a matched-control study. *Am J Drug Alcohol Abuse*, 1991; 17:355-368.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00107-01 PTL

Title of Project: Esterase activity in human cocaine abusers

Principal Investigators: David Gorelick, M.D., Ph.D., Linda Weinhold, Ph.D., Raymond Woosley, M.D.

Cooperating Units: Department of Pharmacology, Georgetown University

Lab/Branch: Pharmacotherapy Lab/Treatment Branch

Section: NONE

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 0.35

Professional: 0.1

Other: 0.25

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

Summary of Work

Esterase enzymes in blood are the major metabolic pathway for cocaine in humans. There is population variability in enzyme activity, some of which is genetically based, yet no published studies to date have evaluated enzyme activity in cocaine abusers or the correlation between enzyme activity and response to cocaine. This study, done in collaboration with Dr. Raymond Woosley, Department of Pharmacology, Georgetown University, measures plasma and RBC esterase activity in cocaine abusing research subjects at the ARC to determine the influence of this metabolic parameter on response to cocaine and on treatment outcome.

2. Clinical Trials Laboratory - Paul Fudala, Ph.D., Chief

Overview

The goal of the Clinical Trials Laboratory is to test the safety and efficacy of new treatments for drug abuse, including both pharmacologic and non-pharmacologic (psychosocial) treatments and their interactions. Studies are conducted in a realistic community (outpatient) setting to gain clues to the effectiveness, safety, and mechanism of action of new treatments that might lead to more intensive study, and to assess various environmental factors and patient characteristics (e.g., availability of illicit drugs, personality traits) affect compliance, treatment outcome, duration in treatment, and other clinically relevant variables. Long-term follow-up is conducted to assess the duration of beneficial, as well as potentially adverse, effects of treatment.

Summary of Research

A. Efficacy of fluoxetine and desipramine in the treatment of cocaine and PCP dependence.

The first phase of this outpatient study assessed the efficacy of fluoxetine, a serotonergic reuptake blocker, for the treatment of cocaine dependence. Fifty-three subjects were admitted to the study; analyzable data was obtained for 46 of these. All subjects received counseling twice weekly. No significant differences were found between treatment groups (fluoxetine 20, 40, 60 mg, or active placebo) for any dependent variable (e.g., cocaine-positive urine, subject-reported craving for cocaine), regardless of whether subjects were grouped by fluoxetine dosage or plasma levels. The second phase of this study involved comparisons between fluoxetine and placebo in PCP abusers and desipramine and placebo in cocaine abusers. Forty-seven subjects were enrolled into the desipramine protocol. Subjects received either desipramine, 300 mg per day or inactive placebo for 12 weeks. All subjects received counseling twice weekly. Forty-four subjects were enrolled into the fluoxetine protocol. Subjects received either fluoxetine, 20 mg per day or active placebo (diphenhydramine 12.5 per day) for 12 weeks. All subjects received counseling once weekly. Data analysis is currently ongoing.

B. Buprenorphine/methadone comparison - maintenance and detoxification

The purpose of this study was to determine the effectiveness of buprenorphine in maintaining opiate-dependent individuals in non-residential treatment as compared to the prototypic treatment drug methadone. Additional information regarding the medical safety of the two treatments, as well as pharmacokinetic data, were obtained from analyses of blood and urine. Preliminary analyses of the data have indicated that: 1) no differences were observed between treatment groups for self-reported opiate withdrawal symptoms, 2) no pattern of results was observed between groups with respect to subject-reported adverse effects which could be related to the study medications, 3) the percentage of missed clinic visits did not differ significantly between treatment groups, 4) subject retention rates at the completion of the maintenance phase (study day 119) were approximately double for the buprenorphine and the higher-dose methadone treatment groups compared to the lower-dose methadone group, 5) buprenorphine treatment was associated with more urine samples negative for opiates compared to either methadone group, and 6) no significant or consistent differences were observed between groups for cocaine-positive urine samples. It is anticipated that this will be considered a pivotal study by the FDA, potentially leading to the approval of buprenorphine as a pharmacotherapy for opiate dependence.

C. Assessment of nalmefene glucuronide as a selective antagonist of gut opioid action

A single-blind ascending dose study was conducted to determine whether nalmefene glucuronide

precipitates withdrawal symptomatology in opiate-(methadone-) dependent individuals. If the glucuronide were shown to exert a selective effect on the enteric nervous system without antagonizing central opiate actions, it could have utility for patients who require high doses of opiates but who suffer from gastrointestinal side effects (e.g., constipation). However, withdrawal symptoms were induced at relatively low doses (e.g., 1 mg po daily). Thus, nalmefene glucuronide does not appear to be useful for constipation associated with the administration of exogenous opiates.

D. Impact of differing intensities of drug abuse counseling

While much research attention has focused on pharmacologic treatment for drug abuse, few studies have addressed the efficacy of psychosocial treatments such as counseling. This 12-week outpatient study is evaluating the effectiveness of individual counseling as a treatment for cocaine dependence. Patients are randomly assigned to one of three counseling frequencies: twice weekly, once weekly, or every other week. All counseling is delivered according to a specified therapy manual in which all counselors have been trained, thus assuring that all patients receive the same type of treatment. Treatment outcome measures include urine toxicology, subject-reported drug use, cocaine craving, depressive symptoms, and psychosocial functioning.

E. A double-blind comparison of carbamazepine and placebo for the treatment of cocaine abuse

The anti-convulsant medication carbamazepine has been suggested as a treatment for cocaine abuse, but there are as yet no published double-blind, placebo-controlled treatment studies establishing its efficacy. This eight-week outpatient study uses such a design to evaluate the efficacy and safety of carbamazepine (up to 800 mg daily) plus individual counseling in the treatment of cocaine dependence. Treatment outcome measures include urine toxicology, subject-reported drug use, cocaine craving, depressive symptoms, and psychosocial functioning.

F. Reasons for seeking drug abuse treatment

This study is collecting data on the self-reported reasons why drug abusers seek treatment. Data will be analyzed in terms of differences among drug abusing populations and for possible predictive factors for treatment compliance and outcome.

3. Drug Abuse Treatment Evaluation Unit - John Ball, Ph.D., Chief

The Treatment Evaluation Unit applies a comprehensive schema for evaluating existing drug abuse treatment, assessing 89 variables in four areas: patient history and characteristics, program characteristics, treatment services provided, and treatment outcome. The goal is to determine the efficacy of existing treatment programs and identify variables associated with successful outcome.

Dr. Ball has applied his methodology to the evaluation of methadone maintenance treatment for opiate dependence, with data analysis largely completed. The next study planned will evaluate existing drug abuse treatment programs in the Baltimore area, including those that treat cocaine users.

Title of Project: Buprenorphine/Methadone Comparison - Maintenance and Detoxification

Principal Investigators: R.E. Johnson, Pharm.D., P.J. Fudala, Ph.D., W.R. Lange, M.D.

Cooperating Units:NONE

Lab/Branch: Clinical Trials Lab/Treatment Branch

Section: NONE

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 12.3

Professional: 3.3

Other: 9.0

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

Previous residential studies conducted at the ARC showed that heroin dependent individuals may be rapidly inducted onto buprenorphine without producing clinically significant opiate-withdrawal symptoms, may be maintained on daily or alternate-day buprenorphine dosing schedules, and experience a mild to moderate withdrawal syndrome after abrupt withdrawal of buprenorphine. Results from dose-ranging studies indicated an appropriate dose for use in non-residential maintenance treatment.

The purpose of this study was to determine the effectiveness of buprenorphine (8 mg sl daily) in maintaining opiate-dependent individuals over 6 months of non-residential treatment as compared to the prototypic treatment drug methadone (20 mg or 60 mg daily). 162 opiate-dependent subjects were randomly assigned after stratification by age, sex, and the results of a naloxone challenge.

This study, the largest clinical trial to date assessing the effectiveness of buprenorphine for the treatment of opiate dependence, found buprenorphine as effective as methadone-60 mg on almost all outcome measures, and both significantly more effective than methadone-20 mg. There was no significant difference among groups in urine samples positive for cocaine.

Title of Project: Double-Blind Comparison of Desipramine, Fluoxetine and Bromocriptine for the Treatment of Cocaine and PCP Abuse

Principal Investigators: L. Covi, M.D., C. Baker, M.A., J.M. Hess, M.A.

Cooperating Units: Office Of Medical Affairs

Lab/Branch: Clinical Trials Lab/Treatment Branch

Section: NONE

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD
21224

Total Man Years: 2.0

Professional: 0.5

Other: 1.5

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

Summary of Work

This series of 3 double-blind, placebo-controlled (active placebo = diphenhydramine - 12.5 mg) studies examined the efficacy of medication plus individual counseling (Rounsaville's adaptation of interpersonal psychotherapy) for 12 weeks as outpatient treatment of drug abuse. Outcome was assessed by drug use (both urine toxicology and self-report), drug craving, mood, and psychosocial functioning (Addiction Severity Index). All subjects were followed up 3, 6, 12 months after active treatment.

In the first study, 53 cocaine abusers (ages 21-60) were randomly assigned to receive either fluoxetine-20 mg (n=11), 40 mg (14), 60 mg (12), or placebo (16) daily. All patients also received counseling twice weekly. There were no significant outcome differences among groups, whether analyzed in terms of medication dose or achieved plasma level (> vs < 100 ng/ml). At follow-up, all groups showed some improvement, with no group differences.

In the second study, 45 PCP abusers were randomly assigned to receive either fluoxetine-20 mg daily or placebo, plus counseling twice weekly. In the third study, 46 cocaine abusers were randomly assigned to receive either desipramine-300 mg daily or placebo, plus counseling once weekly. Data from both studies are being analyzed.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00091-01 CTL

Title of Project: Assessment of Nalmefene Glucuronide as a Selective Antagonist of Gut Opioid Action

Principal Investigators: Lawrence J. Cheskin, M.D., R.E. Johnson, Pharm.D.

Cooperating Units: NONE

Lab/Branch: Treatment

Section: NONE

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD
21224

Total Man Years: 0.5

Professional: 0.2

Other: 0.3

Check Appropriate Boxes:

Human Subjects
 Minors
 Interviews

Human Tissues

Neither

Summary of Work

A single-blind ascending dose study was conducted in 5 subjects to determine whether nalmefene glucuronide precipitates withdrawal symptomatology in opiate-(methadone) dependent individuals. If the glucuronide were shown to exert a selective effect on the enteric nervous system without antagonizing central opiate actions, it could be useful in patients requiring high doses of opiates, but who suffer from gastrointestinal side effects (e.g., constipation). However, withdrawal symptoms were induced at relatively low doses (e.g., 1 mg po daily). Thus nalmefene glucuronide does not appear to be useful for constipation associated with the administration of exogenous opiates in opiate-dependent subjects. It may be useful, however, in patients with constipation who are not opiate-dependent, such as persons suffering from constipation - predominant irritable bowel syndrome.

PUBLICATIONS:

Fudala P.J.,Ph.D., Heishman S.J., Ph.D., Henningfield J.E.,Ph.D., and Johnson R.E., PharmD. Human Pharmacology and Abuse Potential of Nalmefene. Clin. Pharm. and Ther. Vol. 49, No. 3, pp. 300-306, March, 1991.

Title of Project: Reasons for seeking drug abuse treatment

Principal Investigators: Lino Covi, M.D., Judy Hess, M.A., C. Haerten, Ph.D.

Cooperating Units: Clinical Pharmacology Branch

Lab/Branch: Clinical Trials/Treatment Branch

Section: NONE

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD
21224

Total Man Years: 0.3 Professional: 0.1 Other 0.2

Check Appropriate Boxes:

Human Subjects Human Tissues Neither
 Minors
 Interviews

Summary of Work

In order to identify factors possibly influencing treatment compliance and retention, 206 applicants for outpatient pharmacological treatment of cocaine or PCP dependence gave self-reported reasons for seeking treatment, using a new questionnaire developed by the P.I. There were significant differences in reasons given between cocaine vs PCP abusers and males vs females. Subjects not motivated by the cost of their drug abuse stayed in treatment twice as long (6 weeks) as those who were motivated by cost. Currently, data are being collected to compare counselors' ratings of treatment motivations with the self-report instrument.

Publication

L. Covi, J.M Hess, CA Haertsen: Why Cocaine and PCP Abusers Seek Treatment. Poster presented at the Science Day - Francis Scott Key Medical Center, May, 1990.

Title of Project: Impact of Differing Intensities of Drug Abuse Counseling

Principal Investigators: L. Covi, M.D., C.Baker, M.A., J. M.Hess, M.A.

Cooperating Units: Office of Medical Affairs

Lab/Branch: Clinical Trials Lab/Treatment Branch

Section: NONE

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2.0

Professional: 0.5

Other: 1.5

Check Appropriate Boxes:

Human Subjects

Human Tissues

Neither

Minors

Interviews

Summary of Work

This study evaluates the influence of frequency of individual counseling on the effectiveness of cocaine abuse treatment. Subjects meeting DSM-III-R criteria for cocaine dependence will be randomly assigned (50 per group) to one of three treatment conditions plus urine monitoring for 12 weeks: a) twice weekly counseling, b) once weekly counseling, or c) counseling every other week.

All counseling is delivered according to a specified therapy manual integrating aspects of interpersonal, cognitive, and behavioral approaches to drug abuse counseling. In the pilot phase, 27 subjects were treated to refine the manual and train counselors in the therapy.

Treatment outcome will be assessed by urine toxicology twice weekly (collected under direct staff observation) , breath alcohol analysis, self-reported drug use and cocaine craving, psychological symptoms, and psychosocial functioning (Addiction Severity Index). Follow-up at 3, 6, and 12 months will assess any long-term effects of treatment.

To date, 25 subjects have entered the study, of whom 6 received initial evaluation only, with no actual treatment.

Publication:

L. Covi, M.D., C.D. Baker, M.A., and J.M. Hess, M.A.: "An Integrated Interpersonal/Cognitive Behavioral Counseling Approach to Cocaine Abuse Treatment". Poster presented at the International Conference on Cognitive Therapy, Philadelphia 10/5/90.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00106-01 CTL

Title of Project: Evaluation of methadone maintenance treatment for opiate dependence

Principal Investigators: John Ball, Ph.D.

Lab/Branch: Treatment Branch

Section: NONE

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

Total Man Years: 2.0

Professional: 1.0

Other: 1.0

Check Appropriate Boxes:

Human Subjects
 Minors
 Interviews

Human Tissues

Neither

Summary of Work

This project applies a comprehensive schema for evaluating existing drug abuse treatment, assessing 89 variables in four areas: patient history and characteristics, program characteristics, treatment services provided, and treatment outcome. The goal is to determine the efficacy of existing treatment programs and identify variables associated with successful outcome.

Dr. Ball has applied this methodology to the evaluation of 6 methadone maintenance treatment programs for opiate dependence, with data analysis largely completed.

The findings from this large-scale, prospective, systemic treatment outcome study indicate that methadone maintenance is effective in reducing drug use, criminal activity and some HIV infection high-risk activities, but that treatment effectiveness can vary widely among programs, depending on several variables such as methadone dose, staff qualifications, and staff turnover.

Publications:

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