Administrative Document

Annual Report of the Addiction Research Center

National Institute on Drug Abuse

Fiscal Year 1986

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration
National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

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Summary Statements and
Individual Project Reports

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Jerome H. Jaffe, M.D., Director

I am pleased to present this Annual Report on the Addiction Research Center (ARC) which represents the progress during the first fiscal year of full operations in the new Baltimore location. It also marks the end of a long transition period that began in 1976. Ten years ago, the decision was made to discontinue the use of federal prisoners in research at the ARC in Lexington, Kentucky. To insure that an adequate number of research volunteers would be available for study, it was necessary to move the ARC to a large metropolitan center. A building on the grounds of Baltimore City Hospital, now the Francis Scott Key Medical Center, was chosen as the new site. The move of the clinical research program to this campus was completed in 1979, and that of the basic research laboratories in 1984.

This period of transition also saw several changes in the leadership of the ARC. For almost 15 years, Dr. William R. Martin had been the Director of the Center. During that time the ARC enjoyed a period of high research productivity, with Dr. Martin and his associates making substantial contributions to our knowledge of drug abuse and fundamental contributions to science.

Dr. Donald R. Jasinski, whose tenure as Director of the ARC began in the midst of this transition, was successful in reestablishing the clinical research program in temporary quarters on the campus in Baltimore, while continuing his important work on the clinical assessment of new pharmacologic agents for the treatment of narcotic dependence.

Later in this transition period, the Center was most fortunate to have the services of one of NIDA's senior managers as Acting Director. Dr. John Scanlon, who served in this role, completed this transition by putting the final touches on the renovation of our facilities, establishing contracts for supporting services, and setting up the administrative and management practices and policies that now govern the Center. Now the Deputy Director, he continues to be indispensible in managing the administration of the program.

About a year after I assumed the directorship of the ARC in May of 1984, I was asked by Dr. Donald Ian Macdonald, the Administrator of ADAMHA, to serve in the additional capacity of Acting Director of NIDA during the search for a successor to Dr. William Pollin, who had been a staunch supporter of the ARC for

many years. Only a few months before the beginning of the period covered by this report, the appointment of Dr. Charles R. Schuster as the NIDA Director allowed me to focus my full time and attention on the Center. Dr. Schuster's continued personal encouragement, his endorsement of the several new objectives set for the ARC, and his public defense of the budget necessary to carry on our research program has made this task easier than it would otherwise have been.

This fiscal year is also the first full year in which the ARC has operated under its current organizational structure. Although some branches and laboratories have been fortunate in having continuity of leadership, others have only recently been established. The full personnel complement of several laboratories, including the laboratory chiefs, has not yet been identified or recruited. These factors are reflected in the very different levels of activity demonstrated by our various organizational components.

This year's annual report also reflects some of the changes in research priorities which have resulted from our continuing critical review and re-appraisal of our research objectives and directions and of our concept of the role of the ARC. In the clinical biology area, new emphasis is being given to the study of individual differences in psychological and physiological responsivity to drugs, including drug-induced subjective changes and vulnerability to dependence and relapse. Additional emphasis on studies of individual differences is also being given in the Cognitive Studies and Human Performance Laboratory in order to more systematically define the correlates and ultimately the determinants of drug abuse and dependence. Our already substantial program in the neurosciences has also been expanded, particularly in molecular pharmacology, and now represents one of the ARC's strongest and most comprehensive areas of concentration. In another new area of emphasis, which is consistent with our effort to be maximally responsive to public health concerns related to drug abuse, an AIDS Laboratory has been established and studies have begun to examine the seroprevalence of HTLV-III virus in drug-abusing populations and the effects of selected drugs on the immune system.

I would like to extend my thanks to the members of the Board of Scientific Counselors who served during the past year. They are: the Chairman, Louis S. Harris, Ph.D. (Medical College of Virginia), Walter M. Booker, Ph.D. (Walter M. Booker Associates), Marian Fischman, Ph.D. (Johns Hopkins University Medical School), Reese Jones, M.D. (University of California at San Francisco), Dorothy Lewis, M.D. (New York University Medical School), Nancy Mello, Ph.D. (McLean Hospital), and Akira E. Takemori, Ph.D. (University of Minnesota Medical School). They have all permitted me to draw freely from their expertise.

I am also grateful to the guest speakers who participated in our seminar series. They include: Karl Olav Fagerstrom, Ph.D. (Helsingborg Hospital, Sweden), Juan Ramos-Sanchez, Ph.D., M.D. (University of Miami), George Bigelow, Ph.D. (Johns Hopkins University School of Medicine), Larry D. Chait, Ph.D. (Pritzker School of Medicine, University of Chicago), K.H. Ginzel, M.D. (University of Arkansas), Lloyd Fricker, Ph.D. (Albert Einstein College of Medicine), Karen Marquis, Ph.D. (University of Maryland School of Pharmacy), W. Scott Young III, M.D., Ph.D. (National Institute of Mental Health), Tony Yaksh, Ph.D. (Mayo Clinic, Rochester, MN), and Robert L. Balster, Ph.D. (Medical College of Virginia).

Members of the ARC staff have also been active in presenting papers at scientific meetings and participating in a variety of conferences and symposia as abundantly reflected in the attached reports on individual projects. It was my own privilege to participate in more than seventeen meetings, conferences and symposia throughout the United States on a variety of topics related to drug abuse and to contribute to five book chapters in the fields of psychiatry and pharmacology. I also had the opportunity to attend several meetings and conferences in foreign countries and to present the Thomas Okey Memorial Lecture at the Institute of Psychiatry of the University of London.

The past year has also seen the development of firmer and even more productive relationships with others who share the campus of the Frances Scott Key Medical Center (FSKMC) or have worked in collaboration with us. These include Dean David Blake of the Johns Hopkins University Medical School, Mr. Ronald Petersen and his staff at FSKMC, Dean John Dennis of the University of Maryland School of Medicine, Dr. John Talbot, Chairman, Department of Psychiatry, University of Maryland School of Medicine, Dr. Edson Albuquerque, Chairman, Department of Pharmacology, University of Maryland School of Medicine, Dr. Philip Zieve, Chairman, Medical Board, Dr. Gary Buefel, Chairman of the Institutional Review Board, and Dr. Richard Grevlich, Director of the Gerontology Research Center of the National Institute on Aging. It has also been our privilege to work in collaboration with many other universities, research institutes and pharmaceutical companies, as well as to serve as host to their guest scientists. Those organizations with whom we have collaborated are indicated following the individual project summaries.

Finally, I am deeply appreciative of the efforts of every member of the ARC staff, of our visiting scientists and research fellows, and of the contract personnel with whom we work on a daily basis. Together I believe we have laid a very strong foundation for the future development of the ARC into an even more productive research enterprise.

Annual Report of the Clinical Biology Branch
Addiction Research Center
October 1, 1985 to September 30, 1986
Jerome H. Jaffe, M.D., Acting Chief

Introduction

The Clinical Biology Research Branch initiates, develops and conducts pharmacological research in human subjects to investigate the abuse potential of drugs as well as studies into the causes, effects, treatment and prevention of addictive processes. This Branch also conducts research designed to characterize the metabolic disposition of drugs of abuse, to analyze drugs of abuse in biological fluids, to identify medical illnesses in drug abusers, and to synthesize suspected metabolites as well as model compounds for pharmacological investigations. This involves development of analytical methods for qualitative and quantitative analysis of drugs of abuse in biological fluids including blood, urine, feces, and other tissue samples from animals and humans. For each clinical protocol, procedures for protection and proper medical care of research subjects are designed and implemented.

Additionally, the Branch devises and submits plans for policy development as well as for development of the clinical pharmacology research program. The Branch designs protocols to examine the effects of drugs on human performance and to investigate the efficacy of new treatments, especially those involving pharmacological agents, for drug dependence. This involves the investigation, development and improvement of treatment modalities for drug intoxication and overdose, detoxification, and long term rehabilitation. Various elements of both drug and drug-free treatment approaches are studied in relation to outcome variables. This research ranges from studies on such aspects as how the nature and dose of a maintenance drug influence the results of urine screening to investigations of the efficacy of different types of counseling and psychotherapy. In addition, the Clinical Biology Branch conducts psychosocial research to determine the nature and extent of various types of drug abuse in designated catchment areas of the City of Baltimore. Patient populations include those such as AIDS patients.

The Clinical Biology Branch consists of three firmly established laboratories (Chemistry and Drug Metabolism Laboratory, Biology of Dependence and Abuse Potential Assessment Laboratory, and Biology of Vulnerability Laboratory) and a fourth, recently formed laboratory devoted to the support of NIDA efforts on AIDS.

Over the past year, the main themes of the Branch have included:

1. The role of nicotine in the nicotine withdrawal syndrome;

2. The metabolism and spectrum of biological effects observed with passively inhaled and orally administered marijuana;

3. Tolerance to cocaine and the pharmacology of chronic cocaine administration;

4. The interactions of acutely administered cocaine with other pharmacological agents;

5. The metabolism of cocaine and its detectability in various body fluids;

6. The role of anxiety in drug taking;

7. Individual differences, of both a psychological and physiological nature, as determinants of differential response to opioids;

8. The role of aggression as a risk factor in drug abuse;

9. Serotonergic mechanisms in aggression;

10. Sites of action of abused drugs in the human brain as determined by studies of glucose metabolism using the PET scanner (in collaboration with the Neuroscience and Psychopathology Branches and Johns Hopkins University School of Medicine);

11. Establishment of a laboratory to support NIDA's efforts on AIDS, including studies of HTLV-III seroprevalence and the effects of drugs of abuse (e.g., amyl nitrite) on the immune system in man;

12. The effects of cholinergic antagonists and other agents on human performance, an Army project.

Additional studies projected for the coming year include investigations of:

1. The effects of inhaled cocaine;

2. The role of pharmacokinetics in determining subjective response.

The interim progress reports for each laboratory present the projects and findings in greater detail. The various projects and ongoing work appear under the section for the laboratory which played the dominant role in data acquisition or analysis.

1. Laboratory of Chemistry and Drug Metabolism -- Edward J. Cone, Ph.D., Chief

Overview

The Laboratory of Chemistry and Drug Metabolism performs chemical, pharmacokinetic, metabolic and pharmacodynamic studies in human subjects in areas related to the chemistry of substance abuse.

Presently studies are underway on the pharmacokinetics and pharmacodynamics of cocaine. These studies are designed to determine the relation of behavioral and physiological effects produced by cocaine to that of cocaine levels in body fluids. In a related study, the validity of current test methods employed to detect cocaine use by measuring a cocaine metabolite in urine specimens is being assessed.

In another study aimed at assessing the effects of passive inhalation of marijuana smoke, the Laboratory found that with high smoke exposure subjects absorbed sufficient amounts of tetrahydrocannabinol (THC) to report feelings of a marijuana-high and tested positive for cannabinoids in urine screening tests.

The Laboratory also performs basic research in the area of methodology development. New analytical methods are being developed for measurement of drugs of abuse in body fluids. These methods would represent an improvement over existing methods in that active substances will be measured in contrast to inactive metabolites.

The Laboratory has also recently devised a specific and sensitive assay for THC, the active constituent of marijuana. This new assay will provide a new analytical tool in the study of the effects and mechanisms of action of marijuana. Research is continuing in the development of new assays for other drugs of abuse.

Collaborative studies performed by the Laboratory with other research groups include a comparison of the effects of opiates on behavior, physiological effects and hormone levels. This study aims to define individual sensitivity to morphine and possible differences in the response of addicts versus non-addicts. In other studies the Laboratory collaborated with a research group at San Francisco General Hospital in a study of the kinetics and

metabolism of nicotine and metabolites in various animal species.

Overall, the Laboratory performs basic research in the area of the chemistry of substance abuse. Studies range from fundamental studies of the mechanisms of action of drugs to practical studies assessing the validity of test methods currently employed for detection of drugs in body fluids.

Summary of Ongoing Research

Specific research projects which were actively pursued in FY '86 are briefly summarized below. Only those findings for which personnel from this Laboratory were the principal investigators are discussed.

A. Effects of Passive Inhalation of Marijuana Smoke in Humans: Cone, E.J.; Collaborating Investigator: Johnson, R.E.

The aim of this study is to determine if multiple passive exposures to marijuana smoke under controlled environmental conditions cause: a) male human subjects to excrete cannabinoid metabolites in their urine, consequently testing positive for cannabinoid use; and b) subjects to develop marijuana-induced behavioral effects, i.e., a "contact high". All subjects who were exposed to the smoke of 16 marijuana cigarettes for 1 hour each day excreted urines which tested positive for cannabinoids. In addition, under double blind conditions, subjects reported no behavioral effects under placebo smoke conditions and reported significant drug effects under passive marijuana smoke conditions.

B. Acute Effects of Smoking Marijuana on Hormones, Subjective Effects and Performance in Male Human Subjects: Cone, E.J.; Collaborating Investigators: Johnson, R.E., Moore, J.D. and Roache, J.D.

The aim of this study is to determine if smoking marijuana causes changes in circulating levels of specific hormones and if hormonal/behavior/performance interactions might exist. Cortisol levels were significantly elevated and luteinizing hormone levels were significantly depressed in 4 male subjects following active smoking of marijuana as compared to smoking placebo marijuana. The changes occurred concurrently with behavioral and psychomotor impairment change, supporting the hypothesis of a hormone/behavior/performance interaction.

C. Behavioral and Urinary Excretion Studies of Marijuana Administered in "Brownies": Cone, E.J.; Collaborating Investigators: Johnson, R.E. and Higgins, S.T.

The aim of this study is to determine if marijuana administered to male human subjects in the form of baked "brownies" produced behavioral effects and appeared in the urine as cannabinoid metabolites. Preliminary findings indicate that subjects experience a marijuana "high" from marijuana-laced brownies similar to that of smoking, but the onset of effects is slower and the time course is prolonged. Also, subjects tested positive by EMIT (Syva) and GC/MS methods for urinary cannabinoids after ingesting marijuana brownies.

D. The Pharmacodynamics of Single Intravenous Bolus Doses of Cocaine in Humans: Cone, E.J.; Collaborating Investigators: Thompson, L., Sherer, M.A. and Kumor, K.M.

The goal of this study is to determine the relationship between blood and saliva levels of cocaine and behavioral and physiological effects induced by the presence (and disappearance) of cocaine. Another aim is to determine the potentially acute effects of cocaine on circulating levels of cocaine on prolactin and growth hormone. The pharmacokinetic profile of cocaine in plasma was similar to that reported in other studies. The presence of cocaine in saliva was unequivocally confirmed for the first time. The relationship of cocaine saliva levels to plasma levels is currently being analyzed along with correlations with other pharmacological measures.

E. Neurohormonal Effects of Tobacco Dependence, Withdrawal and Re-Exposure: Cone, E.J.; Collaborating Investigators: Herning, R.I. and Henningfield, J.E.

The goal of this study is to determine the effects of tobacco dependence, withdrawal and re-exposure on circulating levels of prolactin and cortisol along with concurrent changes in behavioral and physiological measures. Preliminary analysis of the data indicates that minimal changes in prolactin and cortisol occur in male smokers during withdrawal from tobacco use.

F. Drug Assay Development Studies on Drugs of Abuse: Cone, E.J.; Collaborating Investigator: Thompson, L.

The overall aim of this ongoing project is to develop specific, sensitive and reliable assays for drugs of abuse in biological fluids. These assays serve to support pharmacokinetic and pharmacodynamic studies performed at the ARC. Following publication of the assay methodology, the methods become useful to other researchers performing studies on drugs of abuse. A

specific and reliable methodology has been developed for the measurement of tetrahydrocannabinol in plasma by high pressure liquid chromatography with electrochemical detection. This methodology is a significant advance in marijuana assay technology since it is more specific than current radioimmunoassay techniques and much less involved than analysis by gas chromatography/mass spectrometry.

G. Studies on the Validity of Drug Testing Methodology: Cone, E.J.; Collaborating Investigators: Mell, L., and Irving, J., Navy Screening Laboratory, Norfolk, VA.

The goal of this study is to compare test results for cannabinoid metabolites in urine obtained by EMIT analyses (Syva) with test results obtained by gas chromatography/mass spectrometry (GC/MS). Approximately 85% of the samples which tested positive by EMIT assay (20 ng cutoff) were confirmed to be positive by GC/MS.

Ongoing Studies as of September 1986 include the following:

1. Investigations of the pharmacodynamics of single intravenous bolus doses of cocaine in humans.

2. Drug assay development studies on drugs of abuse.

3. Studies on the validity of drug testing methodology.

4. Studies of the pharmacological, behavioral and biochemical effects of clonidine on marijuana smoking.

5. Investigations of the pharmacokinetics and pharmacodynamics of opiate analgesics.

6. Studies on the development of a new generation of drug screening tests.

Publications for Fiscal Year 1986:

Cone, E.J., Gorodetzky, C.W., Yousefnejad, D. and Darwin, W.D.: A ^{63}N electron capture, gas chromatographic assay for buprenorphine and metabolites in human urine and feces. J. Chromatogr. 337: 291, 1985.

Risner, M.E., Jackson-Smith, P.A. and Cone, E.J.: Discriminative stimulus properties and schedule effects of fencamfamine in rats. Pharmacol. Biochem. Behav. 23: 449, 1985.

Risner, M.E., Goldberg, S.R., Prada, J.A. and Cone, E.J.: Effects of nicotine, cocaine and some of their metabolites on

schedule-controlled responding by beagle dogs and squirrel monkeys. J. Pharmacol. Exp. Ther. 234: 113, 1985.

Cone, E.J. and Johnson, R.E.: Contact highs and urinary cannabinoid excretion after passive exposure to marijuana smoke. Clin. Pharmacol. Exp. Ther., September 1986, in press.

Cone, E.J., Johnson, R.E., Moore, J.D. and Roache, J.D.: Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects. Pharmacol. Biochem. Behav. 24: 1749, 1986.

Cone, E.J., Yousefnejad, D., Buchwald, W.F. and Kumor, K.M.: Determination of ketocyclazocine in human plasma by gas chromatography-negative ion chemical ionization mass spectrometry. J. Chromatog., September 1986, in press.

Preston, K.L., Griffiths, R.R., Cone, E.J., Darwin, W.D., and Gorodetzky, C.W.: Diazepam and methadone blood levels following concurrent administration of diazepam and methadone. Drug Alc. Dep., 1986, in press.

Risner, M.E. and Cone, E.J.: Intravenous self-administration of fencamfamine and cocaine by beagle dogs under fixed-ratio and progressive ratio schedules of reinforncement. Drug Alc. Dep. 17: 93, 1986.

Moore, J.D., Cone, E.J., Jaffe, J.H. and Alexander, S.S.: HTLV-III seropositivity in 1971-72 parenteral drug abusers - a case of false positives or evidence of viral exposure. N. Engl. J. Med. 314: 1387, 1986.

Risner, M.E., Cone, E.J., Benowitz, N.L. and Jacob, III, P.: Effects of the stereoisomers of nicotine and nornicotine on schedule-controlled responding and physiological parameters of dogs. Submitted to J. Pharmacol. Exp. Ther. 1986.

Thompson, L.K., Yousefnejad, D., Kumor, K.M., Sherer, M.A. and Cone, E.J.: Confirmation of cocaine in human saliva after intravenous use. Submitted to J. Anal. Toxicol. 1986.

Vaupel, D.B., Cone, E.J., Johnson, R.E. and Su, T.-P.: Evidence for kappa opioid activity of BW942C, an enkephalin-like pentapeptide, based on urination studies in humans and animals. Submitted to J. Pharmacol. Exp. Ther. 1986.

Jacob, III, P., Benowitz, N.L., Copeland, J.R., Risner, M.E. and Cone, E.J.: Nicotine and cotinine enantiomers: synthesis and disposition kinetics in rabbits and beagle dogs. Submitted to J. Pharmacol. Exp. Ther. 1986.

Abstracts for Fiscal Year 1986:

Vaupel, D.B., Cone, E.J. and Johnson, R.E.: An enkephalin-like pentapeptide (BW942C) with partial kappa agonist activity. Neuroscience 1985.

Risner, M.E., Cone, E.J., Benowitz, N.L. and Jacob, III, P.: Effects of the stereoisomers of nicotine and nornicotine on schedule-controlled behavior and physiological parameters of dogs. Pharmacologist 27: 258, 1985.

Jacob, III, P., Benowitz, N.L., Copeland, J.R., Risner, M.E. and Cone, E.J.: Synthesis and metabolic studies of nicotine and nornicotine enantiomers. Pharmacologist 27: 233, 1985.

Cone, E.J., Johnson, R.E. and Moore, J.D.: Subjective and hormonal responses after one and two marijuana cigarettes. Pharmacologist 28:189, 1985.

Cone, E.J. and Johnson, R.E.: Passive inhalation of marijuana smoke. I. EMIT results. Pharmacologist 28: 235, 1985.

Johnson, R.E. and Cone, E.J.: Passive inhalation of marijuana smoke. II. Subjective effects. Pharmacologist 28: 235, 1985.

Noe, D.N., Kumor, K.M., Sherer, M.A. and Thompson, L.K.: A pharmacodynamic model of the chronotropic effect of i.v. cocaine (C) in man after bolus doses with or without subsequent infusion. Pharmacologist 28: 205, 1986.

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

Overview

The Biology of Dependence and Abuse Potential Assessment Laboratory is one of four laboratories of the Clinical Biology Branch of the Addiction Research Center, NIDA. The purposes of this Laboratory are: first, to assess the biological basis of drug dependence using quantitative experimental procedures of the behavioral and pharmacological disciplines; and, second, to assess the abuse liability of selected compounds. These aims are intended to serve the overall mission of the ARC in providing a better foundation for the understanding, rational treatment and prevention of drug dependence.

Most studies are collaborative and multidisciplinary in nature and involve the electrophysiology and psychometric sections of

the Cognitive Laboratory, the diagnostic capabilities of the Psychopathology and Vulnerability Laboratories, the neuroendocrine and pharmacokinetic response assessment capabilities of the Chemistry Laboratory, and the expertise of scientists of the Preclinical and Neuroscience Laboratories. With such multidisciplinary efforts it is possible to quantitate the subjective, physiologic, behavioral, electrophysiologic, cognitive, pharmacodynamic, pharmacokinetic, reinforcing, aversive and other effects of drugs.

Summary of Ongoing Research:

A. Effects of Atropine on Mood, Performance, and Electrophysiological Response in Normal Volunteer Subjects Living on the Residential Research Unit: Higgins, S.T., Lamb, R.J., Herning, R.I., Pickworth, W.G. and Henningfield, J.E.

Laboratory testing for this project will be complete in September, 1986. However, it is clear that one interesting finding is that a single exposure to atropine leads to a marked degree of tolerance to atropine-induced impairment on cognitive/behavioral tests.

B. Effects of Benzodiazepines on Mood Performance and Electrophysiological Responses in Normal Volunteer Subjects Living on the Residential Research Unit: Lamb, R.J., Higgins, S.T., Roache, J.D., Herning, R.I., Pickworth, W.G. and Henningfield, J.E..

The first phase of this experiment will be completed in October, 1986. However, certain results are evident. Effects of diazepam were detected on some performance measures at doses of diazepam as low as 5 mg. However, on other measures, notably subjective reports of drug effect, effects were not detected until doses of 20 or 40 mg of diazepam were administered.

C. Comparative Studies on Intravenous Drug Self-Administration by Monkeys and Human Volunteers: Henningfield, J.E., Goldberg, S.R., Nemeth-Coslett, R.D., and Katz, J.L.

These studies include integrated human and animal components in an effort to yield data not possible from studies conducted with either species alone. Conditioned stimuli were found to markedly increase cocaine self-administration in humans. Under certain conditions, drug self-administration occurs in the absence of self-reported effects.

D. Triazolam Self-Administration: Interactions with Yohimbine: Meisch, R.A., Roache, J.D., Henningfield, J.E. and Jaffe, J.H.

In subjects with histories of sedative abuse who are living on the residential research unit, patterns of triazolam self-administration are being examined with and without yohimbine pretreatment to evaluate whether possible anxiogenic effects of yohimbine may alter the self-administration of the benzodiazepine. Completion of testing on 2 subjects confirms that the self-administration procedure is viable and safe. Higher than predicted dose levels of yohimbine may be required to produce reliable changes in mood and self-administration of triazolam.

E. Archival Database Project: Haertzen, C.A., Chairman, Database Committee.

The main purpose of the database committee is to combine data from diverse studies and perform analyses on the combined data, building on the extensive screening/testing program initiated by Dr. Jaffe at both the recruitment and admission levels. Database activity has been focused on assembling files of scores collected at the two time periods and linking these. This effort has permitted comparisons between tests collected at the two time periods as well as to relate scores on the various tasks.

F. Psychological Assessment and Correlates of Drug Dependence and Abuse, and Evaluation of a Drug Interview Schedule: Haertzen, C.A.

This project utilizes a variety of psychometric instruments to assess vulnerability and other characteristics of drug abusers and to develop new instruments. Data collection for this project is largely completed although further analyses appear to be yielding findings of importance.

G. Characterization and Pharmacologic Treatment of Nicotine Withdrawal during Tobacco Abstinence: Henningfield, J.E., Nemeth-Coslett, R.D., Snyder, F.R., Herning, R.I., Pickworth, W.B. and Cone, E.J.

A multidisciplinary collaborative study was conducted to quantitate a variety of correlates of nicotine abstinence during 10 days of tobacco withdrawal and to assess the effects of substituting various dose levels of nicotine gum.

H. Clinical Pharmacology of Nicotine-Containing Chewing Gum: Henningfield, J.E., Nemeth-Coslett, R.D., Snyder, F.R., Herning, R.I. and Pickworth, W.B.

A series of studies was conducted to further characterize the pharmacology of nicotine chewing gum. Results from currently completed studies have indicated practical implications for more efficacious use of the gum for treatment of tobacco dependence as well as for understanding the behavioral pharmacology of nicotine delivered via this route of administration.

I. Characterization of the Development of Dependence to Nicotine by Smokeless Tobacco Users and Cigarette Smokers: Henningfield, J.E., Nemeth-Coslett, R.D., Radzius, A., Snyder, F.R., Haertzen, C.A. and Fagerstrom, K.O.

A survey was conducted in collaboration with the Johns Hopkins University School of Medicine to retrospectively assess the patterns of use of smokeless tobacco products. Acquisition of tobacco use is marked by an orderly, gradual increase followed by a relatively stable phase of intake. Early correlates (predictors) of tobacco dependence were found.

J. Factors Influencing Behavioral and Physiological Response to Opioids: Higgins, S.T., Preston, K.L., Cone, E.J., Henningfield, J.E. and Jaffe, J.H.

Postaddicts and normals have been reported to respond differentially to opioids. This project was designed to experimentally examine such population differences in response to mu and kappa opioids on subjective, behavioral, physiological and neuroendocrine parameters using postaddicts and opiate-naive normal residential volunteers. Laboratory testing is complete on the first phase of the study.

K. Motivation Assessment Battery: Higgins, S.T. and Henningfield, J.E.

The motivation assessment battery is an assay to investigate factors related to human aggression under controlled laboratory conditions. The first project was being conducted with residential volunteers and examines the relationships between various psychometric measures of hostility and aggression. The second project was conducted with nonresidential volunteers and is an experimental analysis of the effects of common drugs of abuse, beginning with ethanol, on performance on the various components comprising the motivation assessment battery.

L. Effects of Commonly Used Drugs (i.e., Alcohol, Antihistamines) on Behavioral Measures in Normal Subjects: Roache, J.D. and Henningfield, J.E.

This study involves the use of performance assessment and other behavioral measures in an examination of the effects of prescription and nonprescription drugs in normal volunteer subjects in the nonresidential paradigm.

M. Clinical Pharmacology of Nicotine: Henningfield, J.E., Jasinski, D.R., Lange, R., Sampson, A., Rose, J.E. and Fagerstrom, K.O.

Several studies have been completed in which the effects of intravenous and inhaled nicotine were examined on subjective and physiologic responses in the following populations: drug abusing, cigarette smokers, nondrug-abusing cigarette smokers, and never drug abusers/never cigarette smokers.

N. Abuse Liability of Smokeless Tobacco: Henningfield, J.E., Radzius, A., Nemeth-Coslett, R.D. and Cone, E.J.

Laboratory testing of the abuse liability of smokeless tobacco and smokeless cigarettes will be completed in September.

O. Intramuscular Morphine Self-Administration: Lamb, R.J., Goldberg, S.R. and Henningfield, J.E.

In a subject with a history of opioid abuse, intramuscular morphine at doses of 7.5 mg and above maintained response rates above those maintained by placebo. Morphine, at a dose of 3.75 mg, maintained rates of responding similar to those maintained by placebo. Rates and patterns under the FR 30 (FR 100) schedule of intramuscular morphine injection were similar to those obtained in rhesus monkeys responding under a similar schedule of food presentation.

P. Effects of Drugs on Cigarette Smoking and Response to Nicotine: Nemeth-Coslett, R.D., Henningfield, J.R. and Griffiths, R.R.

A variety of experimental preparations were used to assess the direct effects of drugs on cigarette smoking and the response to nicotine.

Special Projects for Other Federal Agencies:

1. NIDA Triennial Report to Congress, Chapter on Nicotine. Drafted by J.E. Henningfield with assistance by R.D. Nemeth-Coslett.

2. Report to the Surgeon General on the Health Effects of Smokeless Tobacco, Chapter on Pharmacokinetics, Addiction, and Other Physiologic Effects. Drafted by J.E. Henningfield with assistance by R.D. Nemeth-Coslett.

3. NIH/NCI Consensus Conference on the Health Effects of Smokeless Tobacco, Report on Abuse Liability and Dependence Potential of Smokeless Tobacco. Prepared and presented by J.E. Henningfield.

4. Testimony to Federal and State Agencies Regarding the Abuse Liability and Dependence Potential of Nicotine Delivering Tobacco Products, J.E. Henningfield with assistance by R.D. Nemeth-Coslett.

Publications for Fiscal Year 1986:

Bickel, W.K., Johnson, R.E., Stitzer, M.L., Bigelow, G.E., Liebson, I.A., and Jasinski, D.R.: A clinical trial of buprenorphine. Arch. Gen. Psychiatry. In press.

Connolly, G.N., Winn, D.M., Hecht, S.S., Henningfield, J.E., Walker, B., and Hoffmann, D.: The reemergence of smokeless tobacco. N. Eng. J. Med. 314: 1020-1027, 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. In press.

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Coslett, R.D., Pickworth, W.B., Rose, J.E., Sampson, A., and Snyder, F.R.: Human studies of the behavioral and pharmacological determinants of nicotine dependence. In L.S. Harris (Ed.) NIDA Research Monograph, Problems of Drug Dependence 1985.

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Nemeth-Coslett, R.D., Henningfield, J.E., O'Keeffe, M.K., and Griffiths, R.R.: Effects of marijuana on human cigarette smoking and physiological response. Pharmacol. Biochem. Behav. In press.

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Abstracts

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Henningfield, J.E.: Human studies of the behavioral and pharmacological determinants of nicotine dependence. Presented at the Committee on Problems of Drug Dependence, Baltimore, MD, June 1985.

Henningfield, J.E.: Tobacco use as an addictive process: Neurosciences and psychopharmacology. Presented at the Working Meeting on Tobacco Use as an Addictive Process, sponsored by NIDA and the John F. Kennedy School of Government of Harvard University, Boston, MA, July 1985.

Henningfield, J.E.: The role of nicotine addiction in the relapse to tobacco use. Presented at the Smoking Relapse Workshop, sponsored by the National Heart, Lung and Blood Institute, Bethesda, MD, July 1985.

Henningfield, J.E., Sampson, A., and Nemeth-Coslett, R.D.: Effects of nicotine replacement in tobacco withdrawal: An empirical study. Presented at the American Psychological Association, Annual Convention, Washington, DC, August 1986.

Henningfield, J.E., Nemeth-Coslett, R.D., Katz, J.L., and Goldberg, S.R.: Cocaine self-administration in humans: Second-order schedules. Presented at the Committee on Problems of Drug Dependence, Lake Tahoe, CA, June 1986.

Henningfield, J.E., and Goldberg, S.R.: Control of behavior by noxious properties of drugs in human and nonhuman research subjects. Presented at the Annual Convention of the Association for Behavior Analysis, Milwaukee, Wisconsin, May 1986.

Henningfield, J.E., and Grabowski, J.: Discussant for symposium (invited) entitled: Tobacco smoke self-administration: The roles of pharmacologic and non-pharmacologic variables. Presented at the Annual Convention of the Association for Behavior Analysis, Milwaukee, Wisconsin, May 1986.

Henningfield, J.E.: Pharmacologic determinants of tobacco self-administration by humans. Presented at the Annual Convention of the American Society for Pharmacology and Experimental Therapeutics, Baltimore, MD, August 1986.

Henningfield, J.E.: New fellows address (invited) entitled: Behavioral pharmacology of nicotine dependence. Presented at the Annual Convention of the American Psychological Association, Washington, DC, August 1986.

Henningfield, J.E.: Discussant for symposium entitled: Nicotine dependence: Withdrawal following cigarette, nicotine gum, and smokeless tobacco use. Presented at the Annual Convention of the American Psychological Association, Washington, DC, August 1986.

Higgins, S.T., and Stitzer, M.L.: A comparison of the acute behavioral effects of secobarbital and diazepam in humans. Pharmacologist 28: 189, 1986.

Johnson, R.E., and Jasinski, D.R.: Opioid profile of meptazinol in man. Presented at the American Society for Pharmacology and Experimental Therapeutics, Boston, MA, August 1985.

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Nemeth-Coslett, R.D., Henningfield, J.E., Griffiths, R.R., and O'Keeffe, M.K.: Effects of marijuana on cigarette smoking behavior and subjective responses. Poster presented at the American Psychological Association Annual Convention, Los Angeles, CA, August 1985.

Nemeth-Coslett, R.D., Henningfield, J.E., O'Keeffe, M.K., and Griffiths, R.R.: Cigarette smoking, subject ratings and plasma nicotine levels: A dose-response experimental analysis of nicotine gum. Presented at the Eastern Psychological Association, Annual Convention, New York, NY, April 1986.

Nemeth-Coslett, R.D., Sampson, A., and Henningfield, J.E.: Subjective and physiological correlates of cigarette deprivation. Presented at the American Psychological Association, Annual Convention, Washington, DC, 1986.

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Nemeth-Coslett, R.D., Goldberg, S.R., Katz, J.L., and Henningfield, J.E.: Effects of cocaine on rate of cigarette smoking. Presented at the American Psychological Association, Annual Convention, Washington, DC, August 1986.

Nemeth-Coslett, R.D., and Henningfield, J.E. (co-chairpersons): Nicotine dependence: Withdrawal following cigarette, nicotine gum and smokeless tobacco use. Presented at the American Psychological Association, Annual Convention, Washington, DC, August 1986.

Nemeth-Coslett, R.D., and Henningfield, J.E. (co-chairpersons): Symposium entitled: Nicotine dependence: Withdrawal following cigarette, nicotine gum, and smokeless tobacco use. Presented at the Annual Convention of the American Psychological Association, Washington, DC, August 1986.

Roache, J.D., and Griffiths, R.R.: Behavioral effects and abuse liability of lorazepam (LZ) and meprobamate (MEP) in humans. Presented at the 1986 annual meeting of the American Society for Pharmacology and Experimental Therapeutics (ASPET), Baltimore, MD, 1986.

Roache, J.D., and Henningfield, J.E.: Proposed behavioral studies of physostigmine and scopolamine drug interactions. Presented at the Quarterly Meeting of the Joint Working Group on Drug Dependent Degradation in Military Performance (JWGD MILPERF), San Antonio, TX, 1986.

Rose, J.E., Sampson, A., and Henningfield, J.E.: Blockade of smoking satisfaction with mecamylamine. Presented at the American Psychological Association, Annual Convention, Los Angeles, CA, August 1985.

Snyder, F.R., and Henningfield, J.E.: A new psychomotor performance assessment battery: Effects of nicotine deprivation and administration. Presented at the Annual Meeting of the Behavioral Pharmacology Society, Wilmington, DE, June 1985.

Snyder, F.R., Davis, F.C., and Henningfield, J.E.: Chronic abstinence reduces information processing capabilities in heavy smokers. Presented at the Annual Convention of the American Psychological Association, Washington, DC, August 1986.

APPENDIX I

The following are reports of projects that were written, or co-authored, by ARC scientists, of studies that were not developed or executed while the scientist was employed at the ARC:

Bigelow, G.E., Bickel, W.K., Roache, J.D., Liebson, I.A., and Nowowieski, P.: Identifying types of drug intoxication: A laboratory evaluation of subject-examination procedures. In L.S. Harris (Ed.) Problems of Drug Dependence 1985, NIDA Research Monograph 67, U.S. Government Printing Office, Washington, DC, p. 491, 1986.

Brady, J.V., Griffiths, R.R., Heinz, R.D., Ator, N.A., Lukas, S.E., and Lamb, R.J.: Assessing drugs for abuse liability and dependence in laboratory primates. In Methods of Assessing the Reinforcing Properties of Abused Drugs. M.A. Bozarth (Ed.). Montreal: Haer Institute Publications, 1986. In press.

Funderburk, F.R., Bigelow, G.E., Liebson, I.A., and Jasinski, D.R.: An initial evaluation of the behavioral pharmacology of flupirtine maleate in human volunteers. In press.

Griffiths, R.R., Ator, N.A., Roache, J.D., and Lamb, R.J.: Benzodiazepine Abuse Liability: Experimental assessment of triazolam in animals and humans. In Selectivity in Psychotropic Drug Action - Promises or Problems. S.M. Paul, L.F. Gram, S. Dahl, and W.Z. Potter (Eds.). Berlin: Springer-Verlag. In press.

Griffiths, R.R., Brady, J.V., Ator, N.A., Lamb, R.J., Bigelow, G.E., and Roache, J.D.: Progress report from the Division of Behavioral Biology, The Johns Hopkins University School of Medicine. In L.S. Harris (Ed.) Problems of Drug Dependence 1985, NIDA Research Monograph 67: 93-97, 1986.

Higgins, S.T., and Stitzer, M.L.: Acute marijuana effects on social conversation. Psychopharmacology 89: 234-238, 1986.

Higgins, S.T., Bickel, W.K., and O'Leary, D.K.: Acute drug effects on the repeated acquisition and performance of response sequences. Experimental Analysis of Human Behavior Bulletin. In press.

Higgins, S.T., Bickel, W.K., O'Leary, D.K., and Yingling, J.: Acute effects of ethanol and diazepam on the repeated acquisition and performance of response sequences. J. Pharmacol. Exp. Ther. Submitted.

Lamb, R.J., and Griffiths, R.R.: Self-injection of MDMA (3,4-methylenedioxy-methamphetamine) in the baboon. Psychopharmacology. In press.

Lamb, R.J., and McMillan, D.E.: Some effects of chlorimipramine and imipramine on the schedule-controlled behavior of the pigeon. Psychopharmacology 87: 7-11, 1986.

Lamb, R.J., and McMillan, D.E.: The effects of some putative antidepressant agents on the schedule-controlled behavior of the pigeon. Psychopharmacology 88: 368-373, 1986.

Roache, J.D., and Griffiths, R.R.: Repeated administration of diazepam and triazolam to subjects with histories of drug abuse. Drug and Alcohol Dependence 17: 15-29, 1986.

Roache, J.D., and Zabik, J.E.: Effects of benzodiazepines on conditioned taste aversions (CTA's) in a two-bottle choice paradigm. Pharmacol. Biochem. Behav. In press.

Zabik, J.E., Binkerd, K., and Roache, J.D.: Serotonin and ethanol aversion in the rat. In Research Advances in New Psychopharmacological Treatments for Alcoholism. C.A. Naranjo and E.M. Sellers (Eds.), Elsevier Science Publishers, B.V., Amsterdam, the Netherlands, pp. 87-101, 1985.

3. Biology of Vulnerability Laboratory -- Jerome H. Jaffe, M.D., Acting Chief

Overview

This Laboratory was established to give greater emphasis to studies of individual differences in acute responses to abused drugs (i.e., reinforcing effects) and to understanding the mechanisms involved in known role factors associated with later drug abuse problems. These include childhood aggression, anti-social personality, biological parents with history of alcoholism. In the course of developing protocols there were also realistic considerations and resource limitations; therefore, this Laboratory assumed the major burden of initiating clinical studies of cocaine at the ARC. For most of this period, the scientific staff consisted of one staff scientist (Dr. K. Kumor) and one staff fellow (Dr. Sherer). More recently the group has been joined by additional scientists.

Summary of Ongoing Research

In its first year of functioning, this Laboratory has undertaken several major studies, including investigations of:

A. Effects of Subchronic Cocaine Administration (Four Hour Infusions);

B. Effects of Acute Cocaine Administration of EEG, Neuroendocrine Functioning, and Detectability of Cocaine in Body Fluids;

C. Interactions of Cocaine and Other Psychoactive Agents (i.e., Studies of the Neurotransmitter(s) Involved in Cocaine Effects Using Haloperidol, Bromocriptine, Ca^{++} Channel Blockers);

D. Differences in Serotonergic Sensitivity among Former Drug Users with High and Low Levels of Self-Reported Aggressive Behavior (the Serotonin Project);

E. Pharmacological Interactions of Naloxone and Putative Kappa Agonists.

The studies on cocaine infusions revealed little tolerance to cardiovascular or subjective effects over a four-hour period. However, the acute euphoric sensation (called "rush") which follows rapid i.v. injections was not prolonged by a cocaine infusion. Further, there is some evidence that paranoia may develop in as brief a period as four hours if plasma levels are maintained at high and relatively constant levels.

The study entitled "Effects of Pharmacologically Induced Changes in Serotonergic Activity on Neuroendocrine Measures in Drug Addicts with and without Aggressiveness" examines central serotonergic systems in relation to levels of aggression in male populations with drug abuse histories as compared to those without such histories. A serotonergic probe, fenfluramine, is administered to inpatients to evaluate the behavioral and neuroendocrine mechanisms regulated by serotonin. Selection criteria for the study include scores on three psychodiagnostic tests which determine group assignments to "high" versus "low" aggressive groups. A five-hour glucose tolerance test, including electrophysiological and insulin measures, precedes the pharmacologic testing since serotonergic activity and glucose metabolism are known to covary. In addition, studies have shown disrupted glucose metabolism in highly aggressive individuals.

On two alternate days, either fenfluramine or placebo is administered using a double-blind procedure. Electrophysiological (EEG, event-related potentials, and skin conductance) and neuroendocrine (prolactin) measures are obtained throughout the day along with a mood state evaluation. Clinical and behavioral tests, including DSM-III diagnoses, are also administered to further establish levels of aggression and substance abuse. To date, eight subjects have been admitted for this study and data on all aforementioned measures have been obtained from three individuals.

Publications and Papers Submitted in FY 1986:

Papers

Kumor, K.M., Haertzen, C.A., Johnson, R.E., Kocher, T.R. and Jasinski, D.R.: The human psychopharmacology of ketocyclazocine as compared to morphine, cyclazocine and placebo. J. Pharmacol. Exp. Ther. In press.

Sherer, M.A., Kumor, K.M., Mahaffey, J., Cone, E.J. and Jaffe, J.H.: Continuous intravenous infusion and cocaine-induced suspiciousness. Submitted September 1986.

Kumor, K.M., Sherer, M.A., Thompson, L.K., Cone, E.J. and Jaffe, J.H.: Lack of cardiovascular tolerance to four-hour continuous infusions of cocaine in human volunteers. Submitted August 1986.

Kumor, K.M., Sherer, M.A., Gomez, J., Cone, E.J. and Jaffe, J.H.: Subjective effects of four-hour cocaine infusions in human volunteers. Submitted September 1986.

Kumor, K.M., Grochow, L.B. and Hausheer, F.: A new opiate withdrawal syndrome? Submitted July 1986.

Kumor, K.M. and Sherer, M.A.: Dystonia in cocaine users exposed to haloperidol. Submitted June 1986.

Abstracts

Noe, D.N., Kumor, K.M., Sherer, M.A., Cone, E.J. and Thompson, L.: A pharmacodynamic model of the chronotropic effect of i.v. cocaine (C) in man after bolus doses with or without subsequent C infusion. Abst. American Society of Pharmacology and Experimental Therapeutics-Society of Toxicology, Baltimore, MD, 1986.

Sherer, M.A., Kumor, K.M., Golden, R. and Jaffe, J.H.: Continuous infusion of cocaine - a model for cocaine psychosis. Society of Biologic Psychiatry, Annual Meeting, Washington, DC, 1986.

Sherer, M.A., Kumor, K.M., Deborja, J., Cone, E.J., Thompson, L.K. and Jaffe, J.H.: Psychiatric effects of four-hour infusions of cocaine. American Psychiatric Association Meeting, Washington, DC, 1986.

Sherer, M.A., Kumor, K.M., Thompson, L.K., Cone, E.J. and Jaffe, J.H.: Psychopharmacologic and cardiovascular responses after two methods of cocaine administration: cocaine bolus versus cocaine bolus with continuous infusion. American College of Neuropsychopharmacology Meeting, Maui, HI, 1986.

Kumor, K.M., Haertzen, C.A., Jasinski, D.R. and Zerbe, R.: Physiologic and pharmacologic studies of ketocyclazocine in man. American Society of Pharmacology and Experimental Therapeutics-Society of Toxicology Meeting, Boston, MA, 1985.

Organizations Collaborating with the Clinical Biology Branch

Addiction Research Foundation, Toronto, Canada.

Navy Drug Screening Laboratory, Norfolk, VA.

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD.

Department of Psychiatry, University of California, San Francisco, CA.

Behavioral Pharmacology Research Unit, Baltimore City Hospital, Baltimore, MD.

Department of Psychiatry, University of California, Los Angeles, CA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00002-01 CDM

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Validity Studies of Commercial Drug Screening Assays

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Cone	Chief	CDM, ARC, NIDA
Others:	D. Darwin	Chemist	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA
	S. Menchen	Lab Tech	ARC, NIDA
	P. Welch	Nurse	ARC, NIDA

COOPERATING UNITS (if any)

Naval Screening Laboratory, Norfolk, VA (J. Mitchell and L. Mell).

LAB/BRANCH: Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

SECTION:

INSTITUTE AND LOCATION: Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	0.25	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

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. Presently, six commercial assays for cocaine are being tested for validity with cocaine specimens. The results are being compared to GC/MS analyses.

These studies test validity of commercial assays on clinical samples instead of "spiked" samples and provide unique information on their time course of detection, specificity and accuracy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00003-01 CDM

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Detection of Drugs of Abuse in Human Saliva

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Cone	Chief,	CDM, ARC, NIDA
Others:	D. Darwin	Chemist	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA
	S. Menchen	Lab Tech	ARC, NIDA
	P. Welch	Nurse	ARC, NIDA
	L. Thompson	Fellow	ARC, NIDA

COOPERATING UNITS (If any)

LAB/BRANCH: Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

SECTION:

INSTITUTE AND LOCATION: Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.25	1.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

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 gas chromatography or RIA. Significant correlations of blood levels with saliva levels were found for cocaine. Investigations are continuing on marijuana and opiates.

These studies provide the scientific basis for development of new non-invasive tests for drug abuse.

Detection of Drugs of Abuse in Human Saliva, Publications - FY 1986

Thompson, L.K., Yousefnejad, D., Kumor, K., Sherer, M. and Cone, E.J.: Confirmation of cocaine in human saliva after intravenous use. J. Anal Toxicol in press, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00004-02 CDM

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Acute Effects of Marijuana in Humans

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.J. Cone	Chief	CDM, ARC, NIDA
Others:	L. Thompson	Fellow	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA
	S. Menchen	Lab Tech	ARC, NIDA
	P. Welch	Nurse	ARC, NIDA

COOPERATING UNITS *(if any)*

Research Technology Branch, ARC, NIDA (R.E. Johnson).

LAB/BRANCH

Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.75	0.5	1.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of marijuana were studied in human male subjects to determine the relationships of blood, saliva and urine drug levels to behavioral effects, hormone release and performance. Marijuana was administered by smoking, oral ingestion and passive inhalation of marijuana smoke.

Healthy male volunteers with a history of marijuana use participated in the study. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. Subjects smoked or consumed the equivalent of one or two standardized marijuana cigarettes (2.8% THC) or were passively exposed to the smoke of 4 or 16 marijuana cigarettes. Physiologic and behavioral measures were taken along with blood, saliva and urine. Hormone and THC measures were made on blood by radioimmunoassay. Cannabinoid metabolites were measured by HPLC and GC/MS. The acute profile of marijuana was seen as resulting from rapid absorption of THC producing behavioral effects and release of cortisol. Excretion of cannabinoid metabolites was prolonged.

The significance of these studies lies in the discovery of marijuana's effects on cortisol release when actively smoked and the appearance of behavioral effects and cannabinoid metabolites of subjects who were passively exposed to marijuana smoke.

Acute Effects of Marijuana in Humans, Publications - FY 1986

Cone, E.J., Roache, J.D. and Johnson, R.E.: Effects of passive exposure to marijuana smoke. Problems of Drug Dependence, NIDA Research Monograph. U.S. Department of Health and Human Services, Public Health Service, Washington, D.C., U.S. Government Printing Office, 1986.

Cone, E.J. and Johnson, R.E.: Contact highs and urinary cannabinoid excretion after passive exposure to marijuana smoke. Clin. Pharmacol. Exp. Ther. 40:247-56, 1986.

Cone, E.J., Johnson, R.E., Moore, J.D. and Roache, J.D.: Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects. Pharmacol. Biochem. Behav. 24:1749-1754, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00005-02 CDM

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Human Pharmacodynamics of Single Doses of Intravenous Cocaine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.J. Cone	Chief,	CDM, ARC, NIDA
Others:	D. Darwin	Chemist	ARC, NIDA
	D. Yousefnejad	Chemist	ARC, NIDA

COOPERATING UNITS *(if any)*

Clinical Biology Branch, NIDA/ARC (K. Kumor and M. Sherer).

LAB/BRANCH

Laboratory of Chemistry and Drug Metabolism, Clinical Biology Branch

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.25	0.5	1.75

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of single, intravenously administered doses of cocaine were studied in male human volunteers in order to determine the relationships of blood and saliva levels of cocaine to pharmacologic effects.

The subjects were healthy males with a history of intravenous cocaine abuse. Informed consent was obtained and all procedures were approved by the hospital Institutional Review Board. Following a pilot dose run-up study, subjects were administered single doses of cocaine (15 mg and 40 mg) and placebo in random order with crossover design. Blood, saliva, physiological and behavioral measures were taken prior to and following drug administration. Plasma and saliva level in cocaine were measured by gas-chromatography. Correlations were made between blood and saliva levels of cocaine and other measures. Cocaine levels of saliva were found to significantly correlate with blood levels and drug-induced feelings.

The significance of these findings lies in the detection and measure of cocaine in saliva and the good correlation with other measures. These findings provide the scientific rationale for the development of a saliva screening test for cocaine and allow cocaine levels to be determined in a non-invasive manner.

Human Pharmacodynamics of Single Doses of Intravenous Cocaine
Publications - FY 1986

Thompson, L.K., Yousefnejad, D., Kumor, K., Sherer, M. and Cone, E.J.: Confirmation of cocaine in human saliva after intravenous use. J. Anal. Toxicol. in press, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 DA 00004-02 BDL

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.): Comparative Studies of Drug Self-Administration in Squirrel Monkeys and Humans: Nicotine, Cocaine and Morphine

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

J.E. Henningfield, Ph.D.	Chief	BDL, NIDA, ARC
*R. Nemeth-Coslett, Ph.D.	Staff Fellow	BLD, NIDA, ARC

COOPERATING UNITS (If any)

(S.R. Goldberg) BPL (J. Katz) BPL (C. Schindler) RSB (R. Lange)

LAB/BRANCH: Clinical Pharmacology Branch

SECTION: Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION: National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.95	.95	1 *(FAES/Merrell Dow = .15 yr)

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This was a major collaborative project with the BPL in which the human research was conducted in the BPL. Only professional time for the human studies is accounted for. In this project a parallel animal-human series of self-administration studies was conducted.

Self-administration (SA) studies permit 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, morphine and nicotine under similar behavioral schedules and experimental conditions provide a means to assess the generality of biological variables influencing drug SA. 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. These studies have shown that responding is maintained in human subjects in the same manner in which it is maintained in non-human experimental 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. Besides yielding specific data of potential theoretical and clinical interest, these studies have demonstrated that a research strategy employing drug self-administration in human subjects can yield all of the important information of a more traditional "single-dose" type of study, and in addition provide information on the direct reinforcing effects of the compound which may be compared to the large base of animal drug self-administration data.

Attachment

Comparative studies of cocaine self-administration in squirrel monkeys and humans, Publications - FY 1986

Goldberg, S.R.: Nicotine as a reinforcer in humans and experimental animals. Pharmacol. Biochem. Behav., in press, 1986.

Henningfield, J.E., Nemeth-Coslett, R. and Goldberg, S.R.: Intravenous cocaine self-administration by human volunteers: Second-order schedules of reinforcement. NIDA Res. Monog. Ser., in press, 1986.

Henningfield, J.E., Goldberg, S.R., Herning, R.I., Jasinski, D.R., Lucas, S.E., Miyasoto, K., Nemeth-Coslett, R., Pickworth, W.B., Rose, J.E., Sampson, A. and Snyder, F.: Human studies of the behavioral pharmacological determinants of nicotine dependence. NIDA Res. Monog. Ser., No. 67, pp. 54-65, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00005-02 BDL

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Abuse Liability of Smokeless Tobacco Products: Snuff and Smokeless Cigarettes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

J.E. Henningfield, Ph.D.	Chief	BDL, NIDA, ARC
R. Nemeth-Coslett, Ph.D.	Staff Fellow	BDL, NIDA, ARC
R.A. Meisch, M.D., Ph.D.	Visiting Scientist	BDL, NIDA, ARC
A. Radzius	Research Assistant	BDL, NIDA, ARC
A. Sampson, LPN	LPN	BDL, NIDA, ARC
*Students		BDL, NIDA, ARC

COOPERATING UNITS (if any)

Chemistry and Drug Metabolism Lab (E.J. Cone)
Research Support Branch (W.R. Lange)

LAB/BRANCH: Clinical Pharmacology Branch

SECTION: Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION: National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.85	.35	.5 *(FAES/Merrell Dow = .3 yr)

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

These studies adopted the basic strategies of abuse liability assessment in order to characterize some of the behavioral and physiological effects of a widely used brand of smokeless tobacco (snuff in pouch form) and a recently marketed smokeless cigarette which does not contain tobacco but delivers nicotine when air is drawn through. The validity of these studies was greatly enhanced by the development of effective placebo versions of both products by Dr. Cone. Both studies were then able to utilize various combinations of the placebo and commercially available product to yield an effective dose range of 0, 1, 2, and 4 units (smokeless tobacco pouches or smokeless cigarettes). The main finding of these studies was that both products produced key subjective and physiologic effects which mimic those produced by administration of nicotine by other routes. Such findings confirmed the basic rationale of replacing one route of nicotine administration with another route of nicotine administration. On the other hand, it is apparent that each route of nicotine administration is also distinguished by a specific pharmacodynamic and pharmacokinetic profile, as well as peripherally-mediated sensory effects, which may be of practical as well as theoretical import. For instance, smokeless tobacco may be a more acceptable alternative for cigarettes than is nicotine chewing gum since the smokeless tobacco product not only provides tobacco-sensory stimuli but also a pharmacodynamic profile which results in elevated abuse liability. The smokeless cigarette on the other hand, seems to provide a high degree of sensory simulation (possibly due to upper air way absorption of nicotine) when only a relatively small amount of nicotine is detectable in the plasma.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00006-01 BDL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Triazolam Self-Administration: Effects of Yohimbine Pretreatment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J.E. Henningfield, Ph.D.	Chief	BDL, NIDA, ARC
J.D. Roache	Staff Fellow	BDL, NIDA, ARC
R.A. Meisch, M.D., Ph.D.	Visiting Scientist	BDL, NIDA, ARC

COOPERATING UNITS *(if any)*

Biology of Vulnerability (J.H. Jaffe)
Research Support Branch (W.R. Lange)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potenial Assessment Laboratory

INSTITUTE AND LOCATION

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.1	1.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study was to examine the effects of yohimbine pretreatment on th self-administration of triazolam in subjects with histories of sedative drug abuse. This study addressed two different issues of relevance to studies in the behavioral pharmacology of drug abuse. First, this study involved the development of procedure measure sedative/anxiolytic drug self-administration in humans (a phenomenon which h been demonstrated in infra-human species but has not been well demonstrated in human experimental models). A second objective of this study was to examine the effects o yohimbine pretreatment on triazolam self-administration. It is of basic theoretical, well as clinical, interest to define methods to detect the effects of one drug on th self-administration of another drug. In addition, yohimbine has been shown to produ neuroendocrine changes and subjective mood states in humans which resemble anxiety a thus it is of theoretical interest to determine whether a chemically-induced anxiety enhance the self-administration of a benzodiazepine having anxiolytic activity.

Preliminary results suggest that triazolam does maintain stable, dose-related self-administration behavior, and that yohimbine does produce anxious-mood states an increases triazolam self-administration. This study should provide valuable informat regarding human experimental models of drug taking behavior and may ultimately relate the "self-medication" or "need" hypotheses frequently proposed to explain the etiolo of drug abuse.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00007-02 BDL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Assessment of the Liability of Adverse Effects: Drug Effects on Human Performance (Army Contract Initiated Study)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J.E. Henningfield, Ph.D.	Chief,	BDL, NIDA, ARC
J.D. Roache, Ph.D.	Staff Fellow	BDL, NIDA, ARC
R.A. Meisch, M.D., Ph.D.	Visiting Scientist	BDL, NIDA, ARC

COOPERATING UNITS *(if any)*

Research Support Branch (W.R. Lange)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.35	1.35	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This research effort involved the development of procedures to permit studies examining the profile of effects of psychoactive drugs in nonresidential "normal" volunteers. In the nonresidential studies, subjects without drug abuse histories were recruited to report to the laboratory on a regular basis for participation in studies involving the daytime administration of psychoactive drugs; subjects were discharged at the end of the day. The objective of these studies was to examine the effect of various drugs on a subject's mood, physiological function, and ability to perform various tasks designed to measure different dimensions of human performance capability. Drugs under investigation include alcohol, chlorpheniramine and amphetamine.

These studies contribute the understanding of the profile of effects associated with drugs of abuse and they considerably extend the performance assessment capabilities of the ARC. In addition, the methods used in nonresidential research may be extended to the impending increase in such efforts planned in the FY 87 budget which include nonresidential subject evaluation and testing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00008-02 BDL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

~~Behavioral Performance and~~ Physiologic Effects of Drugs: Atropine and Diazepam (Army Contract Initiated)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J.E. Henningfield, Ph.D.	Chief	BDL, NIDA, ARC
R. J. Lamb, Ph.D.	Staff Fellow	BDL, NIDA, ARC
S.T. Higgins, Ph.D.	Staff Fellow	BDL, NIDA, ARC

COOPERATING UNITS *(if any)*

Cognitive Studies and Human Performance Lab (R.I. Herning; W.B. Pickworth; F. Snyder)
Research Support Branch (W.R. Lange)

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.1	1.1	2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several protocols had been written and two studies were initiated and conducted durir FY 86 which were of interest to our colleagues in the Joint Working Group of the Army contract as well as of interest to the Addiction Research Center. The thrust of thes studies is two-fold: first to access the effects of the drugs which may be given unc conditions in which the person is expected to maintain safe and effective performance various tasks. This sort of methodology is readily adapted to questions of fundament interest to the ARC such as: does the smoking of one marijuana cigarette per day, o the ingestion of antihistamines or other drugs of widespread use produce an impairmer of intellectual function? The second aspect of this research is to identify electrophysiological correlates including changes in passive EEG as well as evoked cortical potentials. These studies are therefore conducted in cooperation with the Cognitive and Human Performance Laboratory where EEG and evoked potential data are collected. A separate project report from that laboratory will go into greater detai on the progress made in that area. In the Biology of Dependence Laboratory, during F 87, two drugs, atropine and diazepam, have been studied. These studies both showed orderly and dose-related effects of these drugs on a variety of measures of subjectiv response and performance on the computerized Performance Assessment Battery (PAB). T basic methodology has also readily lent itself to studies with a variety of other dru under assessment at the Addiction Research Center including opioids, cocaine, and nicotine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00009-03 BDL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Drug Effects on Cigarette Smoking: Naloxone, Mecamylamine, Nicotine and Marijuana

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J.E. Henningfield, Ph.D. Chief BDL, NIDA, ARC

*R. Nemeth-Coslett, Ph.D. Staff Fellow BDL, NIDA, ARC

COOPERATING UNITS *(if any)*

Roland R. Griffiths, Ph.D.
Johns Hopkins

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.2	*(FAES/Merrell Dow = .15 yr & Hopkins provided all RA Support

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

These studies were conducted in the physical facilities of the Behavioral Pharmacology Research Unit at Johns Hopkins. During the past year, studies with three drugs were completed. Multiple measures of cigarette smoking, subjective effect and physiologic effect were collected during ad lib smoking sessions in normal volunteers following administration of mecamylamine, naloxone, or marijuana.

Mecamylamine increased several measures of cigarette smoking including number of cigarettes, number of puffs per cigarette and expired air carbon monoxide levels. Subjective effects produced by mecamylamine were not characteristic of those produced by psychoactive drugs. Naloxone did not significantly affect any measure of cigarette smoking including number of cigarettes, number of puffs or expired air carbon monoxide. Subjective effects included increases in subject ratings of yawning, stretching and relaxation. Marijuana did not significantly affect any measure of cigarette smoking including number of cigarettes, number of puffs or expired air carbon monoxide level. Marijuana smoking did produce dose-related increases in heart rate, and ratings of dose strength and drug liking.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00010-03 BDL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (40 characters or less. Title must fit on one line between the borders.)

Behavioral and Pharmacologic Factors in Nicotine Replacement for Tobacco Dependence

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

J.E. Henningfield, Ph.D.	Chief	BDL, NIDA, ARC
*R. Nemeth-Coslett, Ph.D.	Staff Fellow	BDL, NIDA, ARC
S.T. Higgins, Ph.D.	Staff Fellow	BDL, NIDA, ARC

*Students

COOPERATING UNITS (If any)

Cognitive Studies and Human Performance Laboratory - R.I. Herning, Ph.D.; W.B. Pickworth, Ph.D.; F. Snyder, Ph.D.
Research Support Branch - W.R. Lange

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.95	.45	15 *(FAES/Merrell Dow = .5 yr)

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Nicotine delivering polacrilex (chewing gum) has been under investigation as a replacement for tobacco-delivered nicotine and also as a useful and practically convenient drug administration modality which provides a model of more general intere for drug dependence researchers. For instance, nicotine gum was employed in our init studies to set up and validate the performance assessment capabilities of our new computerized PAB, as well as to test the capabilities of the electrophysiologic laboratory to measure EEG correlates of performance effects of drug administration. course of research using this compound has been determined by the priorities and interest of the Addiction Research Center and the Chief of the Biology of Dependence Laboratory. However, since such information can provide a potential scientific benef to a pharmaceutical firm (Merrell Dow), we had accepted a grant which covered the salary and benefits of one of the principal investigators on these studies, Dr. Nemeth-Coslett. These studies have included the following: (1) Effects of nicotine replacement on cigarette smoking and tobacco smoke exposure; (2) Pharmacodynamic effects of nicotine 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 on factors which may affect the functional do such as chewing rate and swallowing rate; (5) Effects of nicotine gum administration learning and performance in non-smokers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00011-03 BDL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Physiologic Dependence to Tobacco: Cigarette Withdrawal and Nicotine Substitution

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J.E. Henningfield, Ph.D.	Chief	BDL, NIDA, ARC
*R. Nemeth-Coslett, Ph.D	Staff Fellow	BDL, NIDA, ARC
A. Sampson, LPN	LPN	BDL, NIDA, ARC

COOPERATING UNITS *(If any)*

BPL - S.R. Goldberg, Ph.D.; J. Katz, Ph.D.; C. Schindler, Ph.D.
RSB - W.R. Lange, M.D.

LAB/BRANCH
Clinical Pharmacology

SECTION
Biology of Dependence and Abuse Potential Assessment Laboratory

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	.4	1 *(FAES/Merrell Dow = .3 yr)

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Despite the vast literature related to tobacco withdrawal and physiologic dependence, no single study has rigorously adapted the design of studies that was used to characterize withdrawal from opioids and sedatives. In this study, a relatively homogeneous group of heavy tobacco users was studied on the residential research unit. In the withdrawal study, subjects were assessed along the following dimensions: self-reported mood, feeling and symptomology, performance assessment, sleep patterns, plasma nicotine and cotinine, general cardiovascular functioning, passive EEG and evoked cortical potential, and caloric intake. In the cigarette withdrawal study, baseline values were collected on these measures during the initial week of the subject's stay on the research unit 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. During the cigarette-abstinence days, subjects were given a piece of gum to chew 12 times per day at one hour intervals. The gum contained either 0,2 or 4 mg of nicotine. In brief, these studies showed that an orderly syndrome of rebound withdrawal emerged during tobacco abstinence. The signs and symptoms characterized a true withdrawal syndrome and were not simply a return to baseline upon removal of nicotine-induced effects. Nicotine substitution for cigarettes produced a dose-related reversal of major signs and symptoms of tobacco withdrawal, confirming that the withdrawal was nicotine specific. 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).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00012-03 BDL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J.E. Henningfield, Ph.D.	Chief	BDL, NIDA, ARC
S.T. Higgins, Ph.D.	Staff Fellow	BDL, NIDA, ARC

COOPERATING UNITS *(if any)*

JHU - K.L. Preston, Ph.D. Biology of Vulnerability - J.H. Jaffe
Chemisty and Drug Metabolism - E.J. Cone, Ph.D.

LAB/BRANCH

Clinical Pharmacology

SECTION

Biology of Dependence and Abuse Potential Assessment Laboratory

INSTITUTE AND LOCATION

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	.4	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Following from the observations that post-addicts and non-opioid users are differentially sensitive to opioids, and perhaps even respond qualitatively differe and the possibility that such differences either predispose certain persons to opio abuse and/or contribute to relapse, this study was conducted to experimentally exam such population differences in response to mu and kappa opioids. Prominent measure included discrimination thresholds of behavioral effects, physiologic responses, an neuroendocrine response. Post-addict and opioid-naive subjects were intended to be separately tested for comparison. However, changes in priorities have resulted in termination of the protocol before the opioid-naive subjects were tested. Testing completed, however, on the initial phase involving post-addict volunteers. These d are currently being analyzed.

PHS 6040 (Rev. 1/84)

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 DA 00013-02 BDL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Archival Data Base

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

C. Haertzen	Research Psychologist	BDL, NIDA, ARC
J.E. Henningfield, Ph.D.	Chief	BDL, NIDA, ARC
A. Haynes	Research Technician	BDL, NIDA, ARC

COOPERATING UNITS *(if any)*
Biology of Vulnerability - J.H. Jaffe Johns Hopkins, Addiction Research Foundation
Cognitive Studies and Human Performance Laboratory - F. Snyder

LAB/BRANCH
Clinical Pharmacology

SECTION
Biology of Dependence and Abuse Potential Assessment Laboatory

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.55	1.05	.5

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The principal objective of database activity is to increase access to the data obtained in past experimental studies or standard admission data and to link databases. By combining the results of numerous studies it is possible to determine important relationships which would not be possible in experimental studies using limited N's. In the first model, 750 records of test responses on morphine or placebo, in studies by Drs. W. Martin and D. Jasinski, were placed in a single database. Numerous relationships within this body of data were studied, such as potency and the effectiveness of the various measures used to evaluate the effects of morphine. The potency of intramuscular and subcutaneous injections is equal and half that of intravenous injections. The most effective indicators of the morphine effect are identification of morphine as dope, pupillary diameter, liking the drug, itching, and euphoria (MBG).

More current data obtained by the recruitment staff (Addiction Severity Index, SCL-90, SHIPLEY IQ, Early Childhood Aggression) and admission test data (Diagnostic Interview Schedule, Buss-Durkee Hostility, MMPI, Alcohol Related Behavior Questionnaire, and EEG) have been combined into a single database. Results of these analyses will be reported by those in The Psychology of Vulnerability lab.

The data have also been useful to compare to other similar databases. For instance, correlations of severity of use of alcohol, tobacco, caffeine, and other drugs were possible to ascertain in a population of primarily opioid abusing subjects at the Addiction Research Center with a population of primarily alcohol and sedative abusers at the Addiction Research Foundation in Toronto.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00001-01 BVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Dopaminergic Mechanisms and Cocaine Effects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jerome Jaffe, M.D.	Acting Chief	BVL	ARC
Others:	Karen Kumor, M.D.	Clin. Pharmacologist	BVL	ARC
	Michael Sherer, M.D.	Staff Fellow	BVL	ARC
	Nicola Cascella, Ph.D.	Staff Fellow	BVL	ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH
Biology of Vulnerability

SECTION
Clinical Biology Branch

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.9	0.9	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

1. Cardiovascular mechanisms in the human abuse of cocaine

We assessed the effects of haloperidol, a dopamine blocking agent, on the cardiovascular effects of cocaine, in order to evaluate the relevance of dopaminergic neurotransmission.

As has been demonstrated by earlier work in this laboratory, intravenous doses of cocaine were followed within minutes by elevations in systolic and disastolic blood pressure and heart rate. The dose administered in this study, 40 mg i.v., is perceived by our patients as similar to a moderate street dose of the drug; this is consistent with our selecting experienced cocaine users. In this population 8 mg of haloperidol was not associated with significant declines in blood pressure. However, when administered 20 minutes before cocaine, haloperidol blocked the cocaine induced rise in both systolic and diastolic blood pressures, although there was little effect on cocaine related rise in heart rate.

The findings are consistent with suggestions that the pressor effects of cocaine in man are mediated via catecholaminergic mechanisms; the role of alpha adrenergic neurotransmission appears central to this process.

The significance of this finding lies in the ability to predict clinically relevant interventions for some of the physiologic toxicity of cocaine.

2. Dopaminergic mechanisms and the subjective effects of cocaine

Previous work in our laboratory has confirmed several clusters of subjective and psychiatric effects of intravenous cocaine. Clinical case reports have suggested that although haloperidol is a potent antipsychotic and may block the development of paranoia in human cocaine abusers, it has little effect on the acute subjective effects of the drug. Using the battery of self-ratings developed by our group, we assessed the ability of haloperidol to block these subjective effects. Cocaine was administered to 5 addict volunteers using a dose (40 mg i.v.) which produced subjective effects that resembled their street doses of the drug. Prior to cocaine administration, patients received a dose of 8 mg haloperidol. The study also used control conditions of haloperidol pretreatment followed by placebo administration i.v., and placebo pretreatment followed by 40 mg cocaine. The results indicate that haloperidol pretreatment had no effect on the perception of drug "rush". There was some effect of haloperidol on perception of drug "high" (measured by self analogue self-ratings and by subscales of the Addiction Research Inventory (ARCI). Overall, the cocaine experience was rated as very pleasurable by the addict, despite haloperidol pretreatment.

This work suggests:

1. Differences in neurochemical modulation of various subjective effects of cocaine.

2. That although haloperidol is useful in the treatment of cocaine induced psychosis, it does not appear to be useful, in clinically relevant doses, in the prevention of cocaine induced euphoria.

3. Neurochemical aspects of cocaine infusions

Cocaine has long been assumed to block the synaptic reuptake of catecholamines, including norepinephrine (NE) and dopamine (DA). Despite an abundance of experiments in animals, there have been no studies in humans assessing synaptic transmission of catecholamines following i.v. cocaine administration. We evaluated catecholamine transmission by measuring plasma concentrations of NE and its metabolite MHPG, and the dopaminergic metabolite, homovanillic acid. We also assessed peripheral sympathetic activity by monitoring cardiovascular measures. Cocaine was administered as a continuous intravenous infusion over a period of four hours.

Despite a robust rise in systolic and diastolic blood pressure following cocaine administration, no accompanying rise in plasma NE was seen. Rather a small but significant decrease in plasma NE was seen in comparison with baseline (preinfusion) controls. This decrease was paralleled by a decrease in plasma MHPG. Under certain circumstances desipramine, a prototypic uptake blocker, is associated with declines in plasma norepinephrine; this likely reflects preferential activity at the alpha2 presynaptic receptor site. The dissociation between plasma levels of amines and cardiovascular response suggests differences in the mechanisms of amines which underlie these effects, possibly reflecting differences between central and peripheral compartments.

4. Bromocriptine pretreatment for cocaine abuse

Bromocriptine has been suggested as a potential treatment for cocaine addicts. This is likely related to its action at the dopaminergic receptor. There is currently evidence for both hyper and hypodopaminergic states as a consequence of cocaine abuse. In a group of experienced cocaine users, we are assessing the ability of pretreatment with bromocriptine to block subjective effects of acutely administered intravenous cocaine. Further, we are assessing possible effects of bromocriptine on the craving addicts experience shortly after cocaine administration. Preliminary evidence suggests that while chronic use of bromocriptine may help reduce baseline drug craving, the effects of bromocriptine pretreatment on the subjective effects of cocaine are limited.

5. Description and assessment of "acute" craving after cocaine injection and the effects of the interaction with bromocriptine

If we observe the pattern of cocaine use by addicts, we are able to see that after each injection the subjects will report the presence of a strong desire to repeat the pleasurable experience of the first "high" or "rush" induced by cocaine. Our goal was to describe the phenomenology of this craving, its time course and the effects of bromocriptine, a dopaminergic agonist, on this kind of craving. To date, nine male volunteers have particpated in the study. All were chronic drug users. A double blind design during which the subjects received bromocriptine or placebo at 8 a.m. and cocaine or placebo at 10 a.m. was implied. The assessment of the craving with a "Checklist for drug related feelings" was made five times during the study day. The data, not yet completely analyzed, showed that the cocaine condition increased the craving and that the bromocriptine did not have any effect, "acutely", in reducing this kind of craving.

Publications

Haloperidol induced dystonia in cocaine addicts. Lancet 2:1897, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00002-01 BVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Multidimensional Scaling of Subjectively Induced Drug Effects

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Karen Kumor, M.D.	Clinical Pharmacologist	NIDA/ARC
Others:	Charles Haertzen, Ph.D.	Senior Investigator	NIDA/ARC
	Crawford Clark, Ph.D.	Senior Investigator	Columbia Neuropsychiatric Institute, NY
	James Janal, Ph.D.	Investigator	Columbia Neuropsychiatric Institute, NY

COOPERATING UNITS (if any)
Columbia Neuropsychiatric Institute, NY

LAB/BRANCH
Biology of Vulnerability

SECTION
Clinical Pharmacology

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	0

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [X] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

There are multiple brain receptors which bind opiate drugs. The psychopharmacologic and physiologic effects of agonism at these different receptors is not precisely known in man. This study will attempt to analyze subjective report data using multidimensional scaling techniques. The data are subjectively judged similarities between drugs. Volunteers were given a training series of single injections of unknown opioid drugs (including placebo and naloxone). Then in a second test set of injections they were asked how similar the test drug of that day was to each of the training doses. The data obtained this way can then be analyzed with multidimensional mathematical fitting using sophisticated computer programs. The data may result in maps of the psychopharmacologic space in which drugs are arranged by their similarity to each other. This kind of map may be useful because the number of dimensions and the coordinates of a drug in dimensional space indicate the number of different kinds of receptors at which the drugs mapped are active as well as characterize the receptor type.

The data are collected on this work. We are awaiting the contract approval for the analysis to take place.

Publications:
None

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00003-01 BVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pharmacologic & behavioral effects of calcium channel blockers administered acutely

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jerome Jaffe, M.D.	Director, ARC	NIDA/ARC
Others:	Robert Lange, M.D.	Medical Officer	NIDA/ARC
	Karen Kumor, M.D.	Clinical Pharmacologist	NIDA/ARC
	Ronald Herning, Ph.D.	Senior Investigator	NIDA/ARC
	Wallace Pickworth, Ph.D.	Senior Investigator	NIDA/ARC
	Michael Sherer, M.D.	Fellow	NIDA/ARC
	Nicola Cascella, Ph.D.	Fellow	NIDA/ARC

COOPERATING UNITS *(if any)*
Cognitive Studies and Human Performance Lab

LAB/BRANCH
Biology of Vulnerability

SECTION
Clinical Pharmacology

INSTITUTE AND LOCATION
NIDA/Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study is in its initiation phase. The study will examine the effects of calcium channel blockers on the subjective and physiologic responses to IV cocaine. Nifedipine is the first drug to be studied in a randomized crossover design in which the calcium blocker is given during a one week period every 8 hours with stepwise increases during the week. Cocaine challenges are given at intervals to assess the effect of the blocker drug.

This study was only in the preparatory phases during the period of time covered by this report.

Publications:
None

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00004-01 BVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
The Human Pharmacology of Cocaine

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Jerome Jaffe, M.D.	Director, ARC	ARC/NIDA
Others:	Karen Kumor, M.D.	Clinical Pharmacologist	ARC/NIDA
	Edward Cone; Ph.D.	Section Chief-Chemistry	ARC/NIDA
	Michael Sherer, M.D.	Psychiatrist - Fellow	ARC/NIDA
	Loren Thompson, Ph.D.	Chemist - Fellow	ARC/NIDA

COOPERATING UNITS (if any)
None

LAB/BRANCH
Biology of Vulnerability

SECTION
Clinical Pharmacology

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.2	2.6	1.6

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The effects of cocaine in human cocaine using volunteer subjects were studied in order to evaluate physiologic and subjective effects under various pharmacologic conditions.

A. Continuous Infusion of Cocaine

Tolerance to the subjective and physiologic effects of cocaine has been hypothesized to occur after single IV injections of cocaine. We studied the physiologic and subjective responses of human volunteers during continuous infusions of cocaine which followed bolus injections of cocaine. This regimen was designed to achieve rapidly a steady-state concentration of cocaine and maintain it. Within limits we achieved this goal and compared it with bolus injections of cocaine followed by placebo infusions. The bolus doses were 40 and 60 mg of cocaine with and without cocaine infusion. Eight subjects were studied. Our results indicate: 1) There is no evidence of cardiovascular tolerance to cocaine during continuous infusion; 2) The subjective effects caused by cocaine can be divided into two kinds, those which are cocaine concentration related and those which are not. "Rush" is not related to the cocaine plasma concentration because the experience of rush is unaltered by the cocaine infusion condition; 3) Continuous infusion of cocaine for four hours is associated with a syndrome of feelings of dread, fear of death, paranoia, and hostility. We believe that this syndrome is a prodrome to the paranoid psychosis caused by cocaine.

B. Repeated Bolus Study

This experiment was designed to study the pharmacologic tolerance to repeated dosing of cocaine. Two IV injections of 40 mg of cocaine was given at intervals of 70 minutes or 3 hours and physiologic and subjective effects were studied. The results show that at 70 minutes the rush is greatly diminished with reference to the first cocaine injection. However, the other subjective effects of cocaine are unchanged. This result is in agreement with the results of experiment A, i.e., these effects are cocaine plasma dependent but "Rush" is not. The results of the 3 hrs. experiment are not fully collected nor analyzed at this time.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00005-01 BVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Effect of Naloxone Blockade on Ketocyclazocine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jerome Jaffe, M.D.	Director, ARC	ARC/NIDA
Others:	Karen Kumor, M.D.	Clinical Pharmacologist	ARC/NIDA
	Charles Haertzen, Ph.D.	Psychologist	ARC/NIDA

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Biology of Vulnerability

SECTION
Clinical Pharmacology

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Ketocyclazocine is primarily an opiate kappa receptor agonist. In previous work accomplished by our group we have shown that the drug causes dysphoric effects in opiate experienced human volunteers (drug abusers). We wished to examine the ability of naloxone to block the effects of ketocyclazocine in order to test the hypothesis that the dysphoria was in fact opiate in nature. The experiment consisted of giving 1.2 mg IM of ketocyclazocine in combination with 0-5 mg of naloxone. The response of naloxone on morphine 30 mg IM was also studied as a control.

The results of the experiment clearly demonstrate naloxone blockade of all the subjective and physiologic effects of ketocyclazocine previously observed. We conclude that these effects are therefore by definition opiate in nature. Furthermore, that naloxone is less potent in blocking the effect of ketocyclazocine than morphine but the ratio is less than 3/1. This differs from animal experiments in which the ratios are 10-20/1. The status of this work is that more statistical analyses needs to be done and the paper prepared.

Addendum 1

Additional work was conducted as an addendum to the original study. It has been postulated that pentazocine, at a low dose, exerts opioid effects by selective stimulation of mu or kappa opioid receptors. At a high dose, however, it exhibits psychotomimetic effects which may be mediated through its sigma receptor stimulation. Accordingly, the analgesic and opioid subjective effects of pentazocine should be naloxone reversible, while the psychotomimetic effects mediated presumably through the sigma receptor should not. This work is not completed. More subjects are being recruited.

Publications:
None

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00006-01 BVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
The human psychopharmacology of ketocyclazocine as compared to morphine, cyclazocine, naloxone and placebo

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Donald Jasinski, Ph.D.	Acting Director (now retired)	NIDA/ARC
Others:	Karen Kumor, M.D.	Clinical Pharmacologist	NIDA/ARC
	Charles Haertzen, Ph.D.	Psychologist	NIDA/ARC
	Rolley E. Johnson, Pharm.D.	Pharmacist/Branch Chief	NIDA/ARC

COOPERATING UNITS (if any)
None

LAB/BRANCH
Biology of Vulnerability

SECTION
Clinical Pharmacology

INSTITUTE AND LOCATION
NIDA Addiction Research Center

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

1. The effects of the kappa opioid agonist, ketocyclazocine, in 10 drug using volunteers. The effects of the drug were compared with effects of standard opioid drugs, including cyclazocine, a mixed agonist-antagonist which has a chemical structure similar to ketocyclazocine and is thought to be an agonist of mu, kappa and sigma opioid receptors; morphine, a mu receptor agonist; and naloxone, an opioid antagonist.

Subjective and physiologic measures were employed and new measures of drug identification and judgments of perceived similarity were developed and used. Ketocyclazocine was found to have properties similar to cyclazocine and be very different from morphine and naloxone on subjective, identification and judgment measures. Furthermore, the drug has severe dysphoric and hallucinogenic properties. This suggests, but does not prove, that kappa agonism causes dysphoria or hallucinations.

2. In this study, the doses of naloxone were between 210 and 300 mg give IM. These large doses were employed to assess the subjective, prolactin response and physiologic effects of doses of naloxone measured by our test battery. This work was performed in preparation for kappa agonist blockade studies in which large doses will be used to block the effects of kappa receptor agonists. Results of the physiologic measurements, respiration, temperature and prolactin from 10 drug-using volunteers indicate that, at these large doses, naloxone may have some weak opioid agonist activity. The results of the subjective report data indicate a vague psychopharmacologic stimulus is present which is compatible with weak agonism at a kappa receptor.

Publications

Kumor, K.M., Haertzen, C., Johnson, R., Kocher, T., and Jasinski, D. The human psychopharmacology of ketocyclazocine as compared to cyclazocine,

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00001-02 AID

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Maryland Addict Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jerome Jaffe, M.D.	Director, ARC	PVL/BVL	ARC
Others:	Robert Lange, M.D.	Medical Director	AID	ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH

AIDS

SECTION

Clinical Biology Branch

INSTITUTE AND LOCATION

NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3		

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Three cohorts of Maryland drug addicts are being studied to provide long term outcome with regard to general features and particularly with regard to AIDS and AIDS-related syndromes. Between 5/71 and 5/72 one hundred Marylanders were admitted to the Lexington facility. These subjects will be sought out and followed up or their death records obtained. That cohort will be compared with a cohort consisting of the first 100 admissions to the ARC Baltimore (1979-1980). All ARC research applicants will be studied from 1986 onward.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00002-02 AID

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Lexington Addict Follow Up Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jerome Jaffe, M.D.	Director, ARC	PVL/BVL	ARC
Others:	Robert Lange, M.D.	Medical Director	AID	ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH

AIDS

SECTION

Clinical Biology

INSTITUTE AND LOCATION

NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3		

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In a cohort of 1129 people admitted to Lexington between 5/71 and 5/72 ELISA testing for HIV virus with subsequent Western Blot testing revealed 29 positive tests. All charts of the cases and 3 random controls from each case have been extracted and the data computerized. Input from the Social Security Administration and the National Death Index, National Center for Health Statistics is pending. A mortality followup study is being completed. As well as HIV positivity and AIDS, hepatitis B is also being studied.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00003-01 AID

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
HIV Sero-Prevalence Pilot Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jerome Jaffe, M.D.	Director, ARC	PVL/BVL	ARC
Others:	Robert Lange, M.D.	Medical Director	AID	ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH
AIDS

SECTION
Clinical Biology Branch

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1		

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The aim of this study is to examine the seroprevalence rate of parenteral drug abusers recently enrolled in treatment programs of a geographic cross section of the United States. Blood specimens have been collected from New York, NY; Baltimore, MD; Tampa, FL; San Antonio, TX; and Southern California. Samples from Denver, CO have also been collected, but testing is incomplete. Samples from the other areas have been tested by ELISA with subsequent Western Blot testing on the ELISA positive samples. Results show that more than 50% of those in the New York area are HIV positive by both tests. In Baltimore 29% of those tested were positive. Those tested in other areas show less than 2% were positive. These studies present opportunities for epidemiological followup and preventative medical studies.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00004-01 AID

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Inhalable Nitrites - Abuse Potential and Immune Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jerome Jaffe, M.D.	PVL/BVL	ARC
Others:	Elizabeth Dax, M.D., Ph.D.	AID	ARC
	Robert Lange, M.D.	AID	ARC
	Ronald Herning, Ph.D.	CHP	ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH
AIDS

SECTION
Clinical Biology Branch

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2		

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The intake and frequency of inhalation of inhalable nitrites has been associated with the incidence of Kaposi's sarcoma in people suffering from AIDS. In animals and in vitro studies have shown that immune cell function has been altered by these agents. However, no such study directly relating the effects of nitrites to disturbances of immune function has been performed in humans. We have designed and implemented a study in healthy, HIV negative volunteers. An inhalation protocol where the subject inhales 3 doses of amylnitrite for 3 days and 1 dose on the fourth day is being carried out. A battery of immune function tests are carried out on 2 occasions prior to the inhalation protocol, then immediately following the last dose and at 24 hours, 96 hours, and 7 days after the last dose. Five subjects have completed the protocol. Early results suggest that immune function may be severely disturbed following amylnitrite inhalation as evidenced by changes in natural killer cell activity and alterations in the T cell ratios. Since the addictive potential of these agents has not been studied, to date, such studies are also incorporated into the protocol. To better understand the mechanisms of these agents we have collected plasma samples from the subjects immediately prior to and following inhalation of amylnitrite. The possibility of an important immunoendocrine interaction is also being investigated. Radioimmunoassays for the relevant neurohormones are being established. The more frequently used butylnitrite is sold as a room odorizer. We plan to study the effect of this agent as soon as the impurity content of this agent is established. This study is underway.

GPO 914-918

Annual Report of the Preclinical Pharmacology Branch
Addiction Research Center
October 1, 1985 to September 30, 1986
Steven R. Goldberg, Ph.D., Chief

Introduction

The Preclinical Pharmacology Research Branch conducts research on the reinforcing effects of drugs of abuse, the influence of such drugs on learned operant behavior, and the discriminative stimulus properties of these drugs. The Branch also conducts neuropsychopharmacological studies using animal models to investigate the modes of action of drugs of abuse, the neurobiological basis of reinforcement, and pathologic changes in neural function that predispose to, or are a consequence of, drug abuse. Research is carried out in both primates and non-primates. New drugs are evaluated for abuse potential by examining their reinforcing, aversive and discriminative stimulus effects and comparing the effects of prototypic drugs of abuse with these as well as on effects in well characterized neurophysiologic systems. The Preclinical Pharmacology Research Branch consists of three laboratories.

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

Overview

The Behavioral Pharmacology Laboratory is responsible for investigating the mechanisms whereby drugs gain control over behavior. The role of drugs of abuse from different pharmacological classes, including psychomotor stimulants, opioids, barbiturates and benzodiazepines, are being investigated with respect to how the opportunity for occasional drug self-administration leads to long sequences of integrated behavior culminating in self-administration of the drug and how administration of these drugs alters ongoing behavior controlled by non-drug events, such as food or water presentation or electric shock delivery. The positive reinforcing as well as the punishing properties of these drugs are being studied to develop an understanding and technology of how drug-seeking becomes strong and persistent and how it might be weakened by pharmacological and behavioral means.

These objectives are being pursued using a variety of experimental procedures, including (1) assessing the reinforcing effects of these drugs using intravenous self-administration procedures, (2) examining their effects as noxious stimuli using schedules of punishment of ongoing behavior by i.v. drug injections or termination or postponement of i.v. drug injections, (3) quantifying their behavioral effects using

fixed-interval and fixed-ratio postponement schedules as baselines, and (4) determining their effects as discriminative stimuli using two-lever choice situations.

Collaborative studies are being pursued with various laboratories. For example, comparative studies of repeated sequences of drug-seeking behavior controlled by intermittent i.v. injections of nicotine and cocaine under complex second-order schedules in humans and in non-human primates are being pursued jointly with the Biology of Dependence and Abuse Potential Assessment Laboratory. Also, studies of neurochemical correlates of the behavioral actions of psychomotor stimulants are being pursued with the Neuroscience Branch utilizing studies of receptor binding and local cerebral glucose utilization.

The long term goals of the Behavioral Pharmacology Laboratory will continue to change as new personnel arrive and initiate new programs but there will continue to be a focus on environmental conditions which determine whether drugs have positive reinforcing or aversive effects, on the use of complex second-order schedules of drug injection in humans and non-human primates to investigate the control of drug-seeking behavior by associated environmental stimuli, and on determination of the pharmacological mechanisms of the behavioral effects of drugs of abuse.

Summary of Ongoing Research

A. Effects of Drugs on Schedule-Controlled Behavior of Experimental Animals: Goldberg, S.R. and Katz, J.L.

General information on the behavioral pharmacology of a drug in the pertinent species is necessary to evaluate quantitatively how the drug functions as a reinforcer or a punisher and to establish a profile of behavioral effects. Multiple schedules of food presentation with both fixed-interval and fixed-ratio components have been most frequently used in this type of study since they generate a wide range of rates and patterns of responding within a single 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, including nicotine, caffeine, narcotic agonists and antagonists and psychomotor stimulants, under multiple schedules of food presentation in squirrel monkeys, rats, and pigeons. Because the behavioral effects of certain drugs depend on the type of consequent event that maintains behavior, the effects of drugs on comparable performances maintained by either delivery of electric shock or by termination of a stimulus associated with electric shock are

also studied.

These procedures provide stable, long term, sensitive baselines for quantitative assessment of both stimulant and depressant drug effects. In addition, the long term nature of these baselines makes them ideal for studying tolerance and cross-tolerance development to chronic treatment with various drugs, including cocaine, caffeine, adenosine analogs, and benzodiazepines. These procedures result in comparable rates and patterns of behavior in different species of experimental animals. Since a large body of literature on the effects of a variety of drugs from many pharmacologic classes already exists for comparison, these procedures are valuable for assessing the behavioral pharmacology of other compounds, such as cocaine metabolites and analogs, nicotine-like agonists, narcotic agonists and antagonists, B-carbolines and benzodiazepine antagonists.

B. Suppression of Behavior by Drug Injections: Katz, J.L. and Goldberg, S.R.

Many psychoactive drugs, including cocaine, nicotine and nalorphine, exhibit an important duality shared with certain other agents. That is, they can function effectively as positive reinforcers or as punishers within the same dose range depending on the context of environmental conditions. Systematic evaluation of environmental conditions which determine the type and direction of behavioral effects with a variety of drugs may have practical implications for the control of licit or illicit drug use by humans. Initial studies in this project demonstrated that nicotine can function either as a reinforcer to maintain behavior, or as a punisher (aversive or noxious stimulus) to suppress behavior, depending on the context in which it is administered.

It is the object of this project to extend these studies to additional drugs under a variety of conditions. Responding will be maintained by food presentation in the presence of either of two distinctive visual stimuli. Responses will occasionally produce drug injections in addition to food only in the presence of one of the stimuli (punishment component). Drugs will be studied in squirrel and rhesus monkeys to determine if they selectively suppress responding only in the punishment components of the schedule.

C. Behavioral Effects of Opioid Agonists, Opioid Mixed Agonist-Antagonists, and Other Drugs of Abuse in Pigeons, Squirrel Monkeys and Rhesus Monkeys: Katz, J.L., Goldberg, S.R. and Schindler, C.W.

These studies are designed to provide a characterization of pharmacological effects of opiate mixed agonist-antagonists and other drugs of abuse. Therapeutic utility of analgesics can be limited by their side effects, such as reinforcing or noxious effects. Thus, an assessment of the analgesic potency and effectiveness of a compound is most useful in comparison to the effectiveness and potency with which the drug produces reinforcing or noxious side effects.

These studies will characterize the effects on behavior of opioids and other drugs of abuse in terms of the consequences of responding. Conditions under which the drugs may maintain schedule-controlled responding will be studied. Additionally, the specificity with which the drugs have analgesic effects will be studied by comparing drug-induced disruptions of control exerted by noxious and non-noxious stimuli. Taken together, the results of the present studies would provide a spectrum of activities for a particular drug that may characterize its actions with respect to usefulness as an analgesic and abuse liability.

D. Maintenance of Behavior by Drug Injections: Goldberg, S.R., Katz, J.L., Schindler, C.W. and Hayes, B.

Schedule-controlled performances provide a meaningful way to analyze drug-seeking behavior in the same way as operant behavior maintained by other events, such as food or electric shock. In the present project with squirrel monkeys and rhesus monkeys, the rates and patterns of responding maintained by various drugs, including cocaine, nicotine, caffeine, methohexital, morphine and chlordiazepoxide, are being compared using simple fixed-ratio and fixed-interval schedules and complex second-order schedules with brief stimulus presentation in which the role of brief stimuli in maintaining extended sequences can be assessed.

Studies of the effects of pre-session treatments with a range of doses of pharmacologic agonists and antagonists, such as caffeine, specific D-1 and D-2 dopamine antagonists, serotonergic reuptake inhibitors, and alpha adrenergic antagonists, on responding maintained by i.v. psychomotor stimulant injection or food presentation under fixed-interval, fixed-ratio and second-order schedules will be continued. The interactions of naloxone or naltrexone with behavior maintained under extended second-order schedules of morphine self-administration or food presentation will be continued. These experiments with long

second-order schedules, in which drug is injected only at the end of the session, will be extended to study the reinforcing effects of other drugs, including benzodiazepines and barbiturates. Studies of pharmacological and environmental means of weakening established behavior maintained by different drugs will be continued.

E. Reinforcing and Punishing Effects of Benzodiazepine Receptor Ligands and Other Sedative/Hypnotics: Goldberg, S.R. and Katz, J.L.

Benzodiazepines are among the most widely prescribed drugs. The widespread use of these compounds leads to concerns over their possible abuse. The present studies are designed to provide a characterization of the possible conditions that promote benzodiazepine self-administration. Additionally, behavioral effects of inverse agonists will be investigated. These compounds produce effects that are in many respects opposite those of benzodiazepines. These drugs will be examined as noxious stimuli that may suppress behavior through a punishment process and as pharmacological treatments that may alter the reinforcing effects of benzodiazepines. Benzodiazepine administration may exacerbate the punishing effects of the inverse agonists through the induction of acute dependence.

F. Comparative Studies of Drug Self-Administration by Monkeys and Human Volunteers: Henningfield, J.E., Goldberg, S.R., Katz, J.L. and Nemeth-Coslett, R.D.

One approach to assessing the dependence-producing effects of drugs is to compare the functional characteristics of behavior reinforced by drug injection in different species. In this experiment, a second-order schedule with fixed-ratio (FR) components will be used to compare responding maintained by drug administration in squirrel or rhesus monkeys to that maintained in humans. Under second-order schedules, every time the subject has completed a fixed number of responses (fixed-ratio), he will be presented with a brief stimulus (light/tone) which has been previously associated with an injection of drug; only after a fixed interval of time has passed or a fixed number of fixed-ratio components has been completed will presentation of the brief stimulus actually coincide with injection of drug.

The use of second-order schedules in this study permits repeated sequences of behavior with relatively little disruption by the direct effects of drug administration. Behavioral measures will be similar for humans and monkeys and comparisons will be made between doses and schedules within-species and across species. These studies provide an opportunity to evaluate the role of conditioned stimuli in human and non-human drug-seeking behavior. Additionally, human self-reported subjective

effects will be evaluated for dose-dependent discriminations. Pharmacological manipulations will include a comparison of patterns of self-administration maintained by morphine, cocaine and nicotine, and pretreatment with various drugs including caffeine, naloxone, cocaine, ethanol and mecamylamine.

G. Collaborative Studies on the Behavioral Pharmacology and Central Mechanisms of Action of Psychomotor Stimulant Drugs: Goldberg, S.R., Katz, J.L., Hayes, B., Swedberg, M., Kuhar, M., Ritz, M. and London, E.D.

The objectives of this joint project with the Neuroscience Branch are to determine the behavioral effects and mechanism(s) of action of cocaine and other psychomotor stimulant drugs. These objectives are sought by: (1) assessing the reinforcing effects of these drugs and certain of their metabolites and analogs using intravenous self-administration procedures, (2) quantifying their behavioral effects using schedule-controlled responding as the baseline, (3) determining their discriminative stimulus effects using a two-lever choice task, (4) studying their effects on local cerebral glucose utilization, and (5) comparing displacement of various ligands bound to rat brain membranes.

Studies to delineate the mechanism(s) of action of these drugs are conducted by determining their effects in the presence and absence of various antagonists, especially those that interact with dopaminergic and serotonergic neurotransmitter systems. The specific brain regions where psychomotor stimulants exert their effects will also be studied by determining their effects and those of related compounds (including dopaminergic and serotonergic antagonists) on local cerebral glucose utilization and by quantifying the ability of these same compounds to alter cocaine binding in the rat brain.

H. Opiates: Mechanisms of Action Involved in Effects on Classical Conditioned Responses: Schindler, C.W., Goldberg, S.R. and Harvey, J.

The purpose of this project is to investigate the effects of opiates on classically conditioned responses. The rabbit nictitating membrane preparation will be used because it allows one to unequivocally attribute the effects of a drug to the associative processes involved with classical conditioning, the sensory processing of the conditioned or unconditioned stimuli, or some combination of these processes. The pharmacological specificity of the effects of opiates will be investigated by studying the effects of opiates purported to be agonists/antagonists at mu, kappa, sigma and delta receptors. The physiological specificity of these effects will be studied using the 2-DG method for measuring metabolic activity in specific brain regions.

Publications for Fiscal Year 1986:

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Morse, Goldberg, S.R., and Katz, J.L.: Actions of opiate antagonists in relation to behavioral processes. In Behavioral Pharmacology: The Current Status, Alan R. Liss, New York, 1985, pp. 149-166.

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Weiss, S.J., Thomas, Warren and Schindler, C.: Effects of chlordiazepoxide on operant conditioned inhibition. Pharmacologist 28: 223.

Weiss, S.J. and Schindler, C.: The composite-stimulus analysis and the quantal nature of stimulus control. Psychol. Rec., submitted.

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2. Neuropsychopharmacology Laboratory -- Steven R. Goldberg, Ph.D., Acting Chief

Overview

This Laboratory conducts studies on the neuroanatomical substrates which mediate the acute and chronic effects of substances of abuse. Studies are conducted to examine neuropharmacological modes of action by which drugs of abuse produce discriminative and reinforcing stimuli as well as changes in physiological parameters, including heart rate, pupil diameter, body temperature and spinal cord reflex activity. Studies are also conducted on the neuroanatomical substrates which mediate the behavioral and physiological effects of drugs of abuse by administering drugs into discrete neuroanatomical sites of the central nervous system and by evaluating the effects of neurochemical lesions on the physiologic and behavioral effects of drugs of abuse.

The Laboratory utilizes operant behavior methodologies, pharmacological strategies, such as comparisons of the effects of selective agonists and antagonists and development of tolerance and cross tolerance to different drugs, and neuroanatomical techniques, such as intracranial self-administration of abused substances using electrolytic microinfusion transducer (EMIT) systems. Personnel perform neurosurgery to implant chronic intracerebral injection guide cannulae and conduct neurohistological examinations of tissues. Studies also are conducted to define the role of various neurotransmitters and neuropeptides in the long term changes associated with the persistent self-administration of cocaine and other drugs of abuse. Research is directed toward a more complete understanding of the role of specific brain loci and neurohumors in mediation of the actions of cocaine and other drugs of abuse in producing reinforcing stimuli.

Summary of Ongoing Research

A. Neural Substrates of Reinforcement. Psychomotor Stimulants: Porrino, L.J. and Sharpe, L.G.

The purpose of this project is to investigate neuroanatomical and neurochemical substrates which mediate the reinforcing properties of cocaine and other psychomotor stimulants. Intracranial self-administration along with intracranial self-stimulation will be used to determine those areas of the brain which subserve both the acute and chronic effects of psychomotor stimulants. Various neuroanatomical sites will be tested to determine whether they support intracranial self-administration of psychomotor stimulants. The modification of

this behavior at positive sites by selective antagonists will be examined.

Intracranial self-stimulation can be obtained at a number of brain sites. The neuroanatomical and neurochemical specificity of the effects of cocaine and other stimulants will be investigated by testing the effects of these drugs alone and in conjunction with various antagonists on self-stimulation behavior to different brain areas. Further, by comparing intracranial self-stimulation and self-administration to each other and to other behavioral paradigms, such as food reinforced responding and locomotor activity, the specificity of the effects on reward systems may be determined.

B. Pharmacologic Investigations of Kappa and Sigma Properties of Opioids, Novel Non-Opioid Compounds and Opioid Peptides: Vaupel, D.B., Su, T.-P. and Cone, E.J.

The rationale for this project is to correlate physiological and behavioral effects to binding site information using pharmacological approaches for compounds with kappa opioid and sigma and/or phencyclidine-like effects. The following research goals have been identified and are used as a framework for conducting experiments: (1) to identify and selectively antagonize animal model correlates which have been termed sigma properties from the desired kappa opioid effects; (2) to determine if physiologically or behaviorally distinct actions of d-SKF 10,047 and phencyclidine can be identified using in vivo or in vitro systems; and (3) to interact with the Clinical Branch to explore drug interactions and mechanisms of action of drugs which offer potential therapeutic utility.

Progress within the last year has included: completion of studies on ketocyclazocine and flupirtine as well as a preliminary study in the dog; development of an in vitro system for evaluating sigma and phencyclidine-like effects as well as submitting a related preliminary report for publication; and, completion of a collaborative study on the diuretic property of BW942C in animals and man as well as submitting a related manuscript for publication.

C. Pupillary Responses as a Neuronal Model System in which to Study Site and Mechanism(s) of Action of Addictive Drugs (Project Terminating): Sharpe, L.G.

The opiates and opioid peptides act centrally on parasympathetic preganglionic systems to change pupillary responses of pupil size, light reflex and fluctuation. The three components have been found to be regulated by separate mechanisms in the cat. Changes in pupillary size by the opiates seem to involve only the mu opioid system, whereas changes in light reflex and fluctua-

tion depend on non-mu opioid systems. Neuropharmacologic research on pupillary responses is used as an opioid neuronal model which may provide important information about multiple subtypes of opioid receptors and how they may interact with CNS neurotransmitters.

D. Neuropeptides Involved in the Opiate Withdrawal Syndrome: Sharpe, L. and Jaffe, J.H.

Substance P and other tachykinins are neuropeptide transmitters ubiquitous throughout the central and peripheral nervous system. Since the opiates inhibit their neuronal release, the aim of this project is to investigate their role as a major neurotransmitter involved in the opiate withdrawal syndrome. This research would contribute to the discovery of drugs (e.g., substance P antagonists) which may be effective in the clinical management of opiate detoxification.

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3. Behavioral Genetics Laboratory -- Steven R. Goldberg, Ph.D., Acting Chief

Overview

The Behavioral Genetics Laboratory is responsible for investigating the extent to which genetic factors contribute to the development of behavior controlled by illicit drugs. Abused drugs from several pharmacological classes are studied. Animal pharmacogenetic models are used to investigate the central mechanisms of abused substances, the contributions of genetic factors to drug abuse, and the commonality between various drug-induced behaviors. Cross-disciplinary studies are also conducted with other laboratories which incorporate behavioral genetic designs.

The overall goal of the research is to effectively integrate behavioral, pharmacological and genetic data into a comprehensive understanding of the biological and environmental substrates which mediate the acute and chronic effects of drugs of abuse. Available tools of behavior-genetic analysis are used, including inbred strains and selected lines of rodents, as well as outbred heterogeneous animal stocks, in planning, designing and executing studies concerning the behavioral and biochemical bases of drug action.

By using sophisticated genetic analytical techniques, including correlated characters and Mendelian analysis, the relationships between various drug-related behaviors are studied to ascertain the degree of genetic commonality among acute, chronic, and reinforcing effects of drugs. In addition, these genetic analyses allow examination of the biochemical substrates which may underlie various drug-related behaviors in collaboration with other laboratories at the Addiction Research Center.

This Laboratory also supervises animal breeding programs to provide the Addiction Research Center in particular and the scientific community in general with genetically specified animal populations for use in studies of drug abuse. Drawing upon knowledge of genetic mechanisms and population development, as well as neuropharmacology, behavioral pharmacology and behavioral genetics, the Laboratory personnel are primarily responsible for determining the phenotypes upon which selection studies will be founded.

A. Genetic Factors in the Reinforcing Effects of Drugs: George, F.R. and Goldberg, S.R.

The objectives of the proposed research are to identify genetic and environmental factors that control drug-reinforced behavior using genetically divergent rat and mouse populations. The

focus will be on the variables that control drug reinforced behavior, especially genetic variables. 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) genetic and environmental factors which contribute to drug self-administration, as well as their interactions, will be explored; and, (3) the use of genetically defined animals will provide information concerning the degree to which genetic factors regulate drug seeking behavior. These studies will build upon an infrahuman model of drug reinforced behavior and contribute to a systematized body of knowledge that may aid in the analysis of the complex problems of drug abuse.

B. Genetic Factors in Acute Response to Drugs: George, F.R. and Goldberg, S.R.

It is possible to divide drug effects into two primary categories: (1) the effects of the drug on the organism, and (2) drug-seeking behavior. Acute sensitivity to substances with abuse potential is an important factor governing both the immediate toxic effects of the drug and the potential for further drug intake. In the present project, genetic factors involved in the acute behavioral effects of drug administration will be systematically explored. The drugs to be studied include opiate agonists and antagonists, stimulants, especially cocaine, benzodiazepines, barbiturates, and phencyclidine. The vast majority of pharmacological research has utilized genetically uncontrolled subjects. Therefore, the results of the proposed experiments should serve to demonstrate the importance of genetic control in drug studies.

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Organizations Collaborating with the Preclinical Pharmacology Branch

Department of Pharmacology, Boston University School of Medicine, Boston, MA.

Department of Psychology, The American University, Washington, DC.

Department of Psychology, The University of Iowa, Iowa City, IO.

Department of Psychiatry, Louisiana State University School of Medicine, New Orleans, LA.

Department of Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, MD.

Department of Chemistry, University of Milwaukee, Madison, WI.

Homburg, Degussa Pharma, Frankfurt, FRG

Laboratory of Cerebral Metabolism, National Institute of Mental Health, Bethesda, MD.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00001-02 BPL

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (60 characters or less. Title must fit on one line between the borders.): Maintenance of Behavior by Drug Injections

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Steven R. Goldberg	Chief, Preclinical Pharmacology	BPL,NIDA,ARC
Others:	Jonathan L. Katz	Research Psychologist	BPL,NIDA,ARC
	Charles Schindler	Staff Fellow	BPL,NIDA,ARC
	Michael Swedberg	Foreign Fellow	BPL,NIDA,ARC
	Belinda Hayes	Staff Fellow	BPL,NIDA,ARC
	Jose Prada	Research Psychologist	BPL,NIDA,ARC
	Carlos Muntaner	Foreign Fellow	PVL,NIDA,ARC
	Rick Lamb	Staff Fellow	BDL,NIDA,ARC

COOPERATING UNITS (if any)

LAB/BRANCH: Preclinical Pharmacology Branch

SECTION: Behavioral Pharmacology Laboratory

INSTITUTE AND LOCATION: NIDA Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.14	1.84	.30

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Reinforcing effects of drugs were assessed in squirrel monkeys trained to respond for i.v. injections. A variety of drugs has been studied under different procedures. Under one procedure, each 30th response produces an injection. This procedure has been used to study cocaine and a series of cocaine analogs and metabolites. l-Cocaine, but not d-cocaine, maintained responding at rates above those maintained by vehicle. Norcocaine and pseudococaine also maintained responding but they were less potent than l-cocaine and their potencies correlated well with those obtained in rat brain tissue binding assays. Under another procedure, each 30th response produces a visual stimulus and intermittently, the stimulus and a drug injection. This procedure has been used to study extended sequences of responding maintained by highly intermittent injections of drugs and to study the effects of environmental stimuli associated with drug injections. Cocaine, methohexital, and opioids, such as morphine, effectively maintained responding under this procedure. Additionally, visual stimuli that accompanied the injections also acquired conditioned reinforcing effects. There was some evidence that the visual stimuli accompanying cocaine injections acquired conditioned reinforcing effects over a wider range of conditions than the visual stimuli accompanying methohexital injections.

The involvement of the dopamine receptors in the discriminative stimulus effects of cocaine is being studied in rats trained to discriminate cocaine from saline. The ability of the D-1 agonist, SKF 39393, and the D-2 agonist, quinpirole, to generalize to the cocaine cue has been studied. These compounds lacked cocaine - like discriminative effects. Also, the D-2 antagonist, sulpiride, failed to antagonize the discriminative stimulus effects of cocaine.

Since it has been reported that the phenylisopropylamines possess mixed cocaine/LSD-like effects, several phenylisopropylamines, such as MDMA and MDA, are being characterized more fully in studies of self-administration.

Maintenance of Behavior by Drug Injections, Publications - FY 1986

Katz, J.L. & Goldberg, S.R.: Second-order schedules of drug injection. In: M.A. Bozarth (Ed.) Methods of Assessing the Reinforcing Properties of Abused Drugs. Brunswick, ME: Haer Institute (in press).

Katz, J.L. & Goldberg, S.R.: Second-order schedules of drug injection: Implications for understanding reinforcing effects of abused drugs. In: N.K. Mello (Ed.) Advances in Substance Abuse, Vol. 3. Greenwich, CT: JAI Press Inc., (in press).

Goldberg, S.R. and Henningfield, J.E.: Nicotine as a reinforcer in humans and experimental animals. Pharmacol. Biochem. Behav. in press.

Goldberg, S.R. and Stolerman, I.P. (Eds.): Behavioral Analysis of Drug Dependence. Academic Press, New York, 1986.

Stolerman, I.P. and Goldberg, S.R.: Brief history and scope of behavioral approaches to dependence. In: Behavioral Analysis of Drug Dependence, (ed.) S.R. Goldberg and I.P. Stolerman, Academic Press, New York, pp. 1-8, 1986.

Goldberg, S.R. and Henningfield, J.E.: Progress in understanding the relationship between the pharmacological effects of nicotine and human tobacco dependence. Pharmacol. Biochem. Behav., in press, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00002-02 BPL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Suppression of Behavior by Drug Injections

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Jonathan L. Katz	Research Psychologist	BPL,NIDA,ARC
Others:	Steven R. Goldberg	Branch Chief	BPL,NIDA,ARC
	Jose A. Prada	Research Psychologist	BPL,NIDA,ARC
	Kohji Takada	Foreign Fellow	BPL,NIDA,ARC
	Charles Schindler	Staff Fellow	BPL,NIDA,ARC
	Michael Swedberg	Foreign Fellow	BPL,NIDA,ARC

COOPERATING UNITS (If any)

Department of Psychiatry, Uniformed Services University of the Health Sciences (J.E. Barrett).

LAB/BRANCH

Preclinical Branch

SECTION

Behavioral Pharmacology Laboratory

INSTITUTE AND LOCATION

NIDA Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.35	1.35	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Aversive behavioral effects of drugs were assessed by training squirrel monkeys to respond for food reinforcement in the presence of either of two alternately presented visual stimuli. In the presence of the first stimulus, responses also intermittently produced drug injections, whereas responses only produced food presentation in the presence of the second stimulus. Selective suppression of behavior in the presence of the stimulus associated with drug injections is an indication of an aversive effect of the drug.

The following drugs were found to produce dose-related selective suppression of responding: histamine, nicotine, quipazine, B-carboline ethyl ester, buspirone, and gepirone. The suppressant effects of histamine were antagonized by a series of H_1-receptor antagonists. These antagonists were ineffective in antagonizing the aversive effects of noxious stimuli other than histamine indicating the pharmacological specificity of the effect. Chlordiazepoxide increased rates of responding suppressed by histamine and responding suppressed by other noxious stimuli. The aversive effects of B-carboline ethyl ester were antagonized by the benzodiazepine-receptor antagonist, flumazepil. Drugs that failed to produce selective suppression were cocaine, yohimbine, and midazolam.

The aversive effects of drugs may contribute to an understanding of why some drugs are abused and why others are not.

Suppression of Behavior by Drug Injections - Publications, FY 1986

Katz, J.L. & Goldberg, S.R.: Effects of H_1-receptor antagonists on responding punished by histamine injection or electric shock presentation in squirrel monkeys. Psychopharmacology (in press).

Takada, K., Hagen, T.J., Cook, J.M., Goldberg, S.R. and Katz, J.L.: Discriminative stimulus effects of intravenous nicotine in squirrel monkeys: effects of morphine, cocaine and B-carboline. Pharmacol. Biochem. Behav. (in press).

Henningfield, J.E., Goldberg, S.R. and Jasinski, D.R.: Abuse liability and dependence potential of nicotine. In Tobacco Smoke and Nicotine: A Neurobiologic Approach. (Eds.) W.R. Martin, G.R. Vanloon, E.T. Iwamoto and D.L. Davis, Plenum Press, New York, 1986, pp.00-00 (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00003-02 BPL

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Effects of drugs on schedule-controlled behavior of experimental animals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Steven R. Goldberg	Chief, Preclinical Pharmacology	BPL,NIDA,ARC
Others:	Jonathan L. Katz	Research Psychologist	BPL,NIDA,ARC
	Kohji Takada	Foreign Fellow	BPL,NIDA,ARC
	Jose Prada	Research Psychologist	BPL,NIDA,ARC
	Michael Swedberg	Foreign Fellow	BPL,NIDA,ARC
	Charles Schindler	Staff Fellow	BPL,NIDA,ARC

COOPERATING UNITS (if any)

LAB/BRANCH
Preclinical Pharmacology Branch

SECTION
Behavioral Pharmacology Lab

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.15	1.10	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

General information on the pharmacology of drugs is obtained investigating how the drugs alter ongoing behavior of laboratory animals. These studies investigate the effects of a number of drugs on different types of trained performances in laboratory animals.

Actions of several benzodiazepine-receptor antagonists were investigated in chlordiazepoxide-tolerant and non-tolerant subjects. Flumazepil, BCCT, and CGS-9895 were more potent in tolerant than non-tolerant subjects; the effects of the inverse agonist, BCCE, were unchanged in tolerant subjects. These data suggest that the changes in sensitivity that are conferred to the antagonists with tolerance are not conferred to the inverse agonist.

Actions of cocaine and its metabolites, norcocaine and pseudococaine, on food-maintained behavior of squirrel monkeys and rats were investigated. The potencies of each of these drugs were related to their affinity for binding to rat brain cell membranes.

The proposal that the psychomotor-stimulant effects of caffeine are due to antagonist actions at adenosine receptors was investigated in studies of effects of combinations of caffeine and adenosine receptor agonists. These studies indicated that, while caffeine can function as an adenosine-receptor antagonist, stimulant effects of caffeine are likely not due to its adenosine-receptor antagonist actions.

Stimulant and interoceptive effects of nicotine and its metabolites, nornicotine and cotinine, were studied in rats and squirrel monkeys. These studies indicated that the nicotine metabolites have psychomotor stimulant effects on behavior but were less potent than nicotine. The potencies were related to their affinity for binding to rat brain cell membranes.

Other studies examined the behavioral mechanism by which pentobarbital disrupts control of behavior by visual discriminative stimuli and by interoceptive noxious stimuli.

Effects of drugs on schedule-controlled behavior of experimental animals, Publications - FY 1986

Goldberg, S.R. and Stolerman, I.P. (eds.): Behavioral Analysis of Drug Dependence. Academic Press, New York, 1986.

Goldberg, S.R., Katz, J.L. & Risner, M.E.: Behavioral pharmacology of licit drugs in experimental animals. In: L.S. Harris (ed.) Problems of Drug Dependence, 1985. NIDA Research Monograph #67. Washington, D.C.: U.S. Government Printing Office, 1986, pp. 36-44.

Katz, J.L. Prada, J.A. & Goldberg, S.R.: Psychomotor stimulant effects of caffeine alone and in combination with adenosine analogs in the squirrel monkey. Pharmacology Biochemistry and Behavior (in press).

Katz, J.L.: Tolerance to effects of morphine without cross-tolerance to effects of clonidine on schedule-controlled behavior of pigeons. Psychopharmacology 89:323-326, 1986.

Katz, J.L. and Goldberg, S.R.: Effects of ethylketazocine and morphine on schedule-controlled behavior in pigeons and squirrel monkeys. The Journal of Pharmacology and Experimental Therapeutics 239:433-441, 1986.

London, E.D., Wilkerson, G., Goldberg, S.R. and Risner, M.E.: Selective effects of cocaine on local cerebral glucose utilization in the rat. Neuroscience Letters 68:73-78, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00004-02 BPL

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Comparative studies of drug self-administration in squirrel monkeys and humans.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Steven R. Goldberg	Chief	BPL,NIDA,ARC
Others:	Jonathan L. Katz	Research Psychologist	BPL,NIDA,ARC
	Jack E. Henningfield	Chief, BDL	BDL,NIDA,ARC
	R. Nemeth-Coslett	Staff Fellow	BDL,NIDA,ARC
	Charles Schindler	Staff Fellow	BPL,NIDA,ARC
	Richard Lamb	Staff Fellow	BDL,NIDA,ARC
	Jose Prada	Research Psychologist	BPL,NIDA,ARC

COOPERATING UNITS (if any)

LAB/BRANCH: Preclinical Branch

SECTION: Behavioral Pharmacology Lab

INSTITUTE AND LOCATION: NIDA Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.53	0.48	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Self-administration studies permit an assessment of the relative contribution of environmental and pharmacologic factors to the self-administration of drugs, and to changes in response to drug due to tolerance and sensitization. Parallel comparative studies in squirrel monkeys and humans in which subjects are given the opportunity to self-administer comparable doses of cocaine, morphine and nicotine 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. These studies have shown that responding is maintained in human subjects in the same manner in which it is maintained in non-human experimental subjects. Additionally, behavior in humans and squirrel monkeys appears to be a function of similar variables. The stimuli that are associated with injections of cocaine develop conditioned reinforcing effects in humans in a manner similar to the manner in which these effects develop in squirrel monkeys. In humans, reinforcing effects of cocaine, morphine and nicotine could be detected at doses that did not occasion subjective reports of drug effects or drug liking. These results indicate that reinforcing effects of drugs can occur without traditional indications of abuse liability.

Comparative studies of cocaine self-administration in squirrel monkeys and humans - Publications, FY 1986

Goldberg, S.R.: Nicotine as a reinforcer in humans and experimental animals. Pharmacol Biochem. Behav. in press, 1986.

Henningfield, J.E., Nemeth-Coslett, R. and Goldberg, S.R.: Intravenous cocaine self-administration by human volunteers: Second-order schedules of reinforcement. NIDA Res. Monog. Ser. in press, 1986.

Henningfield, J.E., Goldberg, S.R., Herning, R.I, Jasinski, D.R., Lucas, S.E., Miyasoto, K., Nemeth-Coslett, R., Pickworth, W.B., Rose, J.E., Sampson, A. and Snyder, F.: Human studies of the behavioral pharmacological determinants of nicotine dependence. NIDA Res. Monog. Ser. No. 67, pp. 54-65, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00005-01 BPL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Drug effects on classical conditioning in rabbits

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Steven R. Goldberg	Chief	BPL,NIDA,ARC
Others:	Charles Schindler	Staff Fellow	BPL,NIDA,ARC

COOPERATING UNITS (if any)

Department of Psychology, The University of Iowa, Iowa City, IA (J.A. Harvey, B.G. Scheurs)

LAB/BRANCH

Preclinical Branch

SECTION

Behavioral Pharmacology Lab

INSTITUTE AND LOCATION

NIDA Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.35	0.35	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Opiates were studied in rabbits to determine their effects on learning using classical (Pavlovian) conditioning of the rabbit nictitating membrane response as a model preparation for learning. In addition, studies were also carried out to determine the effects of opiates on locomotor activity in the rabbit.

A. Classical conditioning. Agonists at all three of the opiate receptor subtypes (mu, kappa and sigma receptors) retard the acquisition of the classically conditioned response. This effect of the mu and kappa agonists appears to be due to an effect on the animal's sensory processing of the conditioned stimulus and not the unconditioned stimulus. Further, the effects of both the mu and kappa receptor agonists were antagonized by the opiate receptor antagonist naloxone at similar doses. Much higher doses of naloxone failed to completely antagonize the effects of the sigma receptor agonists. These results suggest that both the mu and kappa agonists affect acquisition in a similar manner and possibly through a similar receptor.

B. Locomotor activity. The opiates affected locomotor activity in the rabbit differently than they did classical conditioning. While the kappa agonists were more potent at retarding acquisition, the mu agonist, morphine, was more potent at reducing locomotor activity in the rabbit. The opiate antagonist, naloxone, also reduced locomotor activity in the rabbit. In addition, naloxone antagonized the effects of the mu receptor agonist at a lower dose than it did the kappa receptor agonists and it failed to antagonize the sigma receptor agonist to any degree.

The significance of this project lies in the finding that opiates can have varying effects depending on the behavior being studied. Thus, a drug identified as having a low abuse potential while still maintaining analgesic potency, may also still maintain many of the other unwanted side-effects of opiates.

Drug Effects on Classical Conditioning in Rabbits - Publications, FY 1986.

Schindler, C.W., Gormezano, I., and Harvey, J.A.: Effect of LSD on acquisition, maintenance, extinction and differentiation of conditioned responses. Pharmacol. Biochem. Behav. 24:1293-1300, 1986.

Schindler, C.W., Lamb, M.R., Gormezano, I., and Harvey, J.A.: Effects of morphine, ethylketocyclazocine, and N-allynormetazocine on classical conditioning of the rabbit nictitating membrane response. Behav. Neurosci. 100: 647-651, 1986.

Weiss, S.J., and Schindler, C.W.: The composite-stimulus analysis and the quantal nature of stimulus control: Response and incentive factors. Psychol. Res. 37: in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00006-02 BPL

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Behavioral effects of opioid agonists, opioid mixed agonist-antagonists, and other.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Jonathan L. Katz	Research Psychologist	BPL,NIDA,ARC
Others:	Steven R. Goldberg	Branch Chief	BPL,NIDA,ARC
	Charles Schindler	Staff Fellow	BPL,NIDA,ARC
	Jose Prada	Research Psychologist	BPL,NIDA,ARC
	Rick Lamb	Staff Fellow	BDL,NIDA,ARC

COOPERATING UNITS (if any)

LAB/BRANCH
Preclinical Pharmacology Branch

SECTION
Behavioral Pharmacology LAboratory

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.13	.83	.30

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Reinforcing effects of opioids were assessed in squirrel monkeys trained to respond for i.v. injections of morphine or fentanyl under second-order schedules of reinforcement. Under these schedules each 30th response produced a visual stimulus and occasionally the 30th response produced the stimulus and an injection of drug. Both drugs effectively maintained responding.

Food reinforcement maintained an amount and pattern of behavior similar to that of opioids. Naloxone blocked the ability of morphine, but not food, to maintain behavior. In addition, a profound supersensitivity to naloxone developed. Initially a dose of 3 mg/kg naloxone was required to antagonize effects of morphine. After repeated injections, however, a dose as low as 0.03 mg/kg was effective.

Following initial training, the removal of either morphine or food reinforcement failed to reduce behavior. This effect was determined to be due to the brief stimuli which were presented throughout the session in order to initially maintain responding. When these stimuli were removed, the animals stopped responding. Responding remained low when the stimuli were put back in. Re-introduction of morphine or food increased the level of behavior to initial values. Subsequently, removal of morphine or food decreased behavior, even in the presence of the brief stimuli.

The significance of these finding is two-fold. First, morphine can maintain a long chain of behavior which would be analogous to the ritual of behavior necessary for the human addict to obtain and administer abused drugs. Second, the results with the manipulation of environmental stimuli point to the importance of these stimuli in maintaining drug seeking behavior and of incorporating the effects of environmental stimuli in any drug treatment program.

Behavioral Effects of Opioid Agonists, Opioid Mixed Agonist-Antagonists, and Other... - Publications, FY 1986.

Katz, J.L. & Goldberg, S.R.: Effects of ethylketazocine and morphine on schedule-controlled behavior in pigeons and squirrel monkeys. J. Pharmacol. Exp. Ther. 239: 433-441, 1986.

Katz, J.L.: Effects of ethylketazocine and morphine alone and in combination with naloxone on schedule-controlled behavior in pigeons. Psychopharmacology (in press).

Katz, J.L. & Valentino, R.J.: Pharmacological and behavioral factors in opioid dependence in animals. In: Behavioral Analysis of Drug Dependence. S.R. Goldberg and I.P. Stolerman (Eds.) New York: Academic Press, 1986, pp. 287-327.

Katz, J.L.: Effects of clonidine and morphine on opioid withdrawal in rhesus monkeys. Psychopharmacology 88:392-397, 1986.

Stolerman, I.P. and Goldberg, S.R.: Brief history and scope of behavioral approaches to dependence. In: Behavioral Analysis of Drug Dependence, (Eds.) S.R. Goldberg and I.P. Stolerman, New York: Academic Press, 1986 pp. 1-8.

Kumor, K., Su, T.P., Vaupel, B., Haertzen, C., Johnson, E. and Goldberg, S.R.: Studies of kappa agonists. NIDA Res. Monog. Ser., No. 67, pp.18-25, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00007-02 BPL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Reinforcing and punishing effects of benzodiazepine receptor ligands and other...

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Jonathan L. Katz	Research Psychologist	BPL,NIDA,ARC
Others:	Steven R. Goldberg	Chief, Preclinical Pharmacol	BPL,NIDA,ARC
	Jose Prada	Research Psychologist	BPL,NIDA,ARC
	Kohji Takada	Foreign Fellow	BPL,NIDA,ARC

COOPERATING UNITS (if any)

Department of Chemistry, University of Milwaukee at Madison (J.M. Cook)

LAB/BRANCH

Preclinical Pharmacology Branch

SECTION

Behavioral Pharmacology Lab

INSTITUTE AND LOCATION

NIDA Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.15	.85	.30

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Reinforcing effects of sedatives were assessed in squirrel monkeys trained to respond for i.v. injections of methohexital. Methohexital effectively maintained responding. Additionally, visual stimuli that accompanied the methohexital injections also acquired conditioned reinforcing effects. Several benzodiazepines will be studied for their potential to maintain responding in a manner similar to methohexital.

Punishing effects of drugs were assessed by training squirrel monkeys to respond for food reinforcement and scheduling occasional drug injections to follow some responses in the presence of a distinctive stimulus but not in the presence of another stimulus. Selective suppression of behavior in the presence of the stimulus associated with drug injections is an indication of a noxious effect of the drug and was produced by the benzodiazepine inverse agonist, B-carboline ethyl ester but not the agonist, midazolam. The punishing effects of B-carboline ethyl ester were antagonized by the benzodiazepine-receptor antagonist, flumazepil. These results are consistent with reports of axiogenic activity of inverse agonists and provide a means for objectively studying the effects of drugs that may produce dysphoric subjective states.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00008-01 BPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Behavioral pharmacology of non-opioid analgesics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	S. Goldberg	Branch Chief	BPL,NIDA,ARC
Others:	M.D.B. Swedberg	Foreign Fellow	BPL,NIDA,ARC
	H.E. Shannon	Lab Chief,NPP (resigned 7/86)	BPL,NIDA,ARC
	S. Schell	Technician	BPL,NIDA,ARC

COOPERATING UNITS (if any)

B. Nickel, Research Associate, Degussa Pharmaceuticals, Frankfurt, FRG

LAB/BRANCH

Preclinical Pharmacology

SECTION

Behavioral Pharmacology/Neuropharmacollgy (until July 1986)

INSTITUTE AND LOCATION

ARC,NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.70	.60	.10

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Rats were trained to discriminate intraperitoneal injections of either flupirtine (10.0 mg/kg), or, D-16949 (2.0 mg/kg) from the no-drug condition in a two choice shock avoidance procedure. The avoidance or escape from electric shock was contingent upon whether the training drug had been injected prior (flupirtine 10 min., D-16959, 30 min.) to the session or not. Putative agonists were substituted for the training drug and putative antagonists were administered in combination with the training drug, respectively. Results generated by this procedure allow for conclusions regarding the pharmacological mechanisms of action to be drawn.

Flupirtine: Data generated so far indicate alpha adrenergic mechanisms of action to be involved. This study is presently directed towards the separation of the subtypes of alpha-adrenoceptor mechanisms potentially involved.

D-16949: A series of drugs has been tested so far. The opiate antagonist, naltrexone, does not affect the discriminative stimulus properties of this drug, indicating lack of involvement of opiate mechanisms. A variety of 5-HT related compounds has been tested, some of which seem to produce D-16949 like responses. This may indicate the involvement of 5-HT in the mechanisms of action of this analgesic.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00001-03 NPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Pharmacologic interactions of pentazocine and tripelennamine in the dog

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: D.Bruce Vaupel Pharmacologist NPP, NIDA, ARC

COOPERATING UNITS (if any)

LAB/BRANCH

Neuropsychopharmacology Lab, Preclinical Branch

SECTION

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.08	.08	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The acute interactions of pentazocine and tripelennamine, in ratios which have been abused by humans, have been evaluated on the autonomic nervous system, nociceptive reflexes and behavior in the chronic spinal dog. Pentazocine alone produced miosis, hypothermia and analgesia as determined using both spinal and supraspinal nociceptive reflex pathways whereas tripelennamine caused mydriasis, hyperthermia and analgesia. The tripelennamine-induced analgesia was produced only for the skin twitch reflex suggesting a supraspinal mediated analgesic action. No consistent pattern among the interactions emerged. Interactions on pupils appeared additive while tripelennamine antagonized pentazocine-induced hypothermia. Analgesic effects of tripelennamine and pentazocine on the skin twitch reflex interacted additively or infra-additively depending on the dosage ratio. In other experiments, the selective opiate antagonist naltrexone blocked pentazocine's actions but not those of tripelennamine and the sigma-type pharmacologic actions of SKF 10047 were not antagonized by tripelennamine. Depending on the parameter, tripelennamine-pentazocine interactions have shown tripelennamine's actions to summate algebraically with pentazocine, or to antagonize pentazocine. While interactions of this type may contribute to the abuse liability of tripelennamine and pentazocine, these results indicate that the tripelennamine component is not opiate mediated and that tripelennamine does not effectively antagonize sigma activity which has been suggested to be a canine model for dysphoric effects of opiate agonists-antagonists.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00002-06 NPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Assessment of the abuse liability of PCP-like compounds.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	D. Bruce Vaupel	Pharmacologist	NPP, ARC
Others:	Harlan Shannon	Pharmacologist	NPP, ARC
	Marcus Risner	Research-Psychologist	BPP, ARC

COOPERATING UNITS (If any)

LAB BRANCH

Neuropsychopharmacology Lab, Preclinical Branch

SECTION

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.3	.3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Experiments were conducted to evaluate the degree of phencyclidine (PCP)-like activity associated with the dextro and levo enantiomers of the sigma agonist N-allylnormetazocine (NANM). In chronic spinal dogs, d- and l-NANM generally produced similar physiologic and gross animal behavior effects which included mydriasis, tachycardia, hyperthermia, increased secretory activity (lacrimation, rhinorrhea and salivation), nystagmus and stereotyped head movements. For these effects, d- and l-NANM were generally equal in potency and both were about 1/10th as potent as PCP. However, the NANM enantiomers could be differentiated on the basis of their effects on nociceptive reflexes. Comparisons of dose-response curves and efficacies demonstrated that d-NANM was more similar to PCP in its effectiveness in depressing the flexor and skin twitch reflexes than was l-NANM. In addition, naltrexone selectively antagonized or reduced only the effects of l-NANM on reflex activity. In intact dogs, d-NANM and PCP, but not l-NANM maintained self-administration behavior under FR15 or FI9000(FR10:S) schedules of reinforcement. This represented the most stereospecific action of the NANM enantiomers. Additionally, l-NANM failed to maintain self-administration behavior, even following pretreatment with naltrexone, thus suggesting that the opiate activity of l-NANM was not responsible for its lack of reinforcing efficacy. Taken together, the data demonstrate that both d- and l-NANM have PCP-like properties, but d-NANM is pharmacologically more equivalent than l-NANM to PCP and l-NANM has additional activity which is not PCP-like.

PHS 6031 (Rev. 11-83)

Vaupel, D.B., Risner, M.E. and Shannon, H.E.: Pharmacologic and reinforcing properties of phencyclidine and the enantiomers of N-allylnormetazocine in the dog. Drug and Alcohol Dependence, in press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00003-02 NPP

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Investigations of kappa and sigma properties of antinociceptive drugs in the dog.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	D. Bruce Vaupel	Pharmacologist	NPP,NIDA,ARC
Others:	Edward Cone	Senior Scientist	CDM,NIDA,ARC

COOPERATING UNITS (If any)

Degussa Pharmaceuticals, Frankfurt, West Germany (B. Nickel, Research Associate)

LAB/BRANCH: Neuropsychopharmacology Laboratory, Preclinical Pharmacology Branch

SECTION:

INSTITUTE AND LOCATION: ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

1). Chronic spinal dog studies. It was previously demonstrated that the pharmacologic activity of dl-ketocyclazocine is associated with the l-enantiomer; the d-enantiomer being inactive. To show that the actions of l-ketocyclazocine represent kappa and not mu effects, selective antagonism studies with naltrexone were conducted. Relatively low doses of naltrexone (0.01 mg/kg) were required to antagonize morphine whereas relatively high doses (1 mg/kg) were needed to produce a similar antagonism of dl-ketocyclazocine, thus demonstrating that all of the agonist actions of l-ketocyclazocine can be classified as of the kappa type in the dog.

2). Flupirtine is a new analgesic being evaluated in the U.S.A. Its mechanism of action is unknown. To assess the role of opioid mechanisms in flupirtine-induced antinociception, flupirtine was compared to the opioid pentazocine both in single dose studies and in naltrexone antagonism studies in the chronic spinal dog. It was concluded that flupirtine-induced antinociception is not opiate receptor mediated, this action occurs primarily at supraspinal sites and flupirtine is estimated to have 1/12th the antinociceptive potency of pentazocine in the dog.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00004-02NPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Investigations of the kappa and sigma properiftes of opioids and novel non opioids.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Bruce Vaupel	Pharmacologist	NPP,NIDA,ARC
Others:	Tsung-Ping Su	Research Chemist	NPL,NIDA,ARC
	Edward Cone	Senior Scientist	CDM,NIDA,ARC
	Rolley Johnson	Senior Pharmacist	RS,NIDA,ARC
	Mary Gavigan	Stay-in-school	NPP,NIDA,ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychopharmacology Laboratory, Preclinical Pharmacology Branch

SECTION

INSTITUTE AND LOCATION

ARC,NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.00	.45	.55

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

1). The pentapeptide BW942C was examined in humans, rats, mice and squirrel monkeys for its diuretic effect. Its binding affinity for different opioid receptors in guinea pig brain homogenates was also determined. In vivo and in vitro data suggest that BW942C has the property of a partial ketocyclazocine-like kappa opioid agonist in addition to its recognized morphine-like agonist effects.

2). Experiments were conducted to develop an in vitro system for performing bioassay analysis of sigma type drugs. Electrically-induced contractions of the guinea pig vas deferens were potentiated by sigma drugs such as d-pentazocine and phencyclidine. A variety of non sigma drugs did not affect contractions. The potentiating effects were antagonized by haloperidol and BW234U. It was concluded that the guinea pig vas deferens may contain sigma receptors and phencyclidine receptors and therefore this preparation may be a useful tool for studying these two receptors in vitro.

Investigators of the kappa and sigma properties of opioids and novel non opioids, Publications - FY 1986

Kumor, K., Su, T-P., Vaupel, B., Haertzen, C., Johnson, E. and Goldberg, S.: Studies of kappa agonists. In Harris, L.S. (Ed): Problems of Drug Dependence 1985. National Institute on Drug Abuse Research Monograph 67, 1986, pp 18-25, Washington, D.C.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00005-01 NPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The role of neurokinins in the morphine abstinence syndrome.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Lawrence G. Sharpe	Research Psychologist	NPP,NIDA,ARC
Others:	Jerome H. Jaffe	Director	NIDA,ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH

Preclinical Branch

SECTION

Neuropsychopharmacology Laboratory

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.75	0.5	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The neurokinins (substance P neurokinin A and B, physalaemin, etc) are among the most ubiquitous neurotransmitter/neuromodulator substances found in the peripheral and central nervous system. Most all are neuroexcitants and since morphine inhibits and naloxone increases their release in the morphine dependent rat, they may play an important role in the opiate abstinence syndrome. Our purpose is to investigate how these neurokinins may be involved in eliciting naloxone-precipitated withdrawal signs in rats dependent on morphine (75 mg pellet implantation) for 3 days. The approach is to give drugs (before naloxone) that would either increase or decrease the efficacy of endogenous neurokinins in the morphine-dependent rat. Control rats receive the drug vehicle. We gave neonatal rats capsaicin, a drug that permanently destroys small sensory neurons and causes a widespread depletion of substance P and perhaps other neurokinins. When made morphine-dependent as adults, these rats showed less severe abstinence signs of rhinorrhea, lacrimation and salivation than did the controls. The number of wet dog shakes, however, were increased in the capsaicin-treated rats. In another study, morphine-dependent rats were given captopril (0.3 mg/kg, i.p.), a drug that increases the peripheral levels of substance P and other neurokinins by inhibiting the formation of catabolic enzymes. Preliminary results indicated that captopril, given before naloxone (0.5 mg/kg), enhanced several signs of abstinence in the morphine-dependent rat.

The significance of this project is that it may lead to the development of drugs that would aid in the clinical management of opiate detoxification.

The role of neurokinins in the morphine abstinence syndrome, Publications - FY 1986

Sharpe, L.G. and Jaffe, J.H.: Neonatal capsaicin modifies morphine withdrawal signs in the rat. Neurosci. Lett. (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00006-03 NPP

PERIOD COVERED
October 1, 1985 to March 31, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pupillary responses as a neuronal model to study mechanisms of addictive drugs.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L.G. Sharpe	Research Psychologist	NPP,NIDA,ARC
Others:	M. Wright	Stay-in-school Tech.	NPP,NIDA,ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH
Preclinical Branch

SECTION
Neuropsychopharmacology Laboratory

INSTITUTE AND LOCATION
NIDA, ARC, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.25	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Opiates are injected intravenously in the paralyzed cat preparation so that changes in the pupillary-light reflex, pupillary fluctuation and pupillary size can be measured for one hr. The three pupillary responses are recorded by imaging the pupil with an infrared video pupillometer which is connected to a TV monitor and strip chart recorder. The purpose is to use these three responses as an in vivo neuronal model for investigating mechanisms of actions of opiates and other drugs. Morphine (0.06-1.5 mg/kg) increased pupillary size but decreased the light reflex and fluctuations, all of which were dose related. Sufentanil (0.3-10 ug/kg), a more selective mu agonist, was 300 times more potent than morphine in producing mydriasis, 175 times more potent in inhibiting the light reflex and 5 times more potent in inhibiting fluctuations (invalid assay). Naltrexone (10 ug/kg) shifted the sufentanil dose-response curve to the right by a factor of 26 for pupil size, 10 for light reflex and 8 for fluctuations. We concluded from this and other data that separate mechanisms mediate the three pupillary components and that mu systems participate importantly in morphine mydriasis but not in the light reflex and fluctuations.

Studying the changes in pupillary responses produced by opiates may provide new information about the sites and mechanism of action of addictive drugs.

Pupillary responses as a neuronal model to study mechanisms of addictive drugs, Publications - FY 1986

Pickworth, W.B. and Sharpe, L.G.: Morphine-induced mydriasis and inhibition of pupillary light reflex and fluctuation in tne cat. J. Pharmacol. Exp. Ther. 234: 603-606, 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00007-01 NPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurochemical substrates of the motor-activating properties of psychostimulants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Linda Porrino Research Psychologist NPP,NIDA,ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH

Preclinical Branch

SECTION

Neuropsychopharmacology Lab

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Behaviors stimulated by acute treatment with psychostimulants resemble those manifested in conditions of high motivation or arousal. The purpose of this study was to test the effects of pharmacological blockade of either D1 or D2 dopamine receptors on the locomotor response to cocaine administration. Locomotor activity was measured in Omnitech Activity Monitors. Activity counts were measured in 10 minute blocks for 60 minutes following a 20 minute habituation period. Cocaine administration resulted in a dose dependent increase in locomotor activity with peak effects at 20 mg/kg. Preliminary findings demonstrate that the administration of the D2 antagonist, sulpiride, resulted in blockade of the locomotor-activating effects of high doses of cocaine, whereas the administration of the D1 antagonists, SCH-23390, resulted in greater blockade of the motor-activating effects of low doses of cocaine (5 mg/kg) than high doses (20 mg/kg). This suggests that cocaine may have dose-dependent effects at different dopamine receptor subtypes.

The significance of the project lies in the determination of the neurochemical basis of the behavior arousing effects of psychostimulants, a major class of drugs of abuse.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00008-01 NPP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neural Substrates of Behavior Maintained by Intravenous Psychomotor Stimulant Injec..

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Linda J. Porrino	Research Psychologist	NPP,NIDA,ARC
Others:	Nancy Goodman	Pharmacologist	NPP,NIDA,ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH
Preclinical Pharmacology

SECTION
Neuropsychopharmacology Lab

INSTITUTE AND LOCATION
NIDA,ARC, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	.25	.75

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Intravenous self-administration (IVSA) is a paradigm that has been used frequently to assess the reinforcing properties of drugs in several animal species. The purpose of the present work is to determine the neuroanatomical and neurochemical basis of IVSA of cocaine and other psychostimulants in the rat. In these studies lever pressing behavior on a fixed ratio schedule (FR10) was maintained either by i.v. cocaine injection or food presentation. The effects of selective agonists and antagonists of various neurotransmitters will be tested. Preliminary data show that the effects of cocaine on lever pressing maintained by food presentation can be blocked by the selective dopamine D2 antagonist, sulpiride. Further research will test the effects of selective dopamine D1 and serotonin antagonists as well as the effects of the central administraton of these drugs on behavior maintained by food presentation and i.v. injection of cocaine.

The significance of this research is the characterization of the neurohumors and brain loci involved in rewarded behavior and their generality across reinforcers.

PHS 6040 (Rev. 1/84)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00009-01 NPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neural Substrates of reinforcement: Psychomotor Stimulants

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Linda S. Porrino	Research Psychologist	NPP,NIDA,ARC
Others:	Larry G. Sharpe	Research Psychologist	NPP,NIDA,ARC
	Nancy Goodman	Pharmacologist	NPP,NIDA,ARC

COOPERATING UNITS (if any)

LAB/BRANCH

Preclinical Branch

SECTION

Neuropsychopharmacology Lab

INSTITUTE AND LOCATION

ARC, NIDA,Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.75	.50	.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to investigate neuroanatomical and neurochemical substrates that mediate the reinforcing properties of cocaine and other psychomotor stimulants. Intracranial self-administration (ICSA) along with intracranial self-stimulation (ICSS) are used to determine those areas of the brain which subserve the reinforcing effects of psychomotor stimulants. Various neuroanatomical sites are being tested to determine if they support ICSA. The effects of psychomotor stimulants, alone and in conjunction with various antagonists, on ICSS to various brain sites is being tested. Preliminary findings confirm that cocaine decreases the threshold for ICSS to the ventral tegmental area, a brain region implicated in the mediation of reinforced behavior. Further this effect can be blocked by the administration of the D1 antagonist, SCH23390, but not by the D2 antagonist sulpiride

The significance of this project lies in the localization of specific anatomic brain regions which mediate the rewarding effects of cocaine, as well as the identification of the neurochemical basis of these effects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00010-01 NPI

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Metabolic mapping of the brain during reinforced behavior

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Linda J. Porrino Research Psychologist NPP,NIDA,ARC

COOPERATING UNITS (if any) Laboratory of Cerebral Metabolism,NIMH (L. Sokoloff); Department of Pharmacology. Boston Univ. School of Medicine (C. Kornetsky); Department of Psychiatry. Louisiana State Univ. School of Medicine (J. Smith).

LAB/BRANCH

Preclinical Branch

SECTION

Neuropsychopharmacology

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.3	.3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The phenomenon of intracranial self-stimulation (ICSS) is considered a productive way of studying reward systems in the brain. The purpose of this research is the identification of the neural circuits activated during ICSS behavior in rats. The quantitative autoradiographic 2-[14C]deoxyglucose method is being used to map the various brain sites. ICSS to the ventral tegmental area at electrical current levels at or near threshold and those which support maximum rates of ICSS are associated with similar patterns of alterations in glucose utilization in the nucleus accumbens, lateral septum and some thalamic and cortical areas. Further, ICSS to the medial forebrain bundle also results in metabolic changes in these same areas. Present work in association with Dr. James Smith is examining the changes in the turnover of various neurotransmitters in these brain areas. Other work in association with Dr. Conan Kornetsky is examining the metabolic effects of the administration of drugs of abuse on ICSS.

The significance of this project lies in the identification of those brain areas involved in the mediation of reward behavior and the determination of the way these brain circuits are modified by drugs of abuse.

Metabolic mapping of the brain during reinforced behavior - Publications FY 1986

Porrino, L.J.: Cerebral metabolic changes associated with activation of reward systems. In: L. Oreland and J. Engel. (Eds): Brain Reward Systems and Abuse, New York: Raven Press. In press, 1986.

Sokoloff, L., Porrino, L.J.: Some functional considerations in the application of the deoxyglucose method to pharmacological studies. In: J. Krieglstein (Ed): International Symposium on Pharmacology of Cerebral Ischemia, In press, 1986.

Porrino, L.J., Lucignani, G.: Different patterns of local brain energy metabolism associated with high and low doses of methylphenidate: Relevance to its action in hyperactive children. Biol. Psychiat. In press, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 0001-01 BGL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Genetic factors in acute response to drug administration

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: S.R. Goldberg	Branch Chief	BPL,NIDA,ARC
Other: F.R. George	Staff Fellow	BGL,NIDA,ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH
Preclinical Pharmacology Branch

SECTION
Behavioral Genetics Lab

INSTITUTE AND LOCATION
NIDA, Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.55	.55	0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objectives of the proposed research are to identify and study factors that control drug reinforced behavior using genetically divergent rat and mouse 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., food deprivation/satiation and other dietary factors. Emphasis will be given to systematically studying variables over a range of values and interactions among variables will be parametrically explored. 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 that we have developed in this laboratory, and will contribute to a systematized body of knowledge that will aid in the analysis of the complex problems of drug abuse.

Genetic Factors in Acute Response to Drug Administration - Publications, FY 1986

George, F.R.: Prostaglandin involvement in ethanol's mecnanism of action. Alcohol and Acoholism, in press, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00002-01 BGL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Genetic factors in drug self-administration

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S.R. Goldberg	Branch Chief	BPL,NIDA,ARC
Other:	F.R. George	Staff Fellow	BGL,NIDA,ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH
Preclinical Pharmacology Branch

SECTION
Behavioral Genetics

INSTITUTE AND LOCATION
NIDA, Addiction Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.55	.55	0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

With the exception of ethanol, genetic factors have not been widely examined with other abused substances, but existing reports do indicate large genetic differences in both acute sensitivity and predisposition to self-administer drugs, particularly narcotics. In the present project with rats and mice, acute behavioral effects of drug administration will be systematically explored. The drugs to be studied include opiate agonists and antagonists, stimulants, especially cocaine, benzodiazepines, barbiturates, and phencyclidine. Drug effects will be studied using a variety of behavioral tasks, including open field activity, rearing activity, rotational behavior, paw lick, tail flick, sleep time, rotorod stability, and tilt-plane coordination. Simple physiological measures such as body temperature, blood pressure, heart rate and respiration rate may also be assessed. For each drug tested, several doses will be examined to obtain dose-response patterns across a wide range of drug effects. Two to four inbred strains of mice and/or rats will be included in all experiments to determine an estimate of the genetic variation for each behavioral or physiological measure. Where appropriate, these measures will be correlated with each other to estimate the commonality among the acute responses studied. In all of these studies, genotype will be incorporated as an independent variable.

Genetic Factors in Drug Self-Administration - Publications, FY 1986

Ritz, M.F., George, F.R., deFiebre, C. and Meisch, R.A.: Genetic differences in the establishment of ethanol as a reinforcer. Pharmacol Biochem Behav, 24:1089-1094, 1986.

Elmer, G.I., Meisch, R.A. and George, F.R.: Oral ethanol reinforced behavior in inbred mice. Pharmacol Biochem Behav, 24:1417-1421, 1986.

Elmer, G.I., Meisch, R.A. and George, F.R.: Mouse strain differences in operant self-administration of ethanol. Behavior Genetics in press, 1987.

Suzuki, T., George, F.R. and Meisch, R.A.: Differential establishment and maintenance of oral ethanol reinforced behavior in Lewis and Fischer 344 inbred rat strains. J Pharmacol Exp Ther in press, 1987.

Elmer, G.I., Meisch, R.A. and George, F.R.: Differential concentration-response curves for oral ethanol self-administration in C57BL/6J and BALB/cJ mice. Alcohol in press, 1987.

George, F.R.: Genetic and environmental factors in ethanol self-administration. Pharmacol Biochem Behav in press, 1987.

Annual Report of the Neuroscience Branch
Addiction Research Center
October 1, 1985 to September 30, 1986
Michael J. Kuhar, Ph.D., Chief

Introduction

The Neuroscience Research Branch employs a multifaceted research strategy designed to elucidate the effects of abusable substances on neurophysiological systems, the neuroanatomical substrates involved in and the mechanisms of action underlying drug-induced effects. This involves investigating the outcome of both acute and chronic drug exposure on neurotransmitter and neurohormonal systems as well as on endogenous opioid peptide systems using a variety of neurochemical, electrophysiological and biochemical techniques. An important aspect of this research program involves examining pharmacoreceptors for drugs of abuse (e.g., opioid, sedative/hypnotic, and phencyclidine) using drug binding techniques both in in vivo and in vitro receptor and model systems. Immunochemical methods, isotope binding procedures, autoradiography and positron emission tomography (PET) scanning are used to identify neurobiological substrates and anatomical areas which are important correlates of drug exposure in both animals and humans.

Within the Neuroscience Branch, there are two laboratories: Neuropharmacology and Molecular Pharmacology. Over the past year, the Branch expanded to its projected size. Most of the expansion represents recruitment into the new Laboratory for Molecular Pharmacology which was equipped and organized and has begun to function. This Laboratory along with the Neuropharmacology Laboratory provides a broad approach to the study of predisposing factors, mechanisms and sequelae of drug abuse. Thus, the research covers a full range from the molecular genetics of drug action to positron emission tomography (PET) scanning of in vivo drug effects and receptors in human volunteers.

In terms of milestones achieved, the strong program involved with mapping the cerebral metabolic effects of abused substances has generated publications and new data on almost all classes of abused drugs. The work has helped elucidate basic mechanisms of actions and describe anatomical distributions of the effects of certain drugs. Most recently this program has reached the striking goal of PET studies in humans.

Another strong area involves studies of drug receptors. Biochemical investigations have produced new data on receptors for almost all abused drugs and significant related neurohormones. The in vitro experiments conducted provide an

Specific research programs focus on neuroanatomical sites and distributions of drug action, physiological effects of drug interactions, neuroreceptors of abused drugs and related endogenous substances, and physiological correlates of receptor interactions.

The Neuropharmacology Unit has made significant advances in understanding the distribution of CNS responses to various psychoactive drugs. Studies with morphine in human volunteers, using positron emission tomography (PET), demonstrated regionally selective decrements in cerebral metabolic activity which were associated with euphoria and EEG slowing. The effects were contrasted with more restricted alterations in local cerebral glucose utilization (LCGU) observed in rats. In rats, the effects of agonists were compared at different opioid receptor subtypes. Tolerance to opioid effects on LCGU was observed in human subjects as well as in experimental animals, with differing degrees of tolerance in the rat brain and spinal cord. Opioid abstinence in morphine-dependent animals significantly increased glucose metabolism in many brain areas, including those rich in opioid receptors. Metabolic mapping also was used to demonstrate the in vivo cerebral distribution of responses to cocaine, 3,4-methylenedioxymethamphetamine, nicotine, diazepam, phencyclidine, and N-allylnormetazocine, a sigma agonist. The physiological effects of opioids and their interactions with the calcium ion were studied as were opioid effects at the ultrastructural level. Studies on the chronic effects of opioids on neuroreceptors and lymphoid tissue were initiated. Specific binding sites for nicotine and sigma agonists were demonstrated and studied in vivo and in vitro.

The Neurochemistry Unit made what may be considered to be an extremely important finding with the demonstration of endogenous substances in the guinea pig which interact with sigma receptors. Studies of sigma receptors were extended to include investigations with HR-375 and BMY 14802, potential antipsychotic drugs, and in vitro experiments with the guinea pig vas deferens. Studies on kappa receptors were conducted using BM942C, a synthetic pentapeptide. The effects of cocaine, 3,4-methylenedioxyamphetamine (MDA), and 3,4-methylenedioxymethamphetamine (MDMA) on monoamines and their metabolites were studied in brain as was the interaction of pyrilamine with tripelennamine on the urinary excretion of drug metabolites.

A major focus of the Neurophysiology Unit was the effects of nicotinic agonists on single ion channel activity at the frog neuromuscular junction. Several new agonists were synthesized including isoarecolone methiodide, an extremely potent agonist which is useful in receptor and behavioral studies. By systematic, isomorphic substitution on the isoarecolone skeleton, a

quantitative structure-activity relationship emerged. The isolated spinal cord of the neonatal rat was developed as a model in vitro system for the study of opioid effects and withdrawal. This system also appears to be useful for physiological studies to extend information on endogenous and synthetic sigma ligands.

Summary of Ongoing Research

Neuropharmacology Unit:

A. Cerebral Metabolic Studies of Drug-Induced Euphoria: London, E.D. and Broussole, E.P.M.; Collaborating Investigators: Jaffe, J.H., Herning, R., Pickworth, W., Rippetoe, S., Kumor, K.M., Wong, D.F., Links, J., Dannals, R., Wagner, H. (Johns Hopkins Medical Institutions [JHMI]). Previous Collaborators: Johnson, R.E., Jasinski, D. and Margolin, R.W. (Vanderbilt University).

Abused drugs produce a positive affective state termed euphoria. The purpose of this project is to delineate those brain areas that are activated or inhibited during drug-induced euphoria. Inasmuch as the euphorigenic effects of abuse drugs are central to addictive properties, this study may help map the neuroanatomical substrates of addiction. Another objective is to correlate drug-induced EEG changes with effects on rates of local cerebral glucose utilization (LCGU), an index of cerebral function. Such correlations may provide fundamental information about the cortical EEG. Rates of LCGU are measured in human volunteers using [^{18}F]fluorodeoxyglucose (FDG) as a radiotracer for LCGU with positron emission tomography (PET).

Six human volunteers participated in a pilot study on the effects of chronic heroin on LCGU. The subjects were three postaddicts not physically dependent on opioids or other psychoactive agents and three addicts physically dependent and stabilized on heroin. Analysis of scores on the Addiction Research Center Inventory (ARCI) indicated no measurable effects on mood as measured on the MGB, PCAG and LSD subscales at the time of LCGU determination. Rates of LCGU were determined in 74 anatomically-defined brain regions. The pattern of LCGU in postaddicts and active heroin addicts was similar to that reported previously for normal controls. With the smaller number of subjects in the pilot study, no significant group differences in LCGU were obtained although there was a tendency for a reduced LCGU in the basal ganglia and thalamus of active heroin users compared to drug-free postaddicts. The lack of effect in most brain areas was consistent with data obtained by Kimes et al. (see below), indicating tolerance to chronic opioid effects in the brain.

In a second ongoing series of studies, human volunteers with histories of prior opioid abuse are participating in a double-blind

crossover study on the effects of acute morphine on LCGU. Subjects are tested to determine the reliability and strength of their subjective and EEG responses to two doses of morphine (15 and 30 mg, i.m.) as compared to placebo. Any subject who lacks the characteristic responses, measured as EEG slowing and self-reports of euphoria, is excluded from the PET studies.

Preliminary findings suggest a general decrease in LCGU (10-25%), particularly in the basal ganglia and cortex. The LCGU decrement seems to be correlated with the magnitude of subjective responses (self-reports of mood and feeling states) and with the degree of EEG slowing induced by morphine.

The aforementioned studies will be completed and prepared for publication. In addition, a new protocol will be initiated to map the euphorigenic response to cocaine, as measured by LCGU. A major question addressed will relate to the universality of differences in the brain areas or circuits involved in euphoria produced by compounds from different drug classes.

B. Cerebral Distributions and Mechanisms of Action of Cocaine and 3,4-Methylenedioxymethamphetamine ("Ecstasy", MDMA): London, E.D., Wilkerson, G., Kimes, A.S., Weissman, A.D., and Johnson, J.E.; Collaborating Investigators: Battaglia, G. and De Souza, E.B.

The purpose of this project is to delineate the neural effects of cocaine and MDMA and to obtain information about the mechanisms by which these drugs produce psychotropic and possible neurotoxic effects.

The distribution of cocaine's cerebral metabolic effects was studied in the rat using the 2-deoxyglucose technique. Cocaine stimulated rates of local cerebral glucose utilization (LCGU) in components of the extrapyramidal motor system and reduced LCGU in the lateral habenula. The metabolic effects of cocaine resembled findings with amphetamine and apomorphine, and were consistent with a dopaminergic action [Wilkerson et. al., Trans. Am. Soc. Neurochem. 17 (1986) 161; Wilkerson et al., Pharmacologist 28 (1986) 236].

The effects of various dose levels of cocaine were also examined on the fine structure of NG108x15 neuroblastoma cells. Electron microscopic study of the cells after 3 days of treatment with cocaine revealed an interesting effect at low levels (10^{-6} to 10^{-9} M) of cocaine in the cell nucleus, which may have implications for altered genetic transmission (Johnson & Weissman, Soc. Neurosci. Abstr., 12 (1986) in press). The specificity of this effect was demonstrated by the fact that amphetamine and imipramine show a greater toxicity without a concomittant change in nuclear ultrastructure.

The effects of MDMA on LCGU in the rat were also studied. As with cocaine, rates of LCGU were increased in extrapyramidal motor areas and decreased in the lateral habenula. In addition, an activation of some thalamic nuclei and the visual cortex was observed. The findings are consistent with a psychomotor stimulant action of MDMA, similar to that of cocaine and amphetamine, and with the production of visual hallucinations.

Ongoing studies are focused on the effects of dopaminergic and serotonergic antagonists in order to elucidate the neurochemical mechanisms by which cocaine and MDMA may alter behavior and brain function. Strain comparisons have been initiated to correlate the behavioral and cerebral metabolic effects of cocaine as a function of sensitivity to the drug.

Projected studies will use basic neurochemical assays, including measurement of neurotransmitter release and turnover.

Publications for Fiscal Year 1986:

London, E.D., Wilkerson, G., Goldberg, S. and Risner, M.E.: Effects of l-cocaine on local cerebral glucose utilization in the rat. Neurosci. Lett. 68: 73, 1986.

C. Differentiation of Opioid Effects (Mu vs. Kappa) and Studies of the Opioid Abstinence Syndrome by Metabolic Mapping: Fanelli, R.J., Kimes, A.S., Szikszay, M., Cohen, S.R. and London, E.D.; Collaborating Investigators: Bell, J.A. and Sharpe, L.

The purpose of this project is to delineate the anatomical and ultimately neurochemical systems in the brain and spinal cord that mediate the acute and chronic effects of specific opioid agonists and antagonists, and that contribute to the opioid abstinence syndrome.

The mu agonists, morphine and oxymorphone, decreased LCGU in brain regions important in somatosensory processing, including several thalamic nuclei. Nalbuphine, which has kappa agonist and mu antagonist properties, did not produce these effects but stimulated LCGU in nuclei of the spinal tract of the trigeminal nerve. The effects of these drugs on LCGU were blocked by naloxone, indicating specificity for opioid systems. Naloxone alone had no significant effect on LCGU over a wide range of doses, consistent with the view that endogenous opioid systems are activated by specific stimuli and are not tonically active. The findings suggest that different supraspinal mechanisms mediate the actions of mu versus kappa opioids (London et al., Int. Narcotics Res. Conf. (1986) in press; Fanelli et al., Soc. Neurosci. Abstr., 12 (1986) in press). Ongoing and projected experiments to extend these findings will examine the effects of

acutely administered opioids in spinal cord and brain when a painful stimulus is applied and will investigate the acute effects of intracranial microinjections of morphine into brain sites known to play a role in the rewarding and analgesic properties of opioids.

In additional studies, glucose utilization was measured in the brains and spinal cords of rats that were made morphine-dependent by s.c. implantation of morphine pellets for 7 days (chronic treatment). No difference was observed in brain glucose utilization (LCGU in 83 regions), but glucose utilization was reduced in laminae I and II of the dorsal horn of the spinal cord at cervical, thoracic and lumbar levels. Baseline latencies to paw lick in the hot plate test and to tail withdrawal in the immersion test were not different in morphine-pelleted rats compared to controls. Furthermore, an additional injection of morphine (8 mg, s.c.) did not alter hot plate latencies in the morphine-pelleted rats. The morphine-pelleted rats showed a partial tolerance to the morphine injection in the tail immersion test. Thus, cellular adaptations in the brain produced tolerance reflected by normal rates of LCGU and latencies in the hot plate test. The substantia gelatinosa of the spinal cord did not show the same level of tolerance, as evidenced by the local metabolic decrements and the partial tolerance in the tail immersion test. It appeared that tolerance may not develop to the presynaptic action of morphine on primary sensory afferents. This work was presented in part in abstract form (Kimes et al., Winter Conference on Brain Research, 1986).

The effects of chronic (7 day treatment by s.c. pellets) morphine were also examined on choline acetyltransferase and muscarinic cholinergic binding to obtain information about alterations in specific neurochemical parameters in the brain. Morphine produced a decrease in the affinity of muscarinic binding sites and a nonsignificant decrement in the activity of choline acetyltransferase which may be related to inhibitory effects on central cholinergic systems and the development of tolerance.

Glucose utilization was studied in the brain and spinal cord of morphine-dependent rats that were treated with naloxone to precipitate withdrawal. Stimulation of glucose utilization was noted in many brain areas, including thalamic structures and the central amygaloid nucleus (Kimes et al., Soc. Neurosci. Abstr., 11 (1985) 1151). Glucose utilization in the spinal cord was markedly stimulated in the substantia gelantinosa (Bell et al., Soc. Neurosci. Abstr., 11 (1985) 1070). Further work will attempt to quantify the spinal contribution (including the involvement of substance P) to cerebral withdrawal, measured as increases in local rates of glucose utilization. Additionally, how antagonists for substance P and other neuropeptides influence withdrawal-induced hypermetabolism will be determined.

Ultimately, antagonists for substance P or other neuropeptides might be developed to treat withdrawal-associated dysphoria and thus prevent relapse.

Clonidine attenuates many signs of opioid abstinence without ameliorating the subjective signs when used clinically. An action of clonidine on the locus coeruleus has been postulated as a mechanism, but other CNS areas involved could be identified by simultaneously measuring cerebral and spinal glucose utilization and physiological symptoms during opioid withdrawal. In prior work it was observed that the effect of clonidine on attenuating some signs of the opioid abstinence syndrome is associated with a concomitant attenuation of cerebral hypermetabolism during naloxone-precipitated withdrawal (Kimes et al., Soc. Neurosci. Abstr., 12 (1986) in press). Identification of brain regions where withdrawal-induced hypermetabolism persists in clonidine-treated rats may lead to development of agents for blocking withdrawal dysphoria. Therefore, plans are also underway to extend these initial studies to a more complete evaluation of the effects of clonidine on the opioid abstinence syndrome, as measured by effects on glucose utilization in the brain and spinal cord.

Publications for Fiscal Year 1986:

Fanelli, R.J., Dersch, C.M. and London, E.D.: Effects of subchronic morphine on choline acetyltransferase and muscarinic binding in the rat brain. Research Communications in Substances of Abuse 6: 189, 1985.

London, E.D., Fanelli, R.J., Szikszay, M. and Jasinski, D.: Effects of opioid analgesics on local cerebral glucose utilization. Submitted.

Fanelli, R.J., Szikszay, M., Jasinski, D., and London, E.D.: Differential effects of mu and kappa opioid analgesics on cerebral glucose utilization in the rat. Submitted.

Kimes, A.S., Bell, J.A. and London, E.D.: Glucose utilization in the brain and spinal cord during chronic morphine administration. Submitted.

D. Morphine Interactions with Calcium Channel Antagonists: Szikszay, M. and London, E.D.; Collaborating Investigators: Snyder, F.R. and Benedek, G.

Analgesia and respiratory depression in response to opioids are thought to be mediated at different opioid receptor subtypes. It has been shown previously that calcium channel antagonists enhance the antinociceptive and simultaneous thermoregulatory

effects of morphine. The purpose of this project is to investigate the interaction of calcium channel antagonists with other physiological effects of morphine.

The individual and combined effects of subcutaneously administered morphine and diltiazem, a calcium channel inhibitor, on arterial blood gases and pH were assessed in conscious Fischer-344 rats. Morphine (4 mg/kg) produced hypercapnia, hypoxia, and slight acidosis, as compared with control values. Diltiazem alone (10 mg/kg) did not affect these parameters; however, it delayed the aforementioned effects of morphine (Szikszay et al., Soc. Neurosci. Abstr., 11 (1985) 1071; M. Szikszay and E.D. London, Alc. Drug Res., 6 (1985) 237).

As an extension of this work, a major objective was to determine if a negative interaction may be detected between morphine's respiratory depressant effects and another chemical type of calcium channel antagonist. Effects of s.c. morphine and verapamil, alone and in combination, on arterial blood gases and pH, mean blood pressure and heart rate were assessed in partially restrained, awake Fischer-344 rats. As expected, morphine (4-16 mg/kg) produced dose-dependent respiratory depression, indicated by hypoxia, hypercapnia, and acidosis. Verapamil, a calcium channel antagonist, alone (10 mg/kg) did not affect these parameters; however, it significantly attenuated and delayed the aforementioned effects of morphine. Morphine caused a slight increase in mean blood pressure, which was not dose-dependent; whereas verapamil dramatically reduced blood pressure even in the presence of morphine. All groups exhibited some tachycardia, but rats treated with morphine alone exhibited the most pronounced increase in heart rate, which was antagonized by verapamil. It was concluded that the interaction of verapamil with morphine's respiratory depressant effects differed from the previously reported potentiation of morphine's antinociceptive and hypothermic effects. The results are consistent with the view that opioids produce analgesia and respiratory depression through different mechanisms. The combination of calcium channel antagonists with opioids may allow administration of lower opioid doses for analgesia while minimizing the respiratory depressant effects.

Studies of plasma glucose concentrations in rats treated with the calcium channel inhibitors and morphine demonstrated no particular interaction. No significant effect of morphine was observed in fasted conscious rats despite the hyperglycemic effects of diltiazem and verapamil. These findings suggest a general hyperglycemic effect of calcium channel antagonists.

Publications for Fiscal Year 1986:

Szikszay, M., Snyder, F.R. and London, E.D.: Interactions between verapamil and morphine on physiological parameters in rats. J. Pharmacol. Exp. Ther. In press.

Szikszay, M., Snyder, F.R. and London, E.D.: Effects of diltiazem on morphine-induced respiratory decline. J. Pharm. Pharmacol. In press.

Szikszay, M., Snyder, F.R. and London, E.D.: Effects of morphine and calcium antagonists on plasma glucose in male rats. Submitted.

E. Morphine Effect on Kidney Ultrastructure: Johnson, J.E. and London, E.D.; Collaborating Investigators: White, J.J. and Walovitch, R.

Degenerative kidney changes are associated with heroin use in human addicts but it is not known whether these changes result from exposure to the opioid or from contaminants in street heroin. The purpose of this project was to assess the effects of morphine on kidney ultrastructure to obtain information on whether renal degeneration in opioid addicts is due to the opioid per se.

Rats were treated chronically with morphine (s.c. pellets for 7 days) and sacrificed using aldehyde perfusion. The kidneys were excised, sectioned and prepared for scanning electron microscopy. Micrographs taken at 5,000x were scored on the presence of short or long microprojections. Morphine significantly altered the frequencies of scores for long microprojections, suggesting an increased number of microprojections on glomerular polocytes. No changes in filtration slits, pedicels, or blebbing (focal enlargements) were noted. The data support the view that kidney degeneration with opioid abuse reflects effects of opioids per se, and are consistent with microprojection changes as a function of altered intracellular cyclic AMP.

The publication of the resultant manuscript will represent the conclusion of this project.

Publications for Fiscal Year 1986:

Johnson, J.E., Jr., White, J.J., Jr., Walovitch, R. and London, E.D.: Effects of morphine on rat kidney glomerular polocytes: a scanning electron microscopic study. Submitted.

F. Metabolic Studies on the Effects of Capsaicin in the CNS: Szikszay, M. and London, E.D.

Capsaicin has widespread pharmacological effects on the peripheral and central nervous systems, particularly those parts which are involved in sensation. The 2-deoxyglucose procedure was used to assess the distribution of capsaicin's effects on cerebral and spinal rates of glucose utilization to elucidate the anatomical sites involved in the neurotoxic and sensory effects of capsaicin and the neuropeptides that it releases. Subacute capsaicin treatment in adult rats increased rates of glucose utilization in the substantia gelatinosa of the spinal cord (the recipient of primary sensory afferent projections) and the ventromedial aspect of the dorsal horn. Increased rates of glucose utilization were also seen in sensory relay nuclei and other pain-related structures in the brain. Most of the affected structures contain detectable levels of markers for substance P. The work has been presented in abstract form (Szikszay, M. and London, E.D., Soc. Neurosci. Abstr. 12 (1986) In press).

G. Sigma and Phencylidine (PCP) Systems: Neuroanatomical and Metabolic Studies: Weissman, A., Su, T.-P., Brousolle, E. and London, E.D.; Collaborating Investigators: Hedreen, J., Marquis, K. and Moreton, J.E.

The goal of this project is to investigate the nature, distribution and physiological significance of sigma and PCP receptors in the brain. Human autopsy brain tissue has been obtained and is being assayed with several tritiated ligands specific for sigma and PCP receptors. A postmortem study of guinea pig brains is underway to ascertain the stability of these receptors under human autopsy conditions.

In addition, the *in vivo* binding of ligands that interact with sigma receptors, ([^{3}H]+SKF-10,047, [^{3}H]haloperidol and [^{3}H]PCP), is being studied in mice. The resultant information may provide the basis for later *in vivo* studies of sigma receptors in humans using positron emission tomography (PET). Preliminary results indicate that the highest specific binding of ligand to sigma receptors *in vivo* is in the cerebellum, midbrain and medulla pons, consistent with the results of *in vitro* studies. In addition to the studies on receptor characteristics and distribution, it is of interest to investigate the physiological significance of the presence of receptors for these drugs in the brain. Alterations of LCGU induced by pharmacological agents that influence the sigma and PCP systems are being examined. Prior research has shown that PCP has dose-related effects on LCGU in many brain systems including sensory, motor and limbic areas. Most of these effects are apparent as increases in brain metabolism. Some decreases were observed in the frontal cortex and may be linked to PCP's psychotomimetic

actions (London et al., Winter Conference on Brain Research (1986); A.D. Weissman et al., Soc. Neurosci. Abstr., 12 (1986) in press). The effect of the sigma agonist, +SKF-10,1047, was also investigated and found to depress LCGU in several cortical sensory regions and regions of the hippocampus and cerebellum. The pattern of sigma agonist actions on brain metabolism seems to differentiate it from PCP agonists (Weissman et al., The Pharmacologist, 28 (1986) 172; Weissman et al., Soc. Neurosci. Abstr., 12 (1986) in press). Currently efforts are underway to measure the effects of these drugs on LCGU in the presence of specific sigma and PCP antagonists to determine if these two systems utilize functionally different anatomical substrates for their action.

The abuse potential of PCP in humans and the self-administration of the compound by rats have suggested that PCP may affect reward systems. Thus, LCGU is being examined in rats trained to self-administer PCP on a fixed-ratio schedule. Preliminary observations obtained from animals which received PCP and yoked controls receiving saline seem to indicate that the self-administering animals show patterns of LCGU which are similar to naive rats receiving PCP acutely, but at a higher dose.

Publications for Fiscal Year 1986:

Weissman, A.D., Dam, M. and London, E.D.: Alterations in local cerebral glucose utilization induced by phencyclidine. Submitted.

H. Studies of Nicotine Receptors and Their Involvement in the Behavioral and Metabolic Effects of Nicotine: Fanelli, R.J., Broussole, E.P.M., Dam, M. and London, E.D.; Collaborating Investigators: Jaffe, J.H. and Henningfield, J.E.

Previous studies at ARC using light microscopic autoradiography have demonstrated saturable, specific binding of [^{3}H]nicotine ([^{3}H]N) in the rat brain. In addition, it was found that the distribution of the metabolic effects of nicotine follows the localization of [^{3}H]N binding sites, suggesting that the sites are functional receptors (London et al., Soc. Neurosci. Abstr., 11 (1985) 654; Dam et al., soc. Neurosci. Abstr., 11 (1985) 231; Jaffe et al., Third World Cong. Clin. Pharmacol. Ther. (1986). This project is directed toward providing additional information about nicotine receptors so that it might be possible ultimately to study them in the human brain with positron emission tomography (PET). In addition, another goal of the proposed work is to elucidate receptor mechanisms involved in the behavioral effects of chronic nicotine.

[^{3}H]L-nicotine was administered i.v. to mice which were sacrificed at various times later. Brains were dissected for measurement of radioactivity. Nonspecific binding was determined in mice pretreated with unlabelled L-nicotine. There was a rapid entry of [^{3}H]N into the brain and a decline after 7.5 min. Specific binding was maximum at 5 min. (50% in thalamus and superior colliculus) and fell nearly to zero by 30 min. These results suggest that specific binding of [^{3}H]N can be measured in vivo with radiolabeled nicotine. Experiments on the specificity and saturability of binding are in progress. A preliminary report has been submitted (Broussole et al., Soc. Neurosci. Abstr., 12 (1986) in press).

Chronic treatment with nicotine causes an up-regulation of CNS nicotinic cholinergic receptors. Using chronic administration of nicotine to produce supersensitivity and subsequently examining the resulting effects on local rates of glucose utilization in brain, on receptor densities and affinities, and on maze performance may provide insight into the neurochemical and anatomical bases underlying nicotine's chronic effects on behavior. In this regard, the maze performance of animals treated chronically (10 days) with nicotine has been examined and LCGU measured in the same animals. Efforts are ongoing to design a more sensitive learning task in order to demonstrate drug effects. The analysis of receptor dynamics and alterations in LCGU is currently underway.

Publications for Fiscal Year 1986:

Henningfield, J.E., Jaffe, J.H. and London, E.D.: Nicotine reward: studies of abuse liability and physical dependence potential. In Brain Reward Systems and Abuse, Raven Press, New York, In press.

London, E.D., Szikszay, M. and Dam, M.: NIDA Research Monograph 67, Problems of Drug Dependence, L.S. Harris (Ed.), U.S. Government Printing Office, Washington, D.C., pp. 26-36, 1986.

I. Diazepam Effect on LCGU in the Rat: Dam, M., Broussole, E.P.M. and London, E.D.

Diazepam was administered i.v. at different doses and times before [^{14}C]deoxyglucose (DG). Large LCGU decrements were observed in 30 out of 62 brain regions examined which were maximum with 5 mg/kg diazepam at 2 and 30 min. before [^{14}C]DG. The effects occurred preferentially in areas enriched in benzodiazepine type I rather than type II receptors. The results suggested that benzodiazepine receptor subtypes are functionally distinct and that the therapeutic effects of diazepam are mediated by type I receptors (London et al., Soc.

Neurosci. Abstr., 12 (1986) in press). Additional experiments with the selective benzodiazepine type I receptor ligand, CL 218,872, are in progress.

J. Factors which Influence Rates of Local Cerebral Glucose Utilization (LCGU): London, E.D.; Collaborating Investigators: Selmanoff, M., Wise, P.M., Cohen-Becker, I.R., Weiland, N.G. and Walovitch, R.

The 2-deoxyglucose technique for measuring LCGU is used extensively by the Laboratory's research program. It is important to consider various physiological and psychological factors which may influence LCGU and the interpretation of effects of psychoactive drugs on LCGU. Therefore, studies have been initiated on the effects of various conditions on LCGU. Factors considered to date include age, endocrine status, circadian periodicity, restraint stress, and pain.

In keeping with previous findings on effects of age on LCGU, age-associated LCGU declines were observed in all hypothalamic areas examined except the median eminence. Circadian periodicity in LCGU was observed in the suprachiasmatic nucleus and the pineal gland of old and young animals. Old ovariectomized rats primed with estradiol showed an irregularity in the circadian periodicity of LCGU in the suprachiasmatic nucleus, associated with a loss of cyclic reproductive function (Wise et al., Soc. Neurosci. Abstr., 11 (1985) 951; Wise et al., Deutsche Gesellschaft fur Endokrinologie, 30, Symposium 12 (1986) bix 15 Marz, Munchen).

In studies of the effects of prolactin and restraint on LCGU, hyperprolactinemia was associated with decreased LCGU in the medial forebrain bundle and the dorsal hippocampus. Free-ranging rats had significantly higher rates of LCGU than restrained rats in several areas including the medial septal nucleus, rostral striatum, frontoparietal cortex, and median eminence. The results indicate that hyperprolactinemia may be associated with inhibition of brain areas that project to the median eminence, where prolactin stimulates dopamine turnover, and that restraint is a factor which could influence LCGU (Selmanoff et al., Proc. 67th Ann. Meeting Endocrine Soc. 42 (1985).

These studies are being extended to investigate the effects of restraint and pain on drug-induced changes in LCGU.

Publications for Fiscal Year 1986:

Selmanoff, M., Walovitch, R.C., Walker, G.E. and London, E.D.: Effects of hyperprolactinemia on plasma prolactin and glucose and on local cerebral glucose utilization. J. Neurochem. In press.

Wise, P.M., Walovitch, R.C., Cohen-Becker, I.R., Weiland, N.G. and London, E.D.: Effect of age on the circadian rhythm of local cerebral glucose utilization in ovariectomized rats. Submitted.

K. Effects of Chronic Drug Abuse on Lymphoid and Brain Receptors: Kimes, A.S., Ori, C. and London, E.D.

Intravenous drug abusers are at high risk for acquired immunodeficiency syndrome (AIDS), suggesting that chronic exposure to abused substances may alter immune function. To test this hypothesis, receptors for drugs and neurotransmitters are being studied in lymphoid tissue and brains of mice treated chronically with morphine and other abused substances. Assays of opioid receptors, including Scatchard analysis, from brain and spleen homogenates are ongoing. Preliminary results indicate the presence of mu, delta, and kappa receptor binding sites in the brain and mu and kappa sites in the spleen. Further studies will examine the effect of chronic opioid treatment on the densities and affinities of these sites in both tissues. Additional studies on the immune status of opioid-treated mice will be performed and correlated with the receptor studies.

Neurochemistry Unit:

A. Studies on Sigma Receptors: Su, T.-P. and Yeh, S.Y.; Collaborating Investigators: Weissman, A.D. and Vaupel, D.B.

Earlier work in this laboratory demonstrated the existence of endogenous ligands for sigma receptors (Su and Weissman, Soc. Neurosci. Abstr. (1985); Su and Yeh, Abstract, International Narcotics Research Conf., 1986). An endogenous sigma system appears to exist in mammalian brain which may have important pharmacological and physiological roles. Antagonists at sigma receptors may represent a new therapeutic lead to the discovery of potential antipsychotic agents. The sigma antagonists may not elicit undesired extrapyramidal side effects such as those seen with dopamine D_2 antagonists. HR-375 is a drug which in preclinical trials displayed no propensity to elicit extrapyramidal side effects. Ongoing studies have demonstrated that HR-375 was indeed a potent sigma ligand (Su, Pharmacologist 28 (1986) 89), indicating that the potential antipsychotic properties of HR-375 may be attributed, at least

in part, to its interaction with sigma receptors.

The guinea pig vas deferens preparation responded only to sigma and phencyclidine drugs, whereas this preparation exhibited no response to non-sigma drugs such as morphine, DADLE and 1-ketocyclazocine. Therefore, this study provided the first evidence for an in vitro tissue model for sigma receptor activity and strongly suggests that sigma receptors represent biologically functional receptors. It is the continuing effort of this study to discover a tissue preparation which may contain either sigma receptors or phencyclidine receptors.

Publications for Fiscal Year 1986:

Su, T.-P., Weissman, A.D. and Yeh, S.Y.: Endogenous ligands for sigma opioid receptors in the brain ("SIGMAPHIN"): Evidence from binding assays. Life Sci. 38: 2199, 1986.

Su, T.-P.: HR-375: A potential antipsychotic drug that interacts with dopamine D_2 receptors and sigma receptors in the brain. Neurosci. Lett. (1986) In press.

Vaupel, D.B. and Su, T.-P.: Guinea pig vas deferens preparation contains both sigma receptors and phencyclidine receptors. Submitted.

B. Kappa Receptors: Su, T.-P.; Collaborating Investigators: Vaupel, D.B., Johnson, R.E. and Cone, E.J.

A pentapeptide, BW942C, exhibited kappa opioid activity in humans and animals. In receptor binding studies, BW942C possessed high affinities for mu and delta receptors, moderate affinity for kappa receptors, and no affinity for sigma receptors. It is believed that BW942C represents the first synthetic peptide with affinity for kappa opioid receptors. This study provides some interesting insights about the structural requirements for activity at kappa opioid receptors.

Publications for Fiscal Year 1986:

Su, T.-P.: Further demonstration of kappa opioid binding sites in the brain: evidence for heterogeneity. J. Pharmacol. Exp. Ther. 232: 144, 1985.

Vaupel, D.B., Johnson, R.E., Cone, E.J. and Su, T.-P.: Evidence for kappa opiate activity of BW942C, an enkaphalin-like pentapeptide, in humans and animals. Submitted.

C. Genetic Factors in Opioid Dependence: Su, T.-P.

"High" dependent mice and "low" dependent mice are being bred

successfully to the fourth generation at present. There is clearly a separation between the descendants of these two groups of animals. Neurochemical assays will be used to examine the brains of these two groups of animals.

D. Effect of 3,4-Methylenedioxyamphetamine (MDA) and 3,4-Methylenedioxymethamphetamine (MDMA) on Dopamine (DA) and Serotonin (5-HT) in the Rat Brain: Yeh, S.Y.; Collaborating Investigators: Battaglia, G., De Souza, E.B., Kuhar, M.J. and Hsu, F.-Y.

MDA and MDMA possess psychotomimetic and stimulant properties. These so-called "designer drugs" have been popular drugs of abuse. The purpose of this study is to investigate the effects of these drugs on neurotransmitters, especially monoamines and their metabolites. Rats were injected eight times s.c., with either saline, MDA or MDMA (20 mg/kg) every 12 hours. Two weeks following the last injection, the brains were removed and concentrations of monoamines in tissue were measured with HPLC. MDA caused dramatic decreases in serotonin (5-hydroxytryptamine, 5-HT) (65, 26, and 33%) and 5-hydroxyindole acetic acid (5-HIAA) (58, 64, and 40%) in frontal cortex, hippocampus and hypothalamus, respectively. These compounds caused smaller changes in striatal 5-HT content (10-20%), while the decreases in striatal 5-HIAA levels produced by both MDA (33%) and MDMA (36%) were comparable to those observed in other regions (S.Y. Yeh, G. Battaglia, M.J. Kuhar and E.B. De Souza, Soc. Neurosci. Abstr., 12 [1986] in press).

Cytotoxicity was not observed after i.c. injection of 20 ug of MDA and MDMA. The neurotoxicity of MDA and MDMA has been postulated to be due to metabolites of MDA and MDMA, respectively. The effect of 5-HT uptake inhibitors, such as citalopram, on the neurotoxicity of MDMA has been investigated. Citalopram (10 mg/kg) was injected s.c. into rats 45 min. before each MDMA injection, (10 mg/kg, s.c., four times). 5-HT and 5-HIAA contents in the frontal cortex of citalopram- and MDMA-treated animals were not significantly different from those of saline controls. Citalopram also decreased 5-HT in the frontal cortex. The effect of MDMA on 5-HT was dose-dependent. Ongoing studies are focused on the effects of inhibitors of drug metabolizing enzymes on MDMA induced neurotoxicity.

E. Effect of Cocaine on Monoamines and Their Metabolites in Brain: Yeh, S.Y.

The purpose of this study is to determine the effect of short-term cocaine treatment on neurotransmitters, especially monoamines, and their metabolites. Rats were injected s.c. or i.p. with cocaine, 20 mg/kg, or saline every 12 hours for 8 days. Twenty-four hours after the last injection, the animals were sacrificed, the brains removed, and monoamines and their metabolites measured using a HPLC procedure. Cocaine increased hypothalamic content of NE by 133 and 100%, of DA by 177 and 120%, of DOPAC by 68 and 13%, and of HVA by 77 and 58%, after s.c. and i.p. injection, respectively, as compared to that of saline controls. Monoamines and their metabolites in the frontal cortex, striatum, hippocampus, midbrain and pons were not significantly different from saline controls after the short-term cocaine treatment. Ongoing studies are focused on the uptake of NE and DA and tyrosine hydroxylase activity in the hypothalamus of short-term, cocaine-treated rats.

F. Metabolism of Pyrilamine and Tripelennamine: Yeh, S.Y.

The combination of an antihistamine, tripelennamine, and pentazocine, a narcotic agonist/antagonist, has been abused. The purpose of this study is to determine the effect of pentazocine on the urinary metabolic profile of tripelennamine. Urine of rats injected i.p. with either pyrilamine or tripelennamine was hydrolyzed with glusulase and extracted with benzene-isopropanol. The extract was analyzed by thin layer chromatography, gas chromatography and gas chromatography-mass spectrometry. 2-(Dimethylaminoethyl)aminopyridine, 2-(4-hydroxybenzyl)aminopyridine, desmethylpyrilamine, 4-hydroxy-tripelennamine, (4-hydroxy-3-methoxybenzyl)tripelennamine and (3-hydroxy-4-methoxybenzyl)tripelennamine were identified as metabolites of pyrilamine. 2-(Dimethyl-aminoethyl)aminopyridine, 2-(alpha-hydroxybenzyl)aminopyridine, (alpha-hydroxy-benzyl)tri-pelennamine and (4-hydroxybenzyl)tripelennamine were identified as metabolites of tripelennamine. The results confirm debenzylation of tripelennamine and pyrilamine as a new metabolic pathway for these compounds. The results of the study on urine from men administered tripelennamine s.c. were inconclusive [S.Y. Yeh, Pharmacologist 28 (1986) 118].

Publications for Fiscal Year 1986:

Yeh, S.Y.: Potentiation of pentazocine antinociception by tripelennamine in the rat. J. Pharmacol. Exp. Ther. 235: 683, 1985.

Yeh, S.Y.: The effect of antihistamine drugs on pentazocine antinociception in the rat. Pharmacol. Biochem. Behav. 24: 925, 1986.

Yeh, S.Y., Todd, G.D., Johnson, R.E., Gorodetzky, C.W. and Lange, R.: The pharmacokinetics of pentazocine and tripelennamine in humans. Clin. Pharmacol. Ther. Clin. - Pharmacol. 39: 669, 1986.

Neurophysiology Unit:

A. Structure and Activity of Semirigid Nicotinic Agonists: Spivak, C.E.; Collaborating Investigators: Gund, T.M., Liang, R.F. and Waters, J.A.

In fiscal year 1985, this laboratory reported on the discovery of a new, semirigid, cyclic nicotinic agonist, isoarecolone methiodide. This compound, 50 times more potent than carbamylcholine, is one of the most potent agonists tested at the frog neuromuscular junction. Its potency is exceeded only by suberyldicholine, a compound whose flexibility precludes its use in seeking information about how the structure of agonists governs the response of the receptor.

To further pursue the question about what factors contribute to the high potency of isoarecolone methiodide, 13 new agonists have been synthesized and tested during the past year (Gund et al., Soc. Neurosci. Abstr. 12 (1986) in press). Of these, 8 were synthesized in this Laboratory. The most potent agonist, 4.6 times as potent as carbamylcholine, contains a trifluoroacetyl group. Molecular orbital calculations of particle changes show that this compound has an electrostatic field about its acetyl group that is notably different from all the other structurally comparable agonists. It is concluded that such effects are not of primary importance in determining agonist potency. Among the new agonists are three with non-phenolic hydroxy groups. One of these is 2.0 times as potent as carbamylcholine. This finding is novel since such compounds were previously thought to be exceedingly weak agonists (e.g., choline). Three agonists freeze the conformation that believed to be the one necessary for recognition by the receptor into especially rigid structures. The finding that all three are very weak (0.006 to 0.015 times the potency of carbamylcholine) has led to the tentative hypothesis that the agonist is stressed by the receptor during activation such that parts of the agonist must rotate with respect to other parts.

In fiscal year 1985, recordings of single ion channel currents in response to some of the new agonists were initiated. These were from extrajunctional receptors and were relatively easy to record. However, their significance seemed somewhat dubious

and their kinetic analysis very difficult. Therefore, this year junctional regions of muscle fibers were visualized using fluorescent alpha-bungarotoxin so that endplate morphology could be visualized in bright field or Hoffman Modulation optics. Patch clamp recording of junctional receptors was begun and new techniques are being explored in an attempt to enhance the rate of success in recording single ion channel currents.

Publications for Fiscal Year 1986:

Spivak, C.E., Gund, T.M., Liang, R.F. and Waters, J.A.: Structural and electronic requirements for potent agonists at a nicotinic receptor. Eur. J. Pharmacology 120: 127, 1986.

Gund, T.M., Hermsmeier, M., Liang, R.F., Yadav, J., Spivak, C.E. and Waters, J.A.: Molecular modeling approaches for design of receptor agonists and antagonists. Proc. Symp. Three Dimensional Structure and Drug Action. In press.

Gund, T.M., Hermsmeier, M., Liang, R.F., Yadav, J., Spivak, C.E. and Waters, J.A.: Design of acetylcholine receptor agonists and antagonists by computer methods. Sixth Eur. Sympos. on Quantitative Structure Activity Relationships. In press.

Gund, T.M., Hermsmeier, M., Liang, R.F., Yadav, J., Spivak, C.E. and Waters, J.A.: Conformational and electrostatic approaches for design of receptor agonists and antagonists. Gordon Research Conference on Computational Chemistry, August 1986.

B. Studies on the Role of Neuropeptide Transmitters in Opioid Action and Opioid Withdrawal: Bell, J.A.; Collaborating Investigators: Spivak, C.E., Jaffe, J.H. and Su, T.-P.

In studies utilizing the isolated spinal cord of the neonatal rat, capsaicin and synthetic substance P were used to clarify the role of substance P in spinal opioid withdrawal. The capsaicin response was augmented greatly during withdrawal from acute morphine whereas the substance P response was not affected, suggesting that in acute dependence presynaptic changes may be the predominant underlying mechanism.

Studies were performed on the effect of chronic morphine administration on electrophysiological responses in the isolated spinal cord of neonates so treated. To date, no supersensitivity to the action of substance P has been found. Furthermore, the dose response curve to the depolarizing postsynaptic supersensitivity to functional release of substance P has not been observed in the spinal cord of physically dependent neonatal rats.

Antibodies to substance P were successfully raised in rabbits with a titer of about 10,000. Efforts are being focused on utilizing antibodies and substance P antagonists to characterize the involvement of substance P in opiate dependence and withdrawal.

Publication for Fiscal Year 1986:

Bell, J.A. and Jaffe, J.H.: Electrophysiological evidence for a presynaptic mechanism of morphine withdrawal in the neonatal rat spinal cord. Brain Res. (1986) In press.

C. Isolated Spinal Cord of the Neonatal Rat: Role of Neuropeptides at Sigma Receptors: Bell, J.A.; Collaborating Investigator: Su, T.-P.

D-pentazocine, which selectively binds to sigma receptors, has been found to depress C-reflexes and the depolarizing response to capsaicin in the isolated cord, providing a bioassay for sigma activity. Several polypeptides, which have been extracted from guinea pig brain and are active in the sigma binding assay, are being tested on the isolated spinal cord for sigma(D-pentazocine)-like effects. The results may provide information about the possible functional significance of endogenous polypeptides that bind to sigma receptors.

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

Overview

A major effort of this Laboratory has been directed towards elucidating the molecular mechanisms of action of important drugs of abuse. These drugs include cocaine, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxy-methamphetamine (MDMA), and related amphetamine derivatives as well as opiates and benzodiazepines.

With regard to cocaine, a key focus has involved attempts to identify the cocaine receptor. While several binding sites for cocaine have been described in the literature, the receptor or binding site that mediates the reinforcing properties of cocaine has not been identified. Hence, a strategy has been developed and experiments have begun which hopefully will identify the cocaine receptor related to drug abuse.

With regard to MDA, MDMA and related amphetamine derivatives, a major thrust has involved trying to identify the most likely uptake sites or drug receptors which mediate the reinforcing and neurotoxic effects of these drugs. In a variety of in vitro studies, the affinity of these amphetamine derivatives for a

number of drug receptors has been examined. The results indicate that these compounds have relatively high affinities for serotonin uptake sites and serotonin-2 receptors. In addition, a number of in vivo studies have been undertaken and measurements of various monoamines have been made after drug administration. The results indicate that chronic administration of MDA and MDMA results in a drastic reduction in serotonin in various brain areas. Furthermore, the lack of a direct effect of these drugs on brain suggests that it is not the parent compounds, but rather their metabolites, that are toxic.

While very precise and accurate methods exist for studying drug receptors in vitro, the ability to study such receptors in vivo is a current frontier. The Laboratory's approach has been to study drug receptor occupancy in vivo in animal models and to extend the results to human subjects in PET scanning studies. For example, benzodiazepine receptors are well studied in a large number of in vitro experiments. However, there are only a few publications on approaches to study benzodiazepine receptors in vivo. Thus, current efforts are focused on labeling benzodiazepine receptors in vivo with tritiated suriclone. This is important because suriclone is an agonist which gives a high degree of receptor labeling in vivo as indicated by preliminary experiments. Continued success with these experiments should permit the imaging of benzodiazepine receptors in living humans using carbon-11 labeled suriclone for PET scanning. This would afford the opportunity to study these receptors in populations that abuse benzodiazepines and to determine whether or not these receptors might be different in these populations or in other related interesting clinical groups, such as epileptics and patients with anxiety disorders. A strong ongoing collaboration exists with colleagues at the Johns Hopkins University School of Medicine who carry out the PET scanning studies. Currently a productive effort has involved studying dopamine receptors using PET scanning in human populations. Dopamine has been implicated as an important neurotransmitter in reward systems.

Since stress is an important factor in the sociological events that lead to substance abuse, the Laboratory has been investigating molecular mechanisms involved in stress. A key neurochemical in the hypothalamic-pituitary-adrenal stress axis is corticotropin-releasing factor (CRF). At this time, a substantial effort is being directed to studying CRF. A novel finding has been that this compound is not only involved in the hypothalamic-pituitary-adrenal axis but it is also found in brain. Several physiological studies suggest that CRF is a neurotransmitter in the CNS and its action may be related to certain features of the stress response. Much of the Laboratory's work contributes to the notion that CRF is a neurotransmitter in the brain. Moreover, a reliable assay has been established for

measuring CRF receptors in the brain. In addition, detailed studies have been carried out evaluating the second messenger through which CRF may produce its effect in brain cells.

A fortuitous finding was that CRF is reduced in cerebral cortical tissue from patients who died with Alzheimer's disease. This decrease was accompanied by a reciprocal increase in CRF receptors. This finding is unique in the literature since it is one of the first demonstrations of a reciprocal change in a peptide and its receptors in a neurological disorder. The Laboratory also recently found that CRF is altered in other neurological diseases as well. Thus, these data contribute to the idea that CRF is an important neurochemical in animal and human brains and that in the normal situation CRF may be involved in cognition. More recent initiatives with CRF have found that the messenger RNA which produces CRF is found in abundance in the olivo-cerebellar pathway in the brain stem. These data are among the first to strongly suggest that CRF is a neurotransmitter in this pathway.

In summary, the Laboratory is making very substantial progress in providing data indicating that CRF is a major neurotransmitter in the central nervous system, in identifying specific neuronal pathways containing this compound, in characterizing its molecular mechanisms of action at its receptors, and in demonstrating its involvement in the functioning human brain.

A major effort in 1987 will be directed toward studying the CRF receptor and the signal transduction mechanisms at a more detailed molecular level. While certain preliminary data indicate that CRF may produce some of its effects in brain by stimulating adenylate cyclase, other data generated suggest that there may be multiple CRF receptors in brain coupled to multiple signal transduction mechanisms. Thus, the Laboratory has plans to characterize the different types of CRF receptors and examine the effects of CRF on different second messenger systems. By combining radioligand binding techniques with second messenger assays, a greater understanding of the molecular mechanisms by which CRF produces its varied effects in the CNS may result.

Another goal for the upcoming year is to apply molecular biological techniques to the general area of drug abuse. More specifically, this involves an effort to determine the genetic basis for the pharmacological and biochemical actions of drugs on the nervous system. For example, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a substance which elicits neuropathologic changes in man resulting in Parkinson's disease. MPTP is metabolized to MPP^+, which is a highly neurotoxic substance. MPP^+ is neurotoxic to PC12 cells and this toxicity

is mediated by the uptake of MPP^+ by the dopamine uptake site.

Ongoing studies have found that retroviral infection reduces the neurotoxicity of MPP^+ in tissue cultured PC12 cells. Retroviral infection results in an inactivated gene. Thus, these studies indicate that a specific gene may exist which mediates MPTP toxicity. Moreover, this strategy provides an approach by which to identify the gene related to MPTP toxicity. Infected cells which are resistant to MPTP toxicity may be cloned and the retroviral sequence isolated along with the flanking genomic sequence which may encode for the protein related to MPTP toxicity. Based upon the data available, it is quite possible that the related protein is the dopamine uptake site. Consequently, the identification of the gene for the uptake site may permit the determination of the genetic sequence for the dopamine uptake site. This would be the first time that this has been accomplished. This general strategy of identifying specific genes for neurotoxic compounds can be extended to other substances of abuse: for example, MDMA which is known to be toxic to serotonergic neurons.

In addition to the work on MPTP, another important focus of this molecular biological approach is designed to investigate the regulation of the pro-opiomelanocortin (POMC) gene. POMC is a protein which is a precursor for a variety of hormones including the potent opioid peptide, beta-endorphin. While there is apparently only a single functional copy of this gene, it has been clearly established that POMC production is regulated by different hormones in different tissues. For example, POMC in the anterior pituitary is regulated by CRF and glucocorticoids while POMC in the intermediate lobe is regulated by catecholamines. POMC is found in the anterior and intermediate pituitary, in the hypothalamus, in the placenta, in the gut, and possibly in certain lymphocytes. Little is known about the molecular mechanisms and genetic sequences which dictate the differential hormonal responsiveness of the gene in different tissues. The level of POMC production is extremely high in corticotrophs, suggesting the presence of specific genetic elements which may enhance the expression of this gene. Accordingly, the regulatory sequences from the human POMC gene have been subcloned and attached to bacterial genes. This may permit study of the differential responsiveness of various fragments of the POMC regulatory sequence to CRF, steroids and other chemicals in order to identify the nature of the sequences which are responsible for POMC gene regulation. These experiments may also provide definitive information on how the POMC gene and its opioid peptide product may be regulated by multiple hormones.

With respect to AIDS-related studies, since a significant fraction of those who develop AIDS are intravenous drug abusers, the Laboratory has begun a series of AIDS-related studies. A sig-

nificant effort will involve the development of monoclonal antibodies to the human T-lymphotropic virus type III (HTLV-III) virus. A fragment of the viral gene which has already been genetically engineered encodes the envelope protein which is the viral receptor for the human T-helper cells. This recombinant virus may allow safe production of large quantities of the viral envelope protein for antibody production. It is anticipated that this may facilitate the production of a large repertoire of antibodies to surface antigens on the virus, a task which has not proven feasible using conventional methods. Initial objectives will be to obtain antibodies which block viral infection and to identify the viral epitopes to which they bind. A subsequent objective will be to produce, by recombinant DNA techniques, fragments of these viral coat antigens which may be tested for their ability to induce an immune response in animals. The ultimate goal would be to produce a vaccine.

Additional AIDS-related research will be directed toward elucidating the role of CRF and opioid peptides and opiate drugs on immune function. Receptors for CRF and opiates will be identified in mouse spleen, thymus, and human blood leukocytes. In addition, CRF and opiate receptors, as well as cellular response to stimulation by these factors, will be examined before and after infection by viruses and endotoxins as well as following treatment with various opiate drugs and other compounds. The effects of chronic treatment with various drugs of abuse to the point of dependence will also be studied. With regard to the effects of opiates on immune function, a special focus will be on identification and characterization of sigma opioid receptors in rat and human tissues and the modulation of these receptors by chronic opiate treatment.

Summary of Ongoing Research:

A. The Cocaine Receptor

While several binding sites for cocaine have been identified, the binding site related to drug reinforcement and substance abuse has not been identified. These studies are aimed at identifying the cocaine receptor related to addiction and abuse and include:

1.) Mapping cocaine binding sites in rat brain by autoradiography: Goeders, N., Ritz, M. and Kuhar, M.J.

2.) Strategies for finding the cocaine receptor as related to substance abuse: Ritz, M. and Kuhar, M.J.

3.) Studies of the effect of chronic cocaine administration on dopamine receptors in the rat nucleus accumbens: Goeders, N. and Kuhar, M.J.

B. PET Scanning of Receptors

Measuring receptors by positron emission tomography permits the quantification of receptors in the living human brain. Thus, the involvement of receptors in diseases of living clinical populations will be assessed by:

1.) Quantification of neuroreceptors in the living human brain. II. Inhibition studies of receptor density and affinity: Wong, D.F., Gjedde, J., Wagner, Jr., H.N., Dannals, R.F., Douglass, K.H., Links, J.M. and Kuhar, M.J.

2.) ^{3}H-3-N-Methylspiperone labeling of D_2 dopamine receptors in basal ganglia and S_2 serotonin receptors in cerebral cortex: Lyon, R.A., Titeler, M., Frost, J.J., Whitehouse, P.J., Wagner, Jr., H.N., Wong, D.F., Dannals, R.F., Links, J.M. and Kuhar, M.J.

C. Labeling Drug Receptors In Vivo

While studying receptors using in vitro techniques is commonplace, the ability to study drug receptors in vivo is more difficult. The aim of these studies is to identify conditions whereby drug receptors can be studied in an intact animal. The results of these studies which have a direct bearing on the conduct of the PET scanning studies include:

1.) Labeling the benzodiazepine receptor in vivo with suriclone: Ritz, M., Frost, J. and Kuhar, M.

2.) Using buspirone to nonspecifically enhance in vivo labeling of benzodiazepine receptors: Goeders, N.E., Ritz, M. and Kuhar, M.J.

D. Drug Receptor Mapping in Brain: Kuhar, M.J.

Mapping drug receptors may provide an explanation of how a single drug exerts a range of pharmacological effects and a unique view of the biochemical organization of the brain. These studies will focus on receptors for drugs which are abused. They will address the question, Are certain areas of the brain uniquely chemosensitive?

E. The Structural Gene For Angiotensin Converting Enzyme

Angiotensin converting enzyme appears to be expressed uniquely in dopamine containing neurons. The role of angiotensin in these neurons is being explored since these neurons are involved in the endogenous reward system.

Pertinent studies include:

1.) Characterization of the structural gene for rat striatal and lung angiotensin converting enzyme: Lo, M.M.S., Conrad, M.K., Strittmatter, S.M., and McLane, M.

2.) Characterization of the structural gene for rabbit and human striatal and lung angiotensin converting enzyme: Lo, M.M.S, Strittmatter, S.M., Conrad, M.K. and McLane, M.

F. Differential Expression From the Putative 5' Regulatory Sequences of the Human Pro-Opiomelanocortin Gene: Lo, M.M.S. and Dersch, C.M.

This human gene expresses opioid peptides. The factors which regulate the expression of these peptides will be explored.

G. AIDS-Related Studies

Since intravenous drug abusers are at increased risk for developing AIDS complex, a variety of studies will be carried out on the HTLV-III virus, including:

1.) Construction of a highly transmissible HTLV-III retroviral vector: Lo, M.M.S., McLane, M. and C.M. Dersch.

2.) Production of monoclonal antibodies to the envelope protein of the HTLV-III retrovirus: Lo, M.M.S. and Dersch, C.M.

3.) Development of envelope subunit vaccines against the AIDS virus: Lo, M.M.S., Dersch, C.M. and McLane, M.

H. Role of Corticotropin-Releasing Factor (CRF) as a Neurotransmitter in the Central Nervous System

CRF is a peptide that mediates at least some of the stress response. Since stress is often involved in drug abuse, CRF will be explored as a neurotransmitter in the brain by examining:

1.) Corticotropin-releasing factor receptors in the rat central nervous system: Characterization and regional distribution: De Souza, E.B. and Applegate, A.V.

2.) Corticotropin-releasing factor receptors in rat brain which may mediate changes in adenylate cyclase activity: Battaglia, G., Webster, E. and De Souza, E.B.

3.) Corticotropin-releasing factor mRNA in human and baboon inferior olive: Identification using quantitative

hybridization histochemistry: Young, W.S., Price, D., Whitehouse, P.J., Powers, R., Walker, L., Kuhar, M.J. and De Souza, E.B.

4.) Changes in corticotropin-releasing factor (CRF)-like immunoreactivity in cerebral cortex in various neurodegenerative diseases: Whitehouse, P.J., Vale, W.W., Kuhar, M.J., Price, D.L. and De Souza, E.B.

5.) Effects of chronic atropine treatment on corticotropin-releasing factor (CRF) receptors and CRF receptor mediated adenylate cyclase activity in rat brain: De Souza, E.B. and Battaglia, G.

6.) Effects of lesion of ascending cholinergic fibers from the nucleus basalis magnocellularis on corticotropin-releasing factor receptors in rat cortex: De Souza, E.B., Wenk, G. and Whitehouse, P.J.

7.) Effects of protein modifying reagents on corticotropin-releasing factor receptors and CRF-mediated adenylate cyclase in rat brain: Webster, E., Battaglia, G. and De Souza, E.B.

8.) Ontogeny of corticotropin-releasing factor receptors in rat brain: Insel, T.R. and De Souza, E.B.

I. Putative Role of Corticotropin-Releasing Factor on Immune Function

Since stress is known to affect immune function, and since there are CRF receptors in tissues related to the immune response, the CRF receptors will be explored in relation to immune function by:

1.) Characterization and anatomical localization of corticotropin-releasing factor binding sites in thymus and spleen: Webster, E., Kuhar, M.J. and De Souza, E.B.

2.) Characterization of second messenger systems associated with corticotropin-releasing factor receptors in spleen and thymus: Webster, E., Battaglia, G. and De Souza, E.B.

J. Neurochemical Mechanisms Involved in the Action of MDA, MDMA and Related Amphetamine Derivatives

MDA and MDMA are current drugs of abuse. Recent studies have suggested that these compounds are neurotoxic in that they cause degeneration of serotonin containing terminals. These studies aimed at elucidating the mechanism of action of these drugs as well as their neurotoxicity include investigations of:

1.) Effects of MDA, MDMA and related compounds on brain serotonin recognition sites. I: In vitro studies: Battaglia, G., Kuhar, M.J. and De Souza, E.B.

2.) Effects of MDA, MDMA and related compounds on brain serotonin recognition sites. I: In vivo studies: Battaglia, G. and De Souza, E.B.

3.) In vitro and in vivo pharmacological profile of MDA and MDMA on various brain recognition sites: Battaglia, G., Kuhar, M.J. and De Souza, E.B.

4.) Immunocytochemical studies investigating the potential neurotoxic effects of MDA and MDMA on serotonergic neurons in rat brain: O'Hern, E., Battaglia, G., De Souza, E.B., Kuhar, M.J. and Molliver, M.

5.) Neuroendocrine hormone profile of in vivo administration of MDA and MDMA in rats: De Souza, E.B. and Battaglia, G.

6.) Effects of MDA and MDMA on the steady-state concentrations and turnover of biogenic monoamines in rat brain: De Souza, E.B. and Battaglia, G.

K. Receptors in Pituitary Gland

Many of the receptors under study are found in the pituitary. These receptors will be explored and their role in the hypothalamic-pituitary-adrenal stress axis will be explored in studies of:

1.) Serotonin and dopamine receptors in the rat pituitary gland: Autoradiographic identification, characterization and localization: De Souza, E.B.

2.) Identification of alpha-1 adrenergic receptors in the neural lobe of the rat pituitary: De Souza, E.B. and Kuyatt, B.

L. Benzodiazepine Receptors in Rat Brain Are Altered by Adrenalectomy: De Souza, E.B., Goeders, N.E. and Kuhar, M.J.

The role of benzodiazepine receptors in the stress response are being explored.

Organizations Collaborating with the Neurosciences Branch

Clayton Foundation Laboratories for Peptide Biology, Salk Institute, La Jolla, CA.

Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, MD.

Department of Biological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, MD.

Department of Neuroscience, Pharmacology and Experimental Therapeutics, Psychiatry, and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD.

Department of Immunology, The Johns Hopkins University School of Medicine, Baltimore, MD.

Department of Physiology, University of Maryland, School of Medicine, Baltimore, MD.

Division of Neuropathology, The Johns Hopkins University School of Medicine, Baltimore, MD.

Division of Nuclear Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD.

Gerontology Research Center, National Institute on Aging, Baltimore, MD.

Hoechst Company, Munich, Federal Republic of Germany.

New Jersey Institute of Technology, Newark, NJ.

The Medical College of Georgia, Augusta, GA

SMCCR-RSC-O, U.S. Army Research Institute, Aberdeen, MD.

Terre Haute Center for Medical Education, Indiana University School of Medicine, Terre Haute, IN.

University Medical School, Szeged, Hungary.

Department of Psychiatry, Vanderbilt University, Nashville, TN.

Veterans Administration Medical Center and University of Kentucky, Lexington, KY.

Wheaton College, Department of Biology, Wheaton, IL

Whitehead Institute, Massachusetts Institute of Technology, Boston, MA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00200-01 · NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cerebral Metabolic Studies of Drug-Induced Euphoria

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.D. London	Laboratory Chief	NPL, ARC, NIDA
Others:	E.P. Broussolle	Visiting Fellow	NPL, ARC, NIDA
	J.H. Jaffe	Director	ARC, NIDA
	R. Herning	Visiting Scientist	CHP, ARC, NIDA
	W. Pickworth	Pharmacologist	CHP, ARC, NIDA
	S. Rippetoe	Head Nurse	ARC, NIDA
	K. Kumor	Medical Officer	BDL, ARC, NIDA

COOPERATING UNITS *(if any)*

Johns Hopkins Medical Institutions (D.F. Wong, J. Links, R. Dannals, H. Wagner).

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	2.5	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Abused drugs produce a positive affective state, termed euphoria. The purpose of this project is to delineate those brain areas that are activated or inhibited during drug-induced euphoria. Another objective is the correlation of drug-induced EEG changes with effects on rates of local cerebral glucose utilization (LCGU), an index of local cerebral function. Rates of LCGU are measured in human volunteers using [^{18}F]fluorodeoxyglucose (FDG) as a radiotracer for LCGU with positron emission tomography (PET).

Six human volunteers were studied for effects of chronic heroin on LCGU. Scores on the Addiction Research Center Inventory indicated no measurable effects on mood. The pattern of LCGU in postaddicts and active heroin addicts was similar to that reported previously for normal controls. No significant group differences in LCGU were obtained although there was a tendency for a reduced LCGU in the basal ganglia and thalamus of active heroin users compared to drug-free postaddicts. The lack of effect was consistent with data obtained in our laboratory, indicating tolerance to chronic opioid effects in the brain.

In a second ongoing series of studies, human volunteers with histories of prior opioid abuse are participating in a double-blind crossover study on the effects of acute morphine on LCGU. Subjects are tested to determine the reliability and strength of their subjective and EEG responses to two doses of morphine (15 and 30 mg, i.m.) as compared to placebo. Preliminary findings suggest a general decrease in LCGU (10-25%), particularly in the basal ganglia and cortex. The LCGU decrement seems to be correlated with the magnitude of subjective responses and with the degree of EEG slowing induced by morphine.

A new protocol is being initiated to map the euphorigenic responses to cocaine, as measured by LCGU. A major question addressed will be the universality or differences in the brain areas or circuits involved in euphoria produced by agents from different drug classes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00201-02 NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cerebral Distributions and Mechanisms of Action of Cocaine and MDMA ("Ecstasy")

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.D. London	Laboratory Chief	NPL, ARC, NIDA
Others:	A.S. Kimes	Visiting Scientist	NPL, ARC, NIDA
	A.D. Weissman	Staff Fellow	NPL, ARC, NIDA
	J.E. Johnson	Visiting Scientist	NPL, ARC, NIDA
	G. Wilkerson	Bio. Lab. Tech.	NPL, ARC, NIDA

COOPERATING UNITS (if any)

MPL, ARC, NIDA (G. Battaglia, E. B. DeSouza).

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.3	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to delineate the neural effects of cocaine and MDMA and to obtain information about the mechanisms by which these drugs produce psychotropic and possible neurotoxic effects.

The distribution of cocaine's cerebral metabolic effects was studied in the rat using the 2-deoxyglucose technique. Cocaine stimulated rates of local cerebral glucose utilization (LCGU) in components of the extrapyramidal motor system and reduced LCGU in the lateral habenula. The metabolic effects of cocaine resembled findings with amphetamine and apomorphine, and were consistent with a dopaminergic action.

We also examined the effects of cocaine at various doses on the fine structure of NG108x15 neuroblastoma cells. Electron microscopic study of the cells after 3 days of treatment with cocaine revealed an interesting effect of low levels (10^{-6} to 10^{-9} M) of cocaine in the cell nucleus, having implications for altered genetic transmission. The specificity of this effect was demonstrated by the fact that amphetamine and imipramine show a greater toxicity without a concomittant change in nuclear ultrastructure.

The effects of MDMA on LCGU in the rat also were studied. As with cocaine, rates of LCGU were increased in extrapyramidal motor areas and decreased in the lateral habenula. In addition, an activation of some thalamic nuclei and the visual cortex was observed. The findings were consistent with a psychomotor stimulant action of MDMA, similar to that of cocaine and amphetamine, and with the production of visual hallucinations.

Ongoing studies are focused on the effects of dopaminergic and serotonergic antagonists in order to elucidate the neurochemical mechanisms by which cocaine and MDMA alter behavior and brain function. Strain comparisons have been initiated to correlate the behavioral and cerebral metabolic effects of cocaine as a function of sensitivity to the drug. Projected studies will use basic neurochemical assays, including measurement of neurotransmitter release and turnover.

Publications - FY 1986

London, E.D., Wilkerson, G., Goldberg, S. and Risner, M.E.: Effects of l-cocaine on local cerebral glucose utilization in the rat, Neurosci. Lett., 68: 73-78, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00202-03 NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Opioid Effects and the Opioid Abstinence Syndrome Studied by Metabolic Mapping

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R.J. Fanelli	Staff Fellow	NPL, ARC, NIDA
Others:	A.S. Kimes	Visiting Scientist	NPL, ARC, NIDA
	M. Szikszay	Visiting Fellow	NPL, ARC, NIDA
	S.R. Cohen	Visiting Fellow	NPL, ARC, NIDA
	E.D. London	Laboratory Chief	NPL, ARC, NIDA
	J.A. Bell	Pharmacologist	NPL, ARC, NIDA

COOPERATING UNITS *(if any)*

NPP, ARC, NIDA (L. Sharpe)

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.8	3.0	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to delineate the anatomical systems in rat brain and spinal cord that mediate the acute and chronic effects of opioid agonists and antagonists, and that contribute to the opioid abstinence syndrome.

The mu agonists, morphine and oxymorphone, decreased LCGU in brain regions important in somatosensory processing. Nalbuphine, which has kappa agonist and mu antagonist properties, did not produce these effects, but stimulated LCGU in nuclei of the spinal tract of the trigeminal nerve. The findings suggest that different supraspinal mechanisms mediate the actions of mu vs kappa opioids.

Glucose utilization was measured in the brains and spinal cords of rats that were made morphine-dependent by implantation of morphine pellets. No difference in brain glucose utilization (LCGU) was observed, but glucose utilization was reduced in the dorsal horn of the spinal cord. Measures of analgesia were not different in morphine-pelleted rats compared to controls. Thus, cellular adaptations in the brain produced tolerance reflected by normal rates of LCGU and latencies in the hot plate test. The substantia gelatinosa of the spinal cord did not show the same level of tolerance. We also examined the effects of chronic morphine on choline acetyltransferase and muscarinic cholinergic binding. Morphine produced a decrease in the affinity of muscarinic binding sites which may be related to inhibitory effects on central cholinergic systems and the development of tolerance.

Glucose utilization was studied in morphine-dependent rats that were treated with naloxone to precipitate withdrawal. Stimulation of glucose utilization was noted in many brain areas, including thalamic structures and the central amygdaloid nucleus. Glucose utilization in the spinal cord was markedly stimulated in the substantia gelatinosa. Clonidine attenuates many signs of opioid abstinence without ameliorating the subjective signs when used clinically. We have observed that the effect of clonidine to attenuate some signs of the opioid abstinence syndrome is associated with a concomitant attenuation of cerebral hypermetabolism during naloxone-precipiated withdrawal.

Opioid Effects and the Opioid Abstinence Syndrome Studied by Metabolic Mapping

Publications - FY 1986

Fanelli, R.J., Dersch, C.M. and London, E.D.: Effects of subchronic morphine on choline acetyltransferase and muscarinic binding in the rat brain. Research Communications in Substances of Abuse, 6: 189-192, 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00203-02 NPL

PERIOD COVERED
October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Morphine Interactions with Calcium Channel Antagonists

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.D. London	Laboratory Chief	NPL, ARC, NIDA
Others:	M. Szikszay	Visiting Fellow	NPL, ARC, NIDA
	F.R. Snyder	Staff Fellow	CHP, ARC, NIDA

COOPERATING UNITS (if any)
University Medical School, Szeged, Hungary (G. Benedek)

LAB/BRANCH
Neuropharmacology Laboratory

SECTION
Neuroscience Branch

INSTITUTE AND LOCATION
ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	0.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

It has been shown previously that calcium channel antagonists enhance the antinociceptive and thermoregulatory effects of morphine. The purpose of this project is to investigate the interaction of calcium channel antagonists with other physiological effects of morphine.

The individual and combined effects of morphine and diltiazem, a calcium channel inhibitor, on arterial blood gases and pH were assessed in conscious rats. Morphine produced hypercapnia, hypoxia, and slight acidosis. Diltiazem alone did not affect these parameters; however, it delayed the effects of morphine. As an extension of this work, a major objective was to determine if a negative interaction with morphine's respiratory depressant effects could be demonstrated with another type of calcium channel antagonist. Effects of morphine and verapamil, alone and in combination, on arterial blood gases and pH, mean blood pressure and heart rate were assessed in rats. As expected, morphine produced respiratory depression. Verapamil, significantly attenuated and delayed effects of morphine. Morphine caused a slight increase in mean blood pressure; whereas, verapamil reduced blood pressure dramatically even in the presence of morphine. Rats treated with morphine alone showed the most pronounced increase in heart rate which was antagonized by verapamil. We concluded that the interaction of verapamil with morphine's respiratory depressant effects differed from the potentiation of morphine's antinociceptive and hypothermic effects. The results are consistent with the view that opioids produce analgesia and respiratory depression through different mechanisms. The combination of calcium channel antagonists with opioids may allow administration of lower opioid doses for analgesia, while minimizing respiratory depressant effects.

Studies of plasma glucose concentrations in rats treated with the calcium channel inhibitors and morphine demonstrated no particular interaction, no significant effect of morphine in fasted conscious rats, and hyperglycemic effects of diltiazem and verapamil. The findings suggested a general hyperglycemic effect of calcium channel antagonists.

Publications - FY 1986

Szikszay, M., Snyder, F.R. and London, E.D.: Interactions between verapamil and morphine on physiological parameters in rats, J. Pharmacol. Exp. Ther. In press.

Szikszay, M., Snyder, F.R. and London, E.D.: Effects of diltiazem on morphine-induced respiratory decline, J. Pharm. Pharmacol. In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00204-02 NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Morphine Effect on Kidney Ultrastructure

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. D. London	Laboratory Chief	NPL, ARC, NIDA
Others:	J. Johnson	Visiting Scientist	NPL, ARC, NIDA

COOPERATING UNITS *(if any)*

Gerontology Research Center, NIA (J.J. White); and New England Nuclear Corp. (R.C. Walovitch)

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.0.6	0.6	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Degenerative kidney changes are associated with heroin use in human addicts but it is not known whether these changes result from exposure to the opioid or from contaminants in street heroin. The purpose of this project was to assess the effects of morphine on kidney ultrastructure to obtain information on whether renal degeneration in opioid addicts is due to the opioid per se.

Rats were treated chronically with morphine (s.c. pellets for 7 days). The rats were sacrified by aldehyde perfusion and the kidneys excised, sectioned and prepared for scanning electron microscopy. Micrographs taken at 5,000x were scored on the presence of short or long microprojections. Morphine significantly altered the frequencies of scores for long microprojections, suggesting an increased number of microprojections on glomerular podocytes. No changes in filtration slits, pedicels, or blebbing (focal enlargements) were noted. The data supported the view that kidney degeneration with opioid abuse reflects effects of opioids per se and were consistent with microprojection changes as a function of altered intracellular cyclic AMP.

The publication of the resultant manuscript will represent the conclusion of this project.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00205-01 NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Metabolic Studies on the Effects of Capsaicin in the CNS

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E. London	Laboratory Chief	NPL, ARC, NIDA
Others:	M. Szikszay	Visiting Fellow	NPL, ARC, NIDA

COOPERATING UNITS (If any)

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.5	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Capsaicin has widespread pharmacological effects on the peripheral and central nervous systems, particularly those parts which are involved in sensation. We used the 2-deoxyglucose procedure to assess the distribution of capsaicin's effects on cerebral and spinal rates of glucose utilization to elucidate the anatomical sites involved in the neurotoxic and sensory effects of capsaicin and the neuropeptides that it releases. Subacute capsaicin treatment in adult rats increased rates of glucose utilization in the substantia gelatinosa of the spinal cord (the recipient of primary sensory afferent projections) and the ventromedial aspect of the dorsal horn. Increased rates of glucose utilization were also seen in sensory relay nuclei and other pain-related structures in the brain. Most of the affected structures contain detectable levels of markers for substance P.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 DA00206-02 NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Sigma and Phencyclidine (PCP) Systems: Neuroanatomical and Metabolic Studies

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.D. London	Laboratory Chief	NPL, ARC, NIDA
Others:	T.-P. Su	Pharmacologist	NPL, ARC, NIDA
	E. Broussolle	Visiting Fellow	NPL, ARC, NIDA
	A. Weissman	Staff Fellow	NPL, ARC, NIDA

COOPERATING UNITS (if any)

Johns Hopkins School of Medicine (J. Hedreen); and University of Maryland School of Medicine (K. Marquis, J.E. Moreton).

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.9	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The goal of this project is to study the nature, distribution and physiological significance of sigma and PCP receptors in the brain. Human autopsy brain tissue has been obtained and is being assayed with several tritiated ligands specific for sigma and PCP receptors. A postmortem study of guinea pig brains is underway to ascertain the stability of these receptors under human autopsy conditions.

The in vivo binding of ligands that interact with sigma receptors ([^{3}H]+SKF-10,047, [^{3}H]haloperidol and [^{3}H]PCP) is being studied in mice. The resultant information will provide the basis for later in vivo studies of sigma receptors in humans using positron emission tomography (PET). Preliminary results indicate that the highest specific binding of ligand to sigma receptors in vivo is in the cerebellum, midbrain and medulla pons. In addition, alterations of LCGU by pharmacological agents that influence the sigma and PCP systems are being examined. We have shown that PCP has dose-related effects on LCGU in many brain systems including sensory, motor and limbic areas. Most of these effects are apparent as increases in brain metabolism. Some decreases were observed in the frontal cortex and may be linked to PCP's psychotomimetic actions. The effect of the sigma agonist +SKF-10,047 also was investigated and generally found to depress LCGU in several cortical sensory regions and regions of the hippocampus and the cerebellum. The pattern of sigma gonist actions on brain metabolism seems to differentiate it from PCP agonists. We currently are measuring the effects of these drugs on LCGU in the presence of specific sigma and PCP antagonists to determine if these two systems utilize functionally different anatomical substrates for their action.

The abuse potential in humans and the self-administration of PCP by rats has suggested that PCP may affect reward systems. We are examining LCGU in rats trained to self-administer PCP on a fixed-ratio schedule. Preliminary observations obtained from animals which received PCP and yoked controls receiving saline seem to indicate that the self-administering animals show patterns of LCGU which are similiar to naive rats receiving PCP acutely, but at a higher dose.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZQ1 DA 00207-02 NPL

PERIOD COVERED: October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Nicotine Receptors and the Behavioral and Metabolic Effects of Nicotine

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R.J. Fanelli	Staff Fellow	NPL, ARC, NIDA
	E.P. Broussolle	Visiting Fellow	NPL, ARC, NIDA
	M. Dam	Visiting Fellow	NPL, ARC, NIDA
	E.D. London	Laboratory Chief	NPL, ARC, NIDA

COOPERATING UNITS (if any)

Director, ARC, NIDA (J.H. Jaffe); and BDL, ARC, NIDA (J.E. Henningfield)

LAB/BRANCH: Neuropharmacology Laboratory

SECTION: Neuroscience Branch

INSTITUTE AND LOCATION: ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.8	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have previously demonstrated saturable, specific binding of [^{3}H]nicotine ([^{3}H]N) in the rat brain by light microscopic autoradiog- raphy. We also have shown that the distribution of the metabolic effects of nicotine follows the localization of [^{3}H]N binding sites, suggesting that the sites are functional receptors. This project is aimed at providing additional information about nicotine receptors so that we might ultimately study them in the human brain with positron emission tomography (PET) and at elucidating receptor mechanisms involved in the behavioral effects of chronic nicotine.

[^{3}H]L-nicotine was injected i.v. in mice which were sacrificed at various times thereafter. Brains were dissected for measurement of radioactivity. Nonspecific binding was determined in mice pretreated with unlabelled L-nicotine. There was a rapid entry of [^{3}N]N into the brain and a decline after 7.5 min. Specific binding was maximum at 5 min. (50% in thalamus and superior colliculus) and fell nearly to zero by 30 min. These results suggest that specific binding of [^{3}H]N can be measured in vivo with radiolabelled nicotine. Experiments on the specificity and saturability of binding are in progress.

Chronic treatment with nicotine causes an up-regulation of CNS nicotinic cholinergic receptors. Using chronic administration of nicotine to produce supersensitivity, an examination of the resulting effects on local rates of glucose utilization in the brain and correlated effects on receptor densities and affinities and maze performance would be a critical addition to our understanding of the neurochemical and anatomical bases for chronic nicotine effects on behavior. We have treated animals chronically (10 days) with nicotine, examined their maze performance, and measured LCGU in the same animals. We are now designing a more sensitive learning task in order to demonstrate drug effects. The analysis of receptor dynamics and LCGU is currently underway.

Nicotine Receptors and the Behavioral and Metabolic Effects of Nicotine

Publications - FY 1986

Henningfield, J.E., Jaffe, J.H. and London, E.D.: Nicotine reward: studies of abuse liability and physical dependence potential. In Brain Reward Systems and Abuse, Raven press, New York. In press.

London, E.D., Szikszay, M. and Dam, M.: Metabolic mapping of the cerebral effects of abused drugs, NIDA Research Monograph 67 Problems of Drug Dependence, ed. by L.S. Harris, U.S. Government Printing Office, Washington, D.C., 1986 pp 26-36.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00208 -02 NPL

PERIOD COVERED
October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Diazepam Effect on Local Cerebral Glucose Utilization in the Rat

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M. Dam	Visiting Fellow	NPL, ARC, NIDA
Others:	E.P. Broussolle	Visiting Fellow	NPL, ARC, NIDA
	E.D. London	Laboratory Chief	NPL, ARC, NIDA

COOPERATING UNITS (If any)

LAB/BRANCH
Neuropharmacology Laboratory

SECTION
Neuroscience Branch

INSTITUTE AND LOCATION
ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Diazepam was administered i.v. in the rat at different doses and times before [^{14}C]DG. Large LCGU decrements were observed in 30 out of 62 brain regions examined and were maximum with 5 mg/kg diazepam at 2 and 30 min before [^{14}C]DG. The effects occurred preferentially in areas enriched in benzodiazepine type I rather than type II receptors. The results suggested that benzodiazepine receptor subtypes are functionally distinct and that the therapeutic effects of diazepam are mediated by type I receptors. Additional experiments with the selective benzodiazepine type I receptor ligand, CL 218,872, are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00209-03 NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Factors Which Influence Rates of Local Cerebral Glucose Utilization

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E.D. London Laboratory Chief NPL, ARC, NIDA

COOPERATING UNITS (if any)

Dept. Physiology, Univ. of Maryland, School of Medicine (M. Selmanoff, P.M. Wise, I.R. Cohen-Becker, N.G. Weiland); and New England Nuclear Corp. (R.C. Walovitch)

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The 2-deoxyglucose technique for measuring LCGU is used extensively by our research program. It is important to consider various physiological and psychological factors which may influence LCGU and our interpretation of the effects on LCGU of psychoactive drugs. Therefore, we have initiated studies of the effects of various conditions on LCGU in the rat. Factors considered to date include age, endocrine status, circadian periodicity, restraint stress, and pain.

In keeping with previous findings on effects of age on LCGU, age-associated LCGU declines were observed in all hypothalamic areas examined except the median eminence. Circadian periodicity in LCGU was observed in the suprachiasmatic nucleus and the pineal gland of old and young animals. Old ovariectomized rats primed with estradiol showed an irregularity in the circadian periodicity of LCGU in the suprachiasmatic nucleus, associated with a loss of cyclic reproductive function.

In studies of the effects of prolactin and restraint on LCGU, hyperprolactinemia was associated with decreased LCGU in the medial forebrain bundle and the dorsal hippocampus. Free-ranging rats had significantly higher rates of LCGU than restrained rats in several areas including the medial septal nucleus, rostral striatum, frontoparietal cortex, and median eminence. The results indicate that hyperprolactinemia may be associated with inhibition of brain areas that project to the median eminence, where prolactin stimulates dopamine turnover, and that restraint is a factor which could influence LCGU.

These studies are being extended to the effects of restraint and pain on drug-induced changes in LCGU.

Factors Which Influence Rates of Local Cerebral Glucose Utilization

Publications - FY 1986

Selmanoff, M., Walovitch, R.C., Walker, G.E. and London, E.D.: Effects of hyperprolactinemia on plasma prolactin and glucose and on local cerebral utilization, J. Neurochem. In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00210-01 NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Chronic Drug Abuse on Lymphoid and Brain Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A.S. Kimes	Visiting Scientist	NPL, ARC, NIDA
Others:	C. Ori	Visiting Fellow	NPL, ARC, NIDA
	E.D. London	Laboratory Chief	NPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.7	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Intravenous drug abusers are at high risk for acquired immunodeficiency syndrome (AIDS), suggesting that chronic exposure to abused substances may alter immune function. We are testing this hypothesis by studying receptors for drugs and neurotransmitters in lymphoid tissue and the brains of mice treated chronically with morphine and other abused substances. Assays of opioid receptors including Scatchard analysis from brain and spleen homogenates are ongoing. Preliminary results indicate the presence of mu, delta and kappa receptor binding sites in the brain and mu and kappa sites in the spleen. We will study the effect of chronic opioid treatment on the densities and affinities of these sites in both tissues. Additional studies on the immune status of opioid treated mice will be performed and correlated with the receptor studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00211-04 NPL

PERIOD COVERED: October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Studies on Sigma Receptors

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	T.-P. Su	Pharmacologist	NPL, ARC, NIDA
Others:	S.Y. Yeh	Pharmacologist	NPL, ARC, NIDA
	A.D. Weissman	Staff Fellow	NPL, ARC, NIDA
	D.B. Vaupel	Pharmacologist	NPP, ARC, NIDA

COOPERATING UNITS (if any)

LAB/BRANCH: Neuropharmacology Laboratory

SECTION: Neuroscience Branch

INSTITUTE AND LOCATION: ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We demonstrated the existence of endogenous ligands for sigma receptors. Therefore, there appears to exist in mammalian brain, an endogenous sigma system which may have important pharmacological and physiological roles.

Antagonists at sigma receptors may represent a new therapeutic lead to the discovery of potential antipsychotic agents. The sigma antagonists may not elicit undesired extrapyramidal side effects like those of dopamine D_2 antagonists. HR-375 was a drug which in preclinical trials displayed no propensity to elicit extrapyramidal side effects. We demonstrated that HR-375 was indeed a potent sigma ligand, indicating that the potential antipsychotic properties of HR-375 may be attributed, at least in part, to its interaction with the sigma receptors.

The guinea pig vas deferens preparation responded only to sigma and phencyclidine drugs; whereas, this preparation exhibited no response to the non-sigma drugs such as morphine, DADLE and l-ketocyclazocine. The study, therefore, provided the first in vitro tissue model for sigma receptor activity and demonstrates that sigma receptors represent biologically functional receptors. It is the continuing effort of this study to discover a tissue preparation which may contain either sigma receptors or phencyclidine receptors.

Studies on Sigma Receptors

Publications - FY 1986

Su, T.-P., Weissman, A.D. and Yeh, S.Y.: Endogenous ligands for sigma opioid receptors in the brain ("SIGMAPHIN"): Evidence from binding assays. Life Sci. 38: 2199-2210, 1986.

Su, T.-P.: HR 375: A potential antipsychotic drug that interacts with dopamine D_2 receptors and sigma receptors in the brain, Neurosci. Lett. 1986. In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00212-02 NPL

PERIOD COVERED: October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Kappa Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.-P. Su	Pharmacologist	NPL, ARC, NIDA
Others:	D.B. Vaupel	Pharmacologist	NPL, ARC, NIDA
	R.E. Johnson	Laboratory Chief	Research Support, NIDA,ARC
	E.J. Cone	Laboratory Chief	CDM, ARC, NIDA

COOPERATING UNITS *(if any)*:

LAB/BRANCH: Neuropharmacology Laboratory

SECTION: Neuroscience Branch

INSTITUTE AND LOCATION: ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A pentapeptide, BW942C, exhibited kappa opioid activity in humans and animals. In receptor binding studies, BW942C possessed high affinities for mu and delta receptors, moderate affinity for kappa receptor and no affinity at all for sigma receptors. It is believed that BW942C represents the first synthetic peptide with affinity for kappa opioid receptors. This study provides some interesting thoughts about the structural requirements for activity at kappa opioid receptors.

Kappa Receptors

Publications - FY 1986

Su, T.-P.: Further demonstration of kappa opioid binding sites in the brain: evidence for heterogeneity. J. Pharmacol. Exp. Ther., 232: 144-148, 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA00213-01 NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Genetic Factors in Opioid Dependents

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

PI: T.-P. Su Pharmacologist NPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

"High" dependent mice and "low" dependent mice are being bred successfully to the fourth generation at present. There is clearly a separation between the descendants of those two groups of animals. Neurochemical assays will be used to examine the brains of these two groups of animals.

PHS 6040 (Rev. 1/83)

GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00214 -01 NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of MDA and MDMA on Dopamine and Serotonin in the Rat Brain

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	S.Y. Yeh	Pharmacologist	NPL, ARC, NIDA
Others:	G. Battaglia	Staff Fellow	NPL, ARC, NIDA
	E.B. DeSouza	Visiting Scientist	NPL, ARC, NIDA
	M.J. Kuhar	Branch Chief	NPL, ARC, NIDA

COOPERATING UNITS (if any)

Dept. U.S. Army (F.-Y. Hsu)

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.8	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

MDA and MDMA possess psychotomimetic and stimulant properties. The so-called "designer drugs" have been popular drugs of abuse. The purpose of this study is to investigate the effects of these drugs on neurotransmitters, especially monoamines and their metabolites. Rats were injected eight times s.c. with either saline, MDA or MDMA (20 mg/kg) every 12 h. Two weeks following the last injection, the brains were removed, and concentrations of monoamines in the tissues were measured with HPLC. MDA caused dramatic decreases in 5HT (65, 26, and 33%) and 5HIAA (58, 64, and 40%) in frontal cortex, hippocampus and hypothalamus, respectively. MDMA produced similar but less dramatic decreases in 5HT (42, 15, and 18%) and 5HIAA (46, 55 and 26%) in frontal cortex, hippocampus and hypothalamus, respectively. These compounds caused smaller changes in striatal 5HT content (10-20%), while the decreases in striatal 5HIAA levels produced by both MDA (33%) and MDMA (36%) were comparable to those in other regions.

Cytotoxicity was not observed after i.c. injection of 20 ug of MDA and MDMA. The neurotoxicity of MDA and MDMA has been postulated to be due to metabolites of MDA and MDMA, respectively. The effect of 5HT uptake inhibitors, such as citalopram, on the neurotoxicity of MDMA has been investigated. Citalopram, 10 mg/kg, was injected s.c. to rats 45 min before each MDMA injection, (10 mg/kg, s.c., four times). 5HT and 5HIAA contents in the frontal cortex of citalopram- and MDMA-treated animals were not significantly different from those of saline controls. The results suggest that citalopram protects against MDMA toxicity. Citalopram also decreased 5HT in the frontal cortex. The effect of MDMA on 5HT was dose-dependent. Ongoing studies are focused on the effects of drug metabolizing enzyme inhibitors on MDMA-induced neurotoxicity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00215-01 NPL

PERIOD COVERED: October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Cocaine on Monoamines and Their Metabolites in Brain

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: S.Y. Yeh Pharmacologist NPL, ARC, NIDA

COOPERATING UNITS (if any)

LAB/BRANCH: Neuropharmacology Laboratory

SECTION: Neuroscience Branch

INSTITUTE AND LOCATION: NIDA, ARC, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this study is to determine the effect of short-term cocaine treatment on neurotransmitters, especially monoamines and their metabolites. Rats were injected either s.c. or i.p. with cocaine, 20 mg/kg, or saline every 12 h for 8 days. Twenty-four h after the last injection, the animals were sacrificed, the brains were removed, and monoamines and their metabolites were measured with a HPLC procedure. Cocaine increased hypothalamic content of NE by 133 and 100%, of DA by 177 and 120%, of DOPAC by 68 and 13%, and of HVA by 77 and 58%, after s.c. and i.p. injection, respectively, as compared to that of saline controls. Monoamines and their metabolites in the frontal cortex, striatum, hippocampus, midbrain and pons after the short-term cocaine treatment were not significantly different than in saline controls. Ongoing studies are focused on the uptake of NE and DA and tyrosine hydroxylase activity in the hypothalamus of short-term cocaine treated rats.

PHS-6641 Rev. 10-83

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00216-03 NPL

PERIOD COVERED: October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Metabolism of Pyrilamine and Tripelennamine

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

PI: S.Y. Yeh — Pharmacologist — NPL, ARC, NIDA

COOPERATING UNITS *(if any)*

LAB/BRANCH: Neuropharmacology Laboratory

SECTION: Neuroscience Branch

INSTITUTE AND LOCATION: ARC, NIDA, Baltimore, MD 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The combination of an antihistamine, tripelennamine, and pentazocine, a narcotic agonist/antagonist, has been abused. The purpose of this study is to determine the effect of pentazocine on the urinary metabolic profile of tripelennamine. Urine of rats injected i.p. either with pyrilamine or tripelennamine was hydrolyzed with glusulase and extracted with benzene- isopropanol. The extract was analyzed by TLC, GC and GC-MS. 2-(Dimethylaminoethyl)aminopyridine, 2-(4-hydroxybenzyl)aminopyridine, desmethylpyrilamine, 4-hydroxytripelennamine, (4-hydroxy-3-methoxybenzyl)tripelennamine and (3-hydroxy-4-methoxybenzyl)tripelennamine were identified as metabolites of pyrilamine. 2-(Dimethylaminoethyl)aminopyridine, 2-(alpha-hydroxybenzyl)aminopyridine, (alpha-hydroxybenzyl)tripelennamine and (4-hydroxybenzyl)tripelennamine were identified as metabolites of tripelennamine. The results indicate debenzylation of tripelennamine and pyrilamine, a new metabolic pathway for metabolism of tripelennamine and pyrilamine. The results of the study on urine from men administered s.c. tripelennamine were inconclusive.

Metabolism of Pyrilamine and Tripelennamine

Publications - FY 1986

Yeh, S.Y.: Potential of pentazocine antinociception by tripelennamine in the rat; J. Pharm Exp. Ther. 235: 683-689, 1985.

Yeh, S.Y.: The effect of antihistamine drugs on pentazocine antinociception in the rat. Pharmacol. Biochem. Behav. 24: 925-930, 1986.

Yeh, S.Y., Todd, G.D., Johnson, R.E., Gorodetzky, C.W., and Lange, R.: The pharmacokinetics of pentazocine and tripelennamine in humans Clin. Pharmacol. Ther Clin. Pharmacol. 39: 669-676, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00217-02 NPL

PERIOD COVERED: October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Structures and Activity of Semirigid Nicotinic Agonists

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

PI: C.E. Spivak	Pharmacologist	NPL, ARC, NIDA

COOPERATING UNITS *(if any)*

NIH (J.A. Waters); and New Jersey Inst. Technology (T.M. Gund, R.F. Liang)

LAB/BRANCH: Neuropharmacology Laboratory

SECTION: Neuroscience Branch

INSTITUTE AND LOCATION: ARC, NIDA, Baltimore, MD 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In FY85 we discovered a new, semirigid, cyclic nicotinic agonist, isoarecolone methiodide. This compound, 50 times more potent than carbamylcholine, is about the most potent agonist tested at the frog neuromuscular junction. Its potency is exceeded only by suberyldicholine, a compound whose flexibility precludes its use in seeking information on how structure of the agonist governs the response of the receptor.

To pursue further the question of what factors contribute to the high potency of isoarecolone methiodide, 13 new agonists have been synthesized and tested during the past year. The most potent agonist, 4.6 times as potent as carbamylcholine, contains a trifluoroacetyl group. Molecular orbital calculations of particle charges show that this compound has an electrostatic field about its acetyl group that is notably different from all the other structurally comparable agonists. We conclude that such effects are not of primary importance in determining agonist potency. Among the new agonists are three with non-phenolic hydroxyl groups. One of these is 2.0 times as potent as carbamylcholine. This finding is novel because such compounds were previously thought to be exceedingly weak agonist. Three agonists freeze the conformation that we believe to be the one necessary for recognition by the receptor into expecially rigid structures. The finding that all three are very weak (0.006 to 0.015 times the potency of carbamylcholine) has led us to the hypothesis that the agonist is stressed by the receptor during receptor activation such that parts of the agonist must rotate with respect to other parts.

In FY85, recordings of single ion channel currents in response to some of the new agonists were initiated. These were from extrajunctional receptors, easier to record, but whose significance is dubious and whose kinetic analysis is very difficult. This year junctional regions of muscle fibers were visualized with fluorescent alpha-bungarotoxin so that endplate morphology could be recognized in bright field or Hoffman Modulation optics. Then patch clamp recordings of junctional receptors was begun, and new techniques are being explored.

PHS 6040 (Rev. 1/83)

GPO 895-100

Structure and Activity of Semirigid Nicotinic Agonists

Publications - FY 1986

Spivak, C.E., Gund, T.M., Liang, R.F. and Waters, J.A.: Structural and electronic requirements for potent agonists at a nicotinic receptor. Eur. J. Pharmacol. 120: 127-131, 1986.

Gund, T., Hermsmeier, M., Liang, R.F., Yadav, J., Spivak, C.E. and Waters, J.A.: Molecular modeling approaches for design of receptor agonists and antagonists. Proc. Symp. Three Dimensional Structure and Drug Action. In press.

Gund, T., Hermsmeier, M., Liang, R.F., Yadav, J., Spivak, C.E. and Waters, J.A.: Design of acetylcholine receptor agonists and antagonists by computer methods. Sixth Eur. Sympos. on Quantitative Structure Activity Relationships. In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00218-02 NPL

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Role of Neuropeptide Transmitters in Opioid Action and Opioid Withdrawal

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.A. Bell	Pharmacologist	NPL, ARC, NIDA
Others:	C.E. Spivak	Pharmacologist	NPL, ARC, NIDA
	T.-P. Su	Pharmacologist	NPL, ARC, NIDA
	J.H. Jaffe	Director	ARC, NIDA

COOPERATING UNITS *(If any)*

LAB/BRANCH

Neuropharmacology Laboratory

SECTION

Neuroscience Branch

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In studies utilizing the isolated spinal cord of the neonatal rat, capsaicin and synthetic substance P were used to clarify the role of substance P in spinal opioid withdrawal. The capsaicin response was augmented greatly during withdrawal from acute morphine; whereas the substance P response was not affected, suggesting that in acute dependence presynaptic changes may be the predominant underlying mechanism.

Studies were done on the effect of chronic morphine administration on electrophysiologic responses in the isolated spinal cord of neonates so treated. To date, no supersensitivity to the action of substance P has been found. Furthermore, the dose response curve to the depolarizing action of capsaicin is not shifted to the left suggesting that postsynaptic supersensitivity to functional release of substance P is not present in the spinal cord of physically dependent neonatal rats.

Antibodies to substance P were successfully raised in rabbits with a titer of about 10,000. Efforts are being focused on utilizing antibodies and substance P antagonists to characterize the involvement of substance P in opiate dependence and withdrawal.

The Role of Neuropeptide Transmitters in Opioid Action and Opioid Withdrawal

Publications - FY 1986

Bell, J.A. and Jaffe, J.H.: Electrophysiological evidence for a presynaptic mechanism of morphine withdrawal in the neonatal rat spinal cord, Brain Res. 1986. In press.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA00219-01 NPL

PERIOD COVERED: October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Isolated Spinal Cord of Neonatal Rat: Role of Neuropeptides at Sigma Receptors

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.A. Bell	Pharmacologist	NPL, ARC, NIDA
Others:	T.-P. Su	Pharmacologist	NPL, ARC, NIDA

COOPERATING UNITS (if any)

LAB/BRANCH
Neuropharmacology Laboratory

SECTION
Neuroscience Branch

INSTITUTE AND LOCATION
ARC, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We found that D-pentazocine, which selectively binds to sigma receptors, depresses C-reflexes and the depolarizing response to capsaicin in the isolated neoneonatal rat cord, providing a bioassay for sigma activity. Several polypeptides which have been extracted from guinea pig brain and are active in the sigma binding assay are being tested on the isolated spinal cord for sigma(D-pentazocine)-like effects. The results will provide information about the possible functional significance of endogenous polypeptides that bind to sigma receptors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00100-01 MPL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neurotransmitter Receptors in the Pituitary Gland

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.B. De Souza	Unit Chief	MPL, NIDA
Others:	B. Kuyatt	Biolab Technician	MPL, NIDA

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION
Neuropeptide Unit

INSTITUTE AND LOCATION
ARC, NIDA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	0.8	0.6

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Serotonin and catecholamines have been shown to play a major role in regulating pituitary hormone secretion both through effects in brain and direct actions on the pituitary. The goals of the project were to identify, characterize and localize, using in vitro autoradiography, the relative distribution of serotonin-2, dopamine-2, beta-2 adrenergic and alpha-1 adrenergic receptors in the rat pituitary gland. In order to define the role of adrenomedullary catecholamines in regulating pituitary function, we examined the effects of adrenalectomy on beta-2 adrenergic receptors in the rat pituitary gland. The identification of the various receptor described above provides further evidence of the importance of these neurotransmitters in regulating pituitary function and demonstrates conditions in which these receptors can be modulated.

Neurotransmitter Receptors in the Pituitary Gland

PUBLICATIONS

De Souza, E.B.: Serotonin and dopamine receptors in the rat pituitary gland: autoradiographic identification, characterization and localization. Endocrinology 119:1534-1542, 1986.

De Souza, E.B.: Modulation of beta-adrenergic receptors in the pituitary gland following adrenalectomy in rats. Neuroscience Ltrs. (in press).

De Souza, E.B. and Kuyatt, B.L.: Alpha-1 adrenergic receptors in the neural lobe of the rat pituitary: autoradiographic identification and localization. Endocrinology (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00101-01 MPL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Role of Corticotropin-Releasing Factor & Sigma Drugs on Immune Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.B. De Souza	Unit Chief	MPL, NIDA
Others:	E.L. Webster	Graduate Student	MPL, NIDA
	S. Wolf, Jr.	Postdoctoral Fellow	MPL, NIDA
	C. Kulsakdinun	Summer Student	MPL, NIDA

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION
Neuropeptide Unit

INSTITUTE AND LOCATION
ARC, NIDA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	0.5	1.3

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Recent evidence suggests that corticotropin-releasing factor (CRF) and sigma agonists such as phencyclidine (PCP) may have immunomodulatory actions. To evaluate the role of these compounds in regulating immune function, we have carried out studies to identify and localize receptor binding sites in rat and mouse spleen and in human peripheral blood leukocytes (HPBL). With regard to CRF, we have identified and characterized specific high affinity receptors in mouse spleen with characteristics similar to those in brain and pituitary. ^{125}I-CRF binding to mouse spleen is linear with increasing protein concentration, saturable and of a high affinity. In autoradiographic localization studies, CRF binding was localized in red pulp regions and a high density of CRF binding sites were observed in macrophages; there was a notable absence of CRF binding in lymphocytes. The preliminary evidence suggests that CRF receptors are primarily located on splenic macrophages. Sigma receptors were identified and characterized in HPBL and rat spleen; the binding sites had kinetic and pharmacological characteristics similar to those for sigma receptors in brain. The highest density of sigma receptors was found in rat spleen with lower but comparable concentrations in HPBL and rat cerebellum. In preliminary autoradiographic studies, the sigma receptors appear to be localized primarily to lymphocytes. The data demonstrating the presence of CRF and sigma receptors in immune tissue may indicate a physiological role for these endogenous neurotramitters in modulating immune function. Sigma drugs could conceivably alter the release of lymphokines and monokines and provide additional mechanisms for the central action of these drugs. Also, the receptors in HPBL leukocytes may represent useful peripheral markers in humans for assessing the role of these receptors in brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00102-01 MPL

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurotoxic Effects of MDA and MDMA (Ecstasy)

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.B. De Souza	Unit Chief	MPL, NIDA
Others:	G. Battaglia	Staff Fellow	MPL, NIDA
	M.J. Kuhar	Branch Chief	MPL, NIDA
	S.Y. Yeh	Staff Scientist	MPL, NIDA

COOPERATING UNITS (if any)

Department of Neuroscience, JHUMI (Drs. M. Molliver and E. O'Hearne)

LAB/BRANCH: Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION: Neuropeptide Unit

INSTITUTE AND LOCATION: ARC, NIDA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	3.2	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The goal of the project is (1) to study the neurochemical mechanisms through which 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA) and related amphetamine derivatives produce their neurotoxic effects in the central nervous system and (2) to examine the pharmacologic profile of MDA and MDMA at various brain recognition sites.

1. Neurotoxicity: We have examined the effects of chronic in vivo administration of MDA and MDMA on brain monoaminergic systems. These studies have included measurements of the content of a variety of brain monoamines and their respective metabolites, visualization of brain monoaminergic neurons using immunocytochemistry and in vitro autoradiography. We find that chronic administration of MDA and MDMA produces selective decreases in both 5-HT and 5-HIAA with no major changes in the catecholamines in discrete areas of rat brain, drastic reductions in 5-HT uptake sites and massive destruction of 5H-T preterminals. In addition, the immunocytochemical data suggest that it is not the parent compound but rather a metabolite(s) that may be neurotoxic. The autoradiographic data demonstrate that the neurotoxic effects of these compounds on destruction of serotonin terminals is not diffuse but rather is limited to certain brain areas. The neurotoxic effects of MDA and MDMA in rats can be prevented by pretreatment with a selective serotonin uptake blocker, citalopram.
2. The pharmacologic profile of MDA, MDMA and their amphetamine derivatives at various brain receptors were examined using in vitro radioligand binding procedures. MDA and MDMA have relatively high affinities for 5H-T uptake sites, 5H-T_{1A} receptors, 5H-T_2 receptors, and sigma receptors; these compounds have moderate to weak affinities for a variety of other brain recognition sites including pre- and post-synaptic recognition sites for catecholamines, acetylcholine, opioids and various neuropeptides.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00103-01 MPL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Corticotropin-Releasing Factor in Human Neurodegenerative Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.B. De Souza	Unit Chief	MPL, NIDA
Others:	M.J. Kuhar	Branch Chief	MPL, NIDA

COOPERATING UNITS *(if any)*
Neuropathology Laboratory, JHU Sch. Med., Balto., Md. (Drs. D. Price, P.J. Whitehouse, R. Powers and L. Walker); Clayton Foundation Laboratories for Peptide Buiology, The Salk Institute, San Diego, CA (W. Vale).

LAB/BRANCH
Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION
Neuropeptide Unit

INSTITUTE AND LOCATION
ARC, NIDA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.8	2	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The goal of this project is to study the role of brain CRF in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and progressive supranuclear palsy. Initially, we examined in control and Alzheimer's brain tissues pre- and post-synaptic markers for CRF. We found that in Alzheimer's, the concentrations of CRF-like immunoreactivity are reduced and that there are reciprocal increases in CRF receptor binding in affected cerebral cortical areas. These changes are significantly correlated with decrements in choline acetyltransferase activity. Decreases in CRF-like immunoreactivity similar to those described for Alzheimer's disease were also seen in patients who died of Parkinson's disease and progressive supranuclear palsy. In contrast, patients who died of Huntington's disease did not show decrements in CRF-like immunoreactivity in the cerebral cortex but showed a small decrease in CRF-like immunoreactivity in the caudate. More recently, we demonstrated abnormalities in CRF-like immunoreactive neurons in patients who died of Alzheimer's disease in that the CRF-like immunoreactivity was localized to senile plagues. These results strongly support a neurotransmitter role for CRF in brain and demonstrate, for the first time, a modulation of CNS CRF receptors associated with altered CRF content. These observations further suggest a possible role of CRF in the pathophysiology of various neurodegenerative disorders. Future therapies directed at increasing CRF levels in brain may prove useful for the treatment of Alzheimer's disease and other neurodegenerative disorders.

Corticotropin-Releasing Factor in Human Neurodegenerative Diseases

PUBLICATIONS

De Souza, E.B., Whitehouse, P.J., Kuhar, M.J., Price, D.L. and Vale, W.W.: Reciprocal changes in corticotropin-releasing factor (CRF)-like immunoreactivity and CRF receptors in cerebral cortex of Alzheimer's disease. Nature 319:593-595, 1986.

Whitehouse, P.J., Vale, W.W., Zweig, R.M., Price, D.L. and De Souza, E.B.: Reductions in corticotropin-releasing factor-like immunoreactivity in cerebral cortex and Alzheimer's disease, Parkinson's disease and progressive supranuclear palsy. Neurology (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00104-01 MPL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Corticotropin-Releasing Factor as a Stress Neurotransmitter in the CNS

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.B. De Souza	Unit Chief	MPL, NIDA
Others:	M.J. Kuhar	Branch Chief	MPL, NIDA
	G. Battaglia	Staff Fellow	MPL, NIDA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Molecular Pharmacology Laboratory, Neuroscience Branch

SECTION
Neuropeptide Unit

INSTITUTE AND LOCATION
ARC, NIDA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.9	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Corticotropin-releasing factor (CRF) is a critical hormone involved with stress responses. In addition to its role in regulating stress responses via the endocrine system, recent evidence suggests that CRF may act as a neurotransmitter in brain to integrate the overall response of the body to stress. To provide additional evidence for CRF as a neurotransmitter in brain, we have carried out a series of studies to identify receptor binding sites for CRF in the CNS. Biochemical, cellular, pharmacological and neuroanatomical studies have been utilized for studying the characteristics and distributions of CRF and its receptors, the second messenger systems through which CRF produces its many effects, and establishing molecular neurobiological techniques to identify specific intracellular messenger RNA for CRF. We have identified high affinity binding sites for CRF in brain which are distributed throughout the CNS. The anatomical distribution of these sites corresponds with the immunocytochemical distribution of CRF-containing terminals and the pharmacological sites of action of CRF in brain. In addition, we have demonstrated that CRF stimulates adenylate cyclase activity in rat CNS. Also, we have used *in situ* hybridization histochemistry to localize intracellular messenger RNA for CRF in rodent and monkeys. The production of neuroanatomical maps for CRF, mRNA for CRF and CRF receptors has set the basis for subsequent studies to examine the effects of various drugs that modulate CRF neurotransmission and stress responses. These data should be helpful in explaining the mechanisms underlying stress responses.

Corticotropin-Releasing Factor as a Stress Neurotransmitter in the CNS

PUBLICATIONS

De Souza, E.B.: Corticotropin-releasing factor receptors in the rat central nervous system: characterization and regional distribution. J. Neurosci. (in press).

De Souza, E.B. and Battaglia, G.: Increased corticotropin-releasing factor receptors in rat cerebral cortex following chronic atropine treatment. Brain Res. 397: 401-404, 1986.

Young, III, W.S., Walker, L.C., Powers, R.E., De Souza, E.B. and Price, D.L.: Corticotropin-releasing factor mRNA is expressed in the inferior olives of rodents and primates. Molec. Brain Res. 1: 189-192, 1986.

De Souza, E.B. and Kuhar, M.J.: Corticotropin-releasing factor receptors: autoradiographic identification. In Neuropeptides in Neurologic and Psychiatric Diseases, J.B. Martin and J. Barchas (Eds.), Raven Press, New York, 1986, pp. 179-198.

De Souza, E.B. and Kuhar, M.J.: Corticotropin-releasing factor receptors in the pituitary gland and central nervous system. Methods in Enzymology 124:560-590, 1986.

De Souza, E.B.: Corticotropin-releasing factor receptors in brain and pituitary: implications for the stress response. In Neuropeptides and Stress, Y. Tache (Ed.) Springer-Verlag, New York (in press).

De Souza, E.B. and Battaglia, G.: Corticotropin-releasing Hormone (CRH) receptors in brain. In Mechanisms of Physical and Emotional Etress, G. Chroussos (Ed.) Plenum Press, New York (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00105-01 MPL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cloning of Genetic Sequences for a Substance P Degrading Enzyme

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: M.M.S. Lo Unit Chief MPL, ARC, NIDA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Molecular Pharmacology

SECTION

Molecular Biology and Genetics Unit

INSTITUTE AND LOCATION

ARC, NIDA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.25	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Previous studies have demonstrated the importance of substance P in morphine withdrawal. The physiological level of substance P is regulated in vivo by different peptidases which function by either processing the peptide precursor or degrading the bioactive peptide. A putative substance P degrading enzyme has been found in the brain, uniquely localized on striato-nigral neurons, and appears to be closely related to the angiotensin-converting enzyme (ACE) located on lung endothelial cells. Both enzymes are potently inhibited by the ACE inhibitor, captopril. They also share many common pharmacological, biochemical and immunological properties. However, the purified striatal ACE has a different molecular weight compared to the lung form. The pharmacological specificity and regional location of the neuronal ACE strongly implies its role in degrading substance P and substance K in the basal ganglia.

This project is concerned with cloning the gene(s) encoding for the neuronal ACE and identifying the genetic sequences which regulate the expression of this enzyme. A nucleotide sequence deduced from the N-terminus protein sequence of lung ACE was used to synthesize an oligonucleotide probe. Studies with primer extension using purified messenger RNA and the synthetic probe have provided sequence data on 120 nucleotides comprised the signal peptide and the first seven amino acids of ACE. A second probe will be synthesized and used to screen genomic and cDNA libraries. We expect to isolate and sequence the entire gene for this enzyme.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00106-01 MPL

PERIOD COVERED: March 1, 1986 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.): AIDS-Related Research

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M.M.S. Lo	Unit Chief	MPL, ARC, NIDA
Others:	C.M. Dersch	Lab Technician	MPL, ARC, NIDA

COOPERATING UNITS (if any): None

LAB/BRANCH: Molecular Biology and Genetics Unit
Neuroscience Branch, Laboratory of Molecular Pharmacology

SECTION: NONE

INSTITUTE AND LOCATION: ARC, NIDA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The human T-lymphotropic virus (HTLV) III, the causative agent of the Acquired Immunodeficiency Syndrome, propagates through an infectious RNA viral particle. Infection may be prevented by injection with neutralizing antibodies or immunizing with vaccines which induces the production of neutralizing antibodies in man. Monoclonal antibody production is usually hampered by formation of antibodies which are specific for immunodominant sites present on the antigen. These immunodominant sites are highly variable between different strains of the AIDS virus, and therefore severely limit the use of these antibodies as neutralizing reagents.

Preselected cell fusion has proven to produce superior antibodies compared with conventional methods. Preselection also allows the formation of antibodies to sites which are not immunodominant. The objective of this project is to produce antibodies, using preselected fusion techniques, to the AIDS virus. Antibodies will be screened for their ability to block viral infection and subsequent identification of the viral epitope to which they bind. We have genetically engineered a fragment of the HTLV III gene encoding the envelope protein and producing this protein in tissue culture cells. This material is used to produce monoclonal antibodies. A subsequent goal is the production of fragments of the envelope protein and testing of their ability to induce an immune response to the AIDS virus in animals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00107-01 MPL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Labeling Drug Receptors In Vivo

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M.J. Kuhar	Branch Chief	MPL, ARC, NIDA
Others:	M. Ritz	Staff Fellow	MPL, ARC, NIDA
	J. Sharkey	Visiting Fellow	MPL, ARC, NIDA

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION
None

INSTITUTE AND LOCATION
ARC, NIDA, ADAMHA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
½	¼	¼

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

While studying receptors by in vitro biochemical binding techniques is commonplace, the ability to study drug receptors in vivo is more difficult. These studies aim to identify conditions whereby drug receptors can be studied in an intact animal. These efforts bear directly on PET scanning experiments and are required before meaningful PET scanning studies can be attempted in human populations.

The benzodiazepines are widely used drugs that have been abused. These drugs act or exert their action by interacting with a specific receptor site in brain. Suriclone is a drug which binds preferentially to benzodiazepine receptors in vivo. Hence, radiolabeled suriclone will be injected into animals so that the precise conditions in which the bulk of the drug binds to benzodiazepine receptors in brain can be identified.

Buspirone is a novel anxiolytic that does not exert its action by acting at the benzodiazepine receptor. However, it has been found that buspirone enhances the in vivo labeling of benzodiazepine receptors with a benzodiazepine drug, RO15-1788. Thus, a goal is to explore the possibility that this enhancement of benzodiazepine receptor binding is somehow related to the anxiolytic action of buspirone.

In summary, these experiments are a direct extension of biochemical, in vitro experiments and study drug receptors under conditions where they are normally used, that is in vivo. These studies provide a more complete understanding of how drugs interact with receptors in living humans.

Labeling Drug Receptors In Vivo

Publications:

1. De Souza, E.B., Goeders, N.E. and Kuhar, M.J.: Benzodiazepine receptors in rat brain are altered by adrenalectomy. Brain Research 381:176-181, 1986.

2. Kuhar, M.J.: Neuroanatomical substrates of anxiety: a brief survey. Trends in Neuroscience 9(7):307-311, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00108-01 MPL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Cocaine Receptor

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M.J. Kuhar	Branch Chief	MPL, ARC, NIDA
Others:	M. Ritz	Staff Fellow	MPL, ARC, NIDA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION

None

INSTITUTE AND LOCATION

ARC, NIDA, ADAMHA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	½	½

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

While several binding sites for cocaine have been studied, the binding site related to drug reinforcement and substance abuse has not been identified as such. These studies are aimed at identifying the cocaine receptor related to addiction and abuse.

Strategies for finding the cocaine receptor related to substance abuse are being developed. The relative potencies of cocaine and cocaine-like drugs will be tested in animal paradigms of substance abuse and these potencies will be compared to the potencies of these various drugs at different binding sites. The binding site relevant to substance abuse should have a high correlation with the behavioral studies.

Additional studies will focus on the effect of chronic cocaine administration on various biochemical parameters in the brain. The goal of these studies is to test for regulatory processes that occur in response to cocaine's administration and also to identify potential neurotoxic effects of chronic administration.

Another goal is to map cocaine binding sites in brain by autoradiography. A detailed anatomical distribution of cocaine binding sites will help explain how cocaine exerts its various effects on the brain.

The completion of these studies will provide important new information on the mechanism of action of cocaine in the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 00109-01 MPL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Measuring Drug Receptors in Humans by PET Scanning

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M.J. Kuhar	Branch Chief	MPL, ARC, NIDA
Others:	M. Titeler	Associate Prof.	Dept. of Pharmac. & Toxico.
	H.N. Wagner	Professor	JHU Sch. Med.
	D. Wong	Associate Prof.	JHU Sch. Med.

COOPERATING UNITS (if any)

Division of Nuclear Medicine, JHUMI (H.N. Wagner); Department of Pharmacology and Toxicology, Albany Medical School, Albany, New York (M. Titeler)

LAB/BRANCH

Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION

None

INSTITUTE AND LOCATION

ARC, NIDA, ADAMHA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Biochemical measurements of drug receptors in tissue obtained at autopsy have revealed that receptors are changed in various neuropsychiatric disorders. Hence, it is possible that receptor changes may be the cause of some of these disorders. Because of the difficulty in obtaining autopsy tissue of adequate quality and because of the limited supply of this material, autopsy material is hardly adequate for an investigation of receptor changes in neuropsychiatric disorders and addiction. Hence, PET scanning, which is a noninvasive, quantitative measure of receptors in living human populations, is a valuable approach.

Dopamine is a neurotransmitter which has been implicated in mechanisms of reward as well as in the mechanism of action of a variety of abused drugs including cocaine and amphetamines. Hence, a study of dopamine receptors in humans may provide important new information on changes of receptors in clinical populations. Dopamine receptor imaging by PET scanning has been achieved, and efforts are underway to quantify dopamine receptors more accurately in humans.

Because the drug utilized to label D2 dopamine receptors in vivo by PET scanning is 3-N-methylspiperone, a detailed biochemical study of the interaction of this drug with dopamine receptors has been undertaken. It has been found that this drug acts at dopamine receptors with a relatively high affinity and great degree of selectivity. These findings support the use of this agent in PET scanning studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00110-01 MPL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cloning of Genes Regulating the Human POMC Gene

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: M.M.S. Lo Unit Chief MPL, ARC, NIDA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION
Molecular Biology and Genetics Unit

INSTITUTE AND LOCATION
ARC, NIDA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The pro-opiomelanocortin (POMC) is a protein precursor for a variety of hormones including the potent opioid peptide beta endorphin. POMC is produced in the anterior and intermediate pituitary, in the hypothalamus, in the placenta, in the gut and in certain lymphoid populations of the immune system. However, it is clearly established the POMC production is regulated by different hormones in different tissues. For example, POMC in the anterior pituitary is regulated by CRF and steriods, while POMC in the intermediate lobe is regulated by catecholamines. Very little is known about the genetic sequences and cellular mechanisms dictating the differential hormonal responsiveness of the POMC gene in different tissues. Furthermore, the level of POMC production is extremely high in corticotrophs, suggesting the presence of specific genetic elements which enhance the expression of POMC in these cells.

Various fragments of the human POMC gene (containing putative regulatory sequences) were subcloned and attached to bacterial genes. These genetic constructs are then tested by gene transfer into pituitary, neural and fibroblast cell lines and assayed for the production of the bacterial marker protein. Experiments have so far confirmed that the POMC promotor sequence alone is insufficient for POMC expression. We have identified two putative DNA sequences by sequence homology analysis with two other anterior pituitary hormone genes. One sequence may be a putative enhancer sequence which could determine tissue specific expression. Another sequence is a putative steroid receptor binding sequence which may account for the steroid regulation of POMC.

The specific aim of this project is to identify and isolate the regulatory sequences responsible for POMC expression. These experiments will provide definitive information on how the POMC gene and its opioid peptide product are regulated by different hormones.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00111-01 MPL

PERIOD COVERED
April 1, 1986 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cloning of Genetic Sequences Involved in the Neurotoxicity of MPP+

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M.M.S. Lo	Unit Chief	MPL, ARC, NIDA
Others:	C.M. Dersch	Lab. Technician	MPL, ARC, NIDA

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Laboratory of Molecular Pharmacology, Neuroscience Branch

SECTION
Molecular Biology and Genetics Unit

INSTITUTE AND LOCATION
ARC, NIDA, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.25	1.0	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a substance of abuse, is highly neurotoxic and elicits neuropathologic changes in man often resulting in Parkinson's disease. MPTP is also very neurotoxic when exposed to normal pheochromocytoma (PC12) cells. This toxicity is mediated by uptake of MPP+, the toxic metabolite of MPTP, into the cell via the dopamine uptake site. Infection of normal PC12 cells confers resistance to MPP+ in some mutant cells. Retroviruses integrate into the cellular DNA, hence interacting specific genes. This indicates that specific genes exist which mediate MPP+ toxicity in normal cells. Retroviruses infect and integrate into the cell's DNA, therefore inactivating specific genes at the integration site. This also results in the loss of a biological function due to the inactivation of that gene in the mutant cell. This approach makes it possible to identify those specific genes which are involved in MPTP toxicity.

Mutant cells resistant to MPP+ were cloned and characterized for their neurochemical properties. Some mutants were only defective in their ability to take up ^{3}H-dopamine. These mutants were then examined for the number of copy of viral sequence present in their genome by Southern analysis. Retroviral sequences were then isolated along with flanking genomic sequences from mutant cells containing only a single copy of the virus. Using DNA recombinant techniques, we will clone and determine the sequences of these flanking genomic sequences. It is most likely that these genes are part of the dopamine uptake site and, therefore, involved in MPTP toxicity.

The significance of this project is the isolation and identification of genetic sequences encoding the dopamine uptake site. This is an important neurochemical site where cocaine also exerts its effects. This general approach of identifying specific genes for neurotoxic compounds can be extended for other substances of abuse, for example, MDMA which is known to be neurotoxic to serotonergic neurons.

Annual Report of the Psychopathology
Cognitive Studies and Early Intervention Branch
Addiction Research Center
October 1, 1985 to September 30, 1986
Jerome H. Jaffe, M.D., Acting Chief

Introduction

In 1985, the Psychopathology, Cognitive Studies and Early Intervention Branch, with its three component laboratories, was established to give greater emphasis to several research areas which could not be developed while the ARC was located in Lexington, Kentucky. As long as the clinical research of the ARC was limited to studying federal prisoners, outpatient studies to investigate new methods of intervention in drug abuse problems were not possible. Once the ARC moved to Baltimore, the ability to make the transition from basic research to actual studies of drug users living outside the laboratory was identified as an area that should be given priority if and when resources became available.

With respect to the Early Intervention Laboratory, resources for outpatient studies have not yet become available; thus, the title and the unfilled positions within it represent aspirations rather than concrete intentions at this time.

In another area, the psychology of vulnerability, concrete plans have been made to expand the scope of ARC research beyond what was possible at Lexington. The Psychology of Vulnerability Laboratory represents initial efforts to identify mechanisms by which risk factors may contribute to later drug abuse problems. This Laboratory had only one full-time scientist until the Spring of 1986 and a chief has not yet been recruited. Thus, its report is understandably brief. Nevertheless, some preliminary studies on adolescents have been conducted and have yielded interesting findings.

The third laboratory, Cognitive Studies and Human Performance, was established in recognition of the increased emphasis society is placing upon the cognitive and performance impairments produced by the use of psychoactive drugs, as well as the ARC's substantial responsibility under arrangements with the Department of the Army to study the effects of cholinergic blocking agents on human cognition and performance. During a part of last year, the Laboratory of Cognition and Human Performance was guided by Dr. Herbert Weingartner; for the past 5 months Dr. Ronald Herning has been functioning as its principal scientist.

1. Psychology of Vulnerability Laboratory -- Jerome H. Jaffe, M.D., Acting Chief

Overview

The purpose of this Laboratory is to conduct research on the psychological, biological, and family origins of drug dependence and the conduct and personality disorders that are frequently associated with drug dependence. The Laboratory has played a key role in enabling all ARC researchers to give greater attention to these issues by developing a systematic procedure to obtain and integrate data on psychological function and psychiatric diagnosis.

Current research efforts focus on the development and utilization of psychodiagnostic and electrophysiologic measures in studies of adolescent and adult populations considered to be either drug dependent or at risk of becoming dependent. The first study in ARC history to focus on an adolescent population at high risk of developing drug-related problems was designed to compare adolescents expelled from public schools for disciplinary reasons (i.e., fighting and drug/weapons violations) with students from similar backgrounds who seem to be resistant to such behavioral problems. Based on early results of this study, the Laboratory has initiated work with the adult drug-dependent population focusing on the relationship of drug dependence/abuse to psychiatric classification, emotional distress, aggression, and psychopathy.

Summary of Ongoing Research

A. Adolescent Study: Hickey, J.E., Hartsock, P. and Fishbein, D.

Mr. John E. Hickey, Dr. Peter Hartsock and a consultant, Dr. Diana Fishbein, have established working relationships with Baltimore City Public Schools and the Foundation for Youth Impact, a school for students who have been suspended or expelled. Most of the first 24 adolescents involved in the research (12 experimentals, 12 controls) come from these two sources. A comprehensive battery, including Elliott's Delinquency Questionnaire, the computerized Diagnostic Interview Schedule, the California Psychological Inventory, and the Wechsler Intelligence Scales for Children and Adults - Revised, was administered.

Preliminary analysis of data comparing suspended students and matched controls revealed that controls sometimes reported more total antisocial acts than those who had been expelled. There was also a range of attitudes and behaviors among subjects in

both groups, some were positive and constructive while others were involved in using and selling drugs and frequently carrying a gun. These, however, did not always correspond to the individual's status as an experimental or control subject.

When the population (experimental and controls) was divided by a median split using the total number of self-reported acts of aggression, robust differences in EEG patterns were found between the two groups. Those with self-reported histories of more aggression and delinquent acts had depressed P300 evoked responses, a finding reported by Begleiter and colleagues to be characteristic of children of alcoholic parents.

The behavioral and psychological measures that characterized the high aggression adolescent group were applied to an adult population (n=55) who had been previously studied at the ARC. This sample was divided into groups with high or low aggressivity and electrophysiological features were compared between groups. The more aggressive adults exhibited significantly different P 300 event-related potentials and also showed a trend toward increased slow wave and decreased fast wave activity.

These studies are being extended and incorporated into the database. The serotonin projects are described in the reports of other laboratories.

B. Psychobiological Vulnerabilities To Antisocial Behavior: Fishbein, D.H., Hickey, J., Herning, R., Pickworth, W., and Haertzen, C.

Abstract: The present study attempts to identify "markers" for individuals with Antisocial Personality (ASP) disorders and violent tendencies. Standard personality and psychodiagnostic measures were obtained on a sample population of adult males residing on the ward of the research center. These measures have shown to be useful in the identification of ASP and correlate strongly with psychiatric diagnoses, measures of alcohol-related disorders, alcoholism and substance abuse, and levels of aggression. Additionally, physiological indices of psychopathy were assessed using an electrophysiological battery (EEG and evoked potential techniques). Analyses indicate that ASP individuals can be discriminated from a control sample on the basis of these psychodiagnostic, personality and physiological measures. A combination of these features present in a single individual may indicate an "at risk" condition and the application of these techniques to identify markers for ASP may prove useful in the development of appropriate remedial regimens. Presented at the American Society of Criminology Meeting, October 29, 1986, Atlanta, GA.

C. The Assessment of Psychopathy and Opiate Dependence: Hickey, J.E., Fishbein, D.H., Herning, R., Pickworth, W., and Haertzen, C.

Abstract. Historically, the association between psychopathy and opiate dependence has been a subject of considerable inquiry among Addiction Research Center (ARC) scientists (Kolb, 1925; Felix, 1944; Hill, 1962; Martin et al., 1978). In the present study a psychodiagnostic and electrophysiological battery was used to determine whether psychiatric categories or self-report scales correlate with physiological indices of psychopathy. A subject population of adult males was tested utilizing this assessment battery. Significant associations would suggest that accepted psychological measures of psychopathy and opiate dependence (i.e., DIS-NIMH, MMPI, ARCI) are useful in identifying differences in psycho-social orientation between drug dependent and normal populations. Relating these markers to physiological correlates of psychopathy may enhance the understanding of opiate dependence and its correspondent personality disorders. Presented at the American Society of Criminology Meeting, October 29, 1986, Atlanta, GA.

D. Reliability and Validity of An Alcohol-Related Behavior Assessment Device: Fishbein, D.H., Snyder, F., Hickey, J.E., Sherer, M., Hartsock, P., and Jaffe, J.

Abstract: Fifty-one adults were administered the Alcohol-Related Behavior Questionnaire (ARBQ) in addition to control samples of normals. The ARBQ was designed to assess behavioral disorders associated with 3 conditions of nondrinking, usual drinking and heavy drinking. The results indicate that the ARBQ reliably discriminated problem drinkers from nonproblem drinkers and between psychiatric classifications. Several ARBQ scales were significantly related to established measures of behavior disorders, particularly with respect to aggression, further validating the test. These findings were discussed in terms of the need for such a device and its ability to advance the study of alcohol-related behavioral disorders and aggression. Presented at the Eastern Psychological Association Meeting, April 1986, New York, NY.

Publications for Fiscal Year 1986

Fishbein, D.H. and Thatcher, R.W.: New diagnostic means in criminology: assessing organic sources of behavioral disorders. Journal of Research in Crime and Delinquency, In press, August 1986.

Lester, M. and Fishbein, D.H.: Nutrition and neuropsychological development in children, In: Neuropsychological Aspects of Medical Illness. R. Tarter (ed.) Plenum Press, 1986.

Hickey, J., Pickworth, W., Herning, R., Hartsock, P. and Jaffe, J.H.: Altered sensory and cognitive processing in adolescents at risk for drug abuse: electrophysiological evidence. Presented at EPIC, Stanford, CA, June 1986.

Hickey, J.E., Haertzen, C.A. and Henningfield, J.E.: Stimulation of gambling responses on the Addiction Research Center Inventory (ARCI), Addictive Behaviors 11:345-349, 1986.

2. Cognitive Studies and Human Performance Laboratory -- Ronald Herning, M.D., Acting Chief

Overview

The Cognitive Studies and Human Performance Laboratory was established in 1985. Since its inception, the Laboratory has developed fruitful collaborations with the Laboratory of Biology of Dependence and the Laboratory of Vulnerability in the Clinical Branch as well as the Neuropharmacology Laboratory in the Neuroscience Branch within the ARC. While still in its infancy the Laboratory has made significant contributions in various areas of drug abuse. These contributions range from the identification of the role of different opiate receptors in human cognition to the quantification of perceptual and cognitive alterations in adolescents at risk for drug abuse.

To pursue the goals of the Laboratory, current thinking and state-of-the-art methodology from cognitive psychology, psychophysiology, neuropsychology and neurophysiology are focused on the problems of drug abuse in an attempt to bridge the gap between animal studies and classical human clinical studies. Aspects of cognition are quantified and related to the underlying neurophysiology. Differences in cognition can be compared in the drug-free versus the drugged state as well as among persons at risk, persons not at risk, and drug addicts. Cognitive factors contributing to relapse may be identified and appropriate treatment methods determined. This is a relatively new approach; however, recent advances in the above mentioned scientific disciplines may enhance efforts to understand and prevent drug abuse as well as to offer effective treatment programs. Utilizing this fairly novel, multifaceted approach is a main thrust of this Laboratory.

More specifically, the approach taken can be divided into four major areas: (1) quantification of drug-produced alterations in cognition and performance, (2) characterization of cognitive

and performance deficits observed during drug withdrawal, (3) evaluation of sensory and cognitive information processing abilities of populations at risk for drug abuse, and (4) investigation of drug effects on brain electrical activity as both a correlate and as a tool to delineate drug-related activity.

Summary of Ongoing Research

A. Drug-Produced Alterations in Cognition and Performance:

Opiate Studies: The effects of mu and kappa agonists on the EEG and cognitive event-related potentials have recently been reported. Unique mu and kappa effects have been identified. The kappa agonist, ketocyclazocine, diverts attention from external stimuli and decreases the subjects' ability to update working memory. The brain potentials reflecting these effects are maximal at central and right central cortical recording sites. The kappa effect on attention, particularly in the right hemisphere areas, is consistent with the reported propensity of kappa agonists to produce hallucinations. The mu agonist, morphine, delayed stimulus evaluation time as well as reduced the subjects' update working memory but has no apparent effect on attention.

In a second study, preliminary data analysis suggests that both effects mentioned above are blocked by naloxone. An ongoing EEG study has also tentatively found different EEG patterns produced by the mu and kappa agonists. Morphine increased the abundance of delta and theta activity in the spontaneous EEG. This effect is maximal at scalp recording sites over frontal cortex. Ketocyclazocine increased spectral power at 4 Hz in the theta band. This increase in power at 4 Hz is maximal at recording sites in the central cortex, a site at which the event-related potentials reflecting attention were also reduced by the kappa agonist.

Notably, a specific combination of pentazocine and naloxone, which blocks the kappa effect of pentazocine, produces a third unique pattern of the human EEG which appears to be generated by sigma receptor stimulation. Further data analysis is needed before publication of these EEG findings. Pilot work with the pentazocine/naloxone combination indicates that sigma receptor stimulation may alter information processing at stages between attention and stimulus evaluation. Currently effects of morphine on scalp EEG and fluorodeoxyglucose (FDG) positron emission tomography (PET) scans are being compared to further trace the location of these information processing effects in human brain.

The preponderance of EEG and event-related potential alterations produced by opiate receptor stimulation may have implica-

tions for drug abuse and mental illness. There is an abundance of opiate receptors in various sensory and perceptual systems in man. An internal or external imbalance in this system distorts perception. Although this observation is not new, this Laboratory has identified specific information processing alterations produced by two types of opiate receptor interactions and has some evidence for the effects of a third.

Future plans include: 1) finishing the analysis of current work; 2) testing additional subjects in the current experimental protocol; 3) attempting to block any EEG or cognitive event-related potential sigma effect with haloperidol; and, 4) conducting research in an attempt to localize the effects in human brain with BEAM and FDG PET. A clear understanding of this system may aid in the treatment and prevention of both drug abuse and some forms of mental illness.

Cocaine Studies: The effects of cocaine in heavy users were studied over the past year. The focus was on the EEG, cognitive, electrophysiological and behavioral performance. Previous studies in other laboratories in light-to-moderate users have found clear cognitive neurophysiological deficits in some types of behavioral tasks and no deficits in other tasks. In the latter case, cocaine did alter the subjects' cognitive strategy. The event-related potentials to the warning stimuli were found to be enhanced by cocaine. Thus, it appeared that lighter users mustered their attention and stimulus evaluation resources after the warning stimulus in order to perform correctly on the target stimulus when receiving cocaine. While performance did not change, their cognitive strategy did. Cocaine produced an increase in EEG beta power or fast activity and this increase was related to cocaine blood levels.

In an initial study on this topic, an attempt was made to replicate these findings in heavy users. EEG beta power also increased in heavy users and the increase paralleled cocaine blood levels. No tolerance developed to this effect. Cocaine did not disrupt information processing in the heavy users as it did in the light users. On an easy task, an intravenous dose of cocaine (60-80 mg) maintained an electrophysiological index (P300) of stimulus processing as well as performance at pre-drug levels. However, on the placebo day, stimulus processing declined over time. The decline was apparently due to boredom and fatigue. In fact, the decline was more rapid than in non-cocaine users tested on placebo in other studies in the Laboratory.

On a more complex task, the heavy users exhibited no decrease in P300 values on the placebo day and an increase in P300 amplitude after a cocaine bolus. A behavioral measure of performance also increased after the cocaine bolus. The improvement in

cognitive processing and performance seen with cocaine must be considered in light of baseline performance. On the placebo day the heavy cocaine users' performance was poorer than that of non-cocaine users tested on a similar task. Electrophysiological measures also indicated impaired stimulus processing in the heavy users. The heavy cocaine user may require regular stimulant use to maintain optimal cognitive performance. Hence it would seem important that any treatment regimen for the heavy cocaine user should consider embodying a component to aid the patient through a period of cognitive disruption.

Preliminary data suggest that a premotor potential which reflects preparation to make a voluntary movement in the motor and premotor cortical areas is enhanced by cocaine. Further subject testing is needed to resolve this issue. The Laboratory plans to continue its cocaine research program over the coming years. More specifically plans include: 1) a study using calcium channel blockers to antagonize the CNS and cognitive effects of cocaine; 2) a mapping study using BEAM and PET to localize the effects of cocaine in humans; 3) a comparison study investigating both the intravenous and smoked routes of administration of cocaine on cardiovascular, subjective, cognitive and electrophysiological measures; and, 4) a treatment-oriented study which would focus on the time course of the cognitive and performance deficits observed during abstinence from cocaine and their return to normal levels.

Diazepam and Atropine Studies: Two ongoing studies are designed to investigate the sensory, cognitive and behavioral performance effects of diazepam and atropine. In both studies, an extensive battery of nine electrophysiological tasks is being used in an effort to completely characterize sensory and cognitive deficits. In the diazepam study, placebo and five active doses are being given in a counterbalanced, random order. Placebo and three active doses are being given in the atropine study. Both attempt to specifically characterize sensory or cognitive default produced by these drugs which disrupt optimal behavioral performance.

B. Drug Withdrawal-Induced Cognitive and Performance Deficits:

Nicotine Studies: The Laboratory's efforts were also directed toward quantification of the cognitive and performance deficits associated with nicotine withdrawal and the treatment of these deficits with nicotine chewing gum. The EEG, cognitive, and electrophysiological measures examined reflected deficits in cognitive processing 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 (e.g., especially a rapid arithmetic task), and a cognitive event-related potential measure (N100 amplitude). Stimulus evaluation time as measured by P300 latency, the depth of stimulus evaluation as measured by P300 amplitude, and simpler tasks in the computerized battery used 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 may contribute to relapse during treatment. During withdrawal the deficits 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. Since the abstinence period lasted only ten days, this latter deficit may reflect a characterizing trait in those who smoke. The testing of individuals seeking tobacco cessation treatment and actually completing tratment may help resolve this issue.

Three additional studies in various stages of completion were designed to test the efficacy of nicotine chewing gum to prevent the cognitive effects observed during tobacco abstinence. The results of the first two indicate that cognitive deficits were reversed by higher doses of the gum (i.e., 4 mg or more) after 12 hours of tobacco abstinence. When mecamylamine was given to deprived smokers, the EEG alpha frequency was reduced. Since alpha frequency is reliably reduced in tobacco withdrawal, the additional reduction with mecamylamine suggests that mecamylamine administered to nondeprived smokers may precipitate a tobacco withdrawal syndrome. The third study, which has yet to be analyzed, investigates the gum's efficacy in longer periods of abstinence.

Several studies in this area are planned for the coming year. In one, mecamylamine will be used in an attempt to precipitate tobacco withdrawal signs in nondeprived heavy smokers to help better understand the nature of tobacco withdrawal and methods which might be used to prevent it during smoking cessation. In a second study planned, the effects of nicotine will be investigated in nonsmokers.

C. Populations At Risk for Drug Abuse:

Antisocial Adolescents: Adolescents with a history of violence are likely to be at risk for drug abuse. A group of antisocial adolescents and a group of age, IQ, race, and neighborhood matched adolescents participated in a study which included psychometric and electrophysiological testing. The antisocial group differed from the control group on many electrophysiological measures. Wave V of the brainstem

auditory evoked response was significantly longer in the antisocial adolescents. The latency of the N100 of a tone-evoked brain potential was shorter in the antisocial group than in the control group. P300 amplitude to the target tone in a cognitive task was reduced in the antisocial group. EEG alpha activity was reduced and theta power was increased in the violent group.

The constellation of sensory and cognitive differences observed between adolescents with a history of violence and matched controls suggest that adolescents displaying violent antisocial behavior may have a major information processing disorder which is similar in some respects to, and differs in certain respects from, that observed in attentional deficit disorder (ADD). Hence, it might be hypothesized that drugs may be used by these antisocial individuals to normalize cognitive processing.

Future work with violent adolescents will investigate the visual and somatosensory systems in this population. Moreover, the outcome of drug interventions which have been effective in children with ADD may be tested in this population of antisocial adolescents. In addition, other biological and electrophysiological markers will be examined.

Publications for Fiscal Year '86:

Hickey, J.E., Pickworth, W.B., Herning, R.I., Hartsock, P.I., and Jaffe, J.H.: Altered sensory and cognitive processing in adolescents at risk for drug abuse: Electrophysiological evidence. Electroencephalography and Clinical Neurophysiology Sup., June 1986. In press.

Henningfield, J.E., Goldberg, S.R., Herning, R.I., Jasinski, D.R., Lukas, S.E., Miyasato, K., Nemeth-Coslett, R.D., Pickworth, W.B., Rose, J.E., Sampson, A., and Snyder, F.R.: Human studies of the behavioral pharmacological determinants of nicotine dependence 47th CPDD. In Problems of Drug Dependence 1985, L.S. Harris (Ed.), pp. 54-65, 1986.

Pickworth, W.B., and Sharpe, L.G.: Morphine-induced mydriasis and inhibition of pupillary light reflex and fluctuations in the cat. J. Pharmacol. Exp. Therap. 235: 603-606, 1985.

Pickworth, W.B., Neidert, G.L., and Kay, D.C.: Cyclazocine induced sleep disruptions in nondependent addicts. Prog. Neuro-Psychopharmacol. Biol. Psychiat. 10: 77-85, 1986.

Pickworth, W.B., Herning, R.I., and Henningfield, J.E.: Electroencephalographic effects of nicotine chewing gum in humans. Pharmacol. Biochem. Behav., 1986. In press.

Bell, J.A., Sharpe, L.G., and Pickworth, W.B.: Electrophysiologically recorded C-fiber reflexes in the intact cat: absence of naloxone facilitation. Neuropharmacology 26: 555-559, 1985.

Sharpe, L.G., and Pickworth, W.B.: Opposite pupillary size effects in the cat and dog after microinjection of morphine normorphine and clonidine in the Edinger-Westphal nucleus. Brain Res. Bull. 15: 329-333, 1985.

Hickey, J.E., Pickworth, W.B., Herning, R.I., Hartsock, P.I., and Jaffe, J.H.: Altered sensory and cognitive processing in adolescents at risk for drug abuse: electrophysiological evidence EPIC-proceeding, 1986. In press.

Gorodetzky, C.W., Buchwald, W.F., Cone, E.J., Darwin, W.D., Pickworth, W.B., Risner, M.E., and Sharpe, L.G.: Progress report from the NIDA Addiction Research Center (Preclinical Laboratory). In Problems of Drug Dependence 1984, L.S. Harris (Ed.), Rockville, MD, NIDA Research Monograph 55, 32-58, 1985.

Henningfield, J.E., Goldberg, S.R., Herning, R.I., Jasinski, D.R., Lukas, S.E., Miyasato, K., Nemeth-Coslett, R.D., Pickworth, W.B., Rose, J.E., Sampson, A., and Snyder, F.R.: Human studies of the behavioral pharmacological determinants of nicotine dependence 47th CPDD. In Problems of Drug Dependence 1985, L.S. Harris (Ed.), pp. 54-65, 1986.

Abstracts

Pickworth, W.B., and Herning, R.I.: Electroencephalographic effects of nicotine gum in humans. EEG Journal 61: 5171, 1985.

Herning, R.I., and Pickworth, W.B.: Nicotine gum improved stimulus processing during tobacco withdrawal. Psychophysiology 22: 595, 1985.

Pickworth, W.B., and Herning, R.I.: EEG changes following nicotine gum in deprived volunteers. Psychophysiology 22: 608, 1985.

Pickworth, W.B., Herning, R.I., Kumor, K.M., and Sherer, M.A.: Spontaneous EEG during chronic cocaine infusion. Pharmacologist, 1986. In press.

Herning, R.I., Pickworth, W.B., Kumor, K.M., Sherer, M.A., and Cone, E.J.: Cocaine improves information processing in heavy users: electrophysiological evidence. Pharmacologist, 1986. In press.

Pickworth, W.B., Herning, R.I., Hickey, J.E., and Jaffe, J.H.: Spontaneous EEG recordings from adolescents at risk for drug abuse. Psychophysiology, 1986. In press.

Snyder, F.R., and Henningfield, J.E.: Cognitive effects of nicotine deprivation/administration. Paper presented at the annual meeting of the Behavioral Pharmacology Society, Wilmington, DE, June 1985.

Snyder, F.R., Davis, F.C., and Henningfield, J.E.: Effects of tobacco deprivation on cognitive performance. Paper presented at the annual meeting of the Eastern Psychological Association, New York, April 1986.

Pickworth, W.B., Herning, R.I., Snyder, F.R., and Henningfield, J.E.: Cognitive, performance and electrophysiological effects of nicotine deprivation and nicotine gum in human volunteers. Presented at Tobacco Smoking and Health: A Neurobiological Approach, Lexington, KY, December 3, 1985.

Pickworth, W.B., and Herning, R.I.: Electroencephalographic effects of nicotine deprivation in addicted smokers. Am. Psychol. Associat., August 1986.

Herning, R.I., Pickworth, W.B., and Cone, E.J.: Impaired information processing in heavy smokers undergoing withdrawal from tobacco. Am. Psychol. Associat., August 1986.

Herning, R.I., Pickworth, W.B., and Kumor, K.M.: Kappa and mu opiate effects on information processing. Committee on Problems of Drug Dependence, Lake Tahoe, CA, June 1986.

Snyder, F.R., Davis, F.C., and Henningfield, J.E.: Chronic tobacco abstinence reduces information processing capabilities in heavy smokers. Symposium paper presented at the annual meeting of the American Psychological Association, Washington, DC, August 1986.

Snyder, F.R., and Weingartner, H.: State-dependent retrieval of knowledge memory: A psychobiological-cognitive analysis of the discriminative stimulus properties of drugs. Paper presented at the NIAAA/NIDA first national conference on Alcohol and Drug Abuse Prevention, Washington, DC, August 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00001-01 PVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
The Validity of Laboratory Measures of Aggression

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Jerome Jaffe, M.D.	PVL/BVL	ARC
Others:	Diana Fishbein, Ph.D.	PVL	ARC
	Carlos Muntaner, M.D., Ph.D.	PVL	ARC

COOPERATING UNITS (if any)

LAB/BRANCH
Psychology of Vulnerability, Psychopathology Branch

SECTION
Psychopathology and Cognitive Studies

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This study is designed to provide the opportunity for aggressive responses in a laboratory setting in order to measure the degree to which laboratory responses correlate with other measures. All subjects who enter the research ward for an ongoing project are asked to participate in this study after they are released and before they leave the facility. Those subjects who volunteer are seated before a video display terminal where they are instructed that they can earn money for particular responses. An ostensible partner extracts money from them as they play and subjects have the similar ability to extract money from their "partner". Their responses are monitored to determine whether they can be characterized as aggressive or impulsive. After completion, they are debriefed and asked some simple questions indicating their impression of their partner and the game. All data obtained from this experiment will be compared with responses on other psychometric instruments and behavioral questionnaires with respect to psychiatric condition. We will attempt to determine whether responses on this laboratory measure are associated with behavioral, psychological, and psychiatric histories. Additionally, biological measures, such as the EEG and evoked potentials, collected upon admission to the ARC, will be compared with these behavioral data to identify potential correlates.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00002-01 PVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Effects of Serotoninergic Stimulation on Neuroendocrine Measures in Aggressive Addicts

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jerome Jaffe, M.D.	PVL/BVL	ARC
Others:	Diana Fishbein, Ph.D.	PVL	ARC
	David Lozovsky, M.D., Ph.D.	BVL	ARC
	Ronald Herning, Ph.D.	CHP	ARC
	Wallace Pickworth, Ph.D.	CHP	ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH
Biology of Vulnerability and Psychology of Vulnerability

SECTION
Clinical Biology Branch
Psychopathology and Cognitive Studies

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	1	2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study examines central serotoninergic systems in drug addicts with and without high levels of aggressiveness/impulsivity as compared to normal volunteers by evaluating their neuroendocrine and behavioral responses to fenfluramine-induced central serotoninergic stimulation.

Previous studies suggest that serotoninergic activity is blunted in individuals with aggressive and impulsive behaviors. Fenfluramine, a serotoninergic probe, is administered to drug abusers (ages 21 to 50) with and without aggressive and impulsive features and age and sex matched normal volunteers. Neuroendocrine mechanisms regulated by the neurotransmitter, serotonin, are being assessed to determine whether normals and aggressive subjects respond differentially to serotoninergic stimulation. Specifically, anterior pituitary hormones (prolactin, growth hormone, TSH, cortisol) are expected to show differences between groups. Additional measures of psychological and electrophysiological functioning are obtained.

An additional component of this study is the assessment of glucose metabolism, a process influenced by serotoninergic systems. A 5 hour oral glucose tolerance test is administered on the first study day to evaluate possible variations between groups in plasma glucose, insulin and other hormone levels.

The identification of neurotransmitter activity differences between normals and aggressives will enhance understanding of biological mechanisms in aggression and assist in the use of medications designed to normalize these processes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00003-01 PVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Psychological, Behavioral, and Electrophysiological Markers of Antisocial Behavior

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Jerome Jaffe, M.D.	PVL	ARC
Others:	Diana Fishbein, Ph.D.	PVL	ARC
	Ronald Herning, Ph.D.	CHP	ARC
	John Hickey, L.C.S.W.	EIL	ARC
	Wallace Pickworth, Ph.D.	CHP	ARC
	Charles Haertzen, Ph.D.	BDL	ARC

COOPERATING UNITS (if any)

LAB/BRANCH
Psychology of Vulnerability; Cognition and Human Performance; Biology of Dependence

SECTION
Clinical Biology Branch
Psychopathology and Cognitive Studies

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	1.5	1.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This study examines individuals as inpatients to identify the correlates of aggressive tendencies, antisocial behavior and drug addiction. A comprehensive assessment battery has been administered to individuals entering the ARC for one of the ongoing projects. This battery includes psychiatric diagnosis, psychological tests, behavioral measures of aggression and psychopathy, and an electrophysiological test battery. These measures have been entered into an "Admission's Database" and are presently being analyzed to identify significant correlates of drug dependence and behaviors frequently related, such as aggression and psychopathy.

To date, several psycho-diagnostic features significantly related to behavioral measures have been developed into an assessment battery for the identification of behavioral disorders. In addition, several EEG and evoked potentials reflecting cognitive functions appear to discriminate between "normal" subjects and drug abusers with high levels of aggression. Further analyses will be necessary before appropriate interpretations of these data can be formulated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00004-01 PVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Assessment of an Instrument to Measure Alcohol-Related Behaviors

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Jerome Jaffe, M.D.	PVL/BVL	ARC
Others:	Diana Fishbein, Ph.D.	PVL	ARC
	Fred Snyder, Ph.D.	CHP	ARC
	Charles Haertzen, Ph.D.	BDL	ARC
	John Hickey, L.C.S.W.	EIL	ARC
	Carlos Muntaner, M.D., Ph.D.	PVL	ARC

COOPERATING UNITS (if any)

LAB/BRANCH
Psychology of Vulnerability: Cognition and Human Performance

SECTION
Psychopathology and Cognitive Studies

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this study is to assess the reliability and validity of the Alcohol-Related Behavior Questionnaire developed at the Addiction Research Center, NIDA. The ultimate objective of this project is the enhanced ability to prevent and treat alcohol-related disorders and the subsequent development of effective remedial programs.

The questionnaire is designed to determine types of behaviors which are associated with drinking and non-drinking conditions among individuals prone to substance abuse and those without histories of abuse. The questionnaire consists of five behavioral scales reflecting responses associated with drinking behavior. This study assesses the degree to which these behaviors are influenced during simulated conditions of non-drinking, moderate drinking and heavy drinking.

To date, the ARC has obtained nearly 200 completed questionnaires from subjects admitted to the research ward and outpatients. Other psychometric and psychiatric data have been obtained from these same subjects to characterize groups of subjects and determine whether alcohol-related behaviors differ depending upon psychological or psychiatric condition. These data are presently being analyzed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00005-01 PVL

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Aggression Among Drug Users and Normal Controls as a Function of Early Experience

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jerome Jaffe, M.D.	PVL/BVL	ARC
Others:	Charles Haertzen, Ph.D.	BDL	ARC
	Diana Fishbein, Ph.D.	PVL	ARC
	Carlos Muntaner, M.D., Ph.D.	PVL	ARC
	John Hickey, L.C.S.W.	EIL	ARC
	Fred Snyder, Ph.D.	CHP	ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH

Psychology of Vulnerability; Cognition and Human Perofrmance; Biology of Dependence and Abuse Potential

SECTION

Clinical Biology Branch
Psychopathology and Cognitive Studies

INSTITUTE AND LOCATION

NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects
- ☐ (b) Human tissues
- ☐ (c) Neither
- ☐ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study will describe an instrument, the Early Experience Questionnaire (EEQ), that assesses aggressive and antisocial behaviors manifested during childhood. The instrument was designed at the ARC and consists of seven items reflecting aggressive behaviors before the age of 12. Eight additional items have been added to disguise the actual purpose of the test. This questionnaire has been administered to nearly 100 subjects who are either admitted to the research ward at the ARC or who are considered for admission. Initial analyses will describe the reliability and validity of the device. Additional measures of behavior, personality, psychiatric condition and physiology have been obtained and are presently being analyzed to determine whether EEQ differences are associated with distinct personality patterns and behaviors associated with drug and alcohol use during adulthood. In particular, we will explore whether childhood aggression predicts later behaviors in addicts and alcoholics under the influence of their preferred drug.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00006-01 PVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Efficacy of Urine Testing and Family Counseling with Young Chronic Cocaine Users

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Jerome Jaffe, M.D.	PVL/BVL	ARC
Others:	Barry Brown, Ph.D.	EIL	ARC
	William Weddington, M.D.	EIL	ARC
	Marc Rose, Ph.D.	EIL	ARC
	John Hickey, L.C.S.W.	EIL	ARC
	Diana Fishbein, Ph.D.	PVL	ARC
	Ronald Herning, Ph.D.	CHP	ARC
	Wallace Pickworth, Ph.D.	CHP	ARC
	Robert Brooner, Ph.D.		FSKMC

COOPERATING UNITS (if any)
Francis Scott Key Medical Center (FSKMC)

LAB/BRANCH
Early Intervention Branch

SECTION

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	.5

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [X] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This study will examine the deterrent effects of urine testing with chronic young cocaine users. Adolescents and young adults who have sought help for their cocaine usage by phoning the National Institute on Drug Abuse (NIDA) cocaine hotline, or by responding to other media notices, will be provided an opportunity for a comprehensive psychodiagnostic and medical assessment. Volunteers who are living with at least one parent will be assigned to one of three groups: 1) those who receive urine testing with feedback to parents, and family counseling; 2) those who receive counseling alone; and 3) a control group which will receive the benefits of the comprehensive assessment but no subsequent intervention. Levels of cocaine usage for these groups will also be compared at baseline. The objective will be to determine the efficacy of urine testing and family communication about extent of drug use as an intervention in problem cocaine use.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 00007-01 PVL

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Psychodiagnostic and EEG Correlates of Aggression and Drug Use in Adolescents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jerome Jaffe, M.D.	PVL/BVL	ARC
Others:	John Hickey, L.C.S.W.	EIL	ARC
	Ronald Herning, Ph.D.	CHP	ARC
	Wallace Pickworth, Ph.D.	CHP	ARC
	Diana Fishbein, Ph.D.	PVL	ARC

COOPERATING UNITS *(if any)*

LAB/BRANCH
Psychology of Vulnerability; Cognition and Human Performance

SECTION
Psychopathology and Cognitive Studies

INSTITUTE AND LOCATION
NIDA Addiction Research Center, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	.5

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
- [ ] (b) Human tissues
- [ ] (c) Neither
- [x] (a1) Minors
- [ ] (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A group of young adults who had come to the attention of school authorities due to behavioral and disciplinary problems was identified. Cognitive, psychological and electroencephalographic measures were obtained and compared to similar measures obtained from matched controls. The primary hypothesis was that the young men who exhibited or reported more behavioral problems and delinquent behavior were at much higher risk for being drug abusers than control subjects from the same neighborhoods. It was also expected that the more psychopathic, high risk young men, like adult psychopaths examined in previous studies, would differ from controls in the way they processed information as measured by the electroencephalogram.

Preliminary analyses for nineteen subjects showed that several psychological and electrophysiological measures are correlated with antisocial behavior based on self-reports of delinquency. The more antisocial adolescents are the more likely to become involved in drug abuse and to report lower levels of well being and social conformity. Additionally, results for the EEG and event-related potential measures indicate that adolescents reporting more antisocial activity and drug abuse differ from less delinquent and drug using controls throughout the auditory information processing system.

Presently, the study has been expanded to examine a more heterogeneous sample of adolescents and assess additional measures of cognitive performance and physiological responsivity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 DA 02001-01 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mapping the Effects of Opioid Agonists by PET and EEG

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	R.I. Herning	Acting Chief	CHP, NIDA
Others	W.B. Pickworth	Scientist	CHP, NIDA

COOPERATING UNITS *(if any)*

Neuropharmacology Lab (E. London, E. Broussolle)
Johns Hopkins Hospital (D. Wong)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Effects of morphine on the scalp EEG and FDG PET scans are being compared to determine the brain areas invoked in euphoria. The Cognitive Studies and Human Performance Laboratory is collecting and 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 electrophysiologic effects of mu agonist in humans and the cortical distribution of mu effects. The EEG and PET data together may delineate the mechanism responsible for euphoria in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 DA 02101-02 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Acute Abstinence From Tobacco: Electrophysiological and Cognitive Signs

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI	J.E. Henningfield	Chief	BDL, NIDA
Others	W.B. Pickworth	Scientist	CHP, NIDA
	R.I. Herning	Acting Chief	CHP, NIDA
	F. Snyder	Scientist	CHP, NIDA

COOPERATING UNITS (if any)

Biology of Dependence Lab (J. Henningfield, R. Nemeth-Coslett)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

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. Since the abstinence period only lasted ten days, this latter deficit may reflect a characterizing trait in those that smoke. The testing of individuals seeking tobacco cessation treatment and completing treatment can help resolve this issue.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 02301-02 CHP

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.): Interaction of Mecamylamine and Nicotine Gum in Dependent Smokers

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI	J.E. Henningfield	Chief	BDL, NIDA
	R.I. Herning	Acting Chief	CHP, NIDA
Others	W.B. Pickworth	Scientist	CHP, NIDA
	F. Snyder	Scientist	CHP, NIDA

COOPERATING UNITS (if any)

Biology of Dependence Lab (J. Henningfield, R. Nemeth-Coslett)

LAB/BRANCH: Cognitive Studies and Human Performance Laboratory

SECTION:

INSTITUTE AND LOCATION: Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.1	.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Three additional studies at various stages of completion tested the efficacy of nicotine chewing gum in preventing the cognitive deficits observed during tobacco abstinence. The first two found the cognitive deficits were reversed by higher doses of the gum (4 mg or more) after 12 hours of tobacco abstinence. When mecamylamine is given to deprived smokers the EEG alpha frequency is reduced. Since alpha frequency is reliably reduced in tobacco withdrawal, the additional reduction with mecamylamine suggests that mecamylamine administered to nondeprived smokers may precipitate a tobacco withdrawal syndrome. The third study, which is yet to be analyzed, investigates the gum's efficacy in longer periods of abstinence.

We are planning the several studies in this area over the coming year. In the first study mecamylamine will be used to precipitate tobacco withdrawal signs in nondeprived heavy smokers to better understand the nature of tobacco withdrawal and methods to prevent it during smoking cession. The second planned study will investigate the effect of nicotine in nonsmokers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 02801-01 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Human Electrophysiology of Mu and Kappa Opiate Agonists

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI	J. Jaffe	Director	ARC, NIDA
	R.I. Herning	Acting Chief	CHP, NIDA
Others	W.B. Pickworth	Scientist	CHP, NIDA

COOPERATING UNITS (if any)

Biology of Vulnerability (J. Jaffe, K. Kumor)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The effects of mu and kappa agonists on the EEG and cognitive event related potentials were studied in humans. Unique mu and kappa effects have been identified. The kappa agonist, ketocyclazocine, diverts attention of external stimuli and decreases the subjects' ability to update working memory. The brain potentials reflecting these effects are maximal at central and right central cortical recording sites. The kappa effect on attention, particularly in right hemisphere areas, is consistent with the reported propensity of kappa agonists to produce hallucinations. The mu agonist, morphine, delayed stimulus evaluation time as well as reduced the subject's update working memory, but had no effect on attention. In a second study, preliminary data analysis suggests both effects are blocked by naloxone. An ongoing EEG study has also tentatively found morphine increased the abundance of delta and theta in the spontaneous EEG. This effect is maximal at scalp recording sites over frontal cortex. Ketocyclazocine increased spectral power at 4 Hz in the theta band. The increased power at 4 Hz is maximal at recording sites in the central cortex, where the event related potentials reflecting attention were also reduced by the kappa agonist.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 02811-01 CHP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
The Human Electrophysiology of Sigma Opiate Agonist

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI	J. Jaffe	Director	ARC, NIDA
	R.I. Herning	Acting Chief	CHP, NIDA
Others	W.B. Pickworth	Scientist	CHP, NIDA

COOPERATING UNITS (if any)

Biology of Vulnerability (J. Jaffe, K. Kumor)
University of Maryland, School of Pharmacy (N. Khazan, G. Young)

LAB/BRANCH
Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION
Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A limited number of subjects (N=3) has been tested in a dosing paradigm designed to stimulate the sigma receptor in humans. A specific combination of pentazocine and naloxone, which blocks the kappa effect of pentazocine, produces a specific pattern of human EEG (2 Hz spectral peak) which appears to be generated by sigma receptor stimulation. Further data analysis is needed before the publication of these EEG findings. Pilot work with the pentazocine and naloxone combination also indicates that sigma receptor stimulation alters information processing at stages between attention and stimulus evaluation. The sigma receptor stimulation appears to modulate sensory habituation in man. Clarification of the specific sigma subjective effects is also underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 03101-01 CHP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Effects of Atropine on Cognitive Information Processing

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI	J.E. Henningfield	Chief	BDP, NIDA
Others	W.B. Pickworth	Scientist	CHP, NIDA
	R.I. Herning	Acting Chief	CHP, NIDA
	F. Snyder	Scientist	CHP, NIDA

COOPERATING UNITS (if any)

Biology of Dependence Lab (J. Henningfield, R. Lamb)

LAB/BRANCH
Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION
Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.6	.6	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

An extensive battery of sensory and cognitive electrophysiological tasks are being 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) was investigated on two occasions. Eight subjects have been tested on these procedures and data are currently being analyzed.

The purpose of the study is to better understand the effects of cholinergic agents on cognition and performance; in particular, just where in the information processing sequence atropine exerts its effects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 03111-01 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effects of Benzodiazepines on Cognitive Information Processing

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI	R.I. Herning	Acting Chief	CHP, NIDA
Others	W.B. Pickworth	Scientist	CHP, NIDA
	F. Snyder	Scientist	CHP, NIDA

COOPERATING UNITS (if any)

Biology of Dependence Lab (J. Henningfield, J. Roache; R. Lamb)

LAB/BRANCH

Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION

Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.6	.6	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

An extensive battery of sensory and cognitive electrophysiological tasks are being used to assess sensory, cognitive and performance deficits produced by diazepam. The tasks include eyes open and eyes closed EEG, brainstem auditory evoked response, pattern reversal visual evoked response, auditory rare event monitoring task, the auditory continuous performance task and the Sternberg memory task (both immediate and delayed). Six doses (0, 2.5, 5.0, 10.0, 20.0 and 40.0 mg) of diazepam were used. Nine subjects were tested and the data are currently being analyzed.

The purpose of the study is to determine where in the information processing sequence the benzodiazepines exert their effects. Memory deficits have been previously noted, but it is yet unclear whether the deficit is due to poor encoding of the information or loss of the newly formed memory trace. The study is important in understanding the abuse of this class of drugs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 03301-01 CHP

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Electrophysiologic Measures of Conduct Disorder (Aggressive) in Adolescents

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI	J. Jaffe	Director	NIDA/ARC
Others	R.I. Herning	Acting Chief	CHP, NIDA
	W.B. Pickworth	Scientist	CHP, NIDA

COOPERATING UNITS (if any)

Early Intervention Lab (J. Hickey)

LAB/BRANCH
Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION
Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Adolescents with a history of violence are likely to be at risk for drug abuse. This project studies a group of antisocial adolescents and a group of age, IQ, race, and neighborhood matched adolescents who participated in a study which included psychometric and electrophysiological testing. The Cognitive Studies and Human Performance Lab is primarily concerned with the electrophysiological measures. The antisocial group differed from the control group on many electrophysiological measures. Wave V of the brainstem auditory evoked response was significantly longer in the antisocial adolescents. The latency of the N100 of a tone evoked brain potential was shorter in the antisocial group than the control group. P300 amplitude to the target tone in a cognitive task did not show the usual anterior to posterior distribution in the antisocial group. EEG alpha activity was reduced and theta power was increased in the violent group. The constellation of sensory and cognitive differences suggest adolescents displaying violent antisocial behavior have a major information processing disorder, which in some respects is similar ADD and yet differs in other respects. Drugs may be used by these antisocial individuals to normalize cognitive processing.

Our future work with violent adolescents will investigate 1) the visual and somatosensory systems in this population, 2) drug interventions which have been effective in children with ADD, and 3) other biological and electrophysiological markers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 DA 03501-01 CHP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cocaine's Effect on Cognition and Performance: The Heavy User

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.H. Jaffe	Acting Chief	Clin. Biol.
	R.I. Herning	Acting Chief	CHP, NIDA
Others	W.B. Pickworth	Scientist	CHP, NIDA
	F. Synder	Scientist	CHP, NIDA

COOPERATING UNITS *(if any)*
Biology of Vulnerability (J. Jaffe, K. Kumor, M. Sherer)

LAB/BRANCH
Cognitive Studies and Human Performance Laboratory

SECTION

INSTITUTE AND LOCATION
Addiction Research Center, NIDA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.2	

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of cocaine in the heavy users are studied over the past year. The focus of our efforts was on the EEG, cognitive electrophysiology and behavioral performance. Previous studies in light to moderate cocaine users cognitive neurophysiological deficits in some types of behavioral tasks with no deficits in other tasks. Cocaine produced an increase in EEG beta power or fast activity and this increase was related to cocaine blood levels. In our first study we attempted to replicate these findings in heavy users. EEG beta power also increased in heavy users and the increases paralleled cocaine blood levels. No tolerance developed to this effect.

Cocaine did not disrupt information processing in the heavy users as it did in the light users. On an easy task an intravenous dose of cocaine (60-80 mg) maintained an electrophysiological index (P300) of stimulus processing as well as performanmce at pre-drug levels. However, on the placebo day stimulus processing declined over time. The decline was due to boredom and fatigue. In fact the decline was more rapid than that seen in non-cocaine users tested on placebo in other studies in our laboratory. On a more complex task the heavy users had no decrease in P300 on the placebo day and, an increase in P300 amplitude after the cocaine bolus. A behavioral measure of performance also increased after the cocaine bolus. The improvement in cognitive processing and performance with cocaine must be considered in light of poorer baseline performance. The attention and stimulus evaluation abilities as well as task performance is subnormal in the heavy cocaine user. The heavy cocaine user may require regular stimulant use to maintain optimal cognitive performance. Any treatment regimen for the heavy cocaine user should embody a component to aid the patient through a period of cognitive disruption.

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