PROJECT NUMBER.....5 R01 MH19506-19 FY 94

RG/INTRAMURAL UNIT..BNR

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ERFORMING ORGANIZATION: EMORY UNIVERSITY
ITLE HORMONES, BRAIN, AND BEHAVIOR

BSTRACT:

This application for MH 19506-18 is to continue our program of Psychobiological research in the Department of Psychiatry, Emory University School of Medicine. The School of Medicine wishes to support a comprehensive research program that is basic t the problems of brain function, behavior and mental health. The aim is to investigate the physiological and neuroendocrine bases of patterns of primate behavior. Major emphasis is given to the affectional and sexual responses and to the agonistic and aggressive responses. Three interrelated studies are proposed in a social primate, the cynomolgus monkey.

Experiment I will use well-established behavioral techniques systematically to examine, for the first time in a male primate, how aromatizable and non-aromatizable androgens affect different types of male aggression. It will also investigate the social factors that elicit male aggression and how they influence the social bonding of the male-female pair. Experiment II will continue our studies on the behavioral effects in primates of medroxyprogesterone acetate (MPA), which is used clinically to treat violent aggression, particularly violence by men towards women. To understand the brain mechanisms involved, we will use high performance liquid chromatography, autoradiography and immunohistochemistry to study the uptake of androgens and progestins by the male primate brain, and to map the location of androgen- and progestin-target neurons and receptors. Experiment III is concerned with the metabolism of testosterone by brain; and specifically the role of its aromatization to estradiol in the male primate. Aromatization is important for sexual behavior in the male rat, and our preliminary findings with the aromatase inhibitor, Fadrozole, have indicated that this is also the case for the primate, an observation which has importance because of the clinical use of aromatase inhibitors in prostatic disease and cancer. We plan to develop these comparative behavioral and biochemical studies in male monkeys and to extend them to females.

RISP INDEXING TERMS FROM CRISP THESAURUS:

* 4000 0240 S Macaca fascicularis

* INDICATES TERM USED FOR SEARCH
P,S,T = PRIMARY, SECONDARY, TERTIARY EMPHASIS RESPECTIVELY
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PROJECT NUMBER.....5 K05 DA00008-20 FY 94

IRG/INTRAMURAL UNIT..SRCD

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PERFORMING ORGANIZATION: EMORY UNIVERSITY
TITLE BEHAVIORAL PHARMACOLOGY OF OPIOIDS AND CAFFEINE

ABSTRACT:

A program of research is proposed for studying behavioral effects of two types of drugs of major clinical, social , and theoretical important: 1) opioids, which have long represented a significant abuse problem; 2) caffeine, which is the most widely consumed behaviorally-active compound in the world, and which has many of the characteristics of a drug of abuse.

The basic strategy of this research program is to use behavioral methodologies to study interactions of drugs with their neuronal substrates. The objective is to identify and characterize components of drug action that may be relevant to potential for abuse and to related phenomena, such as tolerance and physical dependence. The neuronal substrates of drug action will be characterized with receptor-selective agonists, antagonists, and tolerance and cross-tolerance. Representative compounds will be studied over a range of doses in several behavioral procedures, such as drug discrimination, food-reinforced operant responding, locomotor activity, and autotitration of reinforcement threshold for electrical brain stimulation. Experiments will be performed on rats and, often, on squirrel monkeys. This approach will help in assessing the generality of experimental findings with respect to pharmacological, behavioral, and species variables.

The proposed experiments will address a number of hypotheses. Among these are: 1) Endogenous opioid peptides can modulate the behavioral effects of exogenously administered opioid drugs; 2) Similar components of drug action mediate discriminative stimulus, reinforcing stimulus, and subjective drug effects; 3) The discriminative stimulus effects of low and high doses of caffeine differ qualitatively from each other and reflect components of drug action that underlie, respectively, positive and negative mood states in humans.

CRISP INDEXING TERMS FROM CRISP THESAURUS:

* 0182 1640 T Saimiri

* INDICATES TERM USED FOR SEARCH
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PROJECT NUMBER.....5 R37 DA00541-21

FY 94

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PERFORMING ORGANIZATION: EMORY UNIVERSITY
TITLE BEHAVIORAL PHARMACOLOGY OF NARCOTIC ANTAGONISTS

ABSTRACT:

Opioids comprise a diverse group of compounds that display a broad array of agonist and antagonist properties, apparently as a consequence of differential interactions with multiple populations or receptors. There are major differences in behavioral pharmacology among opioids drugs, which often correspond to differences in abuse potential. This research program will evaluate systematically the behavioral effects of representative opioid drugs having differing spectra of activity in order to identify and study distinct components of drug action that reflect the various receptor types with whch the drugs interact, and which are fundamental determinants of the differences in abuse potential. Particular attention will be given to characterizing the behavioral effects of opioid peptides that interact with defined receptor populations, and to clarifying the role of endogenous opioid systems in the diverseness of the behavioral effects of opioid drugs. Many of the proposed experiments will address different aspects of two hypotheses: 1) activation of delta-opioid receptors can potentiate behavioral effects mediated by mu receptors; 2) mu-receptor agonists (eg, morphine) do not induce tolerance to delta-mediated opioid actions. Behavioral effects of opioid peptides will be determined and compared to those of prototypic opioid alkaloids, and interactions between opioid peptides and opioid agonists and antagonists will be studied. Drugs usually will be examined in two animal species, rat and squirrel monkey, and in several behavioral procedures to generate converging experimental findings having broad applicability. Principal experiments will include: a) evaluating morphine-like and nonmorphine-like discriminative stimulus efects of opioids; b) determining if opioid peptides modify effects of opioid drugs on locomotor activity and food-reinforced operant responding in the same way that they modify discriminative effects, and conversely, determining if behavioral effects of opioid peptides are modified differentially by chronic morphine administration; c) determining if stress-induced potentiation of opioid analgesia can serve as a mdel of "natural" interactions between endogenous opioid systems and opioid drugs; d) characterizing pharmacologically single-dose sensitization by agonists to antagonist-induced disruption of food-maintained operant

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PROJECT NUMBER.....5 R01 DA01161-19

FY 94

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PERFORMING ORGANIZATION: EMORY UNIVERSITY

TITLE BEHAVIORAL AND PHYSIOLOGICAL CONCOMITANTS OF DRUG ABUSE

ABSTRACT:

The purpose of the proposed studies is to identify and characterize the effects of cocaine and related drugs on learned behavior and on physiological activity in nonhuman primates. The experiments are based on the outcome of previous studies in this laboratory showing that cocaine and other drugs with high abuse liability have pronounced effects on behavior, and that behaviorally effective doses of the same drugs can also affect the cardiovascular and thermoregulatory systems. Experiments will be conducted in squirrel monkeys surgically prepared under sterile conditions with chronically indwelling arterial and venous catheters and, in some instances, with osmotic minipumps. Experiments will involve the direct measurements of systemic arterial blood pressure and heart rate as indices of cardiovascular activity, the direct measurement of colonic temperature as an index of thermoregulatory activity, and operantly conditioned behavior as a measure of central nervous system activity. A wide range of doses of selected drugs will be administered alone to determine the direction, magnitude and of rest, and on behavioral and physiological activity during periods of ongoing schedule-controlled behavior. Drugs of primary interest are those that can have central nervous system stimulant effects and include cocaine, d-amphetamine, caffeine, methylphenidate and phencyclidine. In addition, selected pharmacological agonists, antagonists and drugs that alter catecholamine or serotonin synthesis and uptake or receptor activity will be administered in combination with cocaine and other drugs to study the pharmacological basis of the drug effects. Serum blood levels of drugs will be assayed using HPLC to describe the pharmacokinetics of the drugs under study and to correlate these findings with the behavioral and physiological effects. The overall objective of the research program is to determine (1) the effects selected abused drugs with stimulant properties can have on the central nervous system by studying the effects of the drugs on conditioned behavior in squirrel monkeys, (2) the effects these drugs can have on heart rate, blood pressure and temperature at doses that have effects on behavior mediated via the central nervous system, and (3) whether the behavioral, cardiovascular or thermoregulatory effects can be enhanced, attenuated or blocked by other drugs and chemical substances or by behavioral procedures.

CRISP INDEXING TERMS FROM CRISP THESAURUS:

* 0182 1640 T Saimiri

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PROJECT NUMBER.....2 R01 DA05346-06

IRG/INTRAMURAL UNIT..SRCD

FY 94

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TITLE BEHAVIORAL AND RESPIRATORY EFFECTS OF XANTHINES

ABSTRACT:

Caffeine and related xanthines are behaviorally-active drugs used clinically as respiratory stimulants, but biochemical mechanisms that mediate the behavioral and respiratory effects remain undefined. Studies have implicated both antagonism of adenosine receptors and inhibition of phosphodiesterase activity as possible mechanisms that mediate their central effects. Because of the widespread use of xanthines as therapeutic drugs and as constituents of food and beverages, studies are proposed to (1) investigate mechanisms that mediate the behavioral and respiratory-stimulant effects of xanthines, (2) establish a nonhuman primate model of caffeine tolerance, (3) characterize the interactions of caffeine and nicotine during acute and chronic administration of both drugs, and (4) compare the effects of caffeine to those of cocaine to assess the pharmacological specificity of drug effects and to provide critical information regarding the behavioral and respiratory effects of cocaine. Ventilation (minute volume, tidal volume and respiratory frequency) in unanesthetized rhesus monkeys will be monitored continuously with a pressure-displacement, head plethysmograph while a medical gas analyzer monitors carbon dioxide and oxygen tensions in expired air. Drug effects on ventilation will be determined during exposure to normal atmospheric conditions and during conditions of hypercapnia, hypoxia and hyperoxia. Operant behavior will be studied while ventilation is being monitored to provide direct comparisons of drug effects on behavior and on respiration. Additionally, the pharmacokinetics of caffeine and cocaine will be determined by high-performance liquid chromatography analysis. A wide range of doses of caffeine and related drugs with selective actions as adenosine-receptor agonists and antagonists and as phosphodiesterase inhibitors will be determined in caffeine-tolerant and non-tolerant animals. Altered pharmacokinetics and sensitivity to caffeine and related stimulants during chronic drug administration, in conjunction with acute drug interactions, will have important implications for the study of drug abuse and for the establishment of appropriate drug-abuse policy.

CRISP INDEXING TERMS FROM CRISP THESAURUS:

* 0182 1666 T Macaca mulatta

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PROJECT NUMBER.....2 R01 DA06264-04 FY 94

RG/INTRAMURAL UNIT..SRCD

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RFORMING ORGANIZATION: EMORY UNIVERSITY

ITLE CHRONIC COCAINE EXPOSURE DURING GESTATION

BSTRACT:

Clinical reports have indicated that a pregnant woman and her fetus may be subjected to a host of potential problems due to cocaine use. Few studies have examined under controlled laboratory conditions the consequences of cocaine use during pregnancy and, therefore, the effects of cocaine on maternal, fetal and neonatal development and behavior have been poorly documented. This proposal represents plans to continue studies in rhesus monkeys to assess the postnatal consequences of chronic cocaine exposure during gestation. Behavioral, pharmacological and physiological experiments will be performed in young rhesus monkeys previously exposed to cocaine in utero in order to characterize the consequences of prenatal exposure. In addition to defining physical growth characteristics (e.g. body weight, crown-rump length, biparietal diameter, etc.) for cocaine-exposed and pair-fed control subjects, experiments will also be performed to assess the neurobehavioral competence of the monkeys and their responsiveness to cocaine. Three well-established behavioral protocols will be used (delayed matching-to-sample, repeated acquisition and drug self-administration) to test for differences in complex operant performance between drug-exposed and pair-fed control subjects as a function of the gestational age of prenatal exposure and the duration of prenatal exposure. A second set of experiments will be conducted to determine the pharmacokinetic profile of cocaine metabolism in young monkeys previously exposed prenatally to cocaine using HPLC analysis. Finally, prenatally-exposed monkeys will be tested for the effects of cocaine on respiratory function using an established head-plethysmographic technique. For most of these experiments, a full range of doses of cocaine will be studied alone and in combination with other drugs having selective agonist and antagonist actions at various receptors (e.g. dopaminergic, serotonergic, adrenergic, etc.) to determine differences in drug sensitivity among the young monkeys. The prenatally-exposed monkeys will also be monitored and tested for onset of puberty as a measure of the impact of prenatal exposure on the development, maturation and function of the endocrine system (i.e. hypothalamic-pituitary-gonadal axis) controlling reproductive competence. The research will contribute to knowledge of the effects of exposure to cocaine in utero and to the characterization of the rhesus monkey as a model for studying the risks of cocaine use during pregnancy in humans.

ISP INDEXING TERMS FROM CRISP THESAURUS:

0182 1666 T Macaca mulatta

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ROJECT NUMBER.....5 K02 MH01062-02 FY 94

G/INTRAMURAL UNIT.,PYB

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RFORMING ORGANIZATION: EMORY UNIVERSITY
ILE BEHAVIORAL DEVELOPMENT--PRENATAL HORMONAL INFLUENCES

STRACT:

This is a request for an ADAMHA RSDA Level II award. The research investigates gender development in group-living male and female rhesus monkeys exposed to atypical levels of prenatal androgen. These studies will elucidate the role that prenatal androgens play in regulating genital and psychological differentiation in a primate, under social conditions that produce a full range of gender-related social and sexual behavior. By employing short-term treatments during early and late gestation the project seeks to separate the effects of prenatal androgen on masculinization of the genitalia from its effects upon masculinization and defeminization of behavior. These studies are relevant to issues of human gender differentiations and discordances between genital sex and gender role behavior, a clinical problem that affects a substantial number of humans. To achieve these goals, time-mated pregnant rhesus females, living in large age-graded heterosexual groups, will have the sex of their fetus identified using sex chromatin staining. Mothers of female fetuses will be injected with testosterone enanthate (TE) or vehicle for 35 days starting on gestational day 40 or 110. Mothers of male fetuses will be injected with a Nal-Lys GnRH antagonist (Antide), Antide plus TE, or vehicle starting at the same times and for the same duration as the female treatments. Prenatal Antide will suppress testicular function creating males who are androgen deficient for a brief period early or late in gestation. The times selected represent periods during or after genital masculinization and when previous work has shown androgens to differentially affect the sexually dimorphic patterns of rough play and juvenile mounting. Experimental and control animals will be observed behaviorally from birth through the transition into adulthood using methodology that captures traditional sexually dimorphic patterns of behavior and additional patterns of social behavior that are only observable when infants can interact with all ages and sexes in an unrestricted manner. Endocrine and skeletal development will be tracked with systematic collection of serum samples to measure neonatal and peripubertal patterns of hormone secretion and morphometric measures of skeletal growth. Pituitary function will be challenged with exogenous GnRH at several times during development to assess the effects of early androgen exposure on the integrity of the hypothalamo-pituitary-gonadal axis. After the pubertal transition, male and female sexual behavior will be investigated in response to their endogenous hormones. If experimental females produce offspring, the relationship between early androgen

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ROJECT NUMBER.....5 K02 MH01062-02 (Continued)

exposure and maternal behavior will be investigated. These studies provide the first experimental manipulation of prenatal androgen in male primates and will substantially extend our understanding of the role androgen plays in gender differentiation in primates. RSDA support will free the PI from teaching and administrative duties and allow the development of new behavioral and diagnostic techniques for assessing the effects of prenatal androgen manipulations.

ISP INDEXING TERMS FROM CRISP THESAURUS:

* 0182 1666 T Macaca mulatta

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PROJECT NUMBER.....5 R01 NS17678-14 FY 94

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ERFORMING ORGANIZATION: EMORY UNIVERSITY

ITLE MOTOR AND COMPLEX FUNCTIONS OF BASAL GANGLIA AND CORTEX

BSTRACT:

The principal issues addressed in this proposal are: 1) whether motor processing within the basal ganglia-thalamocortical `motor circuit' is organized, at the neuronal level, in a predominantly serial or parallel fashion; and 2) whether there are systematic transformations, at successive stages of the circuit, in the neural representations of variables that have been implicated in different functional `levels' of motor processing. The proposed studies are designed to determine a) whether the same categories of information (i.e., the same motor variables) are proposed at different stages (cortical, striatal, pallidal, thalamic) of the `motor circuit'; b) whether there are systematic changes in the proportionate representation of a given motor variable by neurons at successive stages of the circuit; and c) whether there are systematic shifts, at successive stages of the circuit, in the regression slopes relating variable-specific changes in neuronal discharge rates to gradations in the represented variables. The Specific Aims for the project are as follows: [1] To determine whether, during the planning and execution of visually guided limb movements, multiple `levels' of motor processing are represented in parallel by neuronal activity within each of the precentral motor fields that contribute to the `motor circuit'. The activity of individual neurons in SMA, MC and APA will be recorded in monkeys performing tasks that require them to make reaching movements to position a cursor in two-dimensional space. The tasks involve both the preparation and execution `modes' of motor processing, and will also dissociate variables relevant to different `levels' of processing viz, target level variables, trajectory/kinematic variables, and dynamic/muscle-related variables. Data from the three areas will then be compared, based on results of both categorical and regression analyses. [2] To determine whether, during the planning and execution of visually guided limb movements, multiple `levels' of motor processing are represented in parallel by neuronal activity at the striatal stage of the `motor circuit'. Task-related single unit activity will be sampled from the arm region of the putamen in monkeys performing the same tasks employed in Specific Aim 1. After being subjected to the same set of analyses, the data will be compared with those obtained in Specific Aim 1. [3] To determine whether, during the planning and execution of visually guided limb movements, multiple `levels' of motor processing are represented in parallel by neuronal activity at the pallidal stage of the `motor circuit'. Task-related single unit activity will be sampled from the arm region of GPi in monkeys performing the same tasks used in Specific Aims 1 and 2.

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OJECT NUMBER.....2 R01 NS20855-11A1
FY 94
INTRAMURAL UNIT..ORTH

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FORMING ORGANIZATION: EMORY UNIVERSITY

E SPINAL MECHANISMS REGULATING MUSCLE AND LIMB MECHANICS

TRACT:

The goal of this research program is to understand how the circuits of the spinal cord contribute to coordinated actions of the musculoskeletal system. One way to make sense of spinal circuitry is to evaluate the component reflexes in terms of the mechanical actions, lengths and forces of the associated muscles. For example, the functions of reciprocal inhibition can best be appreciated by knowing that the linked muscles are mutually antagonistic and that the strength of the inhibition depends on muscle length. In general, proprioceptive feedback derives from a number of different receptors and converges and diverges extensively in the spinal cord. A major reason why the functions of these pathways are poorly understood is that information on the three-dimensional actions of muscles and neuromuscular compartments is lacking. Each muscle or compartment acts in a unique direction across one or more joints, and each is associated with a unique pattern of intermuscular reflexes.

The purpose of this research is to establish, for the cat hindlimb, how the organization of spinal reflexes corresponds to the mechanical actions and natural activity patterns of the associated muscles. Mechanical actions will be determined by measuring the torque exerted by a number of muscles about the ankle, knee and hip. Transmission of forces through complex or distributed tendons will be measured by implanted transducers. Reflex linkages between muscles will be investigated in decerebrate cats by applying selective length inputs to one muscle or compartment and recording the force response in the other at different forces and lengths and states of activation. The resulting torque profiles and reflex maps, along with dynamic properties of the limb, will provide basic data for the formulation of models which can explain how the action of spinal circuits contributes to coordinated limb movement and why reflex organization is modified for certain motor tasks, such as locomotion and turning.

The global picture of reflex organization resulting from these studies can potentially guide the formulation of analytical models of information processing in the spinal cord as well as provide a basis for new approaches to the rehabilitation of injury to the motor system. The study of force transmission in tendons may suggest improvements in tendon transfer surgery.

ISP INDEXING TERMS FROM CRISP THESAURUS:

0182 1435 T cat

INDICATES TERM USED FOR SEARCH
T = PRIMARY, SECONDARY, TERTIARY EMPHASIS RESPECTIVELY
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PROJECT NUMBER.....7 R01 NS21023-10

RG/INTRAMURAL UNIT..NEUA

FY 94

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ERFORMING ORGANIZATION: EMORY UNIVERSITY
ITLE FUNCTION AND MODIFIABILITY OF SINGLE MOTONEURON POOLS

BSTRACT:

The long term objective of this study is to identify and characterize different mechanisms used by the nervous system to recruit and modulate the activity of motoneurons during different behaviors. The specific aims are to contrast the recruitment schemes used to control a single muscle when it is excited by diverse sources, and to determine possible functional correlates of those schemes. The results of this work will help to resolve debate about the generality and utility of different recruitment schemes, and may lead to new understanding of the bases of movement disorders, such as spasticity, that involve abnormalities of recruitment or sensory processing.

Using decerebrate cats, the axons of motoneurons supplying either the medial gastrocnemius or biceps femoris muscle will be penetrated in ventral root filaments two at a time. After the physiological makeup of each unit is determined, the sequence of recruitment of the two units will be evaluated during muscle stretch, natural and electrical activation of cutaneous afferents, and electrical stimulation of the mesencephalic locomotor region of the brainstem. Based on work from this and other laboratories, these stimulation regimes are designed to reveal purported shifts in recruitment strategy. Stimuli will also be delivered in combination, in order to test predictions that the firing of certain types of motoneurons may be inhibited in some conditions. Two principal hypotheses will be tested: 1) The activation of motoneurons within a single motor nucleus changes in certain motor tasks. 2) The organization of motor units in different tasks reflects different functional needs.

RISP INDEXING TERMS FROM CRISP THESAURUS:

* 0182 1435 T cat

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