for NE and 5-HT elicit no more than a partial substitution for cocaine, low doses of desipramine and fluoxetine, as well as GBR 12909, enhance the cue produced by low doses of cocaine, a finding which may have important implications in the pharmacotherapy of cocaine abusers with such compounds. Additionally, both D_1 and D_2 DA receptors appear to be critical in the stimulus effects of cocaine. These data support a primary role for DA, but suggest that multiple receptors, and possibly other neural mediators as well, are integral in the discriminative state induced by cocaine.

CHANGES IN NEUROTRANSMITTER TURNOVER ASSOCIATED WITH COCAINE REINFORCEMENT. Steven I. Dworkin. Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC.

Although the major involvement of central dopaminergic pathways in the neurobiologic mechanisms of reinforcement is undeniable, other neurotransmitter systems are also of considerable importance. The drug self-administration paradigm was coupled with an assessment of neurotransmitter turnover in discrete brain regions of the rat in order to determine the neurotransmitter systems involved in the reinforcing effects of cocaine. Members of littermate triads received intravenous presentations of either response-dependent cocaine (self-administered or SA), yoked response-independent cocaine (noncontingent or YC) or yoked saline infusions (YS). After at least 30 stable days of cocaine self-administration by the SA subject, access to cocaine was removed for a 24-hour period. The rats were then pulse labelled with radioactive precursors for the biogenic monoamine and amino acid neurotransmitters and sacrificed after either a 60- or 90-minute pulse period. It was reasoned that any differences observed between the YC and YS groups would be an indication of the pharmacologic actions of cocaine, whereas the differences found between the SA and YC groups would indicate the involvement of neurotransmitter systems in rats exposed to the reinforcing effects of the drug. The response-independent administration of cocaine resulted in 25 significant changes in a total of 15 brain regions. The self-administration of the drug was associated with 30 changes in 17 regions. Both increases and decreases in the turnover of dopamine, serotonin, norepinephrine, GABA, glutamate, glutamine and aspartate were observed. These data indicate that there are significant neurochemical differences associated with the self-administration of cocaine compared to the response-independent administration of the same amount of the drug. Moreover, the neurochemical systems associated with the reinforcing effects of cocaine involve several neurotransmitter systems and pathways in addition to the dopamine system.

RELATIONSHIP OF PSYCHOSTIMULANT MONOAMINERGIC AND BEHAVIORAL RESPONSE PROFILES. Ronald Kuczenski. University of California, San Diego, La Jolla, CA.

The recent application of microdialysis methodology has provided the opportunity to more directly evaluate neuronal-system/behavior relationships, and data obtained using this methodology confirm the profound effects of amphetamine, cocaine, and like stimulants on dopamine systems. However, our concomitant behavior/biochemistry characterizations reveal a clear dissociation between the expression of specific stimulant-induced behaviors and the quantitative aspects of the caudate and accumbens dopaminergic response. Thus we hypothesize that these behaviors involve the interaction of dopamine with other transmitters, including serotonin and norepinephrine, and the present results will extend our characterization of the effects of amphetamine and other stimulants with differing mechanisms of action on regional dopamine, serotonin and norepinephrine.

PAPER SESSION

Imaging Technologies to Study Drugs and Behavior

Chair: *John T. Metz,* University of Chicago, Chicago, IL.

METABOLIC MAPPING OF THE EFFECTS OF ABUSED DRUGS IN ANIMALS. Linda J. Porrino. Bowman Gray School of Medicine, Winston-Salem, NC.

The physiological and behavioral effects of the administration of drugs are the product of multiple processes at a number of anatomical sites. Therefore, to determine the neural substrates of these effects, it is necessary to identify neural events in circuits and pathways throughout the brain with methods capable of surveying the entire brain simultaneously such as the 2-[^{14}C]deoxyglucose (2DG) method. Although the 2DG method may appear to be essentially an anatomical technique on the basis of autoradiographic images that are produced, it is in fact a biochemical method which measures a biological process, glucose utilization or the rate at which energy is consumed in neuroanatomically defined regions in the central nervous system of conscious behaving animals. It is possible, therefore, through the measurement of changes in rates of glucose utilization, to identify brain regions in which functional activity is altered during various experimental manipulations. The advantages and disadvantages of metabolic mapping will be addressed. In addition, there will be a discussion of how the method has been applied to show how the substrates of the effects of cocaine are dependent on the dose, route of administration, behavioral paradigm, as well as the behavioral history of the animal.

METHODOLOGICAL ISSUES IN PET STUDIES OF DRUGS OF ABUSE. Harriet de Wit, John T. Metz and Malcolm Cooper. University of Chicago, Chicago, IL.

Positron emission tomography (PET) represents a unique experimental technique with which to study the effects of drugs on regional cerebral metabolic activity in humans. Several PET studies with abused drugs have now been conducted, using 18F-fluorodeoxyglucose as the tracer. While these studies provide valuable data, they also raise a number of methodological issues which must be taken into consideration when applying the techniques and interpreting the data. The sensitivity of PET is somewhat limited by the relatively poor spatial and temporal resolution of current systems. However, methods are available to overcome these problems, such as the use of oxygen labelled water blood flow studies to provide better temporal resolution, and image-correlation techniques using magnetic resonance imaging to improve the spatial localization. Another methodological consideration is whether the highly technological setting of the PET studies interferes with potential euphorigenic drug effects. This question has been addressed by obtaining data on the mood-altering effects of the drugs in a more naturalistic setting for comparison. Another issue in PET studies is the role of subjects' cognitive activity or behavioral state during the sessions: Subjects in some studies are required to perform a behavioral task to limit variability in their cognitive activity during the

scans. However, it is not clear whether or how this task affects the subjects' metabolic or mood responses to the drug. Finally, both the mood-altering and the metabolic effects may depend critically on the dose of drug tested and on the characteristics of the subjects. It is important that a wide range of doses be tested, and that subject characteristics be examined carefully. These issues will be discussed with respect to selected data from our laboratory.

RECEPTOR LIGAND STUDIES USING PET. Nora Volkow, David Schlyer, Joanna Fowler, Gene Wong, Robert MacGregor and Alfred Wolf. Brookhaven National Laboratory, Upton, NY.

One of the unique advantages which PET has over other types of imaging modalities is the ability to assess receptor dynamics in vivo. By using specific radiolabelled compounds, it is possible to quantitate the availability of particular receptor systems and to define the interactions with other receptor systems. This ability makes PET extremely valuable in studying the mode of action in drugs of abuse. The effect on the receptor systems after chronic use of cocaine and other drugs of abuse can be evaluated and the effects of detoxification on the receptor systems over a period of time can also be determined. In the current studies, the effect of cocaine abuse and detoxification on the dopamine receptor system in terms of the presynaptic dopamine transporter, the postsynaptic dopamine D-2 receptor and the glucose metabolism of the regions involved with the dopamine receptors has been assessed. The studies were carried out in patients soon after detoxification and again after several months to determine the changes in the receptor systems over the period of detoxification. It has been found that the receptor systems and the associated glucose metabolism undergo variations which may be linked to the psychiatric symptoms. These observations may lead to a better understanding of the processes involved at the receptor level in detoxification. An understanding of the mechanism of detoxification could provide insights into more effective therapies.

TOPOGRAPHIC MAPPING AND SOURCE LOCALIZATION OF EEG AND ERP DIPOLES. Scott E. Lukas, Elena Kouri, Michelle Fortin and Leslie Amass. McLean Hospital/Harvard Medical School, Belmont, MA.

Drug-induced intoxication and changes in mood states are associated with episodic alterations in neurophysiological activity that are most easily quantified using topographic mapping techniques. Such techniques permit the simultaneous viewing of electrical activity from all electrode sites on the scalp. Previous studies have shown that ethanol-, marihuana-, morphine-, amphetamine-, pentobarbital- and cocaine-induced states of euphoria are associated with increases in EEG alpha activity, predominantly over occipital and parietal areas. Auditory P300 evoked response potentials (ERPs) provide information about an individual's ability to selectively attend to novel stimuli. Source localization of alpha activity or ERPs can provide new and important information about the similarities and differences among the neurophysiological activities produced by these various drugs. Using mathematical algorithms, the origin of the P300 ERP was calculated to be in the hippocampal formation while the alpha rhythm appeared to originate in the thalamus. Drug-induced states of intoxication disrupt the apparent source of these waves and parallel subjects' inability to selectively attend to novel stimuli. When combined with magnetic resonance imaging techniques, dipole localization can help locate a specific neurophysiological response with a time resolution of only a few milliseconds. (Supported by grants DA03994, DA04059 and DA00115 from the National Institute on Drug Abuse.)

FUNCTIONAL MAGNETIC RESONANCE IMAGING OF COCAINE-TREATED RHESUS MONKEYS. Thomas Aigner and Joseph Frank. NIMH, Bethesda, MD.

Rapid magnetic resonance imaging (MRI) using paramagnetic contrast agents has been shown to be a reliable method for detecting small changes in cerebral circulation. Chronic abuse of cocaine may lead to changes in blood flow as well as in other neuropathological abnormalities, such as subarachnoid hemorrhage and demyelination of white matter. To examine the feasibility of using MRI to document these changes in experimental animals, we compared two monkeys with an extensive history of cocaine self-administration with two normal controls. Scanning was performed in a GE Signa 1.5 T scanner with a 5″ receive-only surface coil. In procedure I, we used a rapid (MR) scanning procedure in combination with dysprosium-DTPA-BMA to examine possible differences in cerebral perfusion in the two groups. This was done during two different scanning sessions, once before and once after a bolus injection of 0.3 mg/kg of cocaine. In procedure II, we used standard MRI techniques to examine grey-white matter differences using scanning parameters that provided a level of detail not previously possible with earlier techniques.

PAPER SESSION

ADHD and Methylphenidate: Dosage Effects on Classroom Functioning and Internalizing Symptomatology

Chair: *Mark D. Rapport*, University of Hawaii, Honolulu, HI.

ATTENTION DEFICIT DISORDER: METHYLPHENIDATE DOSE-RESPONSE EFFECTS ON CLASSROOM BEHAVIOR. Mark D. Rapport. University of Hawaii, Honolulu, HI.

This multi-year investigation was designed to examine the effects of methylphenidate (MPH) at four doses (5, 10, 15, 20 mg) on the attention, academic efficiency, and teacher-rated behavior of 75 children with Attention Deficit Disorder/Hyperactivity (using direct observations), and to compare these effects to functioning under baseline and placebo conditions. MPH significantly improved all areas of classroom functioning in a linear, dose-related fashion. Intermediate and individual level analyses, however, indicated a wide range of optimal response across subjects. Implications for the construction of individual dose-response potency profiles and the ability to predict behavioral response are discussed.

PSYCHOSTIMULANT RESPONSE OF CHILDREN WITH ADHD: INTERACTION WITH INTERNALIZING SYMPTOMS. Russell A. Barkley and George J. DuPaul. University of Massachusetts Medical Center, Worcester, MA.

This investigation was designed to assess whether methylphenidate (MPH) effects on ADHD symptoms differ between children who also display internalizing disturbance relative to those who do not. Significant interactions between MPH Dose and Internalizing Groups were found for only 5 of 28 assessment measures collected across home, school, and clinic settings. The three Internalizing groups evinced similar significant improvements in behavior associated with the two highest MPH