

PSYCHOPHARMACOLOGY NEWSLETTER

(Division 28 - The American Psychological Association)

Issue No. 2, April 1983

D. R. Cherek, Editor

BEHAVIORAL PHARMACOLOGY AT THE ADDICTION RESEARCH CENTER PRECLINICAL LABORATORY

Preclinical behavioral pharmacology at the Addiction Research Center is conducted primarily in the laboratories of Steve Goldberg, Harlan Shannon and Marc Risner. The first laboratory is located on the University of Maryland campus in Baltimore; the latter two are in Lexington, Kentucky. Hopefully, the preclinical and clinical research programs of the ARC will be reunited in mid-1984 on the grounds of Baltimore City Hospital.

Steve Goldberg is currently studying the behavioral pharmacology of nicotine and caffeine in squirrel monkeys using several different schedules of reinforcement. The ability of caffeine, nicotine and several analogs to function as reinforcers and maintain i.v. self-administration behavior under fixed-ratio and second-order schedules is being systematically studied over a range of doses. Low doses of nicotine maintain moderate to high rates of responding. The effects of pre-session treatment with i.m. doses of nicotine, caffeine, mecamylamine and other drugs on self-administration behavior is being systematically explored. Preliminary experiments indicate that pre-session treatment with caffeine increases rates of responding under fixed-ratio schedules of nicotine self-administration. In other studies, the effects of nicotine and caffeine are being studied in squirrel monkeys and rats responding under multiple fixed-interval fixed-ratio schedules of food presentation and in squirrel monkeys responding under fixed-interval schedules of electric shock presentation. When caffeine and nicotine were given in combination, they produced much larger increases in fixed-interval responding than the maximal effects seen when either drug was given alone. Thus, nicotine and caffeine have pronounced effects on behavior under various experimental conditions and these effects may be markedly enhanced when the drugs are given in combination.

Jonathan Katz joined the laboratory of Steve Goldberg in 1983 as a staff-fellow and is studying drug-induced changes in stimulus control

of responding under different schedules of reinforcement. Initial studies conducted in pigeons have indicated that under fixed-interval schedules stimulus control of responding is not affected by drugs such as psychomotor stimulants, sedatives and antipsychotics at low to intermediate doses. These doses, however are effective in modifying temporal patterns and rates of responding. Stimulus control is only affected under fixed-interval schedules at high doses that virtually eliminate responding. Under fixed-ratio schedules, however, pentobarbital affects stimulus control at lower doses that do not affect stimulus control under the fixed-interval schedule and do not dramatically alter response rates. Thus, the schedule of reinforcement can be a critical determinant of whether a drug modifies stimulus control of responding.

Research in Harlan Shannon's laboratory is concerned with two primary topics: (1) behavioral pharmacology of phencyclidine-like drugs and sedative/hypnotic/anesthetic agonists and antagonists; and (2) reinforcing properties of endogenous noncatecholic phenylethylamines. The behavioral pharmacology of phencyclidine-like drugs, including arylcyclohexylamines and certain opioids, has been evaluated using drug discrimination procedures in rodents. The results of these studies have suggested that phencyclidine and opioids such as cyclazocine are sigma receptor agonists. Benzodiazepines and benzodiazepine antagonists also are being evaluated using drug discrimination procedures. The results of these studies demonstrate that benzodiazepine and barbiturates produce very similar discriminative stimuli, but only the effects of benzodiazepines are blocked by benzodiazepine antagonists. The behavioral effects of benzodiazepines on schedule-controlled responding in rodents also can be antagonized by benzodiazepine antagonists. However, benzodiazepine antagonists have effects on schedule-controlled responding in their own right, although these effects differ among the antagonists.

Several noncatecholic phenylethylamines structurally related to amphetamine occur

endogenously in mammalian brain. The effectiveness of these compounds to function as reinforcers in dogs is being evaluated using simple and second-order schedules of drug injection. Phenyethylamine and its N-methyl homolog but not its beta-hydroxy homolog, maintain rates and temporal patterns of responding similar to those maintained by cocaine. These results suggest that phenylethylamine could play a physiological role in the reinforcement process. Currently, work is in progress to determine (a) if drugs therapeutically useful in depression can potentiate phenylethylamine and (b) if drugs therapeutically useful in psychoses can antagonize phenylethylamine.

Finally, research in Marc Risner's laboratory is directed toward (1) assessing the reinforcing properties of drugs using intravenous self-administration procedures, and (2) evaluating the behavioral effects of drugs using a food-maintained, schedule-controlled baseline. Experiments relevant to the first objective are conducted in beagle dogs, a species in which drugs from several pharmacologic categories have been studied over the past several years. In general, the results from many of these previous experiments have shown that response-contingent drug injections maintain behavior that is systematically related to dose and the schedule under which the injections are delivered. Pre-session treatment with selected antagonists has been shown to modify drug-taking behavior; psychostimulant self-administration is especially altered by dopamine antagonists, suggesting that dopamine activation is important for these drugs to function as reinforcers. In one recent study, the reinforcing properties of several compounds structurally related to phencyclidine were assessed. Results from this study suggest that many of these compounds have an abuse potential like that of PCP. Another recent study, done in collaboration with Steve Goldberg, directly compared cocaine and nicotine self-administration behavior. Although both drugs maintained dose-related responding under a fixed-ratio schedule, cocaine maintained considerably higher fixed-ratio values ("break-points") than did nicotine when tested under a progressive-ratio schedule of drug delivery.

The behavioral pharmacology of several sedative-hypnotics, psychostimulants, and related compounds is being evaluated using a food-maintained, schedule-controlled baseline in beagle dogs. In one current experiment, both acutely and chronically administered barbiturates and benzodiazepines produced systematic changes in the

rate and pattern of responding; only some of the changes produced by benzodiazepines could be altered by the co-administration of benzodiazepine antagonists. In another current experiment, the effects of cocaine and nicotine are being compared with some of their metabolites. Although all of the drugs alter schedule-controlled responding, the profile of behavioral effects is not similar across drugs. Studies to evaluate the stereoisomers of several nicotine-related compounds on multiple schedules of reinforcement are in progress.

Marc Risner

COUNCIL REPRESENTATIVE'S REPORT

Council met in Washington, DC on January 21-23, 1983. Almost all the meeting time was spent in consideration of the possible purchase of Psychology Today. Council voted 75 to 27 to authorize the board to negotiate the purchase. My vote was among the 27 "nays". While I do feel that presenting psychology in a positive, educational manner to the general public is a worthwhile endeavor, I felt that the purchase of Psychology Today at close to \$4 million and the commitment to making it a successful publication along the model of the Science 80 series represented too large a portion of our resources (financial and human) in an area that I see as tangential to the main issues of a professional organization. As you know from the March Monitor, the purchase has been completed and the vote at the Board of Director's level was much closer than the Council vote.

At the August business meeting, Bob Schuster and I were asked to monitor proposed federal legislation on the use of animals in experimentation. Then, in September, we were asked to help formulate APA's response to the demonstrations planned for April at four primate centers (New England, Yerkes, Wisconsin and Davis). In doing this, we have worked on two projects with the Board of Scientific Affairs and its Committee on Animals in Research and Experimentation. The first project was to assemble a mailing which you should have received by now. This mailing contains: information on the activities of the group (Mobilization for Animals) planning the demonstrations at the primate centers; an outline of the legislation

proposed on scientific work involving animals in the 97th and 98th congresses; a fact sheet on the bill Senator Dole has introduced, and the rider that Representative Walgren placed on the House NIH appropriation bill, both of which deal with animal experimentation; a summary of outstanding applications of scientific information gained in animal experiments and cogent reasons for supporting this type of scientific work. This information was mailed to members of Divisions 6, 25 and 28 (over 3000 persons), and the chairs of graduate departments of psychology. Persons knowledgeable about experimentation involving animals were encouraged to present a balanced, reasonable argument for work in this area to their local media around the time of the demonstrations planned for April 24. In addition, division members running animal laboratories were asked to invite their representatives to visit their labs and see their work when the representative is in his/her home district. In addition to the mailing, we tried to arrange national publicity portraying scientific work with animals in a positive light. Various persons at APA are attempting to gain editorial support from leading newspapers and national network news interviews with spokespersons who know these issues.

As members of Division 28, each of you should take time to consider the issues of the proposed animal legislation, contact your congresspersons and senators to give them the benefit of your experience and expertise, and, in addition, invite your representatives to visit your lab and become familiar with your work. If you need additional information, or want to update your information, you may call Jeff Stryker (202-833-7596) in APA's Scientific Affairs Office. Jeff is responsible for following this legislation.

M.M. Kilbey

ANIMAL WELFARE LEGISLATION

In March, Senator Robert Dole introduced the "Improved Standards for Laboratory Animals Act", stating that this bill would resolve differences between the research and animal welfare groups. This bill amends the Animal Welfare Act and emphasizes the care and treatment of research animals. The bill will be considered by the Committee on Agriculture. Cosponsors are Senators

John Melcher (D-MO), Jennings Randolph (D-W.VA), John Heinz (R-PA), Charles Percy (R-IL) and Ted Stevens (R-AK).

The bill stipulates an upgrading in the standards for animal care and treatment and enlarges the requirements to include appropriate pre- and post-surgical medical and nursing care and adequate exercise. The bill also would make it easier to promulgate regulations concerning the performance of research. Research facilities will also be required to establish institutional animal study committees to determine the appropriateness of care and treatment of animals. These institutional animal study committees must include at least one veterinarian and one individual not affiliated with the institution who would represent the community. The committee would be required to make inspections twice a year to: (1) evaluate research methods to ensure that animal pain and distress are minimized, (2) to ensure compliance with established standards of care and treatment. The committee would notify the institution of any unacceptable conditions and if not corrected, they would notify federal authorities.

DEVELOPMENT OF CLINICAL ABUSE LIABILITY ASSESSMENT PROCEDURES AT THE BEHAVIORAL PHARMACOLOGY RESEARCH UNIT

For the past 15 years, the Behavioral Pharmacology Research Unit at Baltimore City Hospitals has been conducting studies concerning the self-administration and effects of drugs of abuse in human volunteers. Recently, attention has been focused on the development of clinical testing procedures for the assessment of drug abuse liability in humans. The present report will provide a descriptive overview of this developing research area with illustrative results from individual projects.

In designing clinical research programs, we have attempted to assess four aspects of abuse liability: (1) the extent of maintenance of drug self-administration behavior; (2) the profile of acute subjective and physiological effects; (3) alterations produced in cognitive/psychomotor performance; and (4) alterations produced in global clinical mood and behavior. These dimensions are intended to assess the two crucial

aspects of abuse liability--the likelihood of a compound's being self-administered, and the likelihood of its producing disruptive effects following its administration.

A wide variety of subject populations and clinical research settings have been used for conducting abuse liability assessments as well as a range of measures designed to evaluate behavioral, subjective and physiological variables. One general methodology which has proven valuable involves a series of forced exposure trials to various test doses or test compounds followed by a choice trial, in which the subject chooses which of the previously experienced test conditions she or he will receive. Forced exposure trials permit the evaluation of the profile and time-course of subjective and physiological effects in a manner similar to that traditionally used by the NIDA Addiction Research Center, while the choice trials provide an objective behavioral measure of the relative reinforcing efficacy of the test compounds.

Residential Laboratory. Within our residential Laboratory we have used this alternating forced-exposure/choice-trial procedure to compare diazepam and pentobarbital across a range of doses in experienced sedative abusers. We have reported that subjective liking data generally parallel behavioral choice data--with both active drugs being preferred over placebo, and with higher doses of pentobarbital being preferred over the range tested. Comparisons between the two active drugs, using intermediate doses producing similar magnitudes of overall sedative effect, showed a uniform preference for pentobarbital over diazepam. More recent data from our residential laboratory indicate differential effects of pentobarbital and diazepam upon global clinical mood and behavior; disturbances in mood and behavior were seen following diazepam (50-100 mg/day) which did not occur following pentobarbital (200-400 mg/day).

Intravenous Laboratory. In this setting, subjects participate in sessions of several hours duration several times per week while intensive psychophysiological and subjective data are collected to evaluate the profile and time course of effects of acutely administered drugs. We have described acute physiological and subjective effects of the daily methadone dose which can be measured in methadone maintenance patients. We have also presented data describing the profile and time course of the subjective and physiological effects of a range of intravenous

hydromorphone doses in experienced opioid abusers and describing the attenuation of acute opioid drug effects in methadone maintenance (i.e., opioid tolerant) patients.

Day-Laboratory. We have developed a day-laboratory procedure for evaluating drugs in "recreational" users and in general non-abuser community volunteers who participate in within-subject design studies while spending several hours per day in the laboratory on several days each week. During sessions, behavioral and subjective measures are used to evaluate the intensity and time course of drug effects. Studies of this type have shown that in this subject population, both subjective liking measures and psychomotor/cognitive performance measures were able to sensitively differentiate among various benzodiazepine drugs, including diazepam, lorazepam and clorazepate which were administered in modest oral doses. Further, it was possible in this setting to track the time course of these drug effects and to assess their interaction with ethanol.

Weight Control Clinic. A final setting in which we have conducted comparative clinical evaluations of drugs of potential abuse is a behavioral pharmacological weight control clinic. Here it is possible to evaluate the effects and self-administration of drugs among non-abuser volunteer patients who are exposed to the test drugs for therapeutic reasons. A drug choice procedure has been used in this setting for comparative evaluations of the various phenylethylamine CNS stimulant-anorectics which are marketed for weight control. Results have shown d-amphetamine (5-10 mg tid) preferred over fenfluramine (20-40 mg tid) and diethylpropion (75 mg controlled release) preferred over chlorphentermine (65 mg). The behavioral choice procedure has proven its value by detecting differences between compounds which were not detected by comparing the effects of forced exposure.

In summary, we have found that a variety of settings and subject populations appear adaptable to providing orderly clinical data concerning the relative reinforcing efficacy and abuse liability of drugs. Specifically, we have found that such studies can be conducted in non-residential settings and with volunteer participants without chronic drug abuse histories. Many of the general methods developed by the NIDA-ARC for conducting these evaluations with incarcerated postaddicts have proven adaptable to these other settings and other populations--especially the general approach of examining the profile and time course of the

physiological and subjective drug effects. We have found that there are a variety of other self-report measures which appear to provide sensitive indices of relative drug effects--at times even more sensitively than the ARCI scales. We have emphasized the value of behavioral measures in these procedures. Behavioral choice measures of drug preference would appear to provide the most straightforward and direct measure of the criterion we are trying to predict in abuse liability testing--the relative efficacy of compounds in sustaining self-administration. Finally, behavioral measures of drug effects on skill performance and on global clinical assessments of mood and behavior provide useful complementary data concerning the relative risks which might ensue consequent to the use or abuse of these compounds.

M. Stitzer

* * *

NEW ORGANIZATION

Recently, a special interest group has been organized within the Association for Behavioral Analysis (ABA) by individuals interested in human operant research. The group will promote the experimental analysis of human behavior in fostering communication among researchers interested in this area. Alan Baron, W.F. Buskist, Jim Johnston and Peter Harzem have developed guidelines and objectives for the organization. The group will hold a meeting at the Annual ABA Convention and publish a newsletter. The newsletter will publish annotated bibliographies of relevant articles from a variety of sources, convention and conference notices, course outlines and related materials, and miscellaneous classified ads. Individuals interested in joining the group are asked to pay a five-dollar membership fee which will include a subscription to the newsletter. Along with the check (made payable to **The Human Operant Behavior Special Interest Group**), prospective members are asked to include a 3x5 card containing their name, office address, phone number, and topic areas of interest within the experimental analysis of behavior. Checks and information card should be sent to:

W. F. Buskist, Ph.D.
Department of Psychology
Auburn University
Auburn University, AL 36849

ANNOUNCEMENT FROM APA PUBLIC INFORMATION OFFICE

"Written to any good newspapers or magazines lately? If so, the APA Public Information Office would like your help. The office regularly uses a national clipping service to monitor the trends in news coverage about psychology every month. But while this service covers a wide variety of national and local newspapers and magazines, as well as many newsletters and other periodicals, only rarely does it pick-up letters-to-the-editor by local psychologists concerned about a particular issue.

"Sending APA a copy of your letter is an important and easy way to alert the Public Information Office to newspaper and magazine stories (or radio and TV news items) that were notable enough to inspire you to write. Your letter can help APA to better track the issue and to adjust coverage or handling of that issue accordingly. A copy of your correspondence also will help in coordinating psychology's local and national media relations efforts.

Please send a copy of your letters-to-the-editor to:

APA Public Information Office
1200 Seventeenth Street, NW
Washington, DC 20036."

* * *

**1983 APA CONVENTION
INFORMAL PAPER SESSION**

Individuals wishing to present informal papers of approximately 10 to 15 minutes at the Informal Paper Session should contact:

**Don Cherek
(318)-674-6040
Department of Psychiatry
Louisiana State University
School of Medicine in Shreveport**

* * *

1983 ABA MEETING

The Association for Behavior Analysis will hold its Ninth Annual Meeting at the Hyatt-Regency Hotel in Milwaukee, Wisconsin, May 26-29. Information may be obtained by writing:

**Department of Psychology
Western Michigan University
Kalamazoo, Michigan 49008.**

ADAMHA REAUTHORIZATION HEADED FOR SENATE FLOOR:
Legislation to reauthorize alcohol and drug abuse research is now headed for the Senate floor, after being reported out of the Labor and Human Resources Committee without amendments on March 21. The bill, S. 126, is a compromise based on the House and Senate proposals from the 97th Congress that would renew authority for research on drug abuse at \$56.2 million for FY 1984 and for research on alcoholism and alcohol abuse at \$45.8 million. These ceilings would allow for a 16 percent and a 27 percent increase in funding respectively. The bill would also consolidate all the Alcohol Drug Abuse and Mental Health Administration (ADAMHA) authorities under a new Title V of the Public Health Service Act; mandate creation of an associate administrator for prevention; require establishment of procedures for responding to allegations of fraud and abuse; and address peer review of contracts and intramural research. (APMC President's Weekly Activities Report No. 83-13, March 31, 1983).

Members wishing to submit information or articles for inclusion in future Division 28 Newsletters, should send them to:

**D. R. Cherek
Department of Psychiatry
LSU Medical Center
P.O. Box 33932
Shreveport, LA 71130**