



PRESIDENT

ELLEN A. WALKER, PH.D.

Department of Pharmaceutical Sciences
School of Pharmacy
Temple University
3307 North Broad Street
Philadelphia, PA 19140 USA
(215) 707-6770
(215) 707-3678 (FAX)
E-mail: ellen.walker@temple.edu

PAST-PRESIDENT

MICHAEL SWEDBERG, PH.D.

Astra-Zeneca Research & Development
General Pharmacology
Forskargatan 20
S-151 85 Södertäljel Sweden
46 8553 289 63
46 8553 289 05 (FAX)
E-mail: michael.swedberg@astrazeneca.com

SECRETARY/TREASURER

JOSEPH H. PORTER, PH.D.

Department of Psychology
Virginia Commonwealth University
P.O. Box 842018
808 Franklin Street
Richmond, VA 23284-2018 USA
(804) 828-0096
(804) 828-2237 (FAX)
E-mail: jporter@vcu.edu

WEBMASTER

Adam J. Prus

Virginia Commonwealth University
prusaj@vcu.edu

SSPD News and Notes

Summer is almost here and it is time to update our membership on the current events of our organization. Feel free to forward this newsletter to any colleagues that might be interested in the stimulus properties of drugs. We are continuing to revise our email list for the newsletter and our mailing list for the website. Please forward any new addresses to Joe Porter. In addition, any items of interest that you have for future newsletters may be submitted to the Secretary/Treasurer Joe Porter (jporter@vcu.edu).

The first piece of news to report is that our annual meeting on November 10, 2003 in New Orleans on a **Monday** night was a wonderful success (see our meeting photos at the end of the newsletter). There were so many members and nonmembers in attendance that we needed more chairs! We enjoyed catching up with fellow SSPD members that we haven't seen in many years. In addition, we met some new students interested in joining SSPD. Joe Porter also collected dues from a number of renewing and new members. At the business meeting, the membership was clearly in favor of keeping Monday night for our annual SSPD meeting and keeping the electronic newsletter as our mode of communication. As new business, we discussed access to the drug discrimination database, Ian Stolerman's call for more drug discrimination articles to be published, and updating our email and mailing lists. We also decided to share email lists with the Behavioral Pharmacology Society since many of our members have common interests with this other society.

Our other news is that financially SSPD is back on track due to a number of recent initiatives, donations, and payment of membership dues. First of all, bringing our own laptop and projector to the conference drastically reduced the costs for the annual meeting. We would like to thank John Rosecrans for lending us the projector as well as the VCU crew for lugging the projector through the airports! Most importantly this year, AstraZeneca, Memory Pharmaceuticals, Pierre-Fabre, and Porsolt Associates made generous corporate contributions to SSPD. I would like to thank Charles France and Wouter Koek for assisting me by updating the mailing addresses for our corporate membership. We hope to see as many members and new members in San Diego this year as we did in New Orleans last year. Thanks to all members for their past and recent support.

Ellen Walker, President, SSPD

SSPD WEBSITE:

<http://www.sspd.org.uk/>

DRUG DISCRIMINATION DATABASE:

<http://www.dd-database.org/>

Upcoming SSPD Meeting:

Monday evening, 7:30-10 p.m.
October 25th at the Society for Neuroscience 34rd Annual Meeting, San Diego, CA (October 23 - 27, 2004)

<http://www.sfn.org>

Generous Gifts From Corporate Sponsors

SSPD gratefully acknowledges **AstraZeneca** (Michael Swedberg, Ph.D.), **Memory Pharmaceuticals** (James Barrett, Ph.D.), **Pierre-Fabre** (Francis Colpaert, Ph.D.), and **Porsolt and Partners Pharmacology** (Roger Porsolt, Ph.D.) for their generous financial support. These funds are critically needed to defray the costs of our meetings.

Call For Abstracts for 2004 SSPD Meeting

The 2004 SSPD meeting will be held on Monday, October 25 from 7:30-10 p.m. in San Diego, CA. If you or your students are interested in presenting a 15-20 min informal paper on your research on the stimulus properties of drugs, please submit an abstract to our Secretary/Treasurer Joe Porter (jporter@vcu.edu) by **September 1, 2004** (or sooner if available – abstracts will be accepted in order of receipt).

SSPD Elections

If anyone is interested or would like to nominate someone for SSPD Secretary/Treasurer please email Ellen Walker (ellen.walker@temple.edu) by July 1, 2004. Joe Porter has expressed his willingness to continue as Secretary/Treasurer for one more term.

2003 SSPD Meeting at SFN

Last year, as discussed above, SSPD hosted an evening paper session at the Society for Neurosciences in New Orleans, LA (see photo from the annual meeting at the end of the newsletter). Thanks to Joe Porter for getting our room and snacks organized. We would like to thank our five speakers, Steve Negus, Scott Philibin, Amy Goodwin, Randy James, and Ellen Walker, for presenting such interesting papers and initiating lively discussions on issues relating to the stimulus properties of drugs. The abstracts for the talks are listed below.

2003 Annual Meeting Abstracts

Effects of the selective kappa agonist U50,488 on cocaine discrimination and cocaine self-administration in rhesus monkeys: Do kappa agonists increase the abuse-related effects of cocaine?

S. Stevens Negus

McLean Hospital, Harvard Medical School

Kappa agonists have been reported to attenuate some neurochemical and behavioral effects of cocaine, and kappa agonists constitute one class of drugs being evaluated as potential pharmacotherapies for cocaine dependence. We have conducted an extensive series of studies to examine the effects of kappa agonists on the discriminative stimulus and reinforcing effects of cocaine in rhesus monkeys, and some of these studies will be reviewed. In drug discrimination studies, rhesus monkeys were trained to discriminate 0.4 mg/kg cocaine from saline. Under these conditions, acute pretreatment with the selective kappa agonist U50,488 produced highly variable but naloxone-reversible effects across monkeys, and leftward/upward shifts in the cocaine discrimination dose-effect curve were observed in most monkeys. In one set of drug self-administration studies, rhesus monkeys were trained to respond for cocaine injections or food pellets under a second-order schedule during alternating sessions of cocaine or food availability. The main dependent variables were the total numbers of cocaine injections and food pellets delivered each day. Chronic treatment with U50,488 produced a dose-dependent and nor-binaltorphimine-reversible decrease in cocaine self-administration. However, doses of U50,488 that decreased cocaine self-administration also usually decreased food-maintained responding and produced other effects such as emesis and sedation. Consequently, interpretation of kappa agonist effects on cocaine reinforcement was complicated by the non-selective effects of U50,488. A second set of drug self-administration studies was conducted using a schedule of concurrent choice between food and cocaine. The main dependent measure in this procedure was the allocation of behavior between the food and cocaine choices. This measure of cocaine choice provides a dependent measure that can vary independently from response rates in much the same way that drug-appropriate responding can vary independently from response rates in drug discrimination studies. In this choice study, increasing doses of cocaine produced a dose-dependent and monotonic increase in cocaine choice. Under these conditions, chronic treatment with the selective kappa agonist U50,488 decreased response rates but produced dose-dependent and nor-BNI-reversible *leftward* shifts in the cocaine choice dose-effect curve, suggesting that kappa agonist treatment *increased* the relative reinforcing effects of cocaine. Thus, results from both the cocaine vs. saline discrimination procedure and the cocaine vs. food choice procedure suggest that a kappa agonist may increase the abuse-related effects of cocaine. Choice procedures may provide a useful approach to the study of drug-induced reinforcing effects because these procedures provide a rate-independent measure of reinforcing efficacy.

An analysis of the utility of differential outcome procedures in drug discrimination research.

A.K. Goodwin* and L.E. Baker**

*Johns Hopkins University School of Medicine

**Western Michigan University

Differential outcome procedures correlate unique reinforcers with distinct discriminative stimuli. These procedures can decrease the amount of time needed for response acquisition and improve terminal accuracy of responding. Because the drug discrimination assay relies heavily upon initial response acquisition and continuing terminal accuracy, a procedure successful at shortening acquisition time and improving terminal accuracy would be beneficial. The present studies examined differences in acquisition of drug stimulus control between rats exposed to differential outcome procedures and rats exposed to the outcomes in a non-systematic way. The first experiment examined acquisition of control by MDMA, d-Amphetamine, and saline; the second examined stimulus control by MDMA, LSD, and saline. Neither initial acquisition nor terminal accuracy was influenced by differential outcomes in either experiment. Although the differential outcome effect has been demonstrated in many situations, it does not appear to be useful in the drug discrimination assay.

ACUTE TOLERANCE TO NICOTINE: INDIVIDUAL DIFFERENCES EVALUATED USING DRUG DISCRIMINATION AND ⁸⁶Rb⁺ EFFLUX.

Randy James

Department of Pharmaceutics, School of Pharmacy, Virginia Commonwealth University, Richmond, VA, 23298

The drug discrimination paradigm utilizes a discriminative stimulus (DS) allowing subjects to express the subjective effects of a drug. Male Sprague-Dawley rats were trained to discriminate nicotine (freebase) vs saline in two lever operant chambers. Two acute tolerance testing methods were used over a period of several months; (1) cumulative dosing using the drug discrimination training dose (0.4 mg/kg, s.c.) at 0, 90, 180 and 270 min. (2) challenge dose at time zero (0.8 mg/kg, s.c.) then drug discrimination training dose at 60, 90, 120, 150, 180 and 270 min. Rats in both methods were tested for 2 min. without reinforcement. Evaluation of the chronically treated rats (60 plus doses 0.4 mg/kg nicotine) in both methods showed rats exhibited different levels of acute tolerance in the cumulative dosing method and the challenge dose method. Two distinct groups emerged one exhibited acute tolerance and the other failed to exhibit acute tolerance. A third group of rats had their DS ability attenuated. Correlations between the two methods are presented. This study was performed in an attempt to attribute the varying effects of chronic nicotine administration on rats as observed in a DS behavioural paradigm, to nAChR's in specific brain areas using ⁸⁶Rb⁺ efflux techniques. A ⁸⁶Rb⁺ efflux assay was used to evaluate nicotinic receptor function using synaptosomes from the same rats used in the drug discrimination and acute tolerance testing. Two assays were performed for each brain area using 2 different nicotine concentrations (1uM; 30uM). Significant differences in nicotine-stimulated ⁸⁶Rb⁺ efflux were seen between rats exhibiting

desensitization (DZ) and non-desensitization (NDZ). Significant differences are reported for the following brain areas and concentrations; (1) cortex 30uM, (2) hippocampus 30uM, (3) striatum 1uM, 30uM, (4) thalamus 30uM. Previous work by the author has shown differences in alpha 7 nicotinic receptor populations in these brain areas. Rats exhibiting acute tolerance have more alpha-bungarotoxin binding sites than rats not exhibiting acute tolerance.

Supported by: Philip Morris External Research Program, NIDA, Karolinska Institute and German Council For Smoking

Conflict of Interest: Research funded by a corporation that may benefit financially

Drug discrimination with the atypical antipsychotic clozapine in C57BL/6 mice.

S.D. Philibin, L.E. Wise, A.J. Prus, A.L. Pehrson, & J.H. Porter

Department of Psychology, Virginia Commonwealth University, Richmond VA 23284-2018.

Clozapine (CLZ) is the prototypical atypical antipsychotic drug (APD) and is superior to typical APDs for the treatment of schizophrenia. Understanding the pharmacological properties important for the unique effects of CLZ can help lead to the development of other APDs with greater therapeutic efficacy and less side effect liability. One approach for studying the genetic basis for drug effects on behavior is the use of knockout or transgenic animals. An advantage of these new molecular techniques is the manipulation of neurotransmitter receptors for which pharmacological ligands do not exist. A limitation of this approach is that most knockout animals are currently available only in mice – not rats. One important preclinical assay used in drug development to help identify neurotransmitter receptor targets for putative APDs is drug discrimination. CLZ has previously been studied in the drug discrimination paradigm with rats, pigeons, and non-human primates. The purpose of the present study was to establish CLZ in a two-lever drug discrimination procedure in wild-type C57BL/6 mice and to compare CLZ to other atypical and typical APDs.

C57BL/6 mice (N=17) were trained to discriminate 2.5 mg/kg CLZ (s.c.) from Vehicle using a fixed ratio 10 reinforcement schedule for sweetened-condensed milk. The mice learned the discrimination in an average number of 36.5 training sessions (SEM = 3.47). A dose effect curve for CLZ yielded an ED50 = 1.14 mg/kg (95% C.I. = 0.95 – 1.37 mg/kg) with full generalization at the training dose and at 5.0 mg/kg; however, there were strong rate suppressant effects at the 5.0 dose. The typical APD haloperidol (0.05 – 0.4 mg/kg) did not substitute for CLZ. Other APDs are currently being tested, but these preliminary results demonstrate that CLZ two-lever discrimination can be established in mice and that the results appear to be similar to that seen in other species.

Serotonin_{2C} agonists produce aversive stimulus properties in Swiss-Webster mice

Ellen A. Walker

Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA

The purpose of the present study was to investigate the aversive stimulus effects of two serotonin agonists MK212 and m-chlorophenylpiperazine (mCPP) using a conditioned taste aversion procedure. Swiss Webster male mice weighing 20-35 g were used. For two conditioning days, 30-

min access to a novel flavored solution (conditioned stimulus) was paired with injections of different doses of MK212 or mCPP (unconditioned stimulus). On two alternate conditioning days, a different flavored solution was paired with injections of saline in both training groups. The flavor of the conditioned stimulus was either almond-saccharin solution (almond-scented, 0.15% sodium saccharin) or banana-saline solution (banana-scented, 0.09% sodium chloride) and was counterbalanced within the training groups. The unconditioned stimuli in the different groups of mice were injections of 1.0, 3.2, 10, or 32 mg/kg MK212, i.p., or 1.0, 3.2, 10, 32 mg/kg mCPP, i.p. Under test conditions, the mice were not injected and had access to both flavored solutions. During the choice tests, mice choose the flavor associated with saline and avoided the solution associated with MK212 or mCPP. Furthermore, these conditioned taste aversions were dose-dependent. Nonselective 5-HT_{2C} antagonists, methysergide, 2-bromo-LSD, mianserin, and cyproheptadine blocked the acquisition of conditioned taste aversions produced by either 10 mg/kg MK212 or 10 mg/kg mCPP. These data indicate that the serotonin agonists MK212 and mCPP possess aversive stimulus effects and that these effects are mediated through actions at serotonin receptors. (Supported by USPHS grant DA14673)

Treasurer's Report

As of June 3, 2004 the balance in our checking account is \$5,869.17. A complete report will be presented at the SSPD Business meeting in October.

2005 DUES

Yes – it's that time of year again. I want to thank all of the members who sent in dues payments last year. Most of the membership was one to two years behind in paying dues. As you can see from the checking balance, we need all members to keep up with dues in order to maintain a reasonable balance in our checking account. If you have questions about how much you owe in dues, please contact the Secretary/Treasurer Joe Porter (jporter@vcu.edu).

Please send your check payable to SSPD in the amount of \$20 for your 2005 dues to the Secretary/Treasurer, Joe Porter. If you did not pay your 2004 dues, please make the check out for \$40. If you have been delinquent in your dues for longer than you care to admit – we are offering a special amnesty period – simply pay for 2004 and 2005 (i.e., \$40) and you will be a member in good standing once again. The dues are the primary source of income to pay for the Web Site and the annual meeting so we need all members to stay current in their dues. THANKS!!

WELCOME TO OUR NEWEST SSPD MEMBERS!

Joseph R. Troisi II Saint Anselm College

Zuzana Justinova NIDA-IRP, NIH, DHHS

PLEASE ENCOURAGE YOUR COLLEAGES AND GRADUATE STUDENTS TO JOIN SSPD.
Contact Joe Porter (jporter@vcu.edu) for information.

Lifetime Contribution Award to SSPD Member

A long-standing member of SSPD made an excellent suggestion to resurrect the Lifetime Contribution Award for an individual member that has made significant contributions to the study of the stimulus properties of drug. For example, Donald Overton and John Rosecrans received such recognition in past years. We would like to take some nominations from the membership for individuals that should be acknowledged. Please forward your nominations, suggestions, or comments to Ellen Walker (ellen.walker@temple.edu).

2003 SSPD meeting in New Orleans, LA

