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SSPD

SOCIETY FOR STIMULUS PROPERTIES OF DRUGS

33rd Annual Meeting
November 11, 2011
American University
Washington, D.C.

A Special Celebration of the Life and Research of Francis C. Colpaert (1950 - 2010)

Society for Stimulus Properties of Drugs - 33rd Annual Meeting

Washington, D.C. November 11, 2011
Meeting held at American University

PROGRAM

6:00 - 6:30 pm - Registration, Appetizers and Poster Presentations

6:30 - 7:00 pm - Buffet Dinner and Poster Presentations

7:00 - 7:20 pm - Business Meeting

7:20 - 7:50 pm - Special Presentation of LIFETIME CONTRIBUTION AWARD from SSPD to Francis C. Colpaert (1950 - 2010)

Francis C. Colpaert (1950 - 2010) - A retrospective look at 40 years of research

Joseph H. Porter
Department of Psychology, Virginia Commonwealth University, Richmond, VA

Francis C. Colpaert (1950 - 2010) - Some personal reflections

Wouter Koek
Departments of Psychiatry and Pharmacology, Alcohol and Drug Addiction Division, University of Texas Heath Science Center San Antonio, San Antonio, TX

PRESENTATION OF THE FRANCIS C. COLPAERT STUDENT RESEARCH AWARDS (Sponsored by AstraZeneca Pharmaceuticals)

Oral Presentations (8:00 - 10:00 pm)

(1) ***The discriminative stimulus profiles of low and high efficacy agonists***

Ellen A. Walker[1] and Alice M. Young[2]
[1]Department of Pharmaceutical Sciences, Temple University, Philadelphia, PA
[2]Department of Pharmacology and Neuroscience, Texas Tech University, Lubbock, TX

(2) ***Discriminative stimulus functions of cannabinoid receptor 1 antagonists***

Torbjorn (Toby) Jarbe
Northeastern University, Center for Drug Discovery, Pharmaceutical Sciences, Boston, MA

(3) *A comparison of the modulation of the discriminative-stimulus and reinforcing effects of cocaine by sigma receptor ligands*

Takato Hiranita, Gianluigi Tanda and Jonathan L. Katz
Psychobiology Section, Intramural Research Program,
National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD

(4) *Cannabidiol prevents onset of chemotherapy-induced neuropathic pain: role of 5-HT1A receptors*

Sara Jane Ward
Department of Pharmaceutical Sciences, Temple University, Philadelphia, PA

10 MINUTE BREAK

(5) *The discriminative stimulus functions of nicotine under low- and high-drive states and in the regulation of complex behavioral repertoires in rats: some implications for relapse*

Joseph R. Troisi II
Department of Psychology, Saint Anselm College, Manchester, NH

(6) *The relation between stimulation of mesolimbic dopamine and discriminative-stimulus effects among typical and atypical dopamine uptake inhibitors in rats*

Gianluigi Tanda[1], Stephen J. Kohut[1], Takato Hiranita[1], Soo-Kyung Hong[1,2],Aaron L. Ebbs[1], Valeria Tronci[1], Jennifer Green[1], Linda Garcés-Raimírez[1,3], Lauren Chun[1], Jian Jing Cao[4], Mu-Fa Zou[4], Maddalena Mereu[1], Amy H. Newman[4], and Jonathan L. Katz[1]
[1]Psychobiology and [4]Medicinal Chemistry sections, Intramural Research Program, National Institute on Drug Abuse, NIH/DHHS; [2]Department of Neuroscience, Seoul National University College of Medicine, Seoul, South Korea; [3]Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Mexico City, México.

(7) *Drug-induced state-dependent learning: review of an operant procedure*

Wouter Koek
Departments of Psychiatry and Pharmacology, Alcohol and Drug Addiction Division, University of Texas Heath Science Center San Antonio, San Antonio, TX

Research Posters

(1) *Modafinil potentiates discrimination of low dose amphetamine*

Amanda J. Quisenberry, Jennifer L. Walters, and Lisa E. Baker
Department of Psychology, Western Michigan University, Kalamazoo, MI

(2) *Establishing the atypical antipsychotic amisulpride as a discriminative stimulus*

Timothy J. Donahue[1], Kevin A. Webster[1], Eliseu O. De Oliveira[2], and Joseph H. Porter[1]
[1]Department of Psychology, Virginia Commonwealth University, Richmond, VA;
[2]Department of Oncology - Drug Discovery Program, Georgetown University, Washington, DC

(3) *Effects of acute noxious stimuli on the discriminative stimulus effects of morphine in male and female C57BL/6 mice*

Harshini Neelakantan and Ellen A. Walker
Department of Pharmaceutical Sciences, Temple University, Philadelphia, PA

(4) *Comparison of clozapine's discriminative stimulus in C57BL/6, DBA/2, and 129S2 inbred mouse strains*

Kevin A. Webster[1], Scott D. Philibin[2], D. Matthew Walentiny[1], Sarah A. Vunck[1], and Joseph H. Porter[1]
[1]Department of Psychology, Virginia Commonwealth University, Richmond, VA
[2] Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas, TX USA

(5) *Assessment of dopaminergic involvement in cocaine-induced subjective effects*

Katherine M. Serafine Maria A. Briscione, Kenner C. Rice, and Anthony L. Riley
Department of Psychology, American University, Washington, D.C.

(6) *Fischer and Lewis strain differences in morphine drug discrimination learning*

Catherine M. Davis, Jennifer L. Cobuzzi, and Anthony L. Riley
Department of Psychology, American University, Washington, D.C.

(7) *Effects of nicotine and methylphenidate on a visual stimulus position discrimination task*

Maria A. Greenwood[1] and Katherine L. Nicholson[2]
[1]Department of Psychology, Virginia Commonwealth University, Richmond, VA
[2]Department of Pharmacology & Toxicology, Virginia Commonwealth University, Richmond, VA

(8) *Effects of the neurotensin-1 receptor agonist PD149163 on signal detection performance in rats*

Todd M. Hillhouse[1,2], Ashley A. Schmeling[2], and Adam J. Prus[2]
[1]Department of Psychology, Virginia Commonwealth University, Richmond, VA
[2]Department of Psychology, Northern Michigan University, Marquette, MI

(9) *Differential modulation of cocaine's discriminative cue by predictable and unpredictable stress in rats*

Zachary E. Hurwitz[1], Kathleen L. Decicco-Skinner[2], Anthony L. Riley[1], and Stephen J. Kohut[1]
Departments of [1]Psychology and [2]Biology, American University, Washington, DC

(10) *The discriminative stimulus effects of nitrous oxide*

Kellianne J. Richardson, Galina Slavova-Hernandez, and Keith L. Shelton
Department of Pharmacology & Toxicology, Virginia Commonwealth University, Richmond, VA

(11) *Effects of a typical antipsychotic on the discriminative stimulus effects produced by 22 hours food deprivation*

Amy R. Johnson, Jennifer E. Dobbe, Benjamin A. Kron, and David C. Jewett
Department of Psychology, University of Wisconsin, Eau Claire, WI

ABSTRACTS

ORAL PRESENTATIONS

(1) **The discriminative stimulus profiles of low and high efficacy agonists.**

Ellen A. Walker[1] and Alice M. Young[2]
[1]Department of Pharmaceutical Sciences, Temple University, Philadelphia, PA
[2]Departments of Psychology and Pharmacology and Neuroscience, Texas Tech University, Lubbock, TX

In 1988, Francis Colpaert wrote a theoretical chapter entitled *"Intrinsic activity and the discriminative stimulus effects of drugs"* in a book called Transduction Mechanisms of Drug Stimuli that he co-edited with Robert Balster. In contrast to earlier theories that predicted primarily potency differences among drugs with activity at a common receptor subtype, Colpaert predicts that drugs with different magnitudes of intrinsic activity at a single receptor subtype would be associated with discriminative stimulus effects that differ qualitatively. He proposed a relationship between a quantitative (i.e., magnitude of receptor activation) and a qualitative variable (i.e., quality of discriminative effect). Therefore, the relative intrinsic efficacy of a training drug will control both the potency of other agonists within the assay and the capacity of these other agonists to produce drug-appropriate responding. In the following decades, this theory and additional tenets from his chapter were tested in many laboratories, including our own. In this presentation, we will illustrate the data generated from a number of experiments and demonstrate how Colpaert's reflections on intrinsic activity and discrimination led the way to a more sophisticated appreciation of the subtleties of receptor-drug interactions.

(2) **Discriminative stimulus effects of the cannabinoid receptor 1 antagonist rimonabant: An operant approach using rats.**

T.U.C. Jarbe
Center for Drug Discovery, Northeastern University, Boston, MA 02115

Rationale: Discovery of an endocannabinoid signaling system (ECS) launched the development of rimonabant, a cannabinoid CB1 receptor (CB1R) antagonist/inverse agonist. Due to untoward effects, this medication was withdrawn and efforts have been directed towards discovering chemicals with more benign profiles.
Objective: This study comparatively evaluated new ligands affecting the ECS using rimonabant as a discriminative cue in a fluid-motivated operant procedure.
Methods: Two groups of fluid-restricted rats discriminated between rimonabant (5.6 and 3 mg/kg) and vehicle, administered i.p. 20 min pre-session. The majority of generalization data were obtained in the 3 mg/kg trained rats.
Results: The centrally acting neutral CB1R antagonists AM4113 and AM6527, but not the limited brain penetrating CB1R neutral antagonist AM6545, substituted for rimonabant. The CB2R selective antagonist SR144528 and the cholinergic nicotine did not substitute. The cueing effects of 3 mg/kg rimonabant were attenuated by the CB1R agonist AM5983 (0.03–1.8 mg/kg). Combinations of AM4113 and rimonabant resulted in either no change or additive effects. By varying the injection-to-test interval, we gauged the relative duration of the cueing effects of rimonabant, and the in vivo functional half-life was estimated to be approximately 2 hrs.
Conclusion: Two centrally acting neutral CB1R antagonists (AM4113 and AM6527) produced cueing effects similar to those of rimonabant and generalization likely was centrally mediated. The functional cueing effects of rimonabant are relatively short-acting, pharmacologically selective, and not blocked by a neutral CB1R antagonist.

(3) A Comparison of the Modulation of the Discriminative-Stimulus and Reinforcing Effects of Cocaine by Sigma Receptor Ligands

Takato Hiranita, Gianluigi Tanda, and Jonathan L. Katz
Psychobiology Section, Intramural Research Program,
National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224

Recent studies indicated that sigma-receptor (σR) agonists serve as reinforcers in rats trained to self-administer cocaine. Further, σR antagonists had no effect on cocaine self-administration (SA), despite their blockade of other effects of cocaine. In contrast to cocaine SA, σR agonist SA was dose-dependently blocked by σR antagonists, suggesting reinforcing mechanisms different from those of cocaine. The present study further examined interactions between cocaine and σR ligands in rats trained to discriminate cocaine (10 mg/kg, i.p.) from saline injections. Like cocaine SA, σR antagonists (BD1008, BD1047, BD1063) did not fully substitute in rats discriminating cocaine, though all except BD1063 substituted partially. Unlike cocaine SA, σR agonists (DTG, PRE-084, 5 or 30 min prior, i.p., s.c., or i.v.) did not substitute for cocaine in the drug discrimination (DD) procedure. As with cocaine SA, σR agonist pretreatment dose-dependently shifted the cocaine DD dose-effect curve leftward. Similar effects were obtained with dopamine-uptake inhibitors (WIN 35,428, methylphenidate). Although inactive in cocaine SA, the σR antagonists shifted the cocaine DD dose-effect curve leftward, though not dose-dependently. Leftward shifts in the cocaine DD dose-effect curve produced by σR antagonists were increased by doses of the dopamine-uptake inhibitors that were inactive when administered alone. Higher doses of the dopamine-uptake inhibitors that were active when administered alone were typically not more active with co-administration of σR antagonists. However BD1047 was the exception as it enhanced the leftward shift in the cocaine curve produced by high doses of the dopamine-uptake inhibitors. Finally, the leftward shift in the cocaine DD dose-effect curve produced by the σR agonist, PRE-084, was not antagonized by any of the σR antagonists. The present results further indicate fundamental differences in the mechanisms underlying the effects of σR agonists and dopamine-uptake inhibitors, and that the SA of σR agonists in rats trained on cocaine SA is not due to an overlap of subjective effects. Further, σR agonists and antagonists can enhance the effects of dopamine uptake inhibitors, but these actions are likely not σR mediated.

(4) Cannabidiol prevents onset of chemotherapy-induced neuropathic pain: role of 5-HT1A receptors

Sara Jane Ward
Department of Pharmaceutical Sciences, Temple University, Philadelphia, PA

Paclitaxel (PAC) is associated with a chemotherapy-induced neuropathic pain (CINP) state that can lead to the cessation of treatment in late stage breast cancer patients, even in the absence of alternate therapies. Rodent models of CINP to investigate underlying mechanisms and potential treatments have focused on measurements of thermal and mechanical allodynia following systemic dosing of PAC, while the effect of CINP on pain-depressed and affective behaviors has not been characterized. Also, the non-psychoactive phytocannabinoid cannabidiol (CBD), with known affinity for the 5-HT_{1A} receptor, has been shown to reverse other types of chronic inflammatory and neuropathic pain, but its effect on CINP has not previously been investigated. In the present set of experiments, we investigated the effect of CBD on PAC-induced mechanical allodynia, PAC-induced suppression of food motivation, and PAC-induced place conditioning in female C57Bl/6 mice. PAC administration led to the onset of mechanical allodynia as well as a suppression of progressive ratio responding for palatable food. Treatment with CBD prevented the development of PAC-induced mechanical allodynia, and reversed PAC-induced suppression of food motivation. Also, CBD produced a robust conditioned place preference in PAC-treated but not saline treated mice. Lastly, the ability of CBD treatment to block PAC effects was attenuated by pretreatment with the 5-HT1A antagonist WAY100635. In conclusion, CBD blocks PAC-induced neuropathic pain using pain-stimulated, pain-depressed, and affective analgesia models, and these effects may be mediated by stimulation of 5-HT_{1A} receptors.

(5) The discriminative stimulus functions of nicotine under low- and high-drive states and in the regulation of complex behavioral repertoires in rats: some implications for relapse

Joseph R. Troisi II
Department of Psychology, Saint Anselm College, Manchester, NH

From its inception, the study of the stimulus properties of drugs was intended to functionally investigate the mechanisms underlying interoceptive conditioning. Remarkable similarities have been demonstrated between the discriminative stimulus functions of drugs and stimulus control phenomena evidenced in the traditional animal learning literature (e.g., blocking, overshadowing, extinction, transfer learning). Two studies were carried out in view of this conceptualization. Both studies used nicotine. The first study utilized a counterbalanced one-manipulanda (i.e., nose-poke response) operant procedure. For eight rats, nicotine functioned as an S^D and saline functioned as S^Δ. For the remaining eight rats the roles were reversed. Stimulus control was initially established in a restricted feeding state ("high drive") and then under satiety ("low drive state"). Satiety reduced response rates in the S^D interoceptive condition, but discrimination indices were unchanged. Extinction training was then carried out in the low-drive sated state and tested. Response rates and discriminative control were suppressed, and remained suppressed two-weeks later. However, with this same delay following extinction, rats that were returned to the restricted feeding high drive state showed complete recovery of discriminative control and a significant elevation in response rate specific to the S^D condition. Thus, the discriminative function of nicotine, its extinction and recovery, was conditional on the "drive state". In the second experiment a conditional discrimination was established with a heterogeneous operant chain linked by an exteroceptive conditioned reinforcer (light). In the nicotine condition a lever-press→nose-poke sequence was reinforced by food delivery and in the saline condition a nose-poke→lever-press sequence was reinforced. The order of the sequence was conditional on the presence or absence of nicotine. Brief non-reinforcement probes revealed that the sequence of responses was state-dependent. Extinction training in the saline state undermined response rates of lever-pressing and nose-poking. When nicotine was administered the opposite response sequence recovered and this recovery endured sessions of extinction. Reversal learning was conducted and removal of the light abolished conditional control by nicotine. The findings from both studies collectively suggest that extinction of the discriminative stimulus functions of nicotine can be conditional on: A) other interoceptive events in the organism that may interact conditionally, or B) or other exteroceptive secondary reinforcers. These findings may contribute to understanding mechanisms that modulate relapse.

(6) The Relation between Stimulation of Mesolimbic Dopamine and Discriminative-Stimulus Effects Among Typical and Atypical Dopamine Uptake Inhibitors in Rats

Gianluigi Tanda[1], Stephen J. Kohut[1], Takato Hiranita[1], Soo-Kyung Hong[1,2],Aaron L. Ebbs[1], Valeria Tronci[1], Jennifer Green[1], Linda Garcés-Raimírez[1,3], Lauren Chun[1], Jian Jing Cao[4], Mu-Fa Zou[4], Maddalena Mereu[1], Amy H. Newman[4], and Jonathan L. Katz[1]

[1]Psychobiology and [4]Medicinal Chemistry sections, Intramural Research Program, National Institute on Drug Abuse, NIH/DHHS; [2]Department of Neuroscience, Seoul National University College of Medicine, Seoul, South Korea; [3]Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Mexico City, México.

Compelling evidence indicates that increases in mesolimbic dopamine (DA) produced by abused drugs are related to their abuse liabilities in humans. Most of this evidence comes from studies of cocaine's reinforcing effects, however there is also evidence suggesting a similar involvement in cocaine's discriminative-stimulus effects. Here we studied the relationship between discriminative-stimulus effects and stimulation of mesolimbic-DA levels produced by typical [cocaine, methylphenidate, WIN 35,428], and atypical [N-substituted 4',4"-diF-analogs of benztropine (BZT)] DA-transport (DAT)-blockers. Rats were trained with food reinforcement to discriminate i.p. cocaine (10 mg/kg) from saline injections. Levels of DA were assessed using in vivo microdialysis. All drugs stimulated DA with different maxima obtained at different doses and times after injection. The typical DAT-blockers reliably and fully substituted for

cocaine (>65% drug-appropriate responding) at doses producing 150-200% increases in DA above basal levels. There was a linear relationship between DA concentration and % drug-appropriate responding that was independent of drug, dose, or time after injection. The BZT analogs, AHN 1-055 (N-methyl) and AHN 2-005 (N-allyl), fully substituted only episodically at the highest doses and at selected pretreatment times. On those occasions, substantially greater stimulation of DA levels was necessary (e.g. 400-500 % above basal levels) compared to that required by the typical DAT blockers. JHW 007 (N-butyl) did not fully substitute for cocaine at any dose or time, even those that increased DA by 600 % above basal values. Our data suggest a linear time-independent relationship between subjective effects and elevation of DA levels by typical DAT blockers, which is at variance with that for the atypical DAT-blockers. Pharmacodynamic differences between atypical and typical DAT inhibitors, other than effectiveness in stimulating DA levels, must account for differences in cocaine-like behavioral effects. Finally, we suggest that a time-related desensitization process may contribute to the effects of the atypical DAT-blockers.

(7) Drug-induced state-dependent learning: review of an operant procedure

Wouter Koek
Departments of Psychiatry and Pharmacology, Alcohol and Drug Addiction Division, University of Texas Heath Science Center San Antonio, San Antonio, TX

Abstract: Drug discrimination and drug state dependence are often thought to be based on the same drug actions, and to differ only in the doses needed to produce them, with discrimination occurring at low doses and state dependence at high doses. Testing this hypothesis has been hampered by the use of discrimination and state dependence procedures that differed in many respects. In 1986, Colpaert introduced a procedure to study state dependence in rats that used the same response, the same reinforcer, and the same reinforcement schedule that are commonly used in drug discrimination. Using this procedure, differences between drug state dependence and drug discrimination were found with some drugs (e.g. alcohol), consistent with the hypothesis that the procedures differ in the drug properties they measure, but not with other drugs (e.g. chlordiazepoxide). Thus, state dependence and drug discrimination can generate different outcomes, but the conditions in which they do require further study. However, all the studies conducted with the procedure introduced by Colpaert clearly show that state dependence is not necessarily only a high-dose phenomenon, but can also occur at doses at which many central nervous system drugs produce their characteristic effects. This finding led to the hypothesis that state dependence may be involved in the therapeutic and other effects of psychoactive drugs.

POSTERS

(1) Modafinil potentiates discrimination of low dose amphetamine.

Amanda J. Quisenberry, Jennifer L. Walters, and Lisa E. Baker
Department of Psychology, Western Michigan University, Kalamazoo, MI 49008

Modafinil is a wake promoting stimulant that is FDA approved for the treatment of narcolepsy, shift work sleep disorder, and sleep apnea (Ballon & Feifel, 2006). It is also currently being assessed as a treatment for cocaine and methamphetamine dependence (Vosberg et al., 2010) and has potential for treating cognitive deficits associated with neurological diseases such schizophrenia (Morein-Zamir et al., 2007) and Attention Deficit Hyperactivity Disorder (Rugino, 2007). Previous research indicates that modafinil has a lower abuse liability than d-amphetamine or cocaine (Deroche-Gamonent et al., 2002; Rush et al., 2002). However, the risk for abuse of modafinil in combination with psychomotor stimulants has not been thoroughly investigated. The drug discrimination paradigm is widely used in behavioral pharmacology and offers a useful tool in drug discovery research to screen novel compounds for similarities to drugs with established abuse liability (Moser et al., 2010). The aim of the current study was to assess the effects of modafinil and amphetamine /modafinil combinations in a drug discrimination paradigm. Sixteen male Sprague-Dawley rats were trained to discriminate either 0.3 mg/kg d-amphetamine (0.3 AMPH, n=8) or 1.0 mg/kg d-amphetamine (1.0 AMPH, n=8) from saline under a fixed ratio 20 schedule of food reinforcement. Stimulus generalization tests were conducted with amphetamine

(0.03, 0.1, 0.3, and 1 mg/kg), modafinil (32, 64, 128, and 256 mg/kg), 64 mg/kg modafinil in combination with each of the above AMPH doses, and 0.1 mg/kg AMPH in combination with each of the above modafinil doses. Modafinil produced dose-dependent increases in responding on the AMPH-associated lever, but only partial substitution was observed in both the 0.3 AMPH and 1.0 AMPH groups at 256 mg/kg. At 32, 64 and 128 mg/kg, modafinil produced slightly greater AMPH-lever responding in the 0.3 AMPH group (38-49%) compared to the 1.0 AMPH group (23-29 %). In addition, 64 mg/kg modafinil potentiated the effects of AMPH only in the 0.3 AMPH group. These results indicate the possibility that modafinil may enhance some of the effects of psychomotor stimulants. Further investigations utilizing methods that assess abuse liability (e.g., place conditioning, drug self-administration) with modafinil in combination with other stimulants may be warranted.

(2) Establishing the atypical antipsychotic amisulpride as a discriminative stimulus

Timothy J. Donahue[1], Kevin A. Webster[1], Eliseu O. De Oliveira[2], and Joseph H. Porter[1]
[1]Department of Psychology, Virginia Commonwealth University, Richmond, VA
[2]Department of Oncology - Drug Discovery Program, Georgetown University, Washington, DC

First generation ("typical") antipsychotic drugs like chlorpromazine and haloperidol are relatively effective for treatment of the positive symptoms (e.g. hallucination, delusions) of schizophrenia, but produce extrapyramidal motor side effects (EPS). Second generation ("atypical") antipsychotic drugs like clozapine treat both positive and negative symptoms of schizophrenia and have greatly reduced EPS side effects and other clinical advantages. Since clozapine was introduced, it has remained as the gold-standard "atypical" antipsychotic drug and has led to the development of a number of other "atypical" antipsychotic drugs for the treatment of schizophrenia. While older "typical" antipsychotic drugs like haloperidol preferentially block dopamine D_2 receptors, clozapine has a decreased affinity to these receptors but shows higher affinity to dopaminergic D_4 and serotonergic 5-HT_{2A} (among other receptors). It is assumed that receptor mechanisms other than D_2 receptors may be important for the clinical advantage (e.g. reduced motor side effects) of these newer drugs, but ALL antipsychotic drugs share one property - antagonism of dopamine D_2 receptors.

An interesting atypical antipsychotic drug that has a more selective binding profile is amisulpride. It is approved for the treatment of schizophrenia in Europe and displays an atypical clinical profile with reduced motor side effects and greater reduction of negative symptoms (Mortimer 2004). The typical antipsychotic drug haloperidol is relatively selective for D_2-like receptors (i.e. D_2, D_3, D_4) and also blocksα_1 adrenoceptors. Amisulpride also is relatively selective antagonist at dopamine D_2 and D_3 receptors and blocks serotonin 5-HT_{2B} and 5-HT_7 receptors. In order to determine the subjective effects of these antipsychotic drugs and to study the *in vivo* receptor mechanisms that mediate their discriminative stimuli (and perhaps their therapeutic effects), the present study used drug discrimination, which is a powerful *in vivo* assay that allows for a direct comparison between the atypical antipsychotic amisulpride and the typical antipsychotic haloperidol. Also, by testing selective antagonists at specific receptors it may be possible to determine the differences in receptor mechanisms that play a role in the *in vivo* effects of amisulpride that may be related to its clinical advantages in patients.

In the present study 12 adult C57BL/6 male mice were trained to discriminate 10 mg/kg of amisulpride from vehicle in a two-lever drug discrimination task for food reinforcement (sweetened milk). All 12 mice acquired the amisulpride discriminative stimulus in an average of 37.4 sessions (range 11 to 74 sessions). Five of the mice have finished the amisulpride dose-response curve (0.15625 – 40 mg/kg dose) with an ED_{50} of 2.56 mg/kg (95% confidence interval = 1.13 – 5.34 mg/kg). Full generalization to the amisulpride discriminate stimulus was seen at the training dose of 10 mg/kg and at 20 and 40 mg/kg with no significant changes in response rates. Substitution testing with the typical antipsychotic haloperidol (0.00078 - 0.1 mg/kg) has been completed for 2 amisulpride-trained mice and partially completed for 2 other mice. None of the tested doses of haloperidol substituted for amisulpride. The maximum % drug lever responding (%DLR) produced by haloperidol was 15.0 %DLR at a dose of 0.0125 mg/kg. Responding was suppressed at the 0.10 mg/kg dose of haloperidol. After completion of testing with haloperidol, selective antagonists at serotonin 5-HT_{2B} (e.g. RS127445 or LY-272015) and dopamine

D_3 (e.g. NGB 2904) receptors will be tested to determine the pharmacological basis of amisulpride's discriminative stimulus. These results demonstrate that the atypical antipsychotic amisulpride can be established as a discriminative stimulus in C57BL/6 mice.

(3) Effects of acute noxious stimuli on the discriminative stimulus effects of morphine in male and female C57BL/6 mice

Harshini Neelakantan and Ellen A. Walker
Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA

Recent animal studies have demonstrated current chronic pain to decrease the rewarding properties of prescription opioids. However, the manner in which the stimulus effects of prescription opioids are changed by pain states has not been investigated. Therefore, we are interested in testing the hypothesis that the presence of an acute noxious stimulus will decrease the potency of morphine to produce discriminative stimulus effects in male and female C57BL/6 mice. Mice were trained in a two choice operant experimental chamber to discriminate 3.2 mg/kg morphine or saline. Once the training criterion was met, dose response curves were generated for mice in the absence and presence of 0.4% acetic acid. The acetic acid produced an acute chemically induced nociceptive pain state during the trial sessions. Results showed dose-dependent morphine- appropriate responding in both male and female mice with no differences in the potency of morphine to function as a discriminative cue in either of the sexes. Although the rates of responding were higher in the male mice, the male mice took longer (105 trials) to acquire morphine discrimination when compared to the female mice (77 trials). Combination of acetic acid with morphine doses failed to significantly alter the discriminative effects of morphine in female mice but actually produced a significant rightward shift of the morphine dose response curve in the male mice. These data suggest that an acute pain state may differentially modulate the discriminative stimulus effects of morphine in male and female mice. In addition, these results may have implications with respect to understanding sex differences in the clinical effectiveness of opioids as well as the abuse liability of morphine in the presence of pain.

(4) Comparison of clozapine's discriminative stimulus in C57BL/6, DBA/2, and 129S2 inbred mouse strains

Kevin A. Webster[1], Scott D. Philibin[2], D. Matthew Walentiny[1], Sarah A. Vunck[1], and Joseph H. Porter[1]

[1]Department of Psychology, Virginia Commonwealth University, Richmond, VA USA
[2] Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas, TX USA

Long hailed as the "gold standard" for the clinical treatment of schizophrenia, the atypical antipsychotic clozapine has been established in drug discrimination assays in a variety of species including pigeons, rats, mice and non-human primates. Clozapine's binding profile is one of the more diverse profiles among atypical antipsychotics, binding to multiple sub-receptors of serotonergic, dopaminergic, adrenergic, and muscarinic systems. It is not surprising that rodents trained to discriminate clozapine have a complex and compound discriminative stimulus. The present study examined the underlying receptor mechanisms of clozapine's discriminative stimulus in three inbred mouse strains important for the generation of knockout and transgenic mice: C57BL/6, DBA/2, and 129S2 mice. DBA/2 mice have been shown to have a uniquely functioning dopamine system, which makes it an interesting comparison strain considering the high binding affinity shown by all typical and atypical antipsychotic drugs for the dopaminergic system - specifically D_2 receptor antagonism.

Adult male C57BL/6, DBA/2, and 129S2 mice were trained to discriminate clozapine (2.5 mg/kg for C57BL/2 and DBA/2 mice; 1.25 mg/kg for 129S2 mice) from vehicle in a two-lever drug discrimination task for food reward. In C57BL/6 mice the serotonergic antagonists ritanserin (5-HT_2) and M100907 (selective for 5-HT_{2A}) and the adrenoceptor antagonist prazosin (selective for α_1) fully substituted for clozapine's discriminative stimulus. In 129S2 mice the adrenoceptor antagonist prazosin (selective for α_1) fully substituted for clozapine's discriminative stimulus, while the muscarinic antagonist scopolamine and the serotonergic antagonist M100907 partially substituted. In DBA/2 mice no selective receptor ligands substituted for clozapine's discriminative stimulus, although the muscarinic antagonist scopolamine did produce partial substitution.

These data demonstrate important differences in the atypical antipsychotic clozapine's discriminative stimulus across these three inbred strains of mice. These findings also demonstrate that the nature of clozapine's discriminative cue varies across both species as well as strains of animals. These differences in receptor mechanisms should be taken into consideration when selecting which species or which strain to use in clozapine drug discrimination studies for preclinical assays used to screen potential antipsychotic drugs.

(5) Assessment of dopaminergic involvement in cocaine-induced subjective effects.

Katherine M. Serafine[1], Maria A. Brisclone[1], Kenner C. Rice[2], and Anthony L. Riley[1]
[1]Department of Psychology, American University, Washington, DC. [2]Chemical Biology Research Branch, National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

Although cocaine induces conditioned taste aversions (CTA), little is known about the mechanisms underlying this effect. It has been suggested that cocaine's actions as a nonselective monoamine transport inhibitor may be mediating this suppression. Given the role of dopamine (DA) in cocaine reward, this neurotransmitter system is of particular interest. The present experiments used direct pharmacological antagonism (with DA antagonist haloperidol) to determine a role, if any, of DA in the induction of CTAs by cocaine. Following the determination of behaviorally active doses of haloperidol with no aversive effects on their own (Experiment 1), animals were given 1 mg/kg haloperidol prior to various doses of cocaine in a taste aversion procedure (Experiment 2). Under these conditions, haloperidol blocked cocaine-induced CTAs (at the 18 and 32 mg/kg doses). These results suggest that DA has a role in cocaine-induced CTAs. These results are discussed in context of previous work demonstrating roles for both norepinephrine and serotonin.

Supported by the Mellon Foundation to ALR.

(6) Opioid receptor mediation of morphine's discriminative stimulus effects in the inbred Fischer 344 (F344) and Lewis (LEW) rat strains

Catherine M. Davis[1], Kenner C. Rice[3] and Anthony L. Riley[2]
[1]Division of Behavioral Biology, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD
[2]Psychopharmacology Laboratory, American University, Washington, DC
[3]Drug Design and Synthesis Section, Chemical Biology Research Branch, National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism, Rockville, MD

The present experiment assessed morphine's discriminative stimulus effects in the F344 and LEW inbred rat strains (using the taste aversion baseline of drug discrimination learning) and the relative roles of the mu, kappa and delta opioid receptor subtypes in this discrimination. Specifically, F344, LEW and outbred Sprague Dawley (SD) male rats received an injection of morphine (5.6 mg/kg; i.p.) 30-min prior to 20-min saccharin access which was followed by an injection of lithium chloride (1.8 mEq; F344: $\underline{n}$ = 8; LEW: $\underline{n}$ = 8; SD: $\underline{n}$ = 4) or distilled water (F344: $\underline{n}$ = 8; LEW: $\underline{n}$ = 7; SD: $\underline{n}$ = 4); three recovery days followed during which saline preceded saccharin access. Specific agonists for the kappa [(-)-U50,488H, 0.16-5 mg/kg], delta [SNC80 (0.32-18 mg/kg)] and mu [heroin (0.10-1.8 mg/kg)] opioid receptors, respectively, were then tested for their ability to generalize to the morphine cue. All three strains displayed comparable acquisition of the morphine discrimination and displayed similar morphine dose-substitution curves (1.0-10.0 mg/kg). Paired-samples t-tests revealed that 1.0 and 1.8 mg/kg heroin generalized fully to the morphine training dose in F344 and SD rats. The F344 rats also displayed partial generalization of the 0.56 mg/kg dose of heroin. The LEW strain displayed only partial generalization at 1.8 mg/kg heroin. No strain displayed generalization to any dose of (-)-U50,488H or SNC80 tested. The fact that neither kappa

nor delta compounds substituted for morphine suggests that morphine stimulus control in these strains is solely mu mediated. The basis for the differential substitution by heroin (despite comparable morphine control) suggests differential mediation of the morphine and heroin cues.

Supported by the Mellon Foundation to ALR and intramural funds from NIDA and NIAAA.

(7) Effects of nicotine and methylphenidate on a visual stimulus position discrimination task

Maria A. Greenwood[1] and Katherine L. Nicholson[2]
[1]Department of Psychology, Virginia Commonwealth University, Richmond, VA
[2]Department of Pharmacology & Toxicology, Virginia Commonwealth University, Richmond, VA

(8) Effects of the neurotensin-1 receptor agonist PD149163 on signal detection performance in rats

T. M. HILLHOUSE[1,2], A. A. SCHMELING[2], and A. J. PRUS[2]
[1]Departmetn of Psychology, Virginia Commonwealth University, Richmond, VA
[2]Department of Psychology, Northern Michigan University, Marquette, MI

Neurotensin is a neuropeptide neurotransmitter that has cognitively relevant interactions with multiple neurotransmitter systems. Brain penetrant agonists of neurotensin NT_1 receptors have exhibited atypical antipsychotic drug-like effects in animal models, including reversal of psychotomimetic-induced sensory gating deficits, but have yet to be thoroughly evaluated in animal cognitive models. The present study sought to evaluate the effects of the NT_1 receptor agonist PD149163 on attention using a visual signal detection operant task in rats. PD149163 did not significantly alter the percentage of signals detected (hits) nor alter the percentage of non-signals correctly identified (correct rejections). Both the atypical antipsychotic drug clozapine and the dopamine $D_{2/3}$ receptor antagonist and typical antipsychotic drug raclopride significantly decreased percent hits. Nicotine, used as a positive control, significantly increased both percent hits and percent correct rejections. Based upon these and previous findings, PD149163 is a putative atypical antipsychotic drug that appears neither beneficial nor detrimental for attention.

(9) Differential modulation of cocaine's discriminative cue by predictable and unpredictable stress in rats

Zachary E. Hurwitz[1], Kathleen L. Decicco-Skinner[2], Anthony L. Riley[1], and Stephen J. Kohut[1]
Departments of [1]Psychology and [2]Biology, American University, Washington, DC

Discriminative stimulus functions of drugs of abuse play an important role in the acquisition, maintenance and reinstatement of drug-taking behavior and are altered by a variety of manipulations, including stress. The present study tested whether two different schedules of stressor presentation, i.e., predictable and unpredictable, for 10 days, can modify the discriminative stimulus effects of cocaine in male rats trained to discriminate cocaine (10 mg/kg, i.p.) from saline. Further, dopamine (DAT), serotonin (SERT) and norepinephrine (NET) transporter levels in mesocorticolimbic areas were also measured in a separate cohort of cocaine discriminating animals after stress administration to see if the relative ratio of these proteins may explain, in part, differences found in behavior. In handled controls, ED_{50s} for cocaine-like responding were stable after 10 days of handling compared to baseline. Animals exposed to both predictable and unpredictable stress displayed shifts in the cocaine dose-effect curve but with different patterns of responding. Predictable stress produced a time-dependent left-ward shift in cocaine-like responding, indicating increased sensitivity to the cocaine cue. ED_{50} estimates after unpredictable stress did not differ from baseline; however, maximal cocaine-like responding was lower at the two highest doses of cocaine tested where unpredictably stressed rats switched from predominantly cocaine- to predominantly saline-like responding (i.e., an inverted-U shaped curve). Alterations were found in DAT and NET in the Predictable stress group and in DAT and SERT in the Unpredictable stress group in select brain regions which may explain differences in behavior. These data suggest that predictable stress may heighten cocaine's discriminative stimulus through DAT/NET mechanisms while unpredictable stress may change the stimulus completely, possibly through DAT/SERT mechanisms. This study highlights the utility of drug discrimination as a sensitive tool in studying environmentally-induced brain changes.

Supported by the Mellon Foundation to ALR.

(10) The discriminative stimulus effects of nitrous oxide

Kellianne J. Richardson, Galina Slavova-Hernandez, and Keith L. Shelton
Department of Pharmacology & Toxicology, Virginia Commonwealth University, Richmond, VA

Despite the high prevalence of clinical use as well as illicit abuse, there is a limited understanding of the CNS actions of nitrous oxide (N_2O). *In vitro* studies have shown that N_2O oxide alters the function of NMDA, $GABA_A$, and nicotinic acetylcholine receptors, amongst others. However, the receptor system or systems responsible for the intoxicating, subjective stimulus effects of N_2O are uncertain. Our overarching goal is to use drug discrimination in mice to assess the neurotransmitter systems responsible for producing the discriminative stimulus effects of N_2O. We trained sixteen male B6SJLF1/J mice to discriminate 10 min of exposure to 60% inhaled N_2O/40% oxygen versus 100% oxygen in daily 5-min operant sessions. Subsequently we began substitution tests with other compounds. Positive substitution between nitrous oxide and drugs with well characterized properties suggest similar mechanisms of action. We hypothesize that if the discriminative stimulus effects of N_2O are mediated by NMDA antagonism and/or $GABA_A$ positive modulation, drugs with these mechanisms of action will fully substitute for N_2O. Thus far the NMDA channel blockers ketamine and MK-801 have shown partial substitution for N_2O. Of the 7 mice tested 3 fully substituted at 7 or 10 mg/kg ketamine. Of the 5 animals tested with MK-801, 3 fully substituted at 0.1–0.3 mg/kg. The same mice that fully substituted with ketamine also fully substituted with MK-801. Substitution of NMDA receptor competitive antagonist CGS19755 is currently being conducted. Once complete, the results of these studies will provide important information regarding the receptor systems underlying the abuse-related subjective stimulus properties of N_2O.

(11) Effects of a typical antipsychotic on the discriminative stimulus effects produced by 22 hours food deprivation

Amy R. Johnson, Jennifer E. Dobbe, Benjamin A. Kron, and David .C. Jewett
Department of Psychology, University of Wisconsin, Eau Claire, WI

We have developed and refined a food-deprivation discrimination paradigm that may serve as an animal model of 'hunger'. The dopamine antagonist chlorpromazine has been demonstrated to decrease food intake in several species. We examined the ability of chlorpromazine to reduce the effects of acute food deprivation in rats trained to discriminate between 2 and 22 hrs of acute food deprivation in an operant choice paradigm. Generalization testing began after the discrimination was acquired (~90 daily sessions). During generalization tests, subjects were food deprived for 22 hours. Thirty minutes before the tests, subjects were administered saline or chlorpromazine (0.32 – 3.2 mg/kg, i.p). Chlorpromazine did not affect the discriminative stimulus effects of 22 hour deprivation, although chlorpromazine did decrease response rates at the largest dose examined (3.2 mg/kg). Chlorpromazine also decreased food intake at larger doses tested (1.0 and 3.2 mg/kg). These findings suggest chlorpromazine alters food consumption by mechanisms other than those related to 'hunger.'

Supported by University of Wisconsin – Eau Claire Faculty/Student Research Collaboration grant