

# Behavior, Biology, and Chemistry: Translational Research in Addiction

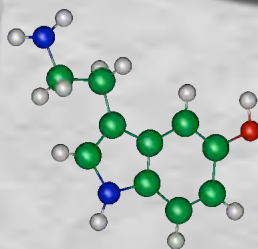


March 3-4, 2012

La Quinta Inn & Suites

Medical Center

San Antonio, TX



# Acknowledgements

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Jun-Xu Li

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# Program Overview

## Friday March 2, 2012

4:00 pm - 7:00 pm	Registration
7:00 pm - 10:00 pm	Opening Reception at Rio Rio on the San Antonio Riverwalk Buses depart from La Quinta at 7:00 PM

## Saturday March 3, 2012

7:00 am - 5:00 pm	Registration
8:00 am - 8:05 am	Welcome and Opening Remarks
8:05 am - 10:25 am	Plenary Symposium: "Relapse to drug taking: focus on corticotropin-releasing factor" Speakers: Yavin Shaham, Eric Zorrilla, Markus Heilig, Harriet de Wit (Chairs: Yavin Shaham and Bill Fantegrossi)
10:25 am - 10:40 am	Coffee Break
10:40 am - 12:00 pm	Open Oral Communications 1 (Chair: Laura O'Dell)

### 12:00 pm - 1:15 pm Lunch

1:15 pm - 2:55 pm	Open Oral Communications 2 (Chair: Jun-Xu Li)
2:55 pm - 3:10 pm	Coffee Break
3:10 pm - 4:10 pm	Special Lecture: David Nichols "Multidisciplinary approaches to the study of the 5-HT <sub>2A</sub> receptor" (Chair: Thomas Prisinzano)
4:10 pm - 4:30 pm	Poster Set-up
4:30 pm - 7:00 pm	Poster Session

### 7:00 pm - 9:00 pm Dinner

	After Dinner Speaker: John Grabowski; "Harm reduction: substitution pharmacotherapy for substance use disorders 'I want a new drug'" (Chair: Richard Meisch)
9:00 pm - 11:00 pm	Hospitality and Entertainment

## Sunday March 4, 2012

8:00 am - 9:40 am	Open Oral Communications 3 (Chair: Celeste Napier)
9:40 am - 9:55 am	Coffee Break
9:55 am - 11:15 am	Open Oral Communications 4 (Chair: Allan Kalueff)
11:15 am - 11:30 am	Coffee Break
11:30 am - 12:30 pm	Special Lecture: Phil Skolnick; "Developing medications to treat substance use disorders: why haven't we been more successful?" (Chair: Alan Frazer)
12:30 am - 12:40 pm	Presentation of travel awards and awards for oral and poster presentations
<b>12:40 pm - 1:30 pm</b>	<b>Lunch</b>
1:30 pm	Closing remarks

# Program Details

## Friday March 2, 2012 (7:00 pm - 10:00 pm)

### Opening Reception

#### Rio Rio on the Riverwalk

7:00 pm	Buses depart from La Quinta
7:30 pm - 10:00 pm	Reception at Rio Rio
9:30 pm	Buses depart for La Quinta

Come and enjoy the beautiful San Antonio Riverwalk. Buses will depart from the La Quinta hotel at 7:00 pm to take you to Rio Rio, a Mexican restaurant on the Riverwalk. Buses will return to La Quinta at 9:30 pm. You will need your badge to board the bus and for dinner. Tickets for spouses and significant others can be purchased in advance or at the registration desk for \$40.00.

## Saturday March 3, 2012

### Welcome and Opening Remarks (8:00 am - 8:05 am)

### Plenary Symposium (Chairs: Yavin Shaham, Bill Fantegrossi)

#### Relapse to drug taking: focus on corticotropin-releasing factor

High relapse rates during abstinence are a pervasive problem in drug addiction treatment. Relapse is often associated with stress exposure, which can provoke a subjective state of drug craving that can also be demonstrated under controlled laboratory conditions. Stress-induced relapse and craving in humans can be modeled in mice, rats and monkeys using a reinstatement model in which drug-taking behaviors are extinguished and then reinstated by acute exposure to certain stressors. The goal of our symposium is to provide an overview on translational research efforts based on the reinstatement model and other animal models, with a particular emphasis on the potential clinical utility of corticotrophin-releasing factor (CRF) receptor antagonists.

8:05 am - 8:40 am	<b>Yavin Shaham</b> ; National Institute on Drug Abuse, NIH Translational research based on the reinstatement model.
8:40 am - 9:15 am	<b>Eric Zorrilla</b> ; The Scripps Research Institute Progress in CRF1 antagonist development: A target at a crossroad.
9:15 am - 9:50 am	<b>Markus Heilig</b> ; National Institute on Alcohol Abuse and Alcoholism, NIH The CRH1 receptor in alcoholism: Target validation, candidate selection and early human translation.
9:50 am - 10:25 am	<b>Harriet de Wit</b> ; University of Chicago Developing translational models of behavior: Risks and rewards.

### Coffee Break (10:25 am - 10:40 am)

**Saturday March 3, 2012 (continued)****Open Oral Communications 1** (Chair: Laura O'Dell)

- 10:40 am - 11:00 am **William Giardino**, Oregon Health & Science University  
Differential involvement of urocortin-1 across several ethanol drinking paradigms in mice.
- 11:00 am - 11:20 am **Meenakshi Subbaraman**, University of California, Berkeley  
Moderation and mediation in the combine study.
- 11:20 am - 11:40 am **Maria Velez-Hernandez**, University of Puerto Rico  
Inhibition of Protein kinase Mzeta (PKM $\zeta$ ) in the mesolimbic system alters cocaine sensitization in rats.
- 11:40 am - 12:00 pm **Rachel Saylor**, Lipscomb University College of Pharmacy  
Synthesis of sterically hindered meperidine analogs: Interactions with CYP3A4 and P-glycoprotein.

**Lunch** (12:00 pm - 1:15 pm)**Open Oral Communications 2** (Chair: Jun-Xu Li)

- 1:15 pm - 1:35 pm **Zachary Pennington**, University of California, Los Angeles  
Caffeine selectively alters choice patterns during the reversal of a visual discrimination.
- 1:35 pm - 1:55 pm **Michael Ballard**, University of Chicago  
Acute d-amphetamine impairs memory retrieval at doses that enhance learning.
- 1:55 pm - 2:15 pm **David Thorn**, University of Buffalo  
Agmatine modulates some behavioral effects of methamphetamine in rats.
- 2:15 pm - 2:35 pm **Steven Graves**, Rush University Medical Center  
Methamphetamine self-administration decreases and 5-HT<sub>2C</sub> receptor agonism increases neuronal excitability in the nucleus accumbens shell.
- 2:35 pm - 2:55 pm **Leah Mayo**, University of Chicago  
Methamphetamine facilitates reward conditioning in healthy volunteers.

**Coffee Break** (2:55 pm - 3:10 pm)**Special Lecture 3:10 pm - 4:10 pm** (Chair: Thomas Prisinzano)

**David Nichols, Purdue University: "Multidisciplinary approaches to the study of the 5-HT<sub>2A</sub> receptor"**

## **Saturday March 3, 2012 (continued)**

### **Poster Set-up (4:10 pm - 4:30 pm)**

### **Poster Session (4:30 pm - 7:00 pm)**

4:30 pm - 5:45 pm Odd numbered posters should be attended by their presenters.

5:45 pm - 7:00 pm Even numbered posters should be attended by their presenters.

Poster Awards: The Awards Committee will hear oral poster presentations (5 min maximum) from students and post-doctoral fellows. One award will be made to the best student poster presentation and one award will be made for the best post-doctoral fellow poster presentation.

Poster judging (for post-doctoral fellows and students) will begin at 4:30 pm or 5:45 pm for odd and even numbered posters, respectively. Judges will begin with the lowest numbered posters and proceed to the higher numbered posters.

If you do not wish to be included in the poster competition, please notify the registration table.

### **Dinner (7:00 pm - 9:00 pm)**

Tickets for spouses and significant others can be purchased in advance or at the registration desk for \$60.00.

### **After Dinner Lecture** (Chair: Richard Meisch)

**John Grabowski, University of Minnesota: "Harm reduction: substitution pharmacotherapy for substance use disorders 'I want a new drug'"**

### **Hospitality and Entertainment (9:00 pm - 11:00 pm)**

Come and enjoy the fun in the ballroom!

**Sunday March 4, 2012****Open Oral Communications 3** (Chair: Celeste Napier)

- 8:00 am - 8:20 am **Carolina Haass-Koffler**, University of California, San Francisco  
The C-terminal fragment of corticotropin releasing factor binding protein (CRF-BP) potentiates CRF-mediated CRF-receptor 2 $\alpha$  (CRF-R2 $\alpha$ ) signaling.
- 8:20 am - 8:40 am **Jonathan Cachat**, Tulane University Medical School  
Effects of the hallucinogenic drug psilocybin on zebrafish behavior and physiology.
- 8:40 am - 9:00 am **Allan Kalueff**, Tulane University Medical School  
Developing innovative zebrafish models for drug abuse research.
- 9:00 am - 9:20 am **Brandi Blaylock**, Wake Forest University  
Effects of dopamine D3 compounds on unconditioned behaviors and food/drug choice in monkeys.
- 9:20 am - 9:40 am **Thomas M. Keck**, National Institute on Drug Abuse  
Novel mGluR5 negative allosteric modulators as tools for in vivo investigation in addiction.

**Coffee Break** (9:40 am - 9:55 am)**Open Oral Communications 4** (Chair: Allan Kalueff)

- 9:55 am - 10:15 am **Jun-Xu Li**, University of Buffalo  
The imidazoline I2 receptor agonist 2-BFI differentially modulates behavioral effects of morphine: implications for pain management.
- 10:15 am - 10:35 am **Xiu Liu**, University of Mississippi Medical Center  
Distinct neuropharmacological substrates for primary and conditioned reinforcement of nicotine in rats.
- 10:35 am - 10:55 am **M. Foster Olive**, Arizona State University  
Self-administration of the synthetic cathinone MDPV in rats and its effects on brain reward function.
- 10:55 am - 11:15 am **Jane Aldrich**, University of Kansas  
Orally active cyclic tetrapeptides as potential treatments for drug abuse.

**Coffee Break** (11:15 am - 11:30 am)**Special Lecture 11:30 am - 12:30 pm** (Chair: Alan Frazer)

**Phil Skolnick, National Institute on Drug Abuse, NIH: "Developing medications to treat substance use disorders: why haven't we been more successful?"**

- 12:30 pm - 12:40 pm Presentation of awards for travel, oral, and poster presentations

**Lunch** (12:40 pm - 1:30 pm)

- 1:30 pm Closing Remarks and Adjournment

# Abstracts

## Oral Communications

1

### Differential involvement of urocortin-1 across several ethanol drinking paradigms in mice

Giardino, William J.<sup>1</sup> and Ryabinin, Andrey E.<sup>1</sup><sup>1</sup>Department of Behavioral Neuroscience, Oregon Health & Science University; Portland OR USA.

Prior work from our laboratory showed that ethanol (EtOH) consumption resulted in robust activation of neurons containing the CRF-related neuropeptide urocortin-1 (Ucn1), and that genetic deletion of Ucn1 dampened EtOH-induced reward. The current studies investigated the experimental variables underlying Ucn1's involvement in several different EtOH drinking paradigms in mice.

Earlier studies showed that genetic deletion of Ucn1 dampened EtOH intake in a continuous access "two-bottle choice" (2-BC) EtOH drinking procedure using 3-10% EtOH, but not in a limited-access "drinking-in-the-dark" (DID) binge model in which mice had access to a single bottle of 20% EtOH. Because these two procedures differ in several aspects (EtOH concentration, concurrent water availability, length of EtOH access), we performed a series of experiments to determine the relative importance of each variable in mediating Ucn1's effects on EtOH intake.

In an altered continuous access 2-BC procedure, genetic deletion of Ucn1 dampened EtOH intake and preference at concentrations of 20% and 40%. In an altered 2-BC/DID hybrid procedure, genetic deletion of Ucn1 had no effect on EtOH intake. These results indicate that the previously observed lack of effect of Ucn1 deletion on EtOH intake in the DID protocol cannot be attributed to the high concentration of EtOH used (20%), nor the absence of water availability during EtOH access.

In conclusion, Ucn1 involvement in EtOH intake depends on the length of EtOH access (or the extent of EtOH history) rather than EtOH concentration or water availability. These findings lend further support for the importance of Ucn1 in development of alcohol use disorders resulting from prolonged alcohol self-administration, and may inform future development of alcoholism therapeutics. This research was supported by NIH grants F31AA021023 (awarded to W.J.G.) and RO1AA013738, UO1AA016647, and P60AA010760 (awarded to A.E.R.).

3

### Inhibition of Protein kinase Mzeta (PKM $\zeta$ ) in the mesolimbic system alters cocaine sensitization in rats

Velez- Hernandez, Maria E

Chronic cocaine use produces long-lasting changes in reward circuits that may underlie the transition from casual to compulsive patterns of drug use. Although strong neuroadaptations within the mesocorticolimbic system are known to occur, the specific role of these drug-induced plasticities on sensitization remains to be elucidated. Here we investigate whether PKM $\zeta$ , a protein involved in maintaining long-term potentiation (LTP), plays a role in these cocaine-induced changes in synaptic strengthening. We performed whole-cell voltage clamp recordings of putative ventral tegmental area (VTA) dopamine (DA) cells 24 hours after five days of 15 mg/kg i.p. cocaine or isovolumetric saline injections. We observed that superfusion of 5 $\mu$ M ZIP (PKM $\zeta$  inhibitory peptide) decreased AMPA currents and AMPA/NMDA ratios only in cocaine sensitized rats. In vivo ZIP microinfusions (10 nmol) into the VTA after cocaine sensitization decreased locomotor activity on a subsequent cocaine challenge only if given ZIP is given before the withdrawal period. On the other hand, ZIP microinfusions into the nucleus accumbens (NAc) core after a seven days withdrawal period disrupt the expression of locomotor sensitization. The present data provide a potentially relevant region, and time-specific PKM $\zeta$ -dependent brain mechanism, that enables sensitization. Our results support the vision that addiction involves a pathological learning process. They imply that if this synaptic strengthening is reversed, changes in the behavioral response may also be overturned.

2

### Moderation and mediation in the combine study

Subbaraman, Meenakshi S.; Lendle, S.; van der Laan, M.J. UC Berkeley

COMBINE investigators aimed to determine whether naltrexone, a drug alleged to reduce cravings for alcohol, combined with a behavioral intervention (CBI) alleged to change stress and coping behaviors, improves drinking outcomes more than either alone. Unexpectedly, the naltrexone + CBI combination did not offer any advantage over either monotherapy. To explain the combination's lack of improvement over each monotherapy, moderation and mediation analyses were performed using targeted maximum likelihood estimation (TMLE). TMLE offers several advantages over traditional approaches such as double-robustness and allowance of treatment\*mediation interaction. Cravings and stress were examined as theoretically informed mediators/moderators. Moderation analyses show that naltrexone, CBI, and the combination all work best when cravings are high, while none work when cravings are low. Similarly, naltrexone and the combination work better when stress is high. Mediation analyses show that all three treatments' effects are at least partially mediated by craving reduction, which explains 50-67% of treatment effects. Furthermore, naltrexone appears to affect cravings earlier while CBI works later. Taken together, the set of results suggests the possibility of a threshold effect: if naltrexone reduces cravings early on and CBI is not effective when cravings are low, then the combination's lack of improvement over either monotherapy should not be surprising.

4

### Synthesis of Sterically Hindered Meperidine Analogs: Interactions with CYP3A4 and P-glycoprotein

Saylor, Rachel M.<sup>1</sup> and Mercer, Susan L.<sup>1,2</sup><sup>1</sup>Department of Pharmaceutical Sciences, Lipscomb University College of Pharmacy, Nashville, TN 37204; <sup>2</sup>Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN 37232

Opioids are the standard drug class used in the treatment of chronic severe pain, providing the patient with analgesia and euphoria. Despite clinical usefulness, chronic opioid treatment leads to side effects such as tolerance, dependence, respiratory depression, nausea, and constipation. Extensive research has investigated the development of central tolerance focused at the cellular and receptor levels; however, recent studies suggest that a systems level approach including metabolism and efflux transporters is involved. The efflux transporter P-glycoprotein (P-gp) is present at the BBB, and being a P-gp substrate, morphine is actively pumped out of the CNS. Animals tolerant to morphine display up-regulation of P-gp and therefore lower levels of morphine in the brain compared to naïve animals, demonstrating that P-gp contributes to central tolerance. P-gp substrates are generally characterized as lipophilic compounds containing basic nitrogens and are also commonly CYP3A4 substrates. Most opioids have these characteristics and therefore most clinically used opioids have P-gp activity. Meperidine is an exception in that it does not have P-gp activity even though it is a lipophilic CYP3A4 substrate with a basic nitrogen, but it is not an optimal pain treatment due to low potency and toxic metabolite formation. CYP3A4 N-demethylates meperidine into normeperidine, a toxic metabolite, which leads to convulsions and potential death in accumulation. Our hypothesis is that meperidine can be optimized by introducing steric hindrance to the piperidine ring at the 2- and 6-positions to eliminate toxic metabolite formation. Preventing CYP3A4 metabolism will eliminate toxic metabolite formation and allow meperidine to be administered over a longer period of time. The synthesis of the 2,6-dimethyl and 2,2,6,6-tetramethyl analogs will be presented, along with biological analyses including opioid binding, P-gp activity, and CYP3A4 metabolism. The ideal meperidine analog maintains opioid activity, lacks P-gp interaction, and is not metabolized by CYP3A4, potentially leading to a novel opioid lacking tolerance development for use in the treatment of chronic, severe pain.



## Oral Communications

5

### Caffeine selectively alters choice patterns during the reversal of a visual discrimination

Zachary T Pennington<sup>1</sup>, Alex S James<sup>1</sup>, Emanuele Seu<sup>1</sup>, and J David Jentsch<sup>1</sup>  
<sup>1</sup>Department of Psychology, UCLA

Caffeine is believed to act primarily as an adenosine receptor antagonist. Importantly, adenosine 2A receptors (A2ARs) are densely located in the striatum, where they form heteromers with dopamine D2 receptors (D2Rs), and A2AR activation appears to functionally antagonize D2R activation. As variation in striatal D2R density and function has been linked to performance on tasks measuring inhibitory control – a phenotype thought to be relevant to the compulsive aspects of drug addiction – caffeine may also target these processes. The present study tested this hypothesis by assessing the effects of caffeine on the performance of a reversal learning task by rats. Using touch-screen based operant chambers, rats (N=22) were trained to discriminate between visual stimuli to earn food rewards. After training, the acquisition of each 3-stimulus set was followed by a reversal stage, wherein a different stimulus was rewarded than during the preceding acquisition. Caffeine (3& 15mg/kg, i.p.) was administered prior to reversal sessions. In addition, we separately examined the effects of caffeine on the acquisition of a novel discrimination, as well as on the retention of a discrimination that had been acquired in a drug-free state. Relative to saline, neither dose of caffeine altered accuracy during reversal, nor did they affect the propensity to respond to the previously rewarded cue. However, the lower dose of caffeine decreased responding to the stimulus rewarded neither during acquisition nor reversal. This same dose of caffeine did not affect the acquisition of a novel discrimination, nor did it affect retention. Additionally, in all phases, caffeine dose -dependently shortened response latencies. These findings might suggest that caffeine is capable of altering distinct learning processes, or alternatively might enable animals to direct behavior towards more task- relevant information. Differences in response latencies are consistent with prior research on dopamine's and adenosine's role in instrumental motivation.

7

### Agmatine modulates some behavioral effects of methamphetamine in rats

Thorn, David A.; Winter, Jerrold C.; Li, Jun-Xu  
 Department of Pharmacology and Toxicology, University at Buffalo, Buffalo, NY 14214, USA

Methamphetamine (MA) abuse and addiction is a significant health care problem but currently there is no effective pharmacotherapy available. The cationic polyamine agmatine attenuates abuse-related effects of opioids in preclinical studies. However, little is known whether agmatine also modifies the effects of other drugs of abuse. MA induces robust rewarding (measured with a conditioned place preference [CPP] paradigm), psychomotor sensitizing, and neurotoxicity (hyperthermia) effects in laboratory animals. This study examined the effects of agmatine on MA-induced CPP, locomotor sensitization and hyperthermia in rats. In experiment 1, MA (0.1-1.0 mg/kg, i.p.) increased the time the subjects spent in MA-paired compartment (place preference) and agmatine (10-32 mg/kg) significantly attenuated the magnitude of this preference. In experiment 2, acute MA (0.32-3.2 mg/kg) treatment increased the locomotor activity and the dose-effect curve was shifted leftward and upward during repeated MA treatment, demonstrating significant locomotor sensitization. Agmatine (32-100 mg/kg) significantly decreased small dose but had no effect on larger doses of MA-induced locomotor sensitization. In experiment 3, a large dose of MA (10 mg/kg) induced a significant hyperthermia. Although agmatine (10-32 mg/kg) alone did not affect the rectal temperature in rats, it markedly decreased MA-induced hyperthermia. Taken together, these results indicate that agmatine attenuated some behavioral effects of MA. To the extent that MA induced CPP and hyperthermia are related to its rewarding effects and neurotoxicity, respectively, these data suggest that agmatine may have some value against MA abuse.

6

### Acute d-amphetamine impairs memory retrieval at doses that enhance learning

Ballard, Michael E.<sup>1</sup>, Gallo, David A.<sup>2</sup>, de Wit, Harriet<sup>1</sup>  
<sup>1</sup>Human Behavioral Pharmacology Laboratory; <sup>2</sup>Memory Research Laboratory  
<sup>1,2</sup>University of Chicago

**Aims:** Moderate doses of stimulant drugs enhance learning in animals and humans. There is also evidence that stimulants can improve retrieval of previously-learned information in animal models, but these drugs' effects on memory retrieval have not been tested in humans. Thus, we set out to determine whether the prototypic stimulant drug d-amphetamine (AMP) enhances memory retrieval in humans at doses known to enhance learning. **Methods:** Healthy volunteers (N=30; 18-35 yrs) received AMP (10, 20 mg) or placebo at the time of retrieval across three sessions, in a double-blind, counterbalanced, crossover design. These doses of AMP were previously shown enhance learning when administered prior to encoding. Each drug condition consisted of two laboratory visits: 1) an Encoding Phase, where participants viewed pictures and words under sober conditions, and 2) a Retrieval Phase 2 days later, where drug or placebo was administered before memory was tested. Participants viewed 60 unique pictures and 30 unique words during each Encoding Phase. At Retrieval, memory was assessed by free recall, and then by recognition among novel distractors. No feedback was provided during testing, and stimuli were not re-used across sessions. Hit and false alarm rates, and overall accuracy (hit – false alarm rates) were analyzed using 2-way repeated- measures ANOVA. **Results:** AMP did not enhance retrieval. Instead, it impaired memory accuracy by increasing false alarm rates without affecting hit rates for previously-studied information. **Conclusions:** At doses that facilitate learning, AMP can impair memory retrieval in humans. This impairment is due to an increased tendency towards false recollection, rather than to reduced access to previously-learned information. That stimulant drugs may interfere with retrieval by increasing false alarms has clinical implications for individuals who use these drugs for cognition-enhancement, and adds to our understanding of how drugs of abuse can influence behavior.

**Supported By:** NIDA DA02812 & T32 DA007255

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### Methamphetamine self-administration decreases and 5-HT2C receptor agonism increases neuronal excitability in the nucleus accumbens shell

SM Graves<sup>1,2</sup>, MJ Clark<sup>3,4</sup>, JR Traynor<sup>3,4</sup>, X-T Hu<sup>1,2</sup>, and TC Napier<sup>1,2</sup>

<sup>1</sup>Dept of Pharmacol; <sup>2</sup>Ctr for Compulsive Behav & Addiction, Rush Univ Med Ctr, Chicago, IL

<sup>3</sup>Dept of Pharmacol; <sup>4</sup>Substance Abuse Res Ctr, Univ of Mich, Ann Arbor, MI

Serotonin2C receptors (5-HT2cR) are promising targets for psychostimulant pharmacotherapy. These receptors are expressed in the nucleus accumbens shell (NAcS), a key region involved in addiction. Here we first examined the consequences of methamphetamine (meth) self-administration on NAcS function and 5-HT2CR-evoked activity using whole-cell current-clamp recordings. To do so, rats were trained to self-administer meth for 14 days (vs. saline-yoked rats). Recordings were performed 1-4 days later from NAcS neurons in ex vivo brain slices. Bath application of 0.1, 1.0, and 10µM of Ro 60-0175 (Ro; 5-HT2C agonist), was compared to control aCSF perfusion. Meth self-administration attenuated action potential generation (0.35nA; \*p<0.05) with no effect on other membrane properties. Neurons from both saline-yoked and meth-treated rats responded to Ro with increased evoked action potentials and decreased afterhyperpolarization amplitudes (10µM; \*p<0.05), suggesting decreased Ca2+-activated K+ channel activity. 5-HT2CRs can engage both Gq and Gi/o. Second, to determine G protein stimulation, the NAc from meth rats was tested for [35S]GTPγS binding under two conditions, one conducive to Gi/o and one conducive to Gq stimulation. Ro (10µM) stimulated [35S]GTPγS binding under Gq but not Gi/o conditions. 5-HT2CRs were not functionally dysregulated by meth. In summary, agonism at the 5-HT2C increased excitability and stimulated Gq but not Gi/o proteins. Supported by USPHSGs DA015760, DA024923, DA04087, and the Daniel F. & Ada L. Rice Foundation

## Oral Communications

9

### Methamphetamine facilitates reward conditioning in healthy volunteers

Leah M. Mayo<sup>1,2</sup>, Diana Fraser<sup>3,4</sup>, Reza Momenan<sup>3</sup>, Daniel W. Hommer<sup>3</sup>, Markus Heilig<sup>3</sup>, Harriet de Wit<sup>2</sup>

<sup>1</sup>Committee on Neurobiology and <sup>2</sup>Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL <sup>3</sup>NIAAA, Bethesda, MD <sup>4</sup>Linköping University, Linköping, Sweden

**Aims:** Studies with laboratory animals indicate that drug-paired stimuli facilitate drug-taking behaviors and that stimulant drugs facilitate the incentive value of reward-paired cues. Previously, we demonstrated that drug conditioning also occurs in humans using a place preference procedure. In the present study, we aimed to see if a stimulant drug would enhance reward-related conditioning of images presented on a computer screen, rewarded with money

**Methods:** Healthy volunteers (18-35 years old; N=64) participated in 4 "conditioning" sessions, 2 with placebo and 2 with methamphetamine (20mg), followed by one "test" session without drug administration. Subjects were randomly assigned to a Paired Group, who received drug paired with a specific background stimulus present during a computer task or an Unpaired Group who received drug without any relation to the task stimuli. Prior to conditioning, subjects rated their preference for several tasks and background pictures. During the conditioning sessions, they performed computer tasks of varying reward pay-off, with distinctive backgrounds present during the tasks. In test sessions, preference for backgrounds was again assessed using the same rating task as before. Measures of subjective drug and mood, and physiological effects were taken several times throughout the session, as well.

**Results:** With approximately half of the subjects completed, methamphetamine induced a preference for the background with which it was paired, without affecting preference in the Unpaired Group.

**Conclusions:** Consistent with previous work, a stimulant drug can affect preference for a neutral cue paired with a reward, in this case money earned in a task.

**Financial Support:** This research was supported by NIDA DA02812 and T32 DA07255, HHMI 56006772.

11

### Effects of the hallucinogenic drug psilocybin on zebrafish behavior and physiology.

Kyza Evan\*, Cachat Jonathan\* [contributed equally], Gaikwad Siddharth, Green Jeremy, Roth Andrew, Collins Christopher, El-Ounsi Mohamed, Davis Ari, Mimi Pham, Kalueff Allan V.

Department of Pharmacology and Neuroscience Program, Tulane University Medical School, New Orleans, LA 70112, USA

Psilocybin is the principal psychoactive compound of the hallucinogenic mushrooms of the *Psilocybe* genus, and has long been known to produce euphoric and entheogenic states in humans. The current study investigated the effects of psilocybin exposure in adult zebrafish, a novel rapidly emerging animal model with significant physiological homology to rodents and humans. At the doses tested (0.5–3 mg/L, 20-min immersion), psilocybin had no overt behavioral effects in the novel tank, light-dark box and social preference tests. However, the drug showed mild hypolocomotor effect in the open field, and increased group cohesion in the shoaling tests (acting somewhat similar to shoaling effects of mescaline, Kyza et al., 2012). Finally, psilocybin produced an increase in systemic cortisol levels, which parallels the action of lysergic acid diethylamide (LSD), a drug which acts similarly to psilocybin, on zebrafish cortisol levels. Collectively, these findings indicate that the tested doses may have been insufficient to produce robust behavioral alterations in some tests, but can produce significant effects on some other fish behavioral phenotypes, as well as on zebrafish physiology (cortisol). Future studies are needed to better dissect the behavioral and physiological effects of psilocybin in adult zebrafish-based models of drug abuse.

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### The C-Terminal Fragment of Corticotropin Releasing Factor Binding Protein (CRF-BP) potentiates CRF-Mediated CRF-Receptor 2 $\alpha$ (CRF-R2 $\alpha$ ) signaling

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A stress response is believed to involve the corticotropin releasing factor (CRF) system and activation of the hypothalamic pituitary axis (HPA). The precise role of CRF-binding protein (CRF-BP) in the brain is still the subject of intense investigation. Due to its high affinity for CRF, it is believed CRF-BP plays a buffer role by reducing the amount of free CRF in the periphery. In the CNS, however, the interaction of CRF-BP with CRF-receptor 2 $\alpha$  (CRF-R2 $\alpha$ ) results in an increase receptor responsiveness to CRF. CRF-BP is susceptible to autocatalytic proteolysis yielding a larger N-terminal fragment of 27-kilodalton, CRF-BP(27kD), which retains the binding site for CRF and a smaller, 9.6-kilodalton C-terminal fragment, CRF-BP(10kD) with no apparent physiological or pathological role. Using a novel cell-based assay, we show that CRF-BP full length (FL), CRF-BP(27kD) and CRF-BP(10kD) can stably be expressed on the plasma membrane. We also demonstrated that only CRF-BP(10kD) is responsible for enhancing CRF-induced CRF-R2 $\alpha$  activity as measured by intracellular calcium release signaling assay. These results suggest that CRF-BP(10kD) may act as an endogenous allosteric modulator of CRF-R2 $\alpha$  signaling.

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### Developing innovative zebrafish models for drug abuse research.

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Drug abuse and addiction represent significant biomedical problems, and require novel therapeutic treatments and screens for compounds that alter drug-seeking behavior. Zebrafish (*Danio rerio*) represent a promising translational animal model with significant physiological homology to humans. Zebrafish are ideal for high-throughput screening due to their low cost, ease of maintenance and genetic manipulations, and robust behavioral responses to various drugs of abuse. Here, we present innovative high-throughput strategies recently developed for the thorough dissection of zebrafish phenotypes in our laboratory. First, we developed tools for 3D spatial and temporal mapping of fish exploratory behavior (Cachat et al., PLoS1, 2011) for the analysis of swimming patterns and various behavioral endpoints (including velocity, angular velocity and turning angle) following LSD, MDMA, mescaline, psilocybin, ketamine, PCP, morphine, alcohol and nicotine treatments. We also applied the Noldus EthoVision tools for analysis and visualization of videos in 3D using Track3D 2.0 software. To reconstruct the 3D position of the fish from 2D images, we used X,Y,Z coordinates and entered them in the calibration software included in Track3D suite. This approach provided a wide range of movement parameters, including speed and heading in each plane and in the 3D space. This method also offered options for data filtering, interpolation, lens correction and analysis in 3D, as well as for generating the animated 3D tracks of fish following the exposure to various drugs of abuse. The ongoing collaborative study presented here is successfully modeling the effects of numerous drugs of abuse in zebrafish behavioral paradigms, revealing their high sensitivity to various psychotropic compounds.

## Oral Communications

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### Effects of Dopamine D3 compounds on unconditioned behaviors and food/drug choice in monkeys

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Dopamine (DA) D3 receptors have been proposed as therapeutic targets for psychostimulant abuse due to their restricted pattern of distribution to meso-limbic brain regions. In this study, we investigated the behavioral effects of the D3-preferring agonist quinpirole (QNP, 0.01-0.3 mg/kg), the D3-selective partial agonist PG 619 (0.03-0.3 mg/kg), and the D2-like antagonist bupirone (BUS, 0.01-0.056) in male rhesus monkeys. First, all compounds were examined in drug-naïve monkeys (n=4) for the ability to influence yawning (D3-mediated) and hypothermia (D2-mediated). QNP dose-dependently elicited yawning that was characterized as an inverted U-shaped function, with an ascending limb (0.01-0.03 mg/kg) and a descending limb (0.1-0.3 mg/kg) which also elicited hypothermia. PG 619 attenuated QNP-elicited yawning, but not hypothermia suggesting selectivity at D3 receptors. BUS exhibited D2 actions by attenuating QNP-induced hypothermia while not altering yawning. Next, DA compounds were evaluated in food/drug choice self-administration studies for their ability to alter the reinforcing strength of cocaine (COC) and methamphetamine (METH) in monkeys (n=4/group). The lowest dose of QNP (0.03 mg/kg) attenuated both COC and METH choice with the most robust effects observed following 5-day treatments. Higher doses (0.1-0.3 mg/kg) potentiated COC and METH choice with both acute and repeated treatment. PG 619 dose-dependently attenuated drug choice in both COC and METH self-administering monkeys and this effect was greater following 5-day treatments. Though 0.056 mg/kg BUS slightly attenuated drug choice in both groups, the number of overall reinforcers was reduced indicating non-selective effects in decreasing food reinforcement. Altogether, these findings support the rationale for developing D3-selective agonists and partial agonists for the treatment of COC and METH abuse. Supported by DA12460 and NIDA-IRP.

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### The imidazoline I2 receptor agonist 2-BFI differentially modulate behavioral effects of morphine: implications for pain management

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Pain affects > 30% of US population. Opioids are effective for treating moderate to severe pain; however, their use is limited due to the unwanted effects, particularly in the treatment of chronic pain. We recently found that imidazoline I2 receptor agonists have antinociceptive activities and increase morphine antinociception for acute pain, but little is known of the effects of these drugs on chronic pain. This study examined the effects of an I2 receptor agonist 2-BFI on the antinociceptive and discriminative stimulus effects of morphine in rats. In rats with complete Freund's adjuvant-induced inflammatory pain, 2-BFI (3.2-17.8 mg/kg) and morphine (1-10 mg/kg) both dose-dependently produced significant antinociception and when both drugs were studied in combination, a synergistic interaction was observed. In rats with chronic constriction injury-induced neuropathic pain, 2-BFI (3.2-10 mg/kg) produced marked antinociception and the effects remained stable during 10 daily treatments. Daily treatment with morphine (32 mg/kg) for 7 days shifted the dose-effect curve of morphine 13-fold rightward in a procedure of acute nociception (warm water tail withdrawal, 50 °C), and co-treatment with 10 mg/kg 2-BFI and morphine shifted the dose-effect curve 3-fold rightward, demonstrating that 2-BFI attenuated the development of tolerance to morphine. In rats discriminating 3.2 mg/kg morphine from saline, 2-BFI did not produce morphine-like discriminative stimulus effects but decreased the potency of morphine under the same condition. Together, these studies suggest that 2-BFI is not only an effective analgesic for chronic pain, it also synergistically increases the therapeutic (analgesia) but decreases some unwanted (tolerance and abuse-related) effects of morphine. This interaction profile between 2-BFI and morphine suggests that the two classes of drugs could be an effective combination therapy strategy for the treatment of chronic pain.

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### Novel mGluR5 negative allosteric modulators as tools for in vivo investigation in addiction

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National Institute on Drug Abuse Intramural Research Program, NIH

The metabotropic glutamate receptor subtype 5 (mGluR5) is a promising pharmacotherapeutic target in preclinical models for a variety of conditions, including Parkinson's disease, anxiety and drug abuse. Prototypic mGluR5 negative allosteric modulators (NAMs), MPEP (Ki=16 nM) and MTEP (Ki=42 nM), have limitations on receptor affinity and selectivity. We present a novel series of aryl-substituted alkynyl analogues synthesized to evaluate structure-activity relationships and identify modifications to the MPEP pharmacophore that optimize binding affinity at mGluR5. Several novel compounds had nanomolar affinities for mGluR5 and were highly potent in an in vitro test of Gq activity. The novel high-affinity NAMs MFZ 10-7 (Ki=0.67 nM) and ZP 3-74 (Ki=2.8 nM) produced anxiolysis more potently than MPEP or MTEP in mouse models of anxiety-like behaviors. In rats, MFZ 10-7 potently inhibited cocaine self-administration and cocaine-seeking behavior in models of reinstatement and incubation of craving. Collectively, these studies have enabled us to identify novel mGluR5 NAMs as potential therapeutic tools for in vivo investigation for addiction.

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### Distinct neuropharmacological substrates for primary and conditioned reinforcement of nicotine in rats.

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Increasing evidence suggests that primary and conditioned reinforcement of drugs of abuse may be mediated by dissociable, yet connected, neurobiological mechanisms. However, less is known about the difference in neurobiological substrates for the primary reinforcement of nicotine and conditioned incentive properties of nicotine-associated cues. We used animal models of nicotine self-administration and cue-induced reinstatement of nicotine-seeking behavior to examine effects of pharmacological blockade of specific neurotransmitter receptors on nicotine intake and conditioned cued nicotine-seeking. Male Sprague-Dawley rats were trained to intravenously self-administer nicotine (0.03 mg/kg/infusion, free base) on a fixed ratio 5 schedule of reinforcement. To establish a nicotine conditioned cue, an auditory/visual stimulus (5-s tone/20-s lever light on) was associated with each nicotine infusions. The cue-induced reinstatement tests were performed after lever responding was extinguished by withholding nicotine and its cue presentation. Before the self-administration and the reinstatement test sessions, antagonists were given to block activation of specific neurotransmitter receptors. The opioid antagonist naltrexone effectively attenuated the behavioral motivational effect of nicotine cue but did not change self-administration of nicotine. In contrast, bupropion enhanced conditioned cued reinstatement of nicotine-seeking behavior although it suppressed nicotine self-administration. Antagonism of the  $\alpha 7$  but not  $\alpha 4\beta 2$  nicotinic acetylcholine receptors reversed cue-induced reinstatement of nicotine-seeking responses, which is in contrast with nicotine self-administration literature. These results suggest distinct neuropharmacological substrates underlying nicotine primary and conditioned reinforcement. This line of information would help direct clinical effort to develop pharmacotherapies aimed at reducing nicotine consumption in current smokers and preventing environmental cue-triggered relapse in abstinent smokers.

## Oral Communications

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### Self-administration of the synthetic cathinone MDPV in rats and its effects on brain reward function

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In recent years, there has been a rapid increase in the use of synthetic cathinones, often called “bath salts” or “legal highs”. The purpose of the present study was to evaluate the abuse potential of the synthetic cathinone methylenedioxypyrovalerone (MDPV). In experiment 1, three groups of rats (MDPV doses of 0.05, 0.1, and 0.2 mg/kg/infusion) were placed into 2 hr daily self-administration (SA) sessions for 10 days followed by a single 16 hr overnight progressive ratio (PR) session. Next, rat groups were split into 2 hr short access (ShA) or 6 hr long access (LgA) daily sessions for 10 days. In experiment 2, rats were implanted with electrodes into the medial forebrain bundle and trained to respond for intracranial self-stimulation (ICSS). All rats were then tested for changes in threshold ICSS values following MDPV treatment (within-subject, vehicle, 0.1, 0.5, 1.0, and 2.0 mg/kg i.p.). SA experiments revealed successful discrimination of active and inactive levers by day 5 for each dose as well as clear dose effects for total number of infusions obtained per session. The PR test revealed a significant dose effect for breakpoints indicating a greater reinforcing efficacy at higher doses. Additionally, LgA rats exhibited an escalated intake of 0.1 and 0.2 mg/kg MDPV infusions across the final 10 days of SA. A dose-dependent reduction in ICSS thresholds was observed with significant decreases at the 0.5, 1.0, and 2.0 mg/kg doses of MDPV versus vehicle. Together, these results reveal that MDPV is a potent reinforcer and activates the brain reward circuitry, suggesting a potential for abuse and dependence. This work was supported by DA025606.

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### Orally Active Cyclic Tetrapeptides as Potential Treatments for Drug Abuse.

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We are exploring a series of novel cyclic tetrapeptides possessing activity at kappa opioid receptors (KOR) as potential treatments for drug abuse. Cyclic tetrapeptides are stable to proteases, and therefore we expected them to remain active following systemic, including oral, administration. A lead cyclic tetrapeptide dose-dependently antagonized the antinociception induced by the KOR selective agonist U50,488 in C57BL/6J mice tested in the 55°C warm water tail withdrawal assay following both subcutaneous and oral administration. Furthermore, following oral administration this peptide dose-dependently antagonized antinociception induced by U50,488 administered centrally (100 nmol intracerebroventricular), and could be detected in the brain by LC-MS/MS, demonstrating that the orally administered peptide crosses the blood-brain barrier to antagonize KOR in the central nervous system. This peptide administered orally also prevented stress-induced reinstatement of cocaine conditioned place preference, consistent with previous demonstrations with KOR antagonists. These data validate the use of cyclic peptides that are stable to metabolism as potentially useful therapeutics. Research supported by NIDA grant R01 DA023924 and by the State of Florida.

## Poster Communications

1

**The organic cation transporter blocker, decynium-22, enhances the ability of the SSRI fluvoxamine to inhibit serotonin clearance and produce antidepressant-like behavioral effects in mice: novel targets to treat depression**

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Mood disorders cause much suffering and lost productivity worldwide. This is compounded by the fact that at least half of patients are not effectively treated by currently available medications. The most commonly prescribed antidepressant drugs are the selective serotonin (5-HT) reuptake inhibitors (SSRIs), which act by blocking the high-affinity 5-HT transporter (SERT). The increase in extracellular 5-HT produced by SSRIs is thought to be critical to initiate downstream events needed for therapeutic effects. A potential explanation for their limited therapeutic efficacy is the recently characterized presence of low-affinity, high-capacity transporters for 5-HT in brain, [i.e. organic cation transporters (OCTs) and plasma membrane monoamine transporter (PMAT)], which may limit the ability of SSRIs to increase extracellular 5-HT. Decynium-22 (D-22) is a blocker of these transporters, and using this compound we recently uncovered a significant role for OCTs in 5-HT uptake in mice genetically modified to have reduced or no SERT expression (1). This raised the possibility that pharmacological inactivation of D-22-sensitive transporters might enhance the neurochemical and behavioral effects of SSRIs. Here we show that in wild-type mice [3H]D-22 binding sites are richly expressed in hippocampus, and that D-22 enhances the effects of the SSRI fluvoxamine to inhibit 5-HT clearance and to produce antidepressant-like activity. Our findings provide a mechanistic basis for poor therapeutic outcome following treatment with SSRIs, and point to D-22-sensitive transporters as novel targets for new antidepressant drugs with improved therapeutic potential.

3

**The Role of mGluR2 in the Discriminative Stimulus Effects of Hallucinogens**

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Unlike most abused drugs, the mechanism of action of hallucinogens is not well understood. Metabotropic glutamate 2 receptors (mGluR2) may be necessary for manifestation of hallucinogenic effects. DMT produces short visual, episodic hallucinations. In contrast, DiPT is a structurally similar analogue that produces auditory effects. The role of mGluR2 in mediating behavioral effects of DiPT and DMT was investigated using drug discrimination. LY379268 (mGluR2/3 agonist) was tested for blockade and LY341495 (mGluR2/3 antagonist) for facilitation of discriminative stimulus effects. LY379268 partially blocked the discriminative stimulus effects of DMT, but not of DiPT. Low dose LY341495 facilitated the effects of DMT, whereas only the high dose facilitated the effects of DiPT. These findings indicate that the mGluR2 does modulate the discriminative stimulus effect of serotonergic hallucinogens and may have a greater effect on visual than auditory hallucinations. Research on DiPT and DMT may give further insight into the mechanisms of auditory versus visual hallucinations, which may be of direct relevance to understanding both why humans use hallucinogens and the mechanisms of auditory hallucinations that occur with schizophrenia.  
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**Priming-Induced Reinstatement of Drug-Seeking Behavior under Choice Conditions.**

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The present studies were conducted to study the reinstatement of drug-seeking behavior by reinforcing drugs when other reinforcement is available. First, monkeys were trained to self-administer cocaine, ketamine, or oxycodone under concurrent schedules of i.v. drug self-administration and food delivery (choice conditions). Reinstatement by priming with drug injection was studied during sessions in which saline was available for self-administration; under control conditions, behavior was allocated exclusively to the schedule of food reinforcement during sessions of saline availability. First, the ability of self-administered or pharmacologically-related drugs to instigate drug-seeking behavior was compared to results of previous reinstatement studies using other means, e.g., during extinction in conditioned place preference or single-schedule self-administration procedures. Next, studies were conducted to examine the ability of daily buprenorphine (0.1-0.32 mg/kg/day) to attenuate the priming effects of oxycodone or other opioids. Results of initial experiments indicate that, under choice conditions, priming injections of reinforcing drugs may vary in their ability to instigate drug-seeking behavior under choice conditions: opioids or monoaminergic stimulants such as cocaine were fully effective in reinstating drug-seeking behavior, dopamine D2 agonists had mixed effects, and ketamine, though it displayed consistent reinforcing effects under choice conditions, was an ineffective priming stimulus. In subsequent studies, previously-effective doses of both high- and low-efficacy opioids (e.g., oxycodone and nalbuphine, respectively) lost their ability to reinstate drug-seeking behavior in buprenorphine-treated monkeys; experimental data suggest this reflected buprenorphine-induced tolerance. Of interest, the priming effects of high-efficacy, but not low-efficacy, opioids was regained by increasing priming dose. These data suggest that, in clients treated with buprenorphine, opioids may retain their ability to provoke relapse (or to produce other opioid effects) in an efficacy-dependent manner. Overall, these studies illustrate the utility of choice procedures for studies of relapse-related phenomena in non-human primates.

4

**Discovery of Novel Potent Positive Allosteric Modulators of AMPA Receptors for Preventing Neuroapoptosis**

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Early postnatal glutamatergic hypofunction induced by blocking NMDA receptors (NMDARs) with open channel blockers causes robust acute neuroapoptosis in developing brains of rodents and nonhuman primates. AMPA receptor (AMPA) activation is essential for NMDAR-mediated glutamatergic neurotransmission since the activation of AMPARs and subsequent depolarization of the postsynaptic membrane relieves the voltage-dependent Mg<sup>2+</sup> block of the NMDAR channels, which in turn augments NMDAR function and enhances synaptic efficacy. Therefore, the development of potent AMPAR positive allosteric modulators (PAMs) aimed at correcting NMDAR-mediated glutamatergic hypofunction has translational value in fostering novel strategies as therapeutic interventions for relevant cognitive abnormalities involving glutamatergic hypofunction including schizophrenia, Alzheimer's disease, addiction, and ADHD. In this work, we designed, synthesized and pharmacologically evaluated a new class of bivalent ligands targeting dimeric AMPARs subunits (i.e. GluA1 and GluA3) with the aid of molecular modeling. From our preliminary studies, we have identified two potent bivalent AMPAR ligands HJC-1-22 and HJC-1-24 that significantly modulate the effect of phencyclidine (PCP)-induced caspase-3 activities in organotypic slices with IC50 values of 15 nM and 5 nM, respectively. These bivalent ligands are at least 200-fold more potent than cyclothiazide (CTZ) and amiracetam, the two commercially available AMPAR PAMs. Moreover, HJC-1-22 pretreatment (0.1-10 mg/kg, s.c.) has been demonstrated to significantly reduce PCP (10 mg/kg)-induced cleaved caspase-3 immunoreactive neurons in frontal cortex (M2/1) of PND7 rats. These newly identified AMPAR PAMs will advance the search for new drugs effective in the treatment of human diseases involving cognitive deficits, including schizophrenia and potentially addiction.

## Poster Communications

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### Effects of the hallucinogenic drug psilocybin on zebrafish behavior and physiology: importance of neuroendocrine biomarkers.

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Psilocybin is the principal psychoactive compound present in the hallucinogenic mushrooms of the *Psilocybe* genus. This compound has been used by native peoples for centuries for its ability to produce euphoric and entheogenic states. The current study investigated the effects of psilocybin exposure in adult zebrafish, a novel rapidly emerging animal model with significant physiological homology to rodents and humans. At the doses tested (0.5, 1 and 3 mg/L), psilocybin had no overt behavioral/locomotor effects in the novel tank test, upon a 20-min exposure via immersion. Also, psilocybin had no effect on zebrafish behavior in the light-dark box, open field, social preference and shoaling tests at these doses. However, psilocybin produced a consistent increase in systemic (whole-body) cortisol levels (assessed by ELISA), which are generally associated with responsiveness to stress, but may also reflect specific hallucinogenic-like states (Kyzar et al., 2012). These physiological effects parallel the action of lysergic acid diethylamide (LSD), a drug which acts similarly to psilocybin, on zebrafish cortisol levels. Future studies are needed to determine the behaviorally relevant dose range of psilocybin in adult zebrafish. Collectively, our findings indicate that although the tested doses may have been insufficient to produce robust behavioral alterations, they were sufficient in producing significant effects on zebrafish physiology, emphasizing the importance of novel neuroendocrine biomarkers of drug abuse and addiction-related states.

7

### Discriminative stimulus effects of mecamylamine in nicotine-treated and untreated rhesus monkeys.

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Nicotine withdrawal is one of the challenges associated with quit attempts in cigarette smokers. This study examined mecamylamine-induced nicotine withdrawal using drug discrimination in rhesus monkeys. As a control, the capacity of mecamylamine to serve as a discriminative stimulus in the absence of nicotine treatment was examined. Four rhesus monkeys received continuous s.c. infusion of 5.6 mg/kg/day of nicotine base and discriminated 1.78 mg/kg s.c. mecamylamine from saline under a fixed ratio 5 schedule of stimulus-shock termination. The same schedule parameters were used to train mecamylamine (5.6 mg/kg) as a discriminative stimulus in the absence of nicotine treatment in four separate rhesus monkeys. Mecamylamine increased drug-lever responding in both nicotine-treated and untreated monkeys; ED50 values of mecamylamine were 0.86 mg/kg and 2.5 mg/kg, respectively. Nicotine, when administered acutely up to a dose of 5.6 mg/kg base in addition to chronic nicotine treatment (5.6 mg/kg/day) didn't attenuate the discriminative stimulus effects of mecamylamine. Similar results were obtained in untreated monkeys, i.e., nicotine (up to 10 mg/kg) failed to attenuate the mecamylamine discriminative stimulus. Discontinuation of nicotine treatment resulted in an immediate (i.e., within 24 h) switch from the vehicle to the mecamylamine lever in some but not all monkeys. Mecamylamine was more potent as a discriminative stimulus in nicotine-treated as compared with untreated monkeys. This might reflect a qualitative difference among the discriminations, with the effects of mecamylamine in nicotine-treated monkeys being due to antagonism of nicotine and perhaps nicotine withdrawal. However, discontinuation of continuous nicotine treatment didn't mimic the effects of mecamylamine in all monkeys and increasing doses of nicotine did not attenuate the effects of mecamylamine. The non-competitive antagonism of nicotine by mecamylamine appears to limit the utility of this approach as a strategy for examining pharmacologic modification of nicotine withdrawal.

6

### Two weeks of exposure to cocaine impairs performance in attentional set shifting task.

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Attentional set shifting tasks, a rodent analog of the Wisconsin Sorting Task (WST), measure executive functioning in the frontal cortex of a rodent model, namely rule learning and decision making. Two week exposure to cocaine has been shown to impair performance on reversals in stimuli. Interestingly, not much work has been done in a specific type of stimuli shifts, the extradimensional shift (EDS) in which the irrelevant medium (odor or digging) becomes the relevant medium. This study focused on the impact of cocaine on extradimensional shift (digging medium to odor and vice versa). Rats were food restricted to 85% body weight and then trained to dig in flower pots for a food reward. After learning the behavior of digging to obtain food, the rats were tested in a series of trials where they must dig to obtain food, as during training, but now the pot with food has either a specific scent or a digging medium. Performance was measured by the number of trials needed to get six correct responses. In general, rats exposed to two weeks of cocaine (12mg/kg) required more trials (M=17) than control rats (M=11.75) in the extradimensional shift. More specifically, two-week cocaine exposure has an impact on the medium switch depending on either odor to digging or digging to odor. Exposure to daily cocaine infusions for two weeks negatively impaired the rats when the relevant stimuli in the EDS becomes odor more so than when the relevant stimuli in the EDS becomes digging medium (p=.01). Future studies aim to get a better idea of the level of effect long-term exposure to cocaine has on attentional set shifting, a model of frontal cortex function.

8

### Exploration of Synthetic Approaches and Pharmacological Evaluation of PNU-69176E and Its Stereoisomer as 5-HT<sub>2C</sub> Receptor Allosteric Modulators

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Allosteric modulators of the 5-HT<sub>2C</sub> receptor (5-HT<sub>2CR</sub>) present a unique drug design strategy to augment the response to endogenous 5-HT in a site- and event-specific manner with great potential as novel central nervous system probes and therapeutics. To date, PNU-69176E is the only reported selective positive allosteric modulator of 5-HT<sub>2CR</sub>. For the first time, an optimized synthetic route to readily access PNU-69176E (1) and its diastereomer 2 has been established in 3.2% and 3.6% overall yields, respectively, over ten steps starting from commercially available picolinic acid. This synthetic approach not only enables a feasible preparation of a sufficient amount of PNU-69176E for use as a reference compound for secondary pharmacological studies, but also provides an efficient synthesis of key intermediates to develop novel and simplified 5-HT<sub>2CR</sub> allosteric modulators. PNU-69176E (1) was functionally characterized as a selective positive allosteric modulator of 5-HT<sub>2CR</sub> using an intracellular calcium (Ca<sup>2+</sup>) release assay in a cell culture model, while its diastereomer (2) demonstrated no allosteric modulation of 5-HT<sub>2CR</sub> function in this assay. The *in vivo* behavioral studies of PNU-69176E in cocaine addiction animal models are under way.

## Poster Communications

9

### **It may leave a bitter taste in your mouth: Negative after effects of sucrose fading on ethanol consumption**

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**Abstract:** Several procedures have been developed to establish ethanol drinking in rodents. Two commonly used are the "sucrose-fading" procedure (Samson, 1986) and the intermittent-access procedure (Simms et al., 2009). Though both procedures have advocates, there is little work directly comparing their effects. The purpose of the present experiment was to compare the procedures in a within-subject design. Six rats were trained to drink a 16% (w/v) ethanol solution via intermittent access; ethanol was available in the home cage 24 hrs per day for 3 days each week. Once rats began drinking reliably, rats were moved to lickometers to measure drinking and the daily access reduced to 8% ethanol for 30 min per day. After 30 days, rats were exposed to a sucrose fading procedure, where 10% (w/v) sucrose was added to ethanol and faded out completely over ten sessions. Following intermittent access, rats drank pharmacologically active doses of ethanol (0.5 g/kg per 30 min). Addition of sucrose substantially increased intake. Interestingly, as sucrose was faded from the solution, intake levels dropped below those established via intermittent access and did not recover after 30 days. The results suggest that training with sucrose may be detrimental to alcohol initiation in rodents.

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### **The role of NGF and PLAMS in the transition from acute to chronic pain**

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The management of pain remains a major health care problem due to an incomplete understanding of pain mechanisms, especially those involved in the transition from the acute to the persistent/chronic pain state. Several reports suggest that NGF appears to be a sufficient stimulus, in humans, to trigger the transition to a persistent pain state. However the mechanisms mediating this transition are unknown. We have tested the central hypothesis that NGF regulates the transition from acute pain to chronic pain via increased TRPV1 activities endogenous TRPV1 agonists, the oxidized linoleic acid metabolites (OLAMs). Rats were injected with NGF for 5d and then tested for thermal and mechanical allodynia in the hind paw up to 15 days after the last injection. Data were analyzed by ANOVA. NGF triggered a persistent thermal and mechanical allodynia that extended up to 11d. Further, the allodynia was significantly reversed by a protein synthesis inhibitor ( $p < 0.01$ ) and by capsaizepine ( $p < 0.001$ ). Thus, NGF induction of a prolonged thermal and mechanical pain state requires de novo protein synthesis and is TRPV1-dependent. To further understand the mechanism of NGF effects on chronic pain, NGF-treated rats were injected with a CYP/LOX inhibitor, NDGA. Our data showed that NDGA reduced NGF effects ( $p < 0.001$ ). We have previously shown that NDGA blocks OLAM synthesis suggesting that the effects of NGF on chronic pain may be in part due to increased OLAM activities in the body. Taken together, the results demonstrate that NGF produces prolonged thermal and mechanical allodynia after injections into rats, and this requires de novo protein synthesis and appears to produce mechanical allodynia via the formation of oxidized agonists to TRP channels. Demonstration of the mechanisms by which NGF triggers the transition to a persistent/chronic pain state may have considerable medical implications by identifying novel targets for analgesic development and equally important scientific implications by revealing critical mechanisms of chronic pain.

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### **Firing properties of dopamine neurons in the ventral tegmental area of Grb10-knockout mice.**

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Growth factor receptor-bound protein 10 (Grb10) is an adaptor protein that interacts directly with the insulin receptor (IR), insulin-like growth factor-I receptor (IGF-IR), and other mitogenic receptor tyrosine kinases. Endogenous Grb10 has been shown to be a negative regulator of insulin signaling and action in vivo. The Grb10 gene is located near dopa decarboxylase, an enzyme that catalyzes the synthesis of dopamine. We found that Grb10 is highly expressed in the ventral tegmental area (VTA) and localized in tyrosine hydroxylase (TH)-positive dopamine neurons in this region. In this study, we examined firing properties of VTA dopamine neurons in mice with targeted deletion of Grb10 in the brain. Extracellular recordings of individual dopamine neurons revealed a significantly lower average firing rate and a tendency to decrease in burst firing of Grb10-deficient mice when compared to their wildtype littermates. Locomotor activity was monitored for 24 h and showed an increase in the dark cycle in brain-specific Grb10-deficient mice. These results suggest that Grb10 is involved in the regulation of VTA dopamine neuron firing and locomotion.

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### **Reward thresholds in rats selectively bred for high (HiS) and low (LoS) saccharin intake during acute morphine administration and morphine withdrawal.**

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Rats that have been selectively bred for high (HiS) or low (LoS) saccharin intake display drug-prone and -resistant profiles, respectively. To investigate the mechanisms driving these divergent traits, we examined reward thresholds using the intracranial self-stimulation paradigm under various conditions in the HiS and LoS rats. Using a discrete trial procedure, animals were trained to self-administer an electrical current to the medial forebrain bundle via surgically implanted electrodes. Following training, reward thresholds were established by assessing the minimum current that would maintain contingent responding for stimulation by the animals. Once stable baselines were reached, thresholds were again assessed 4-hrs after a morphine injection (10 mg/kg) for 8 days. Next, rats received only saline injections until they again reached stable threshold baselines. Last, we examined thresholds during precipitated withdrawal. During this 4-day phase, testing occurred 5-min after a naloxone injection (1 mg/kg) that was preceded 3-hrs and 55-min by a morphine injection (10 mg/kg). Results indicated that acute morphine administration lowered thresholds in the HiS rats more than the LoS rats. Obversely, precipitated morphine withdrawal increased reward thresholds in the LoS rats more than the HiS rats. These results suggest that HiS rats may be more sensitive to the acute effects of morphine and less sensitive to morphine withdrawal compared to the LoS rats. Thus, phenotypic variation in addiction vulnerability may result from differential sensitivity to both the rewarding and aversive effects of abused drugs.

## Poster Communications

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### The apparent relationship between cannabinoid agonist efficacy and tolerance/cross-tolerance in rhesus monkeys.

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In recent years, several products sold as incense in headshops, such as K2, have rapidly emerged as legal substitutes for cannabis due to their cannabinimetic effects when smoked or consumed. The synthetic cannabinoids often found in these products, such as JWH-018 and JWH-073, mimic Δ9-THC by acting on cannabinoid (CB) receptors. However, compared to marijuana, use of these alternatives of cannabis is associated with an apparently higher prevalence of severe adverse affects, such as hypertension, tachycardia, agitation, seizures or panic attacks. One potential reason for the adverse effects is higher efficacy of JWH-018 and JWH-073 related to Δ9-THC. One approach that is sensitive to differences in efficacy is to reduce receptor reserve by chronic agonist administration. When tolerance and cross-tolerance develop, the magnitude of change is less for the agonist with high efficacy as compared to the agonist with low efficacy. The present study used drug discrimination to test the hypothesis that the magnitude of tolerance and cross-tolerance produced by Δ9-tetrahydrocannabinol (Δ9-THC) varies inversely with cannabinoid agonist efficacy. Four rhesus monkeys discriminated 0.1 mg/kg of Δ9-THC i.v. from vehicle under a fixed ratio 5 schedule. Sensitivity to cannabinoid agonists (rank order efficacy in vitro reported to be CP 55940 = JWH-018 = JWH-073 > Δ9-THC) was determined before and after 14 days of Δ9-THC treatment (1 mg/kg/day s.c.). CP 55940, JWH-018 and JWH-073 fully substituted for the discriminative stimulus effects of Δ9-THC. After 14 days of Δ9-THC treatment, the potency of all cannabinoid agonists to produce discriminative stimulus effect was decreased. ED50 values were increased for Δ9-THC 8.3-fold, for CP 55940 4.2-fold, for JWH-018 3.3-fold and for JWH-073 5.4-fold. The greater magnitude of change in sensitivity to Δ9-THC relative to CP 55940, JWH-018 and JWH-073 in this study suggests that cannabinoid agonist efficacy is an important determinant of behavioral effects especially under conditions of chronic Δ9-THC treatment. Supported by USPHS grant DA 19222.

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### Functional selectivity of kappa opioid receptor (KOR) agonists in peripheral sensory neurons.

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Functional selectivity is a term used to describe the ability of drugs to differentially activate signaling cascades coupled to a single receptor subtype. Here we studied the functional selectivity of two KOR agonists, U50488 and Salvinorin A (Sal A), measuring activation of Extracellular Signal-Regulated Kinase (ERK) and inhibition of PGE2-stimulated cAMP accumulation in primary sensory neuron cultures, and inhibition of PGE2-stimulated thermal allodynia following intraplantar (i.pl.) injection in the rat hindpaw. In vitro, both agonists inhibited PGE2-stimulated cAMP accumulation in a pertussis toxin (PTx)-sensitive manner and increased ERK activity. However, although U50488-stimulated ERK activity was sensitive to treatment with PTx (i.e., Gi-protein mediated), Sal A-stimulated ERK activity was PTx insensitive (i.e., Gi-protein independent). In vivo, U50488 and Sal A reduced PGE2-induced thermal allodynia; however for both agonists, the dose-response curve for anti-allodynia was an inverted U-shape. Consistent with reports of increased ERK activity leading to pro-nociception, the downward phase of the inverted U-shaped curve for U50488 was reversed by a MEK inhibitor, U0126, which prevents activation of ERK. However, the MEK inhibitor did not affect the inverted U-shaped curve for Sal A. Since previous studies have shown that activation of c-Jun N-terminal kinase (JNK) disrupts KOR signaling, we examined the effect of JNK inhibition on Sal A-mediated thermal anti-allodynia. In the presence of the JNK inhibitor, SP600125, the downward phase of the inverted U-shaped curve for Sal A was reversed. These data suggest that KOR agonists, U50488 and Sal A, differentially activate ERK and JNK, respectively and underscore the functional selectivity profile of KOR agonists in peripheral sensory neurons. Understanding mechanisms by which KOR agonist efficacy in the periphery is regulated may lead to improved pharmacotherapy for treatment of pain with reduced adverse effects.

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### Changes in potency of benzodiazepines and not neuroactive steroids with repeated benzodiazepine administration in rats discriminating midazolam

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Benzodiazepines and neuroactive steroids are positive GABAA modulators, although they act at different sites on GABAA receptors. After prolonged clinical use, tolerance develops to benzodiazepines, requiring larger doses of the drug in order to have the same, desired effects. In contrast, cross tolerance does not develop to neuroactive steroids, indicating the possibility of using neuroactive steroids as a therapeutic alternative to benzodiazepines. The purpose of this study was to identify whether cross tolerance developed to the discriminative stimulus effects of neuroactive steroids in benzodiazepine-tolerant rats. Four rats discriminated 0.32 mg/kg of the benzodiazepine midazolam under a fixed-ratio 10 schedule of food presentation. Dose-effect curves for midazolam and the neuroactive steroid pregnanolone were generated prior to and after 3 days of daily treatment with 3.2 mg/kg of the benzodiazepine flunitrazepam. Midazolam and pregnanolone both produced ≥80% drug-lever responding in otherwise untreated rats. After 3 days of flunitrazepam treatment, the midazolam dose-effect curve was shifted 3-fold to the right, and the pregnanolone dose-effect curve was not changed. Thus, tolerance develops to the discriminative stimulus effects of benzodiazepines and cross tolerance does not develop to the discriminative stimulus effects of neuroactive steroids; suggesting that neuroactive steroids might provide clinical benefits by retaining the therapeutic effects of benzodiazepines while reducing one prominent adverse effect. Research supported by the USPHS grant R01 DA017240 and R25 GM097632.

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### Empirical Validation of a Novel Touch-Sensitive Apparatus to Test Drug Effects in Squirrel Monkeys

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Despite the increasing sophistication and affordability of touch-sensitive technology, its use in the behavioral and pharmacological sciences has been limited. This poster describes the design and empirical validation of a novel isolated touch-sensitive operant conditioning chamber for use with squirrel monkeys. In addition, an overview of studies on Repeated Acquisition and Discrimination Reversal (animal models of learning) are presented. Results indicate that response rates on the screen approximate those obtained using conventional manipulanda (e.g., response levers) and provide evidence of the reliability and sensitivity of the screen as a response transducer. Rate of discrimination acquisition increased across sessions indicating that squirrel monkeys can effectively learn new discriminations (and reversals) with complex visual stimuli. In addition, a stable baseline of acquisition rate can be obtained for the assessment of drug effects on learning. Data from studies with Δ9-THC reveal orderly dose-related effects on performance that agree with previous reports using conventional approaches. Overall, the ability to program 1) near-limitless variety of complex stimuli and 2) variability in spatial location define two major advantages of this touch-sensitive operant apparatus.



## Poster Communications

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### Deepened Extinction of Cocaine Cues

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Research with non-drug cues has shown that simultaneously presenting (compounding) those cues during extinction can enhance the effectiveness of extinction. The present study investigated whether this procedure could be used to similarly deepen the extinction of cocaine cues. Rats were first trained to self-administer cocaine during tone, click, and light stimuli. Then, these stimuli were subjected to extinction in an initial phase where they were presented individually. In a second extinction phase, one of the auditory stimuli (counterbalanced) was compounded with the light. The other auditory stimulus continued to be presented alone. Rats were then given a week of rest in their homecages prior to testing for spontaneous recovery of cocaine seeking. The cue subjected to the deepened extinction treatment occasioned less spontaneous recovery than the cue that was always presented individually during extinction. Increasing the number of compound cue extinction sessions did not enhance the effect. Results of the present experiment extend the deepened extinction effect from non-drug cues to drug cues. Incorporating deepened extinction into extinction-based drug abuse treatments could help to neutralize the power of drug cues.

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### Extended access to methamphetamine self-administration alters dopaminergic systems in adult male rats.

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Previous studies have demonstrated that repeated administration of methamphetamine produces persistent deficits in dopaminergic systems; and that in rat models extended access to methamphetamine in a self-administration paradigm results in escalation of drug intake versus limited access animals. In order to compare molecular changes in the dopaminergic system under conditions of extended access (binge model), adult male Wistar rats (n=5 extended, n=3 limited, n=4 naïve) were allowed either an extended (6 hr) or limited (1hr) access to methamphetamine for self administration for a period of 30 days. Control rats received surgical implantation of intravenous catheters, but were not given access to methamphetamine. All rats were sacrificed 72 hours after the final self-administration session and striatal tissues were then subjected to Western blot analysis for levels of tyrosine hydroxylase (TH) and dopamine transporter (DAT). Results demonstrate that rats given extended access to methamphetamine displayed escalation within the first 60 minutes of each session, an effect not seen in the limited access group. Western-blot analyses of striatal tissue revealed a decrease in immunoreactivity for TH and an increase for DAT in both groups of methamphetamine self-administration rats as compared to naïve controls. Ongoing studies will examine whether observed changes in the dopaminergic systems are related to compensatory and/or neurotoxicity associated with methamphetamine use and withdrawal. This study was funded by the following grants: 1 R24 DA029989, 5 G12 RR008124, and 2T34GM008048

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### Effects of eating high-fat chow and of repeated cocaine treatment on sensitization to cocaine in female rats.

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Cocaine, a drug that alters dopamine systems, is used recreationally and can lead to addiction. Eating a diet high in fat has been shown to modify sensitivity to the effects of cocaine on locomotion in rats. This ongoing study examines whether a history of eating high-fat chow or a history of repeated testing with cocaine alters sensitivity to locomotor effects of cocaine. Cocaine was studied in 5 groups of adolescent (starting at PND 26) female rats: 1 group had free access to standard chow (5.7% fat) and was tested once per week with cocaine for 8 weeks; 2 groups had restricted access to high- (34.3%) fat chow throughout (body weight matched to rats eating standard chow); and 2 groups had restricted access to high-fat chow for 4 weeks followed by free access to standard chow for 4 weeks. Half of the rats eating high-fat chow for 8 weeks and half eating high-fat chow then standard chow were tested with cocaine weekly for 8 weeks; the other half of rats were tested with cocaine for 4 weeks then with saline for 3 weeks followed by a final cocaine test. Across weekly tests, sensitivity to cocaine increased in all rats, although to a much greater extent in rats eating high-fat chow. When rats that previously ate high-fat chow ate standard chow, their sensitivity to cocaine returned to what was observed in rats eating only standard chow. Rats that ate high-fat chow throughout the study, but were not tested with cocaine for 3 weeks before a final cocaine test, continued to show a greater response to cocaine as compared with rats eating standard chow and tested every week with cocaine. These results suggest that increased sensitivity to cocaine in adolescent female rats eating high-fat chow is reversible; however, increased sensitivity to cocaine persists in rats eating high-fat chow even when rats are no longer receiving cocaine. Supported by K05DA17918 (CPF).

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### Interactions between the CB1-receptor agonist CP55940 and $\mu$ -opioid receptor agonists in rhesus monkeys: antinociception, discrimination, and self-administration.

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Cannabinoid receptor agonists can alter the behavioral effects of  $\mu$ -opioid receptor agonists in rhesus monkeys. The nature of the interaction suggests that the combination of cannabinoid and  $\mu$ -opioid receptor agonists might enhance some of the therapeutic effects of opioids (e.g., analgesia) without similarly enhancing their abuse-related effects. The current study examined the effects of acute administration of the high-efficacy CB1-receptor agonist CP55940 in combination with  $\mu$ -opioid receptor agonists under thermal-antinociception, drug-discrimination, and self-administration procedures in rhesus monkeys. In a warm water tail withdrawal procedure (n=4), morphine (s.c.; 0.32-10.0 mg/kg) dose dependently increased tail withdrawal latency from warm (50 and 55°C) water. CP55940 (s.c.; 0.01-0.056 mg/kg) shifted the morphine dose-effect curve leftward, indicating a clear enhancement of the antinociceptive effects of morphine. In monkeys discriminating 3.2 mg/kg morphine from saline under a stimulus-shock termination schedule (n=3), morphine (s.c.; 0.32-3.2 mg/kg) dose-dependently increased drug-lever responding. CP55940 (s.c.; 0.01-0.056 mg/kg) failed to enhance the discriminative stimulus effects of morphine, resulting in either no shift or rightward shifts in the morphine dose-effect curve. In monkeys lever pressing for i.v. drug infusions (n=5), heroin (0.00032-0.032 mg/kg/infusion) dose-dependently increased then decreased the number of infusions taken per session. CP55940 (i.v.; 0.01-0.032 mg/kg) produced rightward and downward shifts in the heroin dose-effect curve, indicating a failure to enhance the reinforcing effects of heroin. Like other CB1-receptor agonists (e.g.,  $\Delta^9$ -THC), CP55940 enhances the antinociceptive effects of  $\mu$ -opioid receptor agonists at doses that fail to enhance, and in some cases attenuate, their discriminative stimulus and reinforcing effects. These data support the view that combinations of cannabinoid and  $\mu$ -opioid receptor agonists might offer enhanced therapeutic benefit (e.g., analgesia) in the absence of enhanced abuse liability. Supported by USPHS Grants R01DA05018, K05DA17918 (CPF), and T32DA031115 (DRM).

## Poster Communications

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### Delta and Kappa Opioid Receptor (DOR-KOR) Heteromers in Peripheral Sensory Neurons *ex vivo* and *in vivo*.

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Receptor heteromers have unique properties that make them attractive targets for pharmacotherapy including limited cellular/tissue distribution (thereby improving selectivity) and exploitation of allosteric interactions between protomers can permit exquisite fine-tuning of heteromer receptor function. Previous studies have demonstrated the existence of DOR-KOR heteromers in heterologous expression systems and possibly *in vivo* in spinal cord, but not in brain. Recently we reported that DOR-KOR heteromers exist in primary (peripheral) sensory neurons. Further, we found that functional responses of the DOR-KOR heteromer can be either enhanced or reduced depending upon the DOR-KOR ligand pairs. For example, the selective KOR antagonist, nor-BNI, differentially altered the potency and/or efficacy of the DOR agonists, DPDPE and SNC80. In the presence of nor-BNI, the DPDPE responses for both inhibition of cAMP accumulation in primary sensory neuronal cultures and inhibition of thermal allodynia in the rat hindpaw were enhanced, whereas responses to SNC80 were dramatically reduced. Here we describe allosteric effects of a DOR-KOR heteromer-selective monoclonal antibody on DOR agonist responses in peripheral sensory neurons *ex vivo* and *in vivo*. In a rat behavior model of thermal allodynia, the DOR-KOR heteromer selective antibody (10 µg; i.pl) differentially altered antinociceptive responses of DOR agonists. The antibody dramatically enhanced the antinociceptive effect of a subthreshold dose of the DOR agonist, DPDPE (0.2 µg; i.pl), to an extent that exceeded a maximally effective DPDPE dose (20 µg; i.pl). By contrast, the antinociceptive effect of the DOR agonist, SNC80 (5 µg; i.pl), was eliminated in the presence of the heteromer selective antibody. Similarly, in primary sensory neuron cultures, SNC-80-mediated inhibition of cAMP accumulation was eliminated in the presence of the DOR-KOR heteromer antibody, but not by a monoclonal antibody directed against CBI-AT1 receptor heteromers. These data suggest that, similar to allosteric interactions produced with KOR antagonists and DOR agonists, the DOR-KOR heteromer selective antibody also is an allosteric regulator of DOR agonist responses. Approaches to increase antinociceptive efficacy of opioid receptor heteromers on peripheral sensory neurons could lead to improved treatment of pain. (DA026619, DA024865 and DE14318)

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### Quantifying Ethanol Consumption Microstructure

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Recent data suggests that the pattern of ethanol drinking is an important risk factor for the development of alcohol use and abuse disorders (AUDs). Despite the relevance of pattern to risk for AUDs, pattern has received little attention in animal studies. The purpose of the present work was to begin a systematic investigation of variables determining pattern in laboratory rodents. Additionally, we sought to develop a mathematical model to quantify pattern. Pattern can be conceptualized as the relationship between periods of drinking and interbout periods without drinking; these two periods define two populations of behavior: within-bout and between-bout activity. We developed a double exponential model, which has been used to characterizing bout activity in animal foraging studies, to characterize drinking in rats. Six Long Evans rats were trained to drink 8% (w/v) ethanol without the use of sucrose. Later, 10% sucrose was added to the solution for 10 days and then removed. In the absence of sucrose, rats consumed an average of 0.5 g/kg during daily 30-min sessions. The addition of sucrose increased consumption to 1.0 g/kg. In addition, the sucrose adulteration changed the organization of drinking so that rats initiated drinking bouts more often but did not drink longer within a bout. Sucrose's ability to re-organize drinking pattern did not persist after its removal. Previous findings have suggested sucrose only alters the duration of drinking bouts, a conflation with our findings. We show the discrepancy is due to the relatively coarse way microstructure has been defined in prior studies. Our mathematical model has a wide range of applicability and holds promise for understanding and quantifying environmental and genetic determinants of drinking pattern.

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### The Role of NMDA Receptors in the Discriminative Stimulus Effects of Carisoprodol

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Carisoprodol is a commonly prescribed muscle relaxant that is widely abused. Carisoprodol's effects have been attributed to the actions of its active metabolite, meprobamate, at both GABA-A and NMDA receptor sites. However, our earlier findings confirm that carisoprodol itself also has actions at GABA-A receptors and these likely contribute to its discriminative stimulus effects. The purpose of these studies was to determine whether NMDA receptors may also be involved. The GABA-modulating compounds chlordiazepoxide (1-10mg/kg) and pentobarbital (1-25mg/kg), and the NMDA receptor blocker dizocilpine (0.03-0.3mg/kg) were tested for substitution in male Sprague-Dawley rats trained to discriminate carisoprodol (100 mg/kg, ip) from vehicle (2% methylcellulose). Chlordiazepoxide and pentobarbital fully substituted for the discriminative stimulus effects of carisoprodol, and NMDA partially substituted (55%) These findings indicate that both GABA-A and NMDA receptors are involved in mediating the discriminative stimulus effects of carisoprodol.

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### Neurotensin induces long-term depression of dopamine-mediated synaptic currents

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Dopamine (DA) neurons in the substantia nigra (SN) play an important role in movement, reward and addiction and contribute to etiology of Parkinson's disease. Neurotensin (NT), an endogenous peptide, is known to exert a neuro-modulator effect on dopamine D2 autoreceptor function in these neurons. In the present study the interaction between NT (8-13) and DA was examined using whole cell patch clamp recordings of SN dopamine neurons in mouse brain slices. Dendrodendritic dopamine D2-receptor, GIRK channel-mediated inhibitory postsynaptic currents (IPSCs) were evoked by trains of electrical stimuli. Perfusion of NT (8-13) produced an inward change in holding current and decreased the amplitude of DA IPSCs. The decrease in the IPSC persisted for the remainder of each experiment, suggesting that NT induces long-term depression (LTD) of D2 receptor-mediated IPSCs. Chelating intracellular calcium with BAPTA prevented induction of NT-induced LTD suggesting that the effect is calcium-dependent. To test whether NT-induced LTD is specific for D2 receptors or also occurs with other GIRK channel-dependent receptors we examined NT (8-13) effect on GABAB receptor-mediated IPSCs. NT (8-13) briefly decreased the amplitude of GABAB-receptor IPSCs, however the effect recovered completely suggesting that the LTD is specific to D2 receptor-mediated transmission. We next tested whether NT-induced LTD was pre- or post-synaptic by applying a brief ionophoretic application of exogenous DA to produce D2 receptor-mediated outward currents. NT induced a persistent decrease in D2 receptor currents that was smaller in amplitude than the decrease in IPSC amplitude, suggesting that NT may act both pre- and post-synaptically. Taken together, these data suggest that NT can enhance DA release by inducing LTD of D2 receptor-mediated currents in midbrain DA neurons that is D2 receptor-specific, calcium-dependent and at least partially postsynaptic. This form plasticity of dopamine D2 receptor synapses could contribute to the mechanisms of DA-related diseases.

## Poster Communications

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### Discriminative stimulus effects of varenicline, a nicotinic acetylcholine receptor (nAChR) agonist, in mice.

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Varenicline is reported to be a partial nAChR agonist with lower efficacy than nicotine. The effectiveness of varenicline as a smoking cessation aid is proposed to result from attenuation of withdrawal symptoms (i.e., agonism) and attenuation of smoking satisfaction (i.e., nicotine antagonism). In mice discriminating nicotine, varenicline was demonstrated to have a lesser maximum effect than nicotine, consistent with low agonist efficacy. To test the hypothesis that nicotine produces the same maximum effect as varenicline when varenicline is the training drug, C57BL/6J mice (N=8) were trained to discriminate varenicline (3.2 mg/kg s.c.) from saline under a fixed ratio 10 schedule of food delivery. The median number of training sessions to acquisition was 72 among mice. Varenicline dose-dependently increased drug-appropriate responding; the ED50 value was 1.9 mg/kg. The nAChR antagonist mecamylamine (3.2 mg/kg) antagonized the discriminative stimulus effects of varenicline, shifting the dose-response curve of varenicline rightward 2.9-fold. Nicotine dose-dependently increased varenicline-appropriate responding, with a dose of 1 mg/kg producing 93% drug-appropriate responding. The ED50 value of nicotine was 0.33 mg/kg. In contrast, cytosine (the parent compound of varenicline and a smoking cessation aid in Europe) produced a maximum of 52% varenicline-appropriate responding up to a dose that disrupted responding. These results are consistent with the nAChR agonist efficacy of nicotine being equal to or greater than that of varenicline. Failure of cytosine to substitute for varenicline could be due to low agonist efficacy at varenicline-sensitive nAChRs or actions of cytosine at varenicline-insensitive receptors.

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### Reduced ethanol preference and consumption in cocaine- and amphetamine-regulated transcript (CART) knockout mice

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CART is a peptide neurotransmitter implicated in addiction to drugs of abuse. Several studies have characterized the role of CART in addiction to psychostimulants, but few have examined the role of CART in alcohol use disorders including alcoholism. The current study utilized a CART KO mouse model to investigate what role, if any, CART plays in ethanol appetitive behaviors.

CART KO and wild type mice were produced by crossing heterozygote mice to produce litters with CART KO, heterozygote, and WT mice. At 12 weeks, the mice were individually housed and acclimated for 3 weeks to a 12:12 reversed light schedule (lights on at 12 am). A two-bottle choice, unlimited ethanol access paradigm was used to compare ethanol preference and consumption between WT and KO mice of both sexes. The mice were presented with escalating concentrations of an ethanol solution (3%-21%) and water, each for four days with ethanol and water consumption measured daily. Preference for quinine (bitter) and saccharin (sweet) solutions was measured following a two week ethanol abstinent period. Body weights were measured every other day and the position of the ethanol (or tastant) and water bottles was alternated daily to avoid a position preference. Ethanol metabolism rates and ethanol sensitivity were compared between genotypes and sexes with an enzyme assay and the loss-of-righting-reflex assay, respectively.

CART KO mice consumed and preferred ethanol less than their WT counterparts. This genotype effect could not be attributed to differences in bitter or sweet taste perception or ethanol metabolism rates. There was also no difference in ethanol sensitivity in male mice; however, CART KO female mice showed a greater ethanol sensitivity than the WT females. Taken together, these data demonstrate a role for CART in ethanol appetitive behaviors and as a possible therapeutic drug target for drug addiction and abstinence enhancement.

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### Modeling zebrafish habituome - a new concept for cognitive research in drug abuse and addiction

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Habituation is a simple form of working memory widely used to study cognitions and their pharmacological modulation. Representing a reduction in responses to novelty over time, habituation has been evaluated in numerous animal models, including zebrafish (*Danio rerio*). With the growing understanding of the complexity of zebrafish behaviors, the extent to which multiple behaviors habituate remains unclear. Here, we performed a large-scale characterization of multiple behaviors in zebrafish novel tank and open field tests, to identify how their behaviors cluster into distinct groups based on their habituation and anxiety modulated by various pharmacological manipulations, including drugs of abuse (e.g., morphine) and abuse-related states (e.g., morphine withdrawal). Using this approach, we introduce the zebrafish habituome - a new concept and methodological framework to study affective and cognitive phenotypes in zebrafish, with a strong potential for drug abuse research. In particular, the sensitivity to habituation appears to be independent of anxiolytic and anxiogenic states, with numerous behaviors exhibiting a high sensitivity to stress, yet showing a low degree of habituation, and vice-versa. Given the significant conservation in animal novelty exploration, this approach may be also applied to other species to construct habituomes, including rodents and humans, and successfully applied to drug abuse research.

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### Assessment of dopaminergic involvement in cocaine-induced conditioned taste aversions

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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 the DA antagonist haloperidol) as well as cross-drug preexposure (with DA transporter [DAT] inhibitor GBR 12909) 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 18 and 32 mg/kg). In separate experiments, cocaine (18 mg/kg; Experiment 3) or GBR 12909 (32 mg/kg; Experiment 4 or 50 mg/kg; Experiment 5) was administered prior to aversion conditioning with cocaine (18 mg/kg) and GBR 12909 (32 mg/kg). Under these conditions, GBR 12909 (at 50 mg/kg only) blocked cocaine-induced CTAs but the reverse serial presentation did not result in significant cross-drug attenuation, indicating that the aversive properties of GBR 12909 and cocaine are similar, but not identical. Together, these results suggest that DA has a role in cocaine-induced CTAs. These data are discussed in the context of previous work demonstrating roles for both norepinephrine and serotonin in cocaine-induced taste aversion learning as well as research investigating DAT and cocaine in transgenic models.

## Poster Communications

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### Acute injection of a neurotensin receptor agonist decreases intravenous self-administration of methamphetamine in mice.

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Methamphetamine is a psychostimulant that exhibits a significant abuse potential. Although addiction to methamphetamine is a major health and societal concern, at the present time no drug is approved for therapeutic management of methamphetamine addiction. Methamphetamine activates the central dopaminergic "reward" circuitry, and with repeated use increases levels of the neuromodulatory peptide neurotensin (NT) in the nucleus accumbens and ventral tegmental area (VTA). Additionally, neurotensin input into the VTA affects dopamine neuron excitability. Previous studies in rats reported that NT agonism decreases methamphetamine self-administration, but these studies did not examine the effect of NT agonism on the pattern of self-administration. In our studies, we established intravenous methamphetamine self-administration in male, DBA/2J mice (FR3, 2 hr daily sessions) and examined the effect of pretreatment with the NT agonist PD149163 on methamphetamine self-administration behavior. At baseline, mice self-administered an average of approximately 16 infusions (0.8 mg/kg), with almost 90% of responses in the active nosepoke. Pretreatment with PD149163 (0.05 and 0.10 mg/kg, s.c.) significantly decreased methamphetamine self-administration and dose-dependently increased the latency to the first infusion of methamphetamine. No gross effect of PD149163 on locomotor activity was noted, suggesting that NT activity may decrease methamphetamine seeking independent of locomotor effects. Future studies will investigate the mechanisms responsible for the interactions between neurotensin, dopamine and methamphetamine use.

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### Differential effects of bradykinin and exogenous arachidonic acid on delta opioid receptor function in peripheral sensory neurons

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Peripheral administration of delta opioid receptor (DOR) agonists rarely produces analgesic responses in normal (uninflamed) tissue; however, we have found that the DOR system becomes responsive (functionally competent) upon pretreatment ("priming") with inflammatory mediators (e.g., bradykinin (BK) or arachidonic acid (AA)). DOR functional competence produced by either BK or AA-priming occurs rapidly (within 15min) but has a relatively short duration (60min). Here we determined if DOR functional competence could be re-induced by a subsequent BK and/or AA priming stimulus. DPDPE (100nM)-mediated inhibition of PGE2-stimulated cAMP accumulation was measured in primary cultures of rat trigeminal ganglion treated for 15 min with BK (10uM) or exogenous AA (50uM), 60 min after an initial 15 min BK or AA pretreatment. We found DPDPE-mediated responses could be re-induced with BK after an initial BK priming stimulus, but not after an initial AA priming stimulus. We next examined whether different AA metabolic enzymes could be responsible for the subsequent refractory effects of AA priming. In the presence of LOX inhibitors, NGDA (10uM) or DPE (10uM), DOR functional competence was re-established by BK (60 min after initial treatment with AA). In contrast, CYP inhibition (ODYA, 10uM pretreatment) had no effect. These data suggest a LOX-dependent AA metabolite leads to a loss of the ability to induce functional responsiveness of DOR. In addition, initial induction of functional competence by BK was blocked by the COX-1 inhibitor, indomethacin (2uM) whereas AA-priming was blocked by the COX-2 inhibitor, indomethacin (2uM) indicating there are different mechanisms/metabolic pathways associated with AA produced endogenously (i.e., by BK) compared to exogenously applied AA. Furthermore, our results suggest there may be a novel mechanism involving AA metabolites (related to LOX) that is involved in inactivation of the DOR system. Thus inhibition of this pathway combined with a priming stimulus might promote both the initiation and maintenance of peripheral DOR-mediated analgesia.

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### G Protein-coupled Estrogen Receptor 1 (GPER1) Constitutively Inhibits cAMP Production Through a Gi/o-independent Mechanism in Chinese Hamster Ovary Cells.

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G protein-coupled estrogen receptor 1 (GPER1), previously named GPR30 as an orphan, is a G protein-coupled receptor structurally and functionally distinct from nuclear estrogen receptor (ER) ER $\alpha$  and ER $\beta$ . GPER1 has been reported to bind 17 $\beta$ -estradiol with high affinity and to mediate rapid non-genomic estrogenic responses in vitro and in vivo in metabolic regulation, cardiovascular system, nervous system, and immune system. GPER1 is also implicated as a putative prognostic marker and therapeutic target in breast cancer. A GPER1 agonist, G1, was developed and is currently used extensively to probe GPER1 function in various systems. Nevertheless, there remains a debate about the pharmacological profile of GPER1, e.g. whether E2 is the only ligand for this receptor, and the identity of intracellular effectors through which this receptor signals. To shed more light on these questions, we investigated signals emanating from this receptor that modulate cAMP levels in a well-defined model system, Chinese hamster ovary (CHO) cells, transiently transfected with GPER1. Cells were transfected by nucleofection, and cAMP levels were assayed by radioimmunoassay following treatment with and without various agonists. Expression of GPER1 did not influence basal cAMP production but robustly inhibited prostaglandin E2 (PGE2)-stimulated production. The inhibitory effect of GPER1 was not perturbed by pre-treatment with pertussis toxin, which inhibits signaling by G proteins of the Gi/o type. Co-expression of receptor activity-modifying protein 3, which physically interacts with GPER1, also did not influence the GPER1-promoted effect. Finally, G1, which has been reported to be a GPER1 agonist, did not influence cAMP levels either in the absence or presence of the receptor. These results show that GPER1 constitutively inhibits cAMP production through a Gi/o-independent mechanism.

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### Preference for Cocaine vs. Food During Self-administration, Extinction and Reinstatement Testing: Preliminary data.

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Recent studies (for review see Ahmed, 2010) show that when given a mutually exclusive choice between cocaine and food, rats generally choose food. The present experiment investigated potential shifts in preference which might occur during extinction (food and cocaine no longer available) and during footshock-induced and cocaine-primed-reinstatement. During self-administration sessions where food and cocaine were simultaneously available, rats chose food over cocaine on 84% of trials. During extinction when neither reinforcer was available, preference for the food lever decreased until rats responded on the food- and cocaine-associated levers at equally low rates. While footshock had no effect on preference, cocaine priming infusions produced significantly more choice of the cocaine lever over the food lever, a reversal of baseline preference. It appears that although rats generally prefer food over cocaine when presented with a mutually exclusive choice, there are situations in which cocaine-seeking behavior prevails over food-seeking behavior.

## Poster Communications

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### Synthesis and Evaluation of Synthetic Cannabinoids as Potential Appetite Suppressants

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Cannabinoid ligands are a structurally diverse family of compounds that exhibit various biological profiles. Synthetic cannabinoids are members of the cannabinoid ligand family, also recognized as non-classical cannabinoids whose members have a chemically distinct structure from that of  $\Delta^9$ -THC. Aminoalkylindoles (AAIs) are members of this class of synthetic cannabinoids. JWH-018 and JWH-073 are AAIs that were originally synthesized by Dr. John W. Huffman for the purpose of studying structure-activity relationships (SAR) of the cannabinoid receptors (CBs). These compounds were shown to be non-selective CB1/CB2 agonists and more potent than  $\Delta^9$ -THC while exhibiting psychotropic effects that imitate those of marijuana. These characteristics and their non-regulated nature has made them a frequent component of Spice/K2. Despite their high popularity, little is known regarding Spice/K2 metabolism, pharmacology, and toxicology. Recently, a mono-hydroxylated metabolite of JWH-073 that retains CB1 receptor affinity, was discovered. In vivo mice studies confirmed the observed in vitro finding, which lead to the conclusion that the metabolite acts as a neutral CB1 receptor antagonist. The properties of this metabolite make this scaffold interesting for the development of novel anti-obesity drugs.

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### Combined behavioral treatment (wheel running) and medication (progesterone) decrease stress-, drug-, and cue-induced cocaine seeking in female rats

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Individually, both treatment with progesterone (PROG) and concurrent access to an exercise wheel reduce cocaine self-administration under long-access conditions and suppress cocaine (COC)-primed reinstatement in female rats. Treatment with the PROG metabolite allopregnanolone also decreased reinstatement to cocaine seeking by the pharmacological stressor yohimbine (YOH). In the present study, the combined effect of wheel running and PROG on YOH- and COC-induced reinstatement was assessed. Twenty-eight adult female rats were allowed to acquire wheel running and establish a baseline over 3 days. Rats then were catheterized and allowed to self-administer cocaine (0.4 mg/kg, iv) during 6-hr sessions for 10 days without access to the running wheel. Subsequently, auditory and visual stimuli that signaled drug delivery were unplugged, and rats were allowed to extinguish lever pressing for 14 additional sessions. During this period, rats were divided into 2 groups and given access to either a locked or unlocked running wheel. Next, both groups were tested in a within-subjects design for reinstatement of cocaine seeking precipitated by YOH (2.5 mg/kg, ip) or COC (10 mg/kg, ip) alone or YOH+ or COC+cocaine-paired stimuli, in the presence of concurrent wheel access, PROG (0.5 mg/kg, sc), or both. In agreement with prior work, results indicate that concurrent unlocked wheel access decreased responding during extinction of cocaine seeking. Further, in both groups, concurrent wheel running and PROG, separately and combined, decreased YOH-primed, COC-primed, YOH+cue-primed, and COC+cue-primed reinstatement. However, the combination of concurrent wheel running and PROG was the most effective at reducing stress- and drug-induced reinstatement. Thus, joint behavioral (i.e., exercise) and pharmacological (i.e., PROG) interventions are highly successful, possibly more so than either intervention alone. Research supported by R01 DA003240 and K05 DA015267 (MEC).

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### The interaction between flumazenil and midazolam is not changed in benzodiazepine-tolerant rhesus monkeys discriminating midazolam

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Tolerance readily develops to benzodiazepines, although the mechanism that accounts for tolerance in vivo has not been identified. One possibility is that benzodiazepine binding sites on GABAA receptors are changed, and as a consequence, the binding of drugs to that site is altered. If benzodiazepine tolerance is the result of an altered binding, then the interaction between all drugs, including benzodiazepine receptor antagonists, is expected to change. In order to test this hypothesis, the potency of flumazenil to antagonize the discriminative-stimulus effects of midazolam was estimated in untreated monkeys and in monkeys rendered tolerant by an acute injection of chlordiazepoxide. Three female rhesus monkeys discriminated midazolam (0.178 mg/kg) while responding under a fixed-ratio 10 schedule of stimulus-shock termination. Dose-effect curves of midazolam were obtained before and 46 hours after 10 mg/kg of chlordiazepoxide. Midazolam dose-effect curves were re-determined in the presence of flumazenil in chlordiazepoxide-tolerant monkeys and did not change the nature of flumazenil antagonism. Moreover, the potency of flumazenil after acute administration of chlordiazepoxide was similar to its potency in untreated monkeys (range of pA2 values: 7.41 to 7.69). Acute administration of chlordiazepoxide induced tolerance to midazolam and did not change the nature of flumazenil antagonism. Morever, the Schild analysis yielded a slope that was not significantly different from unity and a pA2 value for flumazenil of 7.44 (95% CI: 7.33 to 7.56). Acute administration of chlordiazepoxide induced tolerance to midazolam and did not change the nature of flumazenil antagonism. Moreover, the potency of flumazenil after acute administration of chlordiazepoxide was similar to its potency in untreated monkeys (range of pA2 values: 7.41 to 7.69). These results indicate that mechanisms other than alterations of the benzodiazepine binding site are responsible for tolerance induced by chlordiazepoxide. Supported by USPHS grants R01DA09157 and K05DA017918 (CPF).

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### Effects of amphetamine on delay discounting in rats: impulsivity or something else?

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Drug effects on delay discounting are thought to reflect changes in impulsivity, although other behavioral mechanisms might be important as well. Rats responded under a procedure in which responses on one lever resulted in immediate delivery of one food pellet and responses on the other lever resulted in either immediate or delayed delivery of three food pellets. The delay to the larger reinforcer (4, 8, 16, and 32 s) varied within session; the order of delay presentation was different in each of three groups (ascending, descending, and random). Responding in all three groups was sensitive to reinforcer amount and delay; with no delay rats responded on the lever associated with the larger reinforcer, and as delay increased, responding for the larger reinforcer decreased. The effects of amphetamine (i.p.; 0.1-1.78 mg/kg) on discounting varied across groups. In the ascending delay group, amphetamine enhanced responding for the larger, delayed reinforcer (compared to vehicle sessions) resulting in a shallower discounting function. In the descending delay group, amphetamine decreased responding for the larger reinforcer in all components resulting in a downward shift in the discounting function. The degree of downward shift was more pronounced at the smaller delays. The effects of amphetamine in the random group were mixed both within and across subjects. These data suggest that an increase in perseveration and not reduced sensitivity to reinforcer delay might account for the apparent reduction in impulsivity commonly observed under delay-discounting procedures. Supported by USPHS Grants K05DA017918 (CPF), and T32DA031115 (DRM).

## Poster Communications

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### **Attention, motivation, recovery and relapse.**

Ginsburg, Brett C.

The University of Texas HSC at San Antonio

The most effective therapies for relapse prevention combine a behavioral intervention with a pharmacological treatment. The most effective behavioral interventions reinforce alternative behavior, either explicitly or by reinforcing abstinence. This may reduce attention to stimuli that occasion drug-seeking and explain the consistent decrease in attentional bias and cue-reactivity in recovering, but not relapsed patients. The most effective pharmacological treatments result in satiation or reduced withdrawal, both of which reduce motivation to seek and consume drug. The most common animal models of relapse are sensitive to changes in motivation that result from pharmacological treatments. These effects are seen as reduced persistence of drug-seeking during extinction. However, most of these procedures do not model effective behavioral interventions. Recently, we developed a procedure that models a behavioral intervention, differential reinforcement of alternative behavior, by reducing the response requirement for concurrently available food while the availability of ethanol remains the same. We then examined the ability of stimuli to occasion ethanol-seeking over varying periods of the intervention. We also assessed the persistence of drug-seeking during extinction after similar periods of intervention. The behavioral intervention reduced the ability of stimuli to occasion ethanol-seeking, but did not change the persistence of ethanol-seeking during extinction. This may suggest that behavioral interventions and pharmacological treatments exert their beneficial effects by two different mechanisms: reducing attention to stimuli that occasion drug-seeking and reducing motivation to seek drug. This then provides the potential for improving relapse outcomes by implementing treatments that are more effective at reducing attention AND motivation simultaneously.

## Preparing Effective Oral Presentation Slides

Adapted from [http://www.sfn.org/am2011/index.aspx?pagename=resources\\_presentation#posters](http://www.sfn.org/am2011/index.aspx?pagename=resources_presentation#posters)

**Clear Purpose** - An effective image should have a main point and not be just a collection of available data. Central theme of the image should be readily identified.

**Readily Understood** - The main point should catch the attention of the audience immediately. Audience is not paying attention to the speaker when trying to figure out the image - minimize this.

**Simple Format** - With a simple, uncluttered format, the image is easy to design and directs audience attention to the main point.

**Free of Nonessential Information** - If information doesn't directly support the main point of the image, reserve this content for questions.

**Digestible** - Excess information can confuse the audience. With an average of seven images in a 10-minute paper, roughly one minute is available per image. Restrict information to what is extemporaneously explainable to the uninitiated in the allowed length of time - reading prepared text quickly is a poor substitute for editing.

**Unified** - An image is most effective when information is organized around a single central theme and tells a unified story.

**Graphic Format** – Use graphs to emphasize qualitative relationships "Drug X dose-dependently and markedly increased behavior". Avoid presenting data in Tables.

**Designed for the Current Oral Paper** – Avoid extraneous information; show evidence and conclusions directly related to the subject of the paper; it is not necessary to communicate how much work was done.

**Experimental** - In a 15-min presentation, there is not enough time to teach methods. Only mention what is necessary to develop the theme.

**Visual Contrast** - Contrasts in brightness and tone between illustrations and backgrounds improves legibility. The best color combinations include white letters on black or black on yellow. Never use black letters on a dark background. Many people are red/green color blind - avoid using red and green next to each other.

**Integrated with Verbal Text** - Images should support the verbal text and not merely display numbers. Conversely, verbal text should lay a proper foundation for each image. As each image is shown, give the audience a brief opportunity to become oriented before proceeding.

**Clear Train of Thought** - Ideas developed in the paper and supported by the images should flow smoothly in a logical sequence, without wandering to irrelevant asides or bogging down in detail. Everything presented verbally or visually should have a clear role supporting the paper's central thesis.

If using PowerPoint, consider the following:

Use standard fonts, such as Times, Helvetica, or Arial and Symbol. Space is lost and the amount of information per slide is reduced by repeating graphics (including logos), busy backgrounds, and decorative typefaces.

Enhance the legibility of text and diagrams by maintaining color and intensity contrast. Use white or light yellow text and lines on black backgrounds, and/or use black on white or clear backgrounds. Avoid using colors that do not provide enough contrast red or dark green on blue, and avoid yellow on white.

Test your completed presentation on a separate PC-compatible computer to ensure that fonts are standard and components, such as movies, have been included rather than merely linked.



## Preparing Effective Posters

An effective poster is self-contained and self-explanatory. Viewers can proceed on their own while leaving the author free to discuss points raised in inquiry.

The poster session offers a more intimate forum for discussion than a slide-based presentation, but discussion becomes difficult if the author must explain the poster to a succession of viewers. Time spent at a poster presentation is not determined by the author, but by the viewer – be prepared for 3 min or less.

An effective poster balances figures and text and is not a page-by-page printout of a journal paper or a slide show. Minimize text! Put yourself in the viewers shoes – how much text are you willing to read?

Layout - Organize illustrations and text using a grid plan. Arrange materials in columns rather than rows. Place the most significant findings at eye level immediately below the title bar; place supporting data and/or text in the lower panels. Use line borders to separate areas. Avoid reflective, plastic-coated paper. Use muted background colors - shades of gray are also effective.

Title - Title, author(s), and affiliation should be at least one-inch high.

Illustrations - design figures for viewing from a distance and use clear, visible graphics and large type. Colors are effective if used sparingly; use dark colors on white or pale backgrounds and light colors on dark backgrounds. Figures should illustrate no more than one or two major points. However, simple figures are unnecessary. Make clear main points. Illustration sequences can be specified with numbers or letters. Omit "Fig." or "Figure" - this is unnecessary and occupies excess space.

Text - Each figure or table should have a heading of one or two lines in very large type stating the "take-home" message. Provide additional essential information in the figure itself set in 16 point or larger type. Minimize narrative. Integrate text that would normally appear in the body (Results and Discussion) of a manuscript in figure legends. Concisely describe not only the content of the figure, but also the derived conclusions. Place brief details of methodology at the end of each legend. Numbered or bulleted lists are effective ways to convey a series of points, even for Introduction and Discussion. Do not set entire paragraphs in uppercase (all capitals) or boldface type.

Place an introduction at the upper left and a conclusion at the lower right, both in large type. The abstract should not be included.

## BBC Judge's Evaluation Form

**Presentation number/Presenter:** \_\_\_\_\_

Please assign points for each section and an overall score - (5) Strong to (1) Weak

		STRENGTHS	POINTS	WEAKNESSES	
<b>ABSTRACT</b>	<b>Text:</b> Logical? Clear? Well-organized? Complete? Sufficiently succinct?				
<b>PRESENTATION CONTENT</b>	<b>Introduction:</b> Objectives/background clear? Appropriate rationale?				
	<b>Methods and Results:</b> Appropriate design? Appropriate detail? Clearly explained?				
	<b>Conclusions:</b> More than summary? Supported by the data?				
<b>STYLE/ORGANIZATION/VISUALS</b>	<b>Style:</b> Clear voice? Volume? Appropriate inflection? Eye contact? Pace? Energy?				
	<b>Organization/Timing:</b> Logical sequence? Appropriate time for different sections?				
	<b>Visuals/Graphs:</b> Visible? Clear? Not cluttered? Used appropriately? See guidelines				
<b>OVERALL SCORE (CIRCLE ONE):</b>		<b>POINT TOTAL</b>			
<b>5 Outstanding</b>	<b>4 Excellent</b>	<b>3 Very good</b>	<b>2 Good</b>	<b>1 Fair</b>	

## **Notes**

## **Notes**

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