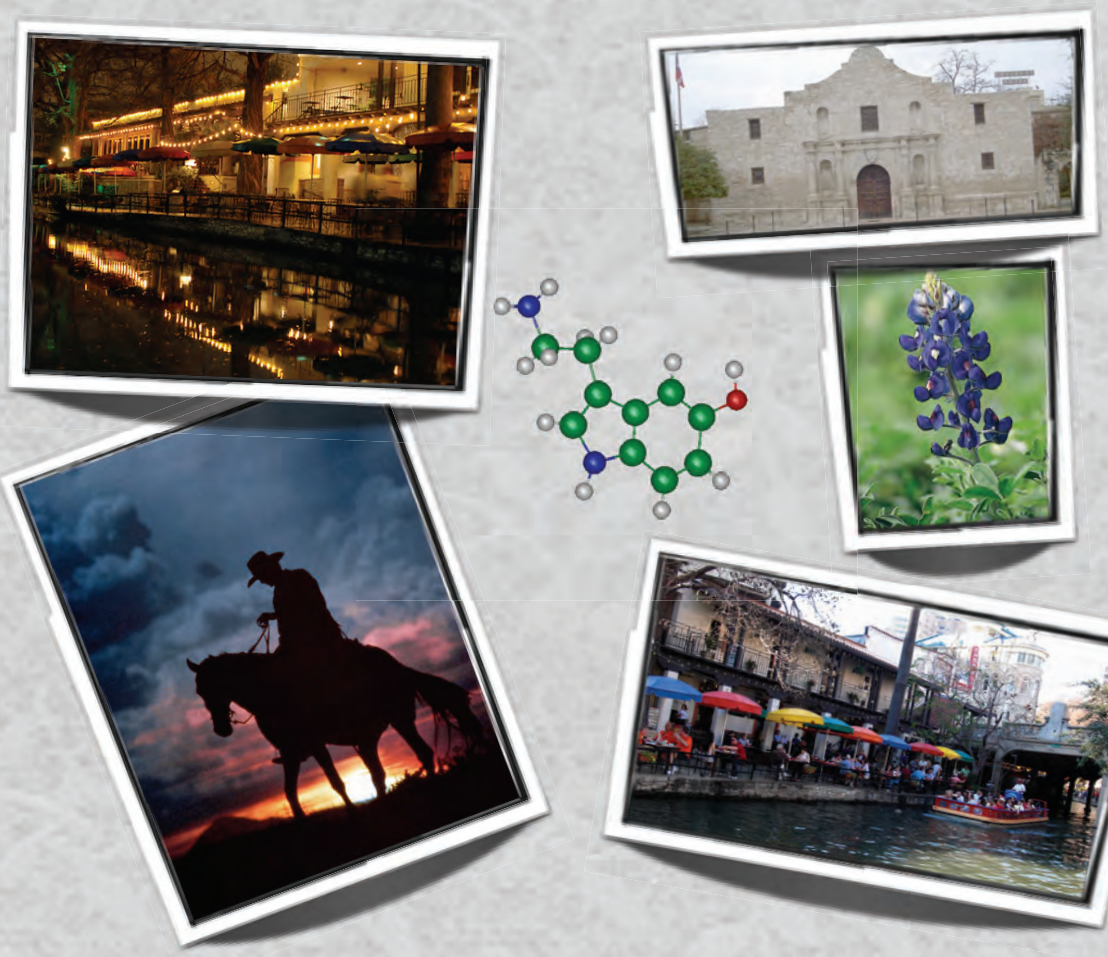
# Behavior, Biology, and Chemistry:
## Translational Research in Addiction

**March 9-10, 2013**

**La Quinta Inn & Suites**

**Medical Center**

**San Antonio, TX**



# Acknowledgements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# *Program Overview*

## Friday March 8, 2013

| | |
|---|---|
| 4:00 pm - 6:00 pm | Registration |
| 6:00 pm - 9:00 pm | Opening Reception at Rio Rio on the San Antonio Riverwalk<br>Buses depart from La Quinta at 6:00 PM |

## Saturday March 9, 2013

| | |
|---|---|
| 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: "Tobacco addiction: from basic science to policy"<br>Speakers: Mariella De Biasi, Peter Crooks, Paul Pentel, Dorothy Hatsukami (Chairs: Dorothy Hatsukami and Kathryn Cunningham) |
| 10:25 am - 10:40 am | Coffee Break |
| 10:40 am - 12:00 pm | Open Oral Communications 1 (Chair: Annette Fleckenstein) |
| **12:00 pm - 1:15 pm** | **Lunch** |
| 1:15 pm - 2:55 pm | Open Oral Communications 2 (Chair: Kevin Freeman) |
| 2:55 pm - 3:10 pm | Coffee Break |
| 3:10 pm - 4:10 pm | Special Lecture: Andrew Coop "Medicinal chemistry of mu opioid agonists" (Chair: Richard Lamb) |
| 4:10 pm - 4:30 pm | Poster Set-up |
| 4:30 pm - 7:00 pm | Poster Session |
| **7:00 pm - 9:00 pm** | **Dinner**<br>After Dinner Speaker: Linda Dykstra; "Opioid dependence: bench, trench, and back again" (Chair: James Woods) |
| 9:00 pm - 11:00 pm | Hospitality and Entertainment |

## Sunday March 10, 2013

| | |
|---|---|
| 8:00 am - 9:40 am | Open Oral Communications 3 (Chair: Lisa Gerak) |
| 9:40 am - 9:55 am | Coffee Break |
| 9:55 am - 11:15 am | Open Oral Communications 4 (Chair: Christopher Cunningham) |
| 11:15 am - 11:30 am | Coffee Break |
| 11:30 am - 12:30 pm | Special Lecture: David Ashley; "How science fits into regulatory decisions" (Chair: Dorothy Hatsukami) |
| 12:30 am - 12:40 pm | Presentation of travel awards and awards for oral and poster presentations |
| **12:40 pm - 1:30 pm** | **Lunch** |
| 1:30 pm | Closing remarks |

***See you at BBC 2014!***

# *Program Details*

## Friday March 8, 2013 (6:00 pm - 9:00 pm)

### Opening Reception

#### Rio Rio on the Riverwalk

| | |
|---|---|
| 6:00 pm | Buses depart from La Quinta |
| 6:30 pm - 9:00 pm | Reception at Rio Rio |
| 9:00 pm | Buses depart for La Quinta |

Come and enjoy the beautiful San Antonio Riverwalk. Buses will depart from the La Quinta hotel at 6:00 pm to take you to Rio Rio, a Mexican restaurant on the Riverwalk. Buses will return to La Quinta at 9:00 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 9, 2013

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

### Plenary Symposium (Chairs: Dorothy Hatsukami and Kathryn Cunningham)

#### Tobacco addiction: from basic science to policy

Nicotine is the agent that leads to addiction to tobacco products. Significant progress has been made in understanding the role of specific nicotine receptors associated with nicotine addiction. This knowledge has led to the exploration or development of new medications for smoking cessation treatment. But another novel approach to treatment has been targeting the nicotine molecule itself through the use of anti-nicotine immunotherapies. Beyond developing new treatments for tobacco dependence, a national policy to reduce the levels of nicotine in cigarettes has been proposed in order to reduce initiation of smoking and to facilitate abstinence. This symposium covers topics ranging from understanding the basic biology of nicotine addiction to policies related to the regulation of nicotine in tobacco products.

| | |
|---|---|
| 8:05 am - 8:35 am | ***Mariella De Biasi***; Baylor College of Medicine<br>Nicotinic receptor subunits and their influence on nicotine addiction and withdrawal |
| 8:35 am - 9:05 am | ***Peter Crooks***; University of Arkansas for Medical Sciences<br>Development of nicotinic receptor antagonists as agents for treating nicotine addiction |
| 9:05 am - 9:35 am | ***Paul Pentel***; University of Minnesota<br>Targeting the drug instead of the brain: nicotine vaccines as a potential treatment for tobacco addiction |
| 9:35 am - 10:05 am | ***Dorothy Hatsukami***; University of Minnesota<br>Nicotine reduction in cigarettes: a national policy measure? |
| 10:05 am - 10:25 am | ***Panel Discussion*** |

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

## Saturday March 9, 2013 (continued)

### Open Oral Communications 1 (Chair: Annette Fleckenstein)

| | |
|---|---|
| 10:40 am -11:00 am | ***Tamara Vasiljevik,*** University of Kansas<br>Structure-activity relationship of a mono-hydroxylated JWH-073 metabolite and the potential for development of alcohol abuse therapies |
| 11:00 am- 11:20 am | ***Sarah Swinford,*** University of Texas Medical Branch<br>Lower serotonin 2C receptor (5-HT2CR) expression in the ventral tegmental area (VTA) associates with elevated cue reactivity following extended forced-abstinence from cocaine-taking |
| 11:20 am - 11:40 am | ***David Thorn,*** University at Buffalo<br>Effects of imidazoline I2 receptor agonist 2-BFI on the development of tolerance and physiological/behavioral dependence to morphine in rats |
| 11:40 am - 12:00 pm | ***Brendan Tunstall,*** American University<br>Reinstatement in a cocaine vs. food choice situation: reversal of preference between drug and non-drug rewards |

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

### Open Oral Communications 2 (Chair: Kevin Freeman)

| | |
|---|---|
| 1:15 pm - 1:35 pm | ***Latham Fink,*** University of Texas Medical Branch<br>A predisposition toward inherent impulsivity is associated with elevated 5-HT2AR expression |
| 1:35 pm - 1:55 pm | ***Bradley Gray,*** University of Arkansas for Medical Sciences<br>In vivo evaluation of CIMBI-256, a novel N-benzylphenethylamine with 100-fold selectivity for 5-HT2A receptors |
| 1:55 pm - 2:15 pm | ***Brian D. Kangas,*** McLean Hospital, Harvard Medical School<br>Novel touchscreen approaches to the study of cognition-related behavior in monkeys |
| 2:15 pm - 2:35 pm | ***Megan Tipps,*** Oregon Health and Science University<br>Alcohol withdrawal-induced enhancement of fear-based learning and memory is attenuated in GIRK3 knock-out mice |
| 2:35 pm - 2:55 pm | ***Dharmendra Goswami,*** Harvard Medical School<br>The large-scale polymorphism discovery in non-human primate G-protein coupled receptors for redefining animal models of drug addiction |

### Coffee Break (2:55 pm - 3:10 pm)

### Special Lecture 3:10 pm - 4:10 pm (Chair: Richard Lamb)

**Andrew Coop, University of Maryland School of Pharmacy: "Medicinal chemistry of mu opioid agonists"**

## Saturday March 9, 2013 (continued)

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

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

Presenters should attend their posters as follows:

**4:30 pm - 5:45 pm odd numbered posters**

**5:45 pm - 7:00 pm even numbered posters**

Poster judging (post-doctoral fellows and students) is scheduled for odd- and even-numbered posters as indicated above. Presenters should be available at their posters until they are judged. Judging begins at the lowest numbered posters and proceeds to higher numbered posters. **There is a 5 min time limit for presentations**. Three awards will be issued for outstanding poster presentations.

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: James Woods)

**Linda Dykstra, University of North Carolina: "Opioid dependence: bench, trench, and back again"**

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

Come and enjoy the fun in the ballroom!

## Sunday March 10, 2013

### Open Oral Communications 3 (Chair: Lisa Gerak)

| | |
|---|---|
| 8:00 am - 8:20 am | ***Noelle Anastasio,*** University of Texas Medical Branch<br>Stop, put that cookie down: impulsivity in the response to eat or overeat |
| 8:20 am - 8:40 am | ***Nora Charles,*** University of Texas Health Science Center at San Antonio<br>The effects of a family history of substance use disorders on different components of impulsivity in children |
| 8:40 am - 9:00 am | ***Hyung Wook Nam,*** Mayo Clinic College of Medicine<br>Adenosine transporter ENT1 regulates the acquisition of goal-directed behavior and ethanol drinking through A2A receptor in the dorsomedial striatum |
| 9:00 am - 9:20 am | ***Jonathan Raybuck,*** Oregon Health & Science University<br>Rescue of cocaine-induced cognitive deficits by medial prefrontal histone deacetylase inhibition in C57BL6 mice |
| 9:20 am - 9:40 am | ***Joshua Ward,*** Harvard Medical School<br>Polymorphisms of the 5-hydroxytryptamine (serotonin) receptors in non-human primates |

### Coffee Break (9:40 am - 9:55 am)

### Open Oral Communications 4 (Chair: Christopher Cunningham)

| | |
|---|---|
| 9:55 am - 10:15 am | ***Kevin Freeman,*** University of Mississippi Medical Center<br>Assessment of the punishing effects of the kappa agonist, salvinorin A, on remifentanil and cocaine self-administration in monkeys |
| 10:15 am - 10:35 am | ***Jun-Xu Li,*** University at Buffalo<br>Delay discounting in rats: impact of neuropathic pain and analgesics |
| 10:35 am - 10:55 am | ***Xiu Liu,*** University of Mississippi Medical Center<br>Desformylflustrabromine, a positive allosteric modulator at α4ß2 nicotinic acetylcholine receptors, reduced nicotine self-administration in rats |
| 10:55 am - 11:15 am | ***Rajeev Desai,*** Harvard Medical School/Mclean Hospital<br>Medication strategies for nicotine addiction |

### Coffee Break (11:15 am - 11:30 am)

### Special Lecture 11:30 am - 12:30 pm (Chair: Dorothy Hatsukami)

**David Ashley, Center for Tobacco Products, Food and Drug Administration: "How science fits into regulatory decisions"**

| | |
|---|---|
| 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

**Structure-Activity Relationship of a Mono-hydroxylated JWH-073 Metabolite and the Potential for Development of Alcohol Abuse Therapies**

Vasiljevik, Tamaraa, Franks, Lirit N.b, Ford, Benjamin M.b, Douglas, Justin T.c, Prather, Paul L.b, Fantegrossi, William E.b, and Prisinzano, Thomas E.a

*aDepartment of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas, bDepartment of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, and cThe University of Kansas, NMR Core Laboratory, Lawrence, Kansas

The abuse of drugs and alcohol is often associated with substantial psychiatric comorbidity and exacerbates the spread of HIV/AIDS and drug resistant tuberculosis. Estimates of the total overall costs of substance abuse in the United States, including productivity and health- and crime-related costs, exceed $600 billion annually. This includes approximately $193 billion for illicit drugs, $193 billion for tobacco, and $235 billion for alcohol. The World Health Organization estimates that approximately 2.5 million people die from alcohol use every year. While several therapies are available for the treatment of alcohol abuse, these existing therapies have only modest efficacy and come with moderate to severe side effects. A growing body of evidence suggests that the endocannabinoid system is involved in some of the abuse related behaviors of drug and alcohol dependence.

We have recently reported that a mono-hydroxylated metabolite of JWH-073, found in the incense blend known as Spice/K2, exhibited neutral antagonist activity at the CB1R. Increased endocanabinoid signaling could be potentially treated with the use of a CB1R neutral antagonist, which will in effect attenuate the endocannabinoid system. Thus, JWH-073 is a lead for the development of alcohol abuse therapies. Systematical modification of the JWH-073 scaffold has led us to two new compounds with dual CB1R antagonist/CB2R agonist activity. TV-5-249 decreases alcohol self-administration, without affecting total fluid intake and TV-6-41 decreases alcohol-conditioned place preference in the same way as rimonabant, without the accompanied inverse agonist activity. Collectively, these initial findings suggest that design and systematic modification of the aminoalkylindoles can lead us to potential alcohol abuse treatments.

### 2

**Lower serotonin 2C receptor (5-HT2CR) expression in the ventral tegmental area (VTA) associates with elevated cue reactivity following extended forced-abstinence from cocaine-taking**

Swinford, Sarah E.1, Anastasio, Noelle C.1, Fox, Robert G.1, Stutz, Sonja J.1 and Cunningham, Kathryn A.

1Center for Addiction Research, Dept. of Pharmacology and Toxicology, UTMB, Galveston, TX

Vulnerability to environmental cues previously associated with cocaine-taking behavior ("cue reactivity") is thought to promote relapse. The VTA has been implicated in cue reactivity such that exposure to cocaine-associated cues has been shown to trigger activation of the VTA in neuroimaging studies of cocaine-dependent individuals. The VTA microcircuitry and afferents that control cue reactivity are underexplored. Serotonergic afferents to the VTA may regulate cue reactivity through metabotropic 5-HT2CRs that exert an overall inhibitory impact over VTA function. Impaired neuronal signal transduction in the VTA through the ERK1/2 pathway may contribute to adaptations underlying responses to cues; however, altered 5-HT2CR expression and signaling as a neurobiological driver of such events underlying cue reactivity is unknown. We tested the hypothesis that extended periods of forced abstinence (FA) from cocaine-taking results in elevated cue reactivity and shifts in the subcellular expression of the 5-HT2CR and pERK1/2. Rats underwent cocaine self-administration followed by 1 or 30 days of FA. Cue reactivity (presses on cocaine-conditioned lever) was measured on FA Day 1 or 30. Rats were immediately sacrificed and VTA harvested. Immunoblotting was performed to assess VTA subcellular localization (membrane, cytosolic, nuclear) of 5-HT2CR and pERK1/2 protein. Cocaine-conditioned lever presses were elevated at FA Day 30 vs. FA Day 1. Expression of membrane 5-HT2CR was lower while nuclear pERK1/2 was higher in the VTA on FA Day 30 vs. FA Day 1. Cytosolic levels of pERK1/2 did not differ on FA Day 1 vs. FA Day 30. Collectively, these data suggest reduced VTA 5-HT2CR expression concomitant with altered pERK1/2 nuclear translocation emerges during prolonged FA from cocaine SA to drive cue reactivity. Future directions will assess the impact of an imbalance in 5-HT2CR homeostasis as a driver of dynamic neurobiological events underlying cocaine cue reactivity. Support: DA07287, DA06511, DA024157

### 3

**Effects of imidazoline I2 receptor agonist 2-BFI on the development of tolerance and physiological/behavioral dependence to morphine in rats**

Thorn, David A and Li, Jun-Xu

Department of Pharmacology and Toxicology, University at Buffalo, Buffalo, NY

Pain is a significant health care challenge and current pharmacotherapy cannot meet increasing clinical needs. Opioids are the drugs of choice for many painful conditions, particularly moderate to severe pain. Accumulating evidence indicates that imidazoline I2 receptor agonists enhance the antinociceptive effects of opioids and therefore may be suitable for combination therapy with opioids for pain treatment. However, little is known of the effects of I2 receptor agonists on the untoward effects of opioids, such as the development of tolerance and physical dependence. In this study, two groups of rats (n=9/group) were trained to lever press for sucrose (10%) presentation under a fixed ratio 10 schedule. Using a cumulative dosing procedure, the rate-suppressing effects of the μ opioid receptor agonist morphine, the imidazoline I2 receptor agonist 2-BFI and the μ opioid receptor antagonist naltrexone were examined each week in rats treated with either (20 mg/kg, s.c.) morphine or (10 mg/kg) 2-BFI in combination with (20 mg/kg) morphine per day for 3 weeks. Chronic morphine administration induced significant tolerance to the rate-suppressing effects of morphine as demonstrated by a greater than 6-fold increase in the ED50 value at week 3, while the chronic administration of 2-BFI plus morphine resulted in a less than 4-fold shift of the morphine ED50 value. In addition, chronic administration of morphine resulted in the development of physical dependence, as evidenced by a marked increase in the sensitivity to the rate-suppressing effects of naltrexone as well as significant body weight loss following the naltrexone test session. Rats treated with daily 2-BFI plus morphine exhibited significantly less naltrexone-induced body weight loss and sensitization to the rate-suppressing effects. Taken together, these results indicate that 2-BFI attenuated the development of tolerance and physical dependence to morphine and further support the therapeutic potential of combining I2 receptor agonists and opioids of pain treatment.

### 4

**Reinstatement in a Cocaine vs. Food Choice Situation: Reversal of Preference between Drug and Non-Drug Rewards.**

Tunstall, Brendan J. and Kearns, David N.

Psychology Department, American University, Washington, DC.

Recent studies (for review see Ahmed, 2010; 2012) show that when given a mutually exclusive choice between cocaine and food, rats almost exclusively choose food. The present experiment investigated potential shifts in preference between levers associated with either food or cocaine which might occur during extinction (food and cocaine no longer available) and during footshock-induced, cocaine-primed, and food-primed reinstatement. During self-administration sessions where food and cocaine were simultaneously available, rats demonstrated a stable food preference, choosing food over cocaine on 83% of trials. During extinction when neither reinforcer was available, no preference between levers was evident and responding decreased until rats responded on the previously food- and cocaine-associated levers at equally low rates. Footshock resulted in a non-specific reinstatement of responding upon both levers, while cocaine priming resulted in a significant preference for cocaine seeking over food seeking. This suggests that the mechanism underlying footshock-induced reinstatement is distinct from that of cocaine-primed reinstatement. Food priming engendered a mild, non-specific increase in responding on both levers. Although rats generally prefer food over cocaine when presented with a choice between these primary reinforcers, the present results suggest that in certain situations cocaine-seeking behavior prevails over food-seeking behavior.

# Oral Communications

## 5

**A predisposition toward inherent impulsivity is associated with elevated 5-HT2AR expression**

L.H.L. Fink,1 N.C. Anastasio,1 R.G. Fox,1 F.G. Moeller,2 and K.A. Cunningham1

1Ctr Addiction Res, Dept Pharm & Tox, UTMB, Galveston, TX, 2Dept Psych & Behav Sci, UTHSC, Houston, TX

Poor inherent response inhibition, or "action without reflection," may set the stage for vulnerability to drug abuse and dependence. Serotonin (5-HT) systems play a nuanced role in impulsive action, perhaps mediated by forebrain 5-HT receptors. Selective 5-HT2A receptor (5-HT2AR) antagonists (e.g., M100907) reduce impulsive action with notable efficacy, suggesting that tonic 5-HT2AR signaling supports impulsive behavior. We sought to test the hypothesis that the inherent predisposition to impulsive action is associated with elevated forebrain 5-HT2AR expression and function. These studies employed the one-choice serial reaction time (1-CSRT) task to identify high (HI) and low (LI) impulsive outbred rats. Rats were trained to nose-poke to receive a food reinforcer on a 5-sec inter-trial interval (ITI) schedule; responses during the ITI (premature responses) resulted in further delays of reward presentation. The upper 25% and lower 25% of animals were identified as HI or LI rats, respectively. Rats were sacrificed and the medial prefrontal cortex (mPFC) was harvested, and crude synaptosomal protein extracted for western blot analysis. In separate sets of animals, the ability of M100907 (0.003, 0.01, 0.03, 0.1 mg/kg, i.p.) to suppress premature responses or the ability of the 5-HT2AR agonist DOI (1 mg/kg, s.c.) to elicit the head twitch response was evaluated in HI and LI rats. HI rats displayed higher 5-HT2AR expression in crude synaptosomal fractions of the mPFC relative to LI rats ($p<0.05$, Student's t-test). Higher doses of M100907 (0.03, 0.1 mg/kg) suppressed premature responses in all rats, but lower doses (0.003, 0.01 mg/kg) suppressed premature responses selectively in HI, but not, LI rats ($p<0.05$, Dunnett's test). DOI elicited a greater head twitch response in HI relative to LI rats ($p<0.05$, Student's t-test). These data demonstrate that high impulsive action is associated with elevated expression and enhanced function of the 5-HT2AR, suggesting that differential 5-HT2AR function in the mPFC may in part drive high and low impulsive action. Supported by DA034488, DA06511, DA024157, DA000403,

## 6

***In vivo* evaluation of CIMBI-256, a novel N-benzylphenethylamine with 100-fold selectivity for 5-HT2A receptors**

Gray, Bradley W1; Hansen, Martin2; Kristensen, Jesper L2; and Fantegrossi, William E3

1College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR 2 Department of Medicinal Chemistry, University of Copenhagen, Copenhagen DK; 3Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR

Serotonin (5-HT) regulates a number of behavioral effects, and abnormalities in 5-HT systems are associated with a range of CNS disorders, such as schizophrenia, depression, anxiety and migraine. The 5-HT2A receptor is the primary excitatory 5-HT receptor in the human brain and mediates both the hallucinogenic effects of serotonergic drugs and the antipsychotic effects of atypicals. Although selective 5-HT2A antagonists have been available for some time, truly selective agonists are extremely rare, and often fail to display in vivo selectivity comparable to what is shown in vitro. The selectivity of N-benzylphenethylamines for 5-HT2A over 5-HT2C was first described by Nichols, and subsequent synthetic efforts yielded CIMBI-256 (4-(2-(2-hydroxybenzylamino)ethyl)-2,5-dimethoxybenzonitrile hydrochloride), which displays over 100-fold selectivity in vitro. These studies represent the first preclinical evaluation of this compound in two assays mediated by 5-HT2A receptors in mice: drug-elicited head twitch, and evaluation of DOI-like (R(-)-2,5-dimethoxy-4-iodoamphetamine) discriminative stimulus effects. In comparison with DOI, CIMBI-256 displayed a partial-agonist profile in both of these assays, eliciting fewer head twitches across the doses tested and substituting only partially for the DOI discriminative stimulus. Importantly, the effects of CIMBI-256 on head twitch behavior were attenuated by the 5-HT2A antagonist M100907, but were not altered by treatment with the 5-HT2C antagonist RS102221. The increased selectivity of compounds like CIMBI-256 will enable further exploration of 5-HT2A receptors, an important target in drug development.

## 7

**Novel touchscreen approaches to the study of cognition-related behavior in monkeys.**

Kangas, Brian D. and Bergman, Jack

Preclinical Pharmacology Laboratory, McLean Hospital, Harvard Medical School, Belmont, MA

The effects of abused drugs on complex behavioral processes are arguably some of the most important and least understood. Modern touchscreen technology provides an extremely flexible means to expose experimental subjects to a variety of behavioral assays. Therefore, our first purpose was to gain a better understanding of how drugs of abuse affect learning, motivation, attention, etc. A second purpose was to devise a means to evaluate the potential side-effects of novel therapeutics. Here, unlike abused drugs which often have deleterious effects on learning, demonstrating a reliable null effect can serve as an important preclinical evaluation of the safety of a given pharmacotherapy. For example, the primary psychoactive ingredient of marijuana, Δ9-tetrahydrocannabinol (THC), has medicinal effects that promote continued development of CB1 agonists as therapeutics but also produces well-documented adverse effects on cognitive endpoints. We will discuss several CB1 agonists – THC, WIN 55,212, AM4054, anandamide (alone and after the FAAH inhibitor URB 597) – that were further evaluated by comparing their effects on cognition in nonhuman primates. Drugs were studied using touchscreen procedures to assay learning (repeated acquisition, reversal), motivation (progressive ratio), and, with novel methodology, attention (titrating vigilance). THC, WIN, and AM4054 produced dose-related impairment of each type of complex behavior. However, drug potency varied across tasks, i.e., particular cognitive endpoints appeared more vulnerable to drug action (e.g., learning<reversal). Anandamide had negligible effects and, even after URB597, produced only minor dose-related impairments. Data and discussion will highlight how investigations of this sort provide preclinical evidence of relative therapeutic safety.

## 8

**Alcohol withdrawal-induced enhancement of fear-based learning and memory is attenuated in GIRK3 knock-out mice.**

Tipps, Megan E1; Raybuck, Jonathan D1; Lattal, Kennon M1; and Buck, Kari J1,2

1Department of Behavioral Neuroscience, Oregon Heath and Science University, Portland, OR USA; 2VA Medical Center, Portland, OR

The involvement of normal learning and memory-related processes in the development of addiction has lead to the hypothesis that addiction is a maladaptive form of learning. While alcohol intoxication has been shown to alter several aspects of learning and memory, less is known about the effects of alcohol withdrawal on these processes. Kcnj9, which codes for a G-protein coupled inwardly rectifying potassium channel subunit (GIRK3), is a high quality quantitative trait gene candidate for physiological dependence to alcohol and the associated withdrawal in mice. The GIRK channel family is a direct target of alcohol and is also involved in the formation of long-term potentiation, a molecular mechanism of learning and memory, suggesting that these channels may play a role in the interaction between alcohol and learning and memory. To test this hypothesis, we trained GIRK3 knock-out (KO), heterozygote (HET) and wild-type (WT) littermates for fear-based learning and memory under both alcohol naïve and acute withdrawal conditions using two forms of fear conditioning (Trace Fear Conditioning and Delay Fear Conditioning). We found that WT mice trained under acute alcohol withdrawal showed increased fear responses 48 h later, suggesting that a single round of acute withdrawal is sufficient to alter long-term learning and memory. In addition, this increase was not observed in the KO mice. Our results implicate GIRK3 in the alcohol withdrawal-induced increase in fear-based learning and specifically highlight the role of GIRK signaling in the hippocampus and amygdala. However, as is the case with traditional KO models, differences from WT mice may also be influenced by potential developmental compensation. Region-specific shRNA-mediated GIRK3 knock-down will be used in future experiments to address this issue.

# Oral Communications

## 9

**The Large-scale polymorphism discovery in non-human primate G-protein coupled receptors for redefining animal models of drug addiction.**

Goswami, Dharmendra B. and Vallender, Eric J.

Dept. of Psychiatry, Harvard University, Harvard Med. School, New England Primate Res. Ctr., Southborough, MA

Several genetic and molecular techniques have selected candidate genes for drug addiction. Good candidate genes usually involved in direct synthesis of an important component of the nervous system, such as a neurotransmitter, neurotransmitter receptor or a protein involved in cellular transmission of information. Typically the G-protein coupled receptors (GPCRs) play an inordinately large role in function of this candidate genes or proteins for addiction. Variation at these genes is associated with basic drug abuse reinforcement ability and pharmacogenetic effects of drug as such, in part, by polymorphisms at these drug targets. While non-human primates are more similar to humans and better face and predictive value in addiction model than rodents, one disadvantage they have had as a model system is a lack of complete control over genetics in inbred as well as outbreed used in behavior experiments. To get the best results and better utilize the non-human primate model, a more complete and thorough understanding of genetic variability is needed. This will give us superior understanding of primate model for best preclinical outcome for drug dependence animal models. Our initial efforts include resequencing 43 Indian-origin rhesus macaques (Macaca mulatta), 20 Chinese-origin rhesus macaques, and 34 cynomolgus macaques (Macaca fascicularis). Using the Agilent target enrichment system, we designed capture baits for GPCRs off the human and rhesus exonic sequence. We used an Illumina HiSeq with single end reads and 24x multiplexing to generate sequencing reads and DNAnexus for initial data analysis. Initial data analysis will proceed through DNAnexus (Palo Alto, CA). All reads will be aligned both to the human genome (GRCh37/hg19) as well as the rhesus genome (rheMac2) and any additional self-genomes that may become available in the interim. Following assembly, we will identify polymorphic sites and catalog frequencies and functional effects, whether the change is synonymous, nonsynonymous (missense), nonsense, or results in a frameshift and also map the SNPs to secondary structures of the GPCRs leading to abuse potential.

## 10

**Stop, put that cookie down: impulsivity in the response to eat or overeat**

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Food intake is essential for survival, but maladaptive patterns of intake, possibly encoded by an individual's preexisting vulnerability coupled with the influence of environmental variables, can modify the reward value of food and food-associated stimuli. Impulsivity, which is defined as a predisposition toward rapid unplanned reactions to stimuli without regard to the negative consequences, has been noted as one of the multifaceted determinants underlying the etiology of dysregulated eating, its evolving pathogenesis, and treatment outcomes. Impulsivity and dysregulated eating converge mechanistically at the level of serotonin (5-HT) neurotransmission at the 5-HT2C receptor (5-HT2CR) within an integrated brain network (e.g., prefrontal cortex, nucleus accumbens), that orchestrates a balance between stimulus-driven and goal-driven behaviors. Disturbances in this system may engender maladaptive eating behaviors [esp., binge eating on palatable high fat/sugar ("sweet-fat) foods] and the response to food stimuli seen in obesity and binge eating disorder. Yet, our understanding of the reciprocal relationships linking impulsivity to binge eating and/or relapse in the presence of food stimuli, and the shared neurobiological mechanisms, is very limited. We tested the hypothesis that binge eating involves an imbalance in the 5-HT2CR "rheostat" within key brain regions that control impulsivity and the desire to binge. Employing interlaced, novel animal models of impulsivity and binge eating, individual differences in impulsivity were quantified in outbred rats, and relative to low impulsive rats, high impulsive rats binged more on sweet-fat food, but not regular chow. A positive correlation was observed between levels of impulsivity and calorie intake during the binge. We also discovered that genetic elimination of the 5-HT2CR in the nucleus accumbens results in aggregate high impulsivity and sweet-fat food binge eating. A greater understanding of the neurobiology of relationship between impulsivity and dysregulated eating has the potential to lead to therapeutically-relevant findings and significantly impact clinical practice for disorders of overeating.

## 11

**The Effects of a Family History of Substance Use Disorders on Different Components of Impulsivity in Children**

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2.

Individuals with family histories of substance use disorders (FH+) are at increased risk for developing substances use disorders relative to those without such histories (FH-). One possible mechanism that may increase risk among FH+ individuals is elevated impulsivity. Importantly, impulsivity is not a unitary process but rather a multi-dimensional construct. A better understanding of how different dimensions of impulsivity are altered in FH+ individuals may provide insights into specific behavioral pathways leading to substance use disorders. In the present study, 281 FH+ children (age 10-12) and 78 FH- children were administered a diverse battery of impulsivity measures including the Kirby Delay Discounting Questionnaire, the Barratt Impulsiveness Scale (BIS-11), the Immediate Memory Task (IMT), and the GoStop Task. FH+ children discounted the value of delayed rewards more and reported more non-planning impulsivity on the BIS-11. FH+ children were not more impulsive on the IMT, indicating normal response initiation impulse control, but were more impulsive on the GoStop task, indicating impaired ability to inhibit already initiated responses. Collectively, these results indicate FH+ children have more impulsive decision-making and planning, as well as poorer inhibition. We will examine how these factors specifically contribute to risk for both the initiation of substance use as well as substance use disorders as part of an ongoing longitudinal project monitoring these children across adolescence.

## 12

**Adenosine Transporter ENT1 Regulates the Acquisition of Goal-Directed Behavior and Ethanol Drinking Through A2A Receptor in the Dorsomedial Striatum**

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Adenosine signaling has been implicated in the pathophysiology of many psychiatric disorders including alcoholism. Striatal adenosine A2A receptors (A2AR) play an essential role in both ethanol drinking and the shift from goal-directed action to habitual behavior. However, direct evidence for a role of striatal A2AR signaling in ethanol drinking and habit development has not been established. Here, we identified that decreased A2AR-mediated CREB activity in the dorsomedial striatum (DMS) enhanced initial behavioral acquisition of goal-directed behaviors and the vulnerability to progress to excessive ethanol drinking during operant conditioning in mice lacking ethanol-sensitive adenosine transporter ENT1 (ENT1–/–). Utilizing mice expressing β-galactosidase (lacZ) under the control of seven-repeated CRE sites in both genotypes (CRE-lacZ/ENT1+/+ mice and CRE-lacZ/ENT1–/– mice) as well as dnCREB (dominant negative form of CREB), we found that reduced CREB activity in the DMS is causally associated with decreased A2AR signaling and increased goal-directed ethanol drinking. Finally, we demonstrated that A2AR antagonist (ZM241385) dampened PKA-activity mediated signaling in the DMS and promoted excessive ethanol drinking in ENT1+/+ mice, but not in ENT1–/– mice. Taken together, our studies indicate that A2AR-mediated CREB signaling in the DMS is a key determinant to enhance the development of goal-directed ethanol drinking in mice.

# Oral Communications

## 13

**Rescue of cocaine-induced cognitive deficits by medial prefrontal histone deacetylase inhibition in C57BL6 mice.**

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Much work has demonstrated that chronic, binge, and repeated psychostimulant exposure produces long-lasting disruption of reward circuitry. Since deficits in executive function result from drug use, as well as predispose individuals to initial and continued substance abuse, a better understanding of the neural and pharmacological targets underlying these deficits may reveal novel approaches to facilitate cessation, as well as mechanisms that may be exploited to prevent long-term effects of drug-exposure. We used trace fear conditioning, a model of working memory dependent associative learning to investigate the effects of short-term binge-cocaine treatment on cognitive function in C57BL6 mice. Binge-cocaine administration produced robust, long-lasting, exposure dependent deficits in trace conditioning, without affecting delay or contextual conditioning, and similar deficits were present in rats following cocaine self-administration. Examination of epigenetic histone acetylation (HA) revealed deficits in learning induced HA in the prelimbic cortex (PrL) of cocaine-treated mice following trace conditioning. Further, systemic (1.2 g/kg NaBut, ip) or local (1 ug/side, SAHA, PrL) histone deacetylase (HDAC) inhibition fully rescued cognitive deficits in cocaine-treated mice. These results suggest (1) that robust deficits in cognitive function follow binge/repeated cocaine exposure, (2) that deficits are mediated by decreased HA in the PrL, and (3) that cognitive deficits can be rescued by either systemic of local administration of HDAC inhibitors. Thus, modulation of HA may serve as a useful target for the treatment of cognitive deficits induced by exposure to cocaine or other psychostimulants. Additionally, HDAC inhibitors may prove to be useful small molecule pharmacotherapies for the treatment of drug-exposure induced cognitive deficits. This research was supported by MH077111, DA025922, JDR supported by F32DA031537.

## 14

**Polymorphisms of the 5-hydroxytryptamine (serotonin) receptors in non-human primates.**

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This study explored 5-hydroxytryptamine (5-HT, serotonin) receptor variation of Indian and Chinese-origin rhesus macaques (Macaca mulatta) and cynomolgus macaques (Macaca fascicularis). Serotonin is an important neurotransmitter, capable of regulating substance-use disorder (SUD) acquisition, maintenance, and recovery. Specific 5-HT polymorphisms have been associated with SUDs. The greater genetic, anatomical, physiological, and behavioral similarities between non-human primates (NHP) and humans increase the translational validity of the NHP model. While NHPs are more similar to humans than rodents, one disadvantage they have had as a model system is a lack of genetic homogeneity. A benefit of rodents is the control over genetics in inbred and transgenic lines. Practical limitations have made this control impossible in NHPs, but as we emerge into the post-genomic era it is becoming not only possible but necessary to expand our knowledge of NHP genetics to improve animal models. DNA was isolated from blood collected from 20 Chinese-origin rhesus, 44 Indian-origin rhesus, and 32 cynomolgus macaques. This study used a custom designed and validated gDNA target enrichment methodology to focus on 5-HT sequences of interest. By employing exomic capture techniques and next generation sequencing, and taking advantage of molecular barcoding for multiplexing, it was possible to efficiently and inexpensively generate significant polymorphism data. Prior to sequencing, samples underwent quality control analysis via qPCR. Over 2,500 5-HT single-nucleotide polymorphisms (SNP) were discovered, including 1,896 non-coding, 235 synonymous, and 378 non-synonymous variants. Further analyses revealed non-synonymous polymorphisms varying in frequency across 12 5-HT receptor family subtypes and different NHP species. Our improved understanding of 5-HT receptor polymorphism in these NHPs allows researchers to better select appropriate NHP models, increasing translational relevance. Looking ahead, 5-HT receptor polymorphisms may direct individualized treatment, reducing the burden caused by addiction.

## 15

**Assessment of the punishing effects of the kappa agonist, salvinorin A, on remifentanil and cocaine self-administration in monkeys**

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The study of drugs as punishers may be useful in the development of abuse-deterrent formulations for prescription medications. Kappa agonists, which have received much experimental attention as therapeutics for drug abuse, are reportedly dysphoric in humans and appear to be aversive in animals. The aim of the current study was to determine if a kappa agonist could punish self-administration of two drug reinforcers from different classes: the mu opioid, remifentanil, and the psychostimulant, cocaine. Using a two-lever operant procedure, 4 monkeys were allowed to choose between equal doses of an intravenous drug reinforcer when the options were the drug alone or the drug mixed with a range of doses of the kappa agonist, salvinorin A (SVA). In separate conditions, the drug reinforcers were 0.1 µg/kg remifentanil (n=2) or 100 µg/kg cocaine (n=2). Daily sessions consisted of 2 forced-choice trials on each lever followed by 10 free-choice trials, and trials were separated by a 10-min timeout. In the absence of SVA, choice for the lever paired with the drug alone option was approximately 50% for both the remifentanil and cocaine conditions. However, adding SVA to the mixture option increased choice for the drug alone option in a manner directly related to SVA dose for both remifentanil and cocaine. At the highest dose of SVA tested (10 µg/kg), choice for the drug alone option was >80% in all monkeys for both drug conditions. These data indicate that the kappa agonist, SVA, can punish self-administration of remifentanil and cocaine in monkeys, which suggests a novel use for kappa agonists as therapeutics for drug abuse. Punishment of self-administration, as a mechanism, offers a specific utility for these compounds that likely capitalizes on their dysphoric effects.

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## 16

**Delay discounting in rats: impact of neuropathic pain and analgesics.**

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Prolonged pain conditions often lead to emotional disturbances and cognitive impairments, such as attention, memory and emotional decision making. In rodents, limited data also suggest an altered emotional decision making capability when persistent pain is present. However, the dynamic process and its response to analgesics of such a change are unknown. Delay discounting is a procedure that measures temporal decision making. This study employed a delay discounting paradigm to examine whether one type of chronic pain (neuropathic pain) alters the delay discounting performance in rats and whether analgesics alter the delay discounting functions with or without chronic pain. Fourteen rats responded under an operant choice procedure whereby responses on one lever resulted in immediate delivery of one 45-mg food pellet and responses on another lever resulted in delivery of three pellets, either immediately or after a delay (5-40 s). The delay to the larger reinforcer increased within-session across discrete blocks allowing for generation of delay discounting functions within sessions. Without delay, rats chose the larger reinforcer nearly exclusively. With increasing delay, rats progressively switched their choice from the larger to the smaller reinforcer in a delay-dependent manner. This delay discounting function remained highly stable across weeks and was shifted leftward by the adrenergic α2 receptor agonist clonidine (0.01-0.1 mg/kg), but was unaltered by morphine (1-5.6 mg/kg) or an imidazoline I2 receptor agonist CR4056 (3.2-10 mg/kg). Chronic constriction injury (CCI), a model of neuropathic pain, produced significant mechanical hyperalgesia in rats and the effect lasted for at least 5 weeks. However, such a persistent pain failed to alter the delay discounting function. Moreover, rats responded to clonidine, morphine and CR4056 similarly under control and persistent pain conditions. Together, these data suggest that chronic neuropathic pain does not alter temporal decision making in rats, nor does such a pain condition alter the response of rats to analgesics. The fact that chronic pain alters some cognitive functions but not others (e.g., temporal decision making) suggest the non-overlapping neural mechanisms of these functions and the specificity of chronic pain on cognition.

# Oral Communications

## 17

### Desformylflustrabromine, a Positive Allosteric Modulator at α4β2 Nicotinic Acetylcholine Receptors, Reduced Nicotine Self-Administration in Rats.

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The α4β2 subtype of nicotinic acetylcholine receptors (nAChRs) plays a central role in the reinforcement of nicotine derived from tobacco smoke. Positive allosteric modulators (PAMs) at α4β2 nAChRs facilitate the intrinsic efficiency of these receptors and thus enhance receptor activation by nicotine, although they do not directly activate the receptors. α4β2 PAMs are hypothesized to reduce nicotine intake in subjects engaged in routine nicotine consumption. The present study used an animal model of nicotine self-administration to examine the effects of a PAM at α4β2 nAChRs on nicotine intake. Male Sprague-Dawley rats were trained in daily 1 h sessions to intravenously self-administer nicotine (0.03 mg/kg/infusion, free base) on a fixed-ratio 5 schedule. After the establishment of stable nicotine self-administration, the effects of the α4β2 PAM desformylflustrabromine (dFBr), α4β2-selective agonist 5-iodo-A-85380, and α7 PAM and acetylcholinesterase inhibitor galantamine on nicotine intake were examined. The ability of dFBr and 5-iodo-A-85380 to substitute for nicotine in maintaining self-administration behavior was also tested. Pretreatment with dFBr and 5-iodo-A-85380 dose-dependently reduced the number of active lever responses and corresponding nicotine infusions without altering food self-administration. Although galantamine decreased nicotine self-administration, it also suppressed lever-press responses for food reinforcement at high doses. Unlike 5-iodo-A-85380, dFBr failed to substitute for nicotine in supporting self-administration behavior. These results demonstrated the effectiveness of dFBr in reducing nicotine intake in rats that regularly self-administered nicotine and the inability of dFBr to support self-administration behavior, indicating a lack of reinforcing actions on its own. These findings suggest that positive allosteric modulation of α4β2 nAChRs may be a promising target for the treatment of nicotine addiction. Moreover, α4β2 PAMs, in contrast to agonist medications, may have clinical advantages because they may have little liability for abuse because of their lack of reinforcing actions on their own.

## 18

### Medication strategies for nicotine addiction

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Smoking behavior and relapse to smoking are mediated in part by the interoceptive stimulus effects of nicotine (NIC), and drug discrimination (DS) studies can be exploited to both identify NIC-like properties of tobacco constituents and evaluate medication strategies against tobacco addiction. Accordingly, the present studies in squirrel monkeys that discriminated IM injections of a nicotinic agonists [0.1 mg/kg, NIC or 0.001 mg/kg (+)-epibatidine(+)-(EPI)] from vehicle were conducted to evaluate: a) the NIC-like DS effects of selected minor tobacco alkaloids [nornicotine (NOR), anabasine (ANA), cotinine (COT), and myosmine (MYO)]; and b) the ability of pharmacological (nicotinic partial agonists) and immunological (anti-NIC vaccine) approaches to attenuate the DS effects of NIC. Results show that in (+)-EPI-trained monkeys, NIC and related compounds produced full [NIC, (+)-EPI, (-)-EPI] or partial [isoarecolone (ISO), varenicline (VAR)], substitution for the training stimulus. The minor tobacco alkaloids displayed a full range of effects in (+)-EPI-trained monkeys. Thus, NOR and ANA fully substituted for (+)-EPI, whereas COT and MYO failed to produce substantial levels of responding on the lever associated with the nicotinic agonist. In additional experiments to evaluate reduction of nicotinic DS effects, results indicate that a) pretreatment with the selective α4β2 nicotinic antagonist DHβE or partial nicotinic agonists (VAR, CYT) can attenuate the stimulus properties of NIC; and b) immunization with an anti-NIC vaccine can prevent the acquisition of NIC but not (+)-EPI (0.001 mg/kg) as a DS. In conjunction, these findings suggest that some minor tobacco alkaloids (NOR, ANA), exhibit NIC-like pharmacological properties that may contribute to tobacco addiction; and b) both pharmacological and immunological strategies could play an important role in future approaches to treating tobacco addiction.

# Poster Communications

## 1

**Chronic Food Restriction increases burst firing of midbrain dopamine neurons**

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Food restriction is commonly used to promote rapid and reliable establishment of drug self- administration in rodent models of drug use. Both feeding and drugs of abuse increase extracellular dopamine levels in the projection regions of midbrain dopamine neurons which is thought to be responsible for many of the reinforcing effects of rewarding stimuli. Glutamate transmission in dopamine neuron cell body regions enables burst firing of dopamine neurons which rapidly increases extracellular dopamine levels at the terminal, so any manipulation that enhances burst firing of dopamine neurons could have a profound impact on reward related behavior. Here we investigated the cellular adaptations responsible for the interplay between feeding state and drug abuse. We examined firing of subtantia nigra dopamine neurons in mice that had either been fed ad libitum or chronically food restricted to 80-85% of their initial body weight. Cells from chronically food restricted mice exhibited increased burst firing in vivo, an effect that was augmented by an i.p. injection of cocaine (10 mg/kg). Electrophysiological recordings in acutely isolated brain slices showed that aspartic acid-induced burst firing was also increased by chronic food restriction, indicating that food restriction-induced adaptations occur postsynaptically in the dopamine neuron cell bodies. Mice re-fed after a chronic food restriction regimen also showed an increase in burst firing while mice acutely food restricted overnight did not. These results suggest food restriction-induced adaptations are not significantly implemented overnight, but persist for at least a week following refeeding. Chronic food restriction also increased AMPA/NMDA ratios indicating an increase in synaptic strength to reinforcing stimuli. Thus, the behavioral consequences of food restriction may be partially attributable to an increase in glutamatergic burst firing of dopamine neurons.

## 2

**Assessment of 5-HT3 receptor antagonism on cocaine-induced conditioned taste aversions.**

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Cocaine, like other drugs of abuse, has both rewarding and aversive effects. The balance of these effects may influence a drug's overall abuse potential. While the rewarding effects of cocaine are well characterized, the mechanisms underlying its aversive effects are less understood. The conditioned taste aversion (CTA) preparation is a common animal model used to assay the aversive effects of drugs. In this procedure, animals avoid consumption of a saccharin solution (a novel taste) after it has been paired with a drug. This decrease in consumption is indicative of the aversive effects of the drug. Previous work has demonstrated that cocaine's actions as a nonselective monoamine reuptake inhibitor may mediate its ability to induce CTAs. Several reports have indicated a possible role of serotonin (5-HT) in the aversive effects of cocaine through cocaine's ability to block the reuptake of 5-HT resulting in increased synaptic 5-HT levels. The present study addressed whether pharmacological antagonism of 5-HT would result in attenuated cocaine-induced CTAs, indicating a role of 5-HT in the aversive-inducing effects of cocaine. The specific 5-HT receptor, 5-HT3, was analyzed given the fact that it is implicated in a number of the behavioral effects of cocaine, including its affective properties. Specifically, rats were given access to a novel saccharin solution followed by an injection of various doses of cocaine (alone or in combination with tropisetron). Under these conditions, animals acquired a robust aversion to the cocaine-paired solution that was generally unaffected by the co-administration of tropisetron, suggesting that cocaine's aversive effects are not mediated by this specific receptor subtype. Research supported by a Robyn Rafferty Mathias award to MAB, AU Artists and Scholars Fellowship to MAB and a grant from the Mellon Foundation to ALR.

## 3

**The role of serotonin 2A and 2C receptors in tryptamine hallucinogens DMT and DiPT**

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Hallucinogens have been used for centuries yet compared to other drug classes, relatively little is known about their mechanism of action. Serotonin (5-HT) 2A and 2C receptors are primary targets for classic serotonin-mediated hallucinogens. Of the groups of classic hallucinogens two tryptamine hallucinogens are futher examined to determine the role of these receptors in mediating behavioral effects. These hallucinogens are N,N-dimethyltryptamine (DMT; visual hallucinations) and N,N-diisopropyltryptamine (DiPT; auditory distortions). Drug discrimination, head twitch and radioligand binding assays were used. Rats were trained to discriminate DMT or DiPT from saline. Antagonists selective for 5-HT2AR (MDL100907) and 5-HT2CR (SB242084) were used to attenuate the discriminative stimulus effects. MDL100907 was used to attenuate DMT/DiPT-induced head twitches in mice. Radioligand binding was performed at the 5-HT2CR in HEK cells for DiPT and compared to pre-existing data for DMT. MDL100907 fully blocked the discriminative stimulus effects of DMT, but only partially blocked DiPT. SB242084 partially attenuated the discriminative stimulus effects of DiPT, but minimally attenuated DMT's effects. Both compounds produced head twitches (DiPT>DMT), which were blocked by MDL1000907. DiPT and DMT had similar binding and were fully efficacious at the 5-HT2C receptor, but DiPT was ~ 20 times less potent at stimulating IP-1 formation. 5-HT2AR and 5-HT2CR play different roles in mediating the discriminative stimulus effects of DMT and DiPT. 5-HT2AR is essential for both compounds, whereas 5-HT2CR may be more important for the stimulus effects of DiPT. DMT has a pharmacological profile similar to other classical hallucinogens. This work was supported by: NBA T32 AG020494 and NIH N01DA-7-8872.

## 4

**Behavioral, biochemical and molecular indices of stress are enhanced in female versus male rats experiencing nicotine withdrawal**

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Background: Stress is a major factor that promotes tobacco use and relapse during withdrawal. Although women are more vulnerable to tobacco use than men, the manner in which stress contributes to tobacco use in women versus men is unclear.

Purpose: The present study compared anxiety-like behaviors, plasma corticosterone levels and changes in gene expression of corticotropin releasing factor (CRH) in various brain regions relevant to drug abuse in male and female rats. Since the effects of nicotine withdrawal are age-dependent, this study also included adolescent rats.

Methods: Rats underwent sham surgery or received subcutaneous pumps that delivered nicotine (4.7 mg/kg/day). After 14 days of nicotine exposure, the pumps were removed to induce spontaneous withdrawal. Twenty-four hours later, anxiety-like behavior was assessed using elevated plus maze and open field maze procedures. After behavioral testing, blood samples were analyzed for corticosterone and cotinine levels. Coronal slices containing the nucleus accumbens (NAcc), amygdala and hypothalamus were also analyzed for CRH gene expression.

Results: Female rats experiencing nicotine withdrawal displayed a significant increase in anxiety-like behaviors, plasma corticosterone levels, and an up-regulation of CRH mRNA expression in the NAcc relative to males. However, during nicotine exposure, adult males exhibited higher levels of corticosterone and CRH mRNA in the amygdala relative to females.

Conclusion: These findings suggest that intense stress produced by nicotine withdrawal may contribute to tobacco use in women.

# Poster Communications

## 5

**Discriminative stimulus effects of quinpirole, a dopamine D3/D2 receptor agonist, in free-feeding and food-restricted mice.**

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The discriminative stimulus effects of direct- and indirect-acting dopamine receptor agonists are mediated by multiple dopamine receptor subtypes. In rats, the relative contribution of D2 and D3 receptors to these effects can be altered by manipulating feeding conditions (e.g., food restriction). In these studies a two-lever discrimination was trained with a direct-acting D3/D2 agonist, quinpirole (0.032 mg/kg), using a fixed ratio 10 schedule of food presentation (50% sweetened condensed milk) in free-fed and food-restricted mice (n=5 per group). Although feeding condition did not affect the rate at which mice acquired the discrimination, free-fed mice responded at lower rates under training conditions and were more sensitive to the rate-suppressant effects of quinpirole. Despite these differences, pramipexole (D3 agonist), sumanirole (D2 agonist), and apomorphine (a non-selective dopamine agonist) each produced dose-dependent increases in quinpirole-appropriate responding over a similar range of doses in free-feeding and food-restricted mice. Although these findings suggest that feeding condition did not alter the potency of these D2-like agonists to produce quinpirole-like discriminative stimulus effects, free-feeding mice were more sensitive to the rate-suppressant effects of each of the direct dopamine receptor agonists. Cocaine, an indirect-acting dopamine receptor agonist, did not systematically increase quinpirole-appropriate responding in either group of mice, suggesting that cocaine does not possess quinpirole-like discriminative stimulus effects in mice. These studies are the first to characterize the relative contribution of D2 and D3 receptors to the interoceptive effects of quinpirole in mice and will serve as the basis for future studies investigating the impact of nutritional factors on the behavioral effects of dopaminergic drugs in mice.

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## 6

**Effect of stimulants on executive functioning as measured by 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 significantly more trials (M=17.6) than control rats (M=9.25), ), $t(11.97)=2.52$, $p=.027$, in the extradimensional shift. Cocaine rats also required significantly more trials to complete the entire task (M= 12.89, M=9.44, $t(9)=3.37$, $p<.01$). A follow up study is currently looking at the role of amphetamine on this same task. Preliminary results show impairments in the reversals for amphetamine (M=15.6) compared to controls (M=9.9), $p>.01$. Future studies aim to obtain a better understanding of the level of effect long-term exposure to amphetamine has on attentional set shifting and how it compares to the impairments associated with cocaine.

## 7

**Loss of sensitivity to varenicline in monkeys receiving chronic nicotine treatment.**

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Given the adverse health consequences of cigarette smoking, there is a need to understand pharmacologic mechanisms underlying the effects of smoking cessation aids and whether those effects vary as a function of nicotine treatment. The effects of nicotine and varenicline (Chantix) were examined in two groups of rhesus monkeys that received markedly different nicotine treatments. One group (n=5) received 1.78 mg/kg of nicotine base as a training drug in a two-lever discrimination procedure. The other group was trained at the same dose of nicotine, but also received post-session administration of 8.9 mg/kg/day of nicotine. Nicotine dose-dependently increased nicotine-lever responding in both groups; the ED50 value (0.47 mg/kg) in the absence of post-session nicotine was not different from that (0.30 mg/kg) in monkeys receiving post-session nicotine. Varenicline produced 98% nicotine-lever responding (ED50 value = 0.53 mg/kg) in the absence of post-session nicotine. In contrast, varenicline produced a maximum of only 10% nicotine-lever responding in monkeys receiving post-session nicotine. To examine whether the marked loss of sensitivity to varenicline was related to low agonist efficacy at nicotinic acetylcholine receptors, varenicline and nicotine were combined. Varenicline did not antagonize the nicotine discriminative stimulus, as might be expected of a low efficacy agonist in combination with a high efficacy agonist. A difference in agonist efficacy at a common receptor type is not sufficient to account for the striking loss of sensitivity to varenicline resulting from nicotine treatment. Instead, nicotine treatment appears to differentially alter multiple subtypes of receptor, one of which is necessary for varenicline to exert its effects.

## 8

**Mixed mu/delta opioid analgesics based on the oxymorphone pharmacophore**

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The rapid development of analgesic tolerance following prolonged administration of mu opioid receptor (MOR) agonists such as morphine and oxycodone is a significant burden facing treatment of chronic severe pain. Previous studies have demonstrated that concomitant pharmacological blockade of the delta opioid receptor (DOR), through receptor knockout models or administration of DOR-selective antagonists, greatly attenuates the development of analgesic tolerance to MOR agonists. Co-administration of MOR agonist with a DOR antagonist is clinically undesirable, as this adds to both the pill burden for the patient and the potential for drug-drug interactions to a patient likely taking various medications. Thus, there is great interest in developing novel analgesics presenting a dual profile of MOR agonism and DOR antagonism. Using the “message-address” concept, a series of hybrid analogues of DOR antagonist benzylidenenaltrexone (BNTX) and MOR agonist oxymorphone was synthesized and evaluated in vitro in opioid receptor binding and efficacy assays. In displacement binding assays, benzylideneoxymorphone (BOM) demonstrated nanomolar affinity to both MOR and DOR, and efficacy studies ([35S]GTP-gamma-S) indicated a profile of MOR partial agonism and DOR antagonism. Attempts to further enhance MOR potency and efficacy through replacement of the N-methyl substituent resulted in an unexpected decrease in MOR affinity. Molecular modeling studies were conducted using the recently-described MOR and DOR crystal structures toward describing this unique activity and devising a rational approach to producing novel analgesics with the desired MOR/DOR pharmacological activity

# Poster Communications

## 9

**Developing Novel Positive Allosteric Modulators of 5-HT2C Receptor as Pharmacotherapy for Psychostimulant Addiction**

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Allosteric modulators of the serotonin (5-HT) 5-HT2C receptor (5-HT2CR) 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. We recently investigated two synthetic routes and established a feasible method to readily access PNU-69176E, the only reported selective positive allosteric modulator for the 5-HT2CR, and its diastereomer for the first time. Meanwhile, the biological characterization using an intracellular calcium (Cai++) release assay revealed that PNU-69176E demonstrated efficacy and potency as a selective allosteric modulator for the 5-HT2CR with no intrinsic agonist activity, while its diastereomer did not alter 5-HT-evoked Cai++ release in either stably-transfected 5-HT2AR- or 5-HT2CR-Chinese Hamster Ovary (CHO) cells nor did PNU-69176E display intrinsic agonist activity (ACS Chem. Neurosci. 2012). The in vivo behavioral studies showed that PNU-69176E (1 and 3 mg/kg, i.p.) dose-dependently decreased basal levels of horizontal and vertical activity consistent with expectations. Intrigued by these exciting findings, we further took advantage of PNU-69176E as a chemical lead to optimize the polar head domain (S3 site) and the lipophilic binding pocket (S2 site) to identify novel positive allosteric modulators of 5-HT2CR. Several novel and simplified PNU-69176E analogues (e.g., CYD-1-79, CYD-6-16-2) have been discovered as drug candidates for further preclinical validation and clinical application in translational research. Our success in the chemical design, synthesis and pharmacological evaluation of these unique small molecules opens new avenues in probing the 5-HT2CR function and developing novel pharmacotherapeutics for brain disorders including addictions and impulse control disorders.

## 10

**Central and peripheral contributions of TRPV1 to a rodent model of nerve growth factor-induced persistent 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 to persistent/chronic pain states. Nerve growth factor (NGF) appears to be a sufficient stimulus in humans to trigger a persistent pain state, but 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 and endogenous TRPV1 agonists, the oxidized linoleic acid metabolites (OLAMs). Using blinded observers, 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. NGF triggered a persistent thermal and mechanical allodynia that extended up to 11d. Further, the allodynia was significantly reversed by systemic administration of anisomycin, a protein synthesis inhibitor ($p<0.01$) and by capsazepine (CPZ, $p<0.001$). Thus, NGF induction of a prolonged thermal and mechanical pain state requires protein synthesis and is TRPV1-dependent. Our data also showed that NDGA, a CYP/LOX inhibitor, reduced NGF effects ($p<0.001$). We have previously shown that NDGA blocks OLAM synthesis in cultured neurons, suggesting that the in vivo effects of NGF on persistent pain may be in part due to increased OLAM activities in the neuronal soma. To further evaluate TRPV1 contributions to persistent NGF-induced allodynia, CPZ was administered peripherally (i.pl.) and centrally (i.t.). Peripheral administration of CPZ attenuated persistent thermal but not mechanical allodynia ($p<0.001$), and intrathecal CPZ attenuated both thermal and mechanical persistent allodynia ($p<0.001$). Taken together, the results demonstrate that NGF produces prolonged thermal and mechanical allodynia after injections into rats, and this requires de novo protein synthesis, is mediated by TRPV1, involves the release of oxidized lipids and produce thermal allodynia by both peripheral and central mechanisms, but produces mechanical allodynia only by central mechanisms. Understanding how NGF triggers persistent/chronic pain state may identify novel targets for analgesic development

## 11

The **effect of the α1- adrenoreceptor antagonism on one-trial nicotine conditioned place preference in adolescent rats.**

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Nicotine is one of the most heavily abused drugs in the United States, and adolescents are especially liable to develop patterns of tobacco use that lead to addiction (Breslau, 1992). This pattern of early drug abuse is supported by a sensitization of the mesolimbic dopamine pathway in the adolescent brain. Our lab has previously demonstrated that adolescent rats, and not adults, form conditioned place preference (CPP) to nicotine after one conditioning trial (Brielmaier et al, 2007). Recent observations in our lab have found that one-trial nicotine CPP is also dependent on differences in anxiety-like responses.
The noradrenergic system, specifically α1-adrenoreceptors, has been implicated in the maintenance of both anxiety and drug reward- related behavior (Weinshenker et al, 2007). Prazosin (PRAZ) is a non-competitive α1-adrenoreceptor antagonist that has been found to attenuate CPP in mice and adult rats when paired with nicotine, morphine or cocaine (Forget et al, 2010; Bernardi et al, 2009). PRAZ also decreases stress and cue- induced ethanol cravings in human adults (Fox et al, 2012). This study investigated the relationship between α1-adrenoreceptor signaling and single trial nicotine CPP in adolescent rodents.
Adolescent rats (P28) were subject to a biased, one- trial nicotine CPP protocol (0.5 mg/kg s.c.). 30 minutes prior to the single nicotine conditioning session (saline for controls), animals were given a 0.5 mg/kg PRAZ injection or vehicle. Adolescent rats pretreated with prazosin formed a significant place preference for the nicotine- paired chamber compared to saline pretreated controls. In light of previous findings, our results suggest that there are differences in the neurochemical substrates defining addiction- related behavior between adolescents and adults that extend beyond dopamine signaling.

## 12

**CHILDHOOD EXPOSURE TO METHYLPHENIDATE ENHANCES COCAINE REWARD IN MALE ADOLESCENT RATS**

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Methylphenidate is the most prescribed drug for the treatment of attention deficit hyperactivity disorder in children. Surprisingly, little research has examined the long-term effects of this early and extended use of this drug, particularly when it is prescribed to preschool age children. In rats, exposure to methylphenidate early in development has been shown to produce long-lasting effects on the sensitivity to cocaine when animals are tested as adults. However, the effect of early methylphenidate exposure on the sensitivity to cocaine in adolescent rats has not been investigated. Using the conditioned place preference (CPP) paradigm, we examined the effects of early methylphenidate exposure on cocaine reward in early and late adolescent rats. Male and female Sprague-Dawley rats were treated twice daily with methylphenidate (0, 2, or 4 mg/kg) from postnatal days (PDs) 11-20, a period of development comparable to preschool age children. Rats were then assessed for cocaine-induced CPP, beginning on PD 27 (early adolescence) or PD 41 (late adolescence), using an 8-day CPP procedure. During days 1 and 8 of the CPP procedure, rats were tested for their preconditioning and postconditioning place preference, respectively, in 15-minute sessions. During days 3-6, rats were conditioned 30-minutes a day with either cocaine (1.25 or 2.5 mg/kg) or saline on alternating days. Days 2 and 7 were rest days. Results showed that early methylphenidate (2.0 mg/kg) exposure enhanced the rewarding effects of a sub-threshold dose of cocaine (1.25 mg/kg) when males were tested during early adolescence (PD34). In contrast, differences in cocaine-induced CPP with the higher dose of cocaine (2.5 mg/kg) were not evident in male or female rats pretreated with methylphenidate and tested during the early or late adolescent period. Thus, early methylphenidate exposure has a modest increase on cocaine-induced CPP. The present data adds to a growing body of evidence that methylphenidate prior to adolescence alters the functional effects of various drugs of abuse later in development.

# Poster Communications

## 13

**Withdrawal from cocaine self-administration alters Activin/Smad3-signaling**

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The addicted phenotype is characterized as a long-lasting, chronically relapsing disorder that persists following long periods of abstinence leading the hypothesis that the addicted brain has been functionally "re-wired". Repeated exposure to psychomotor stimulants results in an increase in dendritic spine density in the brain including the nucleus accumbens (NAc) a critical area of the mesolimbic dopamine circuitry mediating drug addiction. These changes are thought to represent alterations in synaptic connectivity that may underlie the life long battle with addiction. Activin receptor signaling is known to regulate the actin cytoskeleton through both direct regulation of actin dynamics, and more indirectly through changes in gene transcription. Here, we examined the role of activin receptor signaling following withdrawal from cocaine-self administration. Following a seven-day withdrawal period from cocaine self-administration, there was a marked increase in the activin receptor II (ActRII) expression at both the mRNA and protein levels in the NAc. Activin receptor activation leads to the phosphorylation of Smad3, which transduce extracellular signals to the nucleus regulating gene transcription. Consistent with the increased expression of activin receptors, we find an increase in phosphorylated Smad3 (p-Smad3), an effect observed seven days but not one day following cocaine self-administration. These data strongly suggests that withdrawal from cocaine self-administration leads to an induction of the transcription factor Smad3 and subsequent activation of Smad-dependent gene expression in the NAc. Taken together, these data indicate that activin/Smad3 signaling is regulated in a time-dependent manner following cocaine self-administration, and may be the molecular bridge between actin dynamics and long-term transcriptional events that have been associated with drug addiction

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## 14

**Monoamine transporter mediated in vivo effects of abused "bath salt" constituent MDPV in mice: drug discrimination, thermoregulation, and motor activity**

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In recent years, synthetic analogues of naturally-occurring cathinone in commercial "bath salt" preparations have emerged as psychostimulant-like drugs of abuse. 3,4-Methylenedioxypyrovalerone (MDPV) is a common constituent of these illicit products, and recent in vitro studies implicate monoamine transporters as mediators of its pharmacological effects. In these studies, adult male NIH Swiss mice were trained to discriminate 0.3 mg/kg MDPV from saline, and interoceptive effects of a range of substitution doses of MDPV, MDMA and METH (as well as negative controls morphine and JWH-018) were then assessed. In separate groups of mice, surgically-implanted radiotelemetry probes simultaneously monitored thermoregulatory and locomotor responses to various doses of MDPV and MDMA, as a function of ambient temperature. The role of monoamine transporters in these effects were assessed via pretreatment with the non-selective transporter inhibitor imipramine, the serotonin-selective reuptake inhibitor fluoxetine, the norepinephrine-preferring reuptake inhibitor desipramine, or saline, followed by MDPV. We found that mice reliably discriminated the MDPV training dose from saline, and that cumulative doses of MDPV, MDMA, and METH all fully substituted for the MDPV training stimulus with similar ED50 values. Stimulation of motor activity was observed following administration of a wide range of MDPV doses (1 to 30 mg/kg), and the warm ambient temperature potentiated motor activity and elicited profound stereotypy and self-injurious behavior at 30 mg/kg. In contrast, similar MDPV-induced hyperthermic effects were observed in both the cool and warm ambient environments. This pattern of effects is in sharp contrast to MDMA, where ambient temperature interacts with thermoregulation, but not locomotor activity. These studies suggest that while the interoceptive effects of MDPV are similar to those of MDMA and METH, direct effects on thermoregulatory processes and locomotor activity are likely mediated by different mechanisms than those of MDMA. The role of monoamine transporters in these effects will be discussed.

## 15

**Optogenetic investigation of the neurobiology of choice behavior**

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Recent studies have implicated several specific brain regions in the evaluation and commission of a choice between two alternatives. Lesions of the anterior cingulate cortex appear to bias choice toward smaller, lower effort rewards, while lesions of the orbitofrontal cortex appear to bias choice toward smaller, immediately delivered rewards. In contrast, lesions of the nucleus accumbens (Nacc) appear to disrupt instrumental responding without affecting the sensitivity to effort or reward size. Yet, these studies are limited by relatively poor experimental control over the lesion and the behavior. Further, such studies do not allow a comparison with the effect of activating these same regions. Combining optogenetic technology and an operant behavioral techniques overcomes these limitations. Here, we investigate the effects of hyperpolarization of NAcc on a choice between a large or small food reward using optogenetic technology. Rats were infected with an adenovirus containing channelrhodopsin and fitted with a cannula allowing experimenter-illumination of the NAcc using a laser; presumably resulting in hyperpolarization of the NAcc. Rats were then trained to respond on levers resulting in delivery of either 1 or 10 food pellets following 5 or 25 responses, respectively (FR5, FR25) in a concurrent schedule of reinforcement during a 30-min session. Illumination of the laser occurred during a test session and its effects were compared to components within the same session in which the laser was not illuminated, as well as to sessions on other days in which the laser was illuminated in the test chamber, but was not attached to the cannula providing a powerful within-subject (and within-session) evaluation of the effects of activation of the NAcc. Preliminary results are consistent with previous studies showing that disruption of the NAcc during choice evaluation can disrupt instrumental behavior without altering the allocation of the behavior. This study provides the foundation for more extensive investigations of the neurobiology of choice using optogenetic techniques.

## 16

**Inhibition or deletion of PKCβ but not PKCα reduces amphetamine-stimulated behaviors and dopamine efflux**

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The reinforcing properties of amphetamines (AMPH) depend on the level of extracellular dopamine (DAe) which is elevated after AMPH binds to the dopamine transporter. Identifying factors that dampen the ability of AMPH to increase DAe offers new options for treatment of stimulant dependence. The emerging role of protein kinase Cbeta (PKCβ) in AMPH function provides a target worthy of exploration. PKC inhibitors have been shown to inhibit AMPH-induced locomotor behaviors and DA efflux. We demonstrated that inhibition of PKCβ in particular inhibit AMPH-stimulated DA efflux. Because PKCα has also been specifically identified as being located in DA cells projecting to the striatum, we examined whether inhibition of PKCα would alter AMPH-stimulated activities. There is no specific small molecule inhibitor of PKCα, so we conducted studies using PKCα or PKCβ knockout (KO) mice. As compared to wild type (WT) controls, AMPH-stimulated DA efflux in perfused striatal synaptosomes from PKCβ-KO but not PKCα-KO mice was reduced. [3H]DA uptake was not changed from WT control in striatal synaptosomes from either PKCβ-KO or PKCα-KO mice. To examine the reverse effect, we demonstrated that overexpression of PKCβ but not PKCα into heterologous hDAT cells enhanced AMPH-stimulated DA efflux. Locomotor activity in response to 3 mg/kg AMPH i.p. was reduced from WT control values in PKCβ but not PKCα KO mice. Because locomotor activity does not involve a 'reward' component, we determined conditioned place preference to AMPH in PKCβ KO and WT mice. CPP for AMPH was demonstrated in WT but not PKCβ mice. We conclude that PKCβ promotes dopamine transporter-mediated DA efflux but not DA influx. Furthermore, our data suggest that a specific PKCβ inhibitor could be useful in treating AMPH abuse. Funded by DA011697 (MEG).

# Poster Communications

## 17

**BLG: In-Vivo Detection and Assay studies**

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In the 80 years since the discovery of Beta-Lactoglobulin(BLG) in milk a number of experiments have been conducted to ascribe a biological function to the protein. The main biological function continues to elude us. The protein might, in fact, be detrimental to health, not only as an allergen but also as one of the causes of Age Related Macular degeneration (Mol. BioSyst., 2011, 7, 162-168). Previous work in our lab has identified that BLG carries out the cyclodimerisation of terpenals (Mol. BioSyst., 2011, 7, 162-168). BLG's size, stability and unique ability to absorb into the blood stream make it an excellent target as a drug delivery vehicle. Delivery of drugs to the retina continues to be challenging because of the presence of a blood retina barrier. In our research, we aim to show that the protein BLG can cross the blood-retina barrier and enter the retina. To do so, we are making use of a dual-modality optical coherence tomography/fluorescence lifetime imaging microscopy system developed by Dr. Applegate at Texas A&M University. By attaching BLG to a fluorophore, we can directly observe the retina of a live mouse fed a BLG-fluorophore complex to assay for the influx of BLG from the bloodstream. Another aspect of using BLG for drug delivery is the identification of various bioactive compounds that can bind to the protein. To help us screen libraries of bioactive compounds, we are developing an ELISA assay for cyclocitral (a cycloterpenal). One of the first steps to develop an ELISA assay is to generate antibodies against cyclocitral. We are synthesizing an acid derivative of cyclocitral that can be bound to keyhole limpet hemocyanin to make the hapten-protein conjugate which can be used as an antigen.

## 18

**FAMILIARITY, PERCEIVED HARMFULNESS, AND USE OF "LEGAL HIGHS" AMONG COLLEGE STUDENTS LIVING ON THE U.S. / MEXICO BORDER**

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The use of Spice and other "legal highs" is increasingly recognized as a public health concern. However, few studies have examined how familiarity, perceived harmfulness, and related factors influence the use of these substances. This study examined how the latter influence the use of Spice, Salvia, and cough and cold medication containing dextromethorphan. This study also investigated whether age, gender, and estimates of friends' drug use were related to ever having used Spice, Salvia, and dextromethorphan-containing cough and cold medications for the purposes of getting buzzed or high.

Two hundred seventy-eight participants (79% Hispanic; 62.6% female; mean age = 19.62, standard deviation = 2.99) were recruited from a University on the U.S/Mexico border for an online study. Participants completed measures assessing demographics, substance use history, estimates of friends' substance use, and perceived harmfulness of using various drugs. Age, gender, and friends' substance use were entered into three separate logistic regression analyses, with lifetime use of Spice, Salvia, and cough and cold medication as the dependent variables.

Approximately, 9%, 3%, and 7% of the sample reported prior use of Spice, Salvia, or cough and cold medications, respectively. Only 4%, 17%, and 1% of the sample reported being unfamiliar with Spice, Salvia, and cough and cold medications, respectively. Approximately 22%, 24%, and 15% of the sample reported that experimental use of these drugs would lead to "very great harm."

The use of Spice and related synthetic marijuana products was significantly associated with being male (OR 3.18, $p = .05$) and friends' substance use (OR 1.12, $p = .007$). The use of Salvia was significantly associated with friends' substance use (OR 1.17, $p = .01$). The abuse of cough and cold medication was significantly associated with being male (OR 8.23, $p = .009$) and friends' use (OR 1.16, $p = .003$)

## 19

**Effects of amphetamine on delay discounting depend upon the context in which it is studied**

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Stimulants tend to increase choice of larger, delayed reinforcers under delay discounting procedures, suggesting that they attenuate delay discounting (i.e., decrease impulsivity). However, recent data from our laboratory indicate that amphetamine either increases or decreases choice of larger, delayed reinforcers depending upon the order in which delays are presented within the session. Because the previous study compared drug effects and delay order between different groups of subjects, differences might be due to factors other than or in addition to delay order (e.g., history of responding exclusively with one order of delay presentation). The current study examined the effects of amphetamine in a single group of rats (n=8) that were trained and tested under both ascending and descending orders of delay presentation. Responses on one lever delivered one food pellet immediately and responses on the other lever delivered three food pellets either immediately or after a delay (4, 8, 16, and 32 s); delay to the larger reinforcer varied within session. Responding under both orders was sensitive to reinforcer amount and delay; with no delay rats responded exclusively for the larger reinforcer and, as the delay increased, responded progressively less for the larger reinforcer and more for the smaller reinforcer. Delay functions obtained under the ascending and descending order were not significantly different within subjects. For some rats (n=4), the effects of amphetamine (i.p.; 0.32-1.78 mg/kg) on discounting varied markedly across delay order. Under the ascending series, amphetamine either had no effect or enhanced responding for the larger, delayed reinforcer, whereas under the descending series, amphetamine reduced responding for the larger reinforcer in all components. For the remaining rats (n=4), amphetamine tended to decrease choice of the larger reinforcer under both orders of delay but did so to a greater degree under the descending series. These data indicate that the effects of amphetamine on discounting can differ markedly, even in the same individual, depending upon the conditions under which they were studied.

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## 20

**Interaction between FAAH and MAGL inhibitors in mice discriminating delta-9-THC.**

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The CB1 receptor-mediated in vivo effects of delta-9-THC were compared to those of anandamide and 2-AG and their respective degradative enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) in male C57BL6/J mice discriminating delta-9-THC (5.6 mg/kg i.p.). Delta-9-THC dose-dependently increased delta-9-THC appropriate responses with an ED50 value of 3.2 mg/kg. Mice did not respond as though they received delta-9-THC when instead they received anandamide, 2-AG, or inhibitors with selectivity for FAAH (PF-3845) or MAGL (JZL-184). Mice also did not respond as though they received delta-9-THC when anandamide (1-10 mg/kg) was combined with PF-3845 (10 mg/kg) or when 2-AG (0.32-10 mg/kg) was combined with JZL-184 (40 mg/kg). In contrast, the same amount of delta-9-THC appropriate responding as that produced by delta-9-THC itself was produced by a combination of PF-3845 (10 mg/kg) and JZL-184 (12-120 mg/kg) (ED50 value = 29 mg/kg) and also by drugs that inhibit both FAAH and MAGL, including SA-57 (ED50 value = 2.6 mg/kg) and JZL-195 (ED50 value = 25 mg/kg). The CB1 receptor-selective antagonist rimonabant attenuated the effects of SA-57, JZL-195 and delta-9-THC. According to these results, inhibition of both FAAH and MAGL is needed to produce CB1 receptor agonism of the type produced by delta-9-THC, perhaps reflecting more widespread CB1 receptor stimulation in brain as compared with inhibition of the degradation of anandamide or 2-AG alone.

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# Poster Communications

## 21

**Discriminative stimulus effects of direct- and indirect- acting dopamine receptor agonists in free-feeding and food-restricted mice**

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Manipulation of feeding conditions (e.g., food restriction) has been shown to alter the specific dopamine receptor subtypes that mediate the discriminative stimulus effects of direct- and indirect-acting dopamine receptor agonists in rats. These studies examined whether the relative contribution of dopamine D2 and D3 receptors in mediating the discriminative stimulus effects of cocaine are different in food-restricted (2.5g/day) or free-feeding mice. Both groups of mice were trained to discriminate cocaine (10.0 mg/kg) using a two-lever discrimination under a fixed ratio 10 schedule of food (50% sweetened condensed milk) presentation. Both groups of mice learned the discrimination; however, food-restricted mice acquired the discrimination significantly faster than mice with unrestricted access to food. Direct-acting D2-like receptor agonists, quinpirole (D2/D3), sumanirole (D2), pramipexole (D3), and an indirect-acting dopamine receptor agonist, amphetamine, each dose-dependently increased cocaine-appropriate responding in food-restricted, but not free-feeding mice. Although this may reflect a difference in the relative contribution of D2-like receptors in mediating the discriminative stimulus effects of cocaine, it is important to note that free-feeding mice were more sensitive to the rate-suppressant effects of direct- and indirect-acting dopamine receptor agonists. Given these differences, it is likely that the increased sensitivity of the free-feeding mice to the rate-suppressant effects of both dopamine and non-dopamine (midazolam) drugs limited the range of doses that could be assessed, and precluded accurate assessments of the relative contribution of D2 and D3 receptors to the discriminative stimulus effects of cocaine. These results provide a foundation for future studies aimed at identifying how feeding conditions impact the behavioral effects of dopamine drugs in mice.

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## 22

**Prolonged reduction in kappa opioid receptor function after a single administration of the antagonist, norBNI, in peripheral sensory neurons ex vivo and in vivo.**

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The kappa opioid receptor (KOR) is known to couple to a variety of intracellular signaling cascades. Although not as well studied, activation of KOR increases the activity of c-Jun N-terminal kinase (JNK). Interestingly, in the CNS as well as in HEK cells, certain KOR antagonists, such as norBNI, display agonist activity toward JNK, which in turn produces long-term inactivation (lasting weeks) of KOR function. Here, we sought to assess the possible long-term regulation of KOR function by norBNI in peripheral sensory neurons. Using a rodent behavioral model of pain, we measured paw withdrawal latencies following intraplantar (i.pl. 50 µl) injection of PGE2 (0.3µg) with and without the KOR agonist, U50488 (0.1µg), 2 and 7 days after a single injection with norBNI (30 ng; ~3 nM, 100xKi) or vehicle. U50488-mediated reduction in PGE2–induced thermal allodynia was completely abolished both 2 and 7 days following a single norBNI injection. In the presence of a selective JNK inhibitor, SP600125 (1µg, i.pl.) prior to norBNI, the long-term inhibition of KOR-mediated anti-allodynia was completely abolished. To determine if prolonged reduction on KOR signaling occurs with a single norBNI treatment ex vivo, primary cultures of adult rat peripheral sensory neurons were incubated with norBNI (3nM) for 1 hour (followed by washing), 24h before measurement of U50488-mediated inhibition of AC and activation of ERK. Inhibition of AC was completely eliminated following norBNI treatment, whereas activation of ERK by U50488 was unaffected. Further, the effect of norBNI on U50488-mediated inhibition of AC was abolished in cells pre-treated with JNK inhibitor, SP600125. Taken together, these data suggest that activation of JNK by norBNI leads to prolonged reduction in some, but not all, KOR functional responses in peripheral sensory neurons and provides strong evidence that norBNI is a protean ligand.

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## 23

**New 5-HT2A Receptor Ligands via Structural Exploration of Aporphines**

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Naturally occurring aporphine alkaloids as well as synthetic and semi-synthetic derivatives have been explored as ligands for various CNS targets including dopamine D1 and D2 receptors, the serotonin 5-HT1A receptor and α-adrenergic receptors.

We recently discovered that modifications on aryl ring A (viz. C1 and C3 positions) of the aporphine alkaloid nantenine, may afford significant improvements in 5-HT2A antagonist potency. This revelation has prompted further modifications on the aporphine template as a means of delineating critical elements of the aporphine core scaffold that are required for antagonism of the 5-HT2A receptor as well as selectivity vs other CNS receptors. Such a study has the potential to uncover new potent and selective 5-HT2A antagonists as well as multi-receptor ligands that may be useful as biological tools or in drug abuse applications.

Against this background, we designed and synthesized a series of C4 nantenine analogues that contain known 5-HT2A antagonist pharmacophores embedded in the aporphine core structure. Our synthetic route here featured a Michael addition and a high yielding microwave-assisted direct arylation as key steps. In addition, we implemented an oxa-Pictet-Spengler cyclization and microwave-assisted direct arylation in the construction of a novel series of heterocyclic analogues in which the sole nitrogen atom was substituted by oxygen. Further details on our synthetic work as well as biological evaluation of the analogues at CNS receptors will be presented.

## 24

**Cocaine Cues vs. Food Cues: Strength as Reinstaters and Conditioned Reinforcers**

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Recent studies show that rats greatly prefer natural rewards (e.g., food, saccharin) over cocaine, suggesting that cocaine is a relatively weak reinforcer (Ahmed, 2012). The present study explored whether a similar difference would be observed when the conditioned (rather than primary) reinforcing effects of cocaine and food were compared. This was accomplished by measuring the effects of cocaine cues and food cues within a cue-induced reinstatement design and within a novel operant acquisition procedure. In Experiment 1, rats were first trained to press one lever to receive cocaine infusions and another lever to receive food pellets. Delivery of each reinforcer was accompanied by a distinct audiovisual cue. When given a choice, rats chose to press the food lever 80% of the time. In the next phase, lever pressing on both levers was extinguished. Lever presses did not result in food, cocaine, or their associated cues during this phase. Once responding on both levers was eliminated, a cue-induced reinstatement test was administered. Pressing a lever resulted in presentation of the associated audiovisual cue, but not cocaine or food. Cocaine cues and food cues were found to be equally effective reinstaters of reward-seeking behavior on this test. Experiment 2 tested the effectiveness of cocaine cues and food cues as reinforcers in the acquisition of a novel operant response. Rats trained to lever press for food and for cocaine again greatly preferred food. But cues previously associated with cocaine or food were equally effective in reinforcing a novel nose-poke operant response. These results show that while food may act as a stronger primary reinforcer than cocaine, cues associated with cocaine or food are similarly powerful as reinstaters and conditioned reinforcers.

# Poster Communications

## 25

Characterization of the behavioral effects of varenicline (VAR) and meca-**mylamine (MECA) in monkey models of nicotine (NIC) and cocaine (COC) abuse**.

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Emerging preclinical and clinical data indicate that brain nicotinic acetylcholine receptors (nAChRs) could function as critical targets for the development of pharmacotherapies for a range of disorders from Tourette's syndrome to drug abuse and dependence. As the efficacy of novel pharmacotherapies targeting nAChRs are being evaluated, the abuse potential of these compounds must also be assessed. VAR is a low-efficacy α4β2* subtype-selective agonist that has shown success in smoking cessation and has low abuse liability in monkey models of COC abuse (Gould et al. 2011). The current study further characterized VAR by examining its reinforcing effects in a monkey model trained to self-administer (SA) NIC and its ability to decrease NIC SA. We also examined the effects of MECA, a noncompetitive nAChR antagonist, on NIC SA. Previous research has shown that MECA can promote smoking abstinence in humans (Rose, 2006), and it has also been shown beneficial effects in depression in more recent clinical trials. Since MECA demonstrates clinical efficacy in a variety of diseases, drug history of the population could be an important factor to consider when assessing how MECA may function. Therefore, abuse potential of mecamylamine in monkeys SA either NIC or COC was also investigated. VAR dose-dependently attenuated NIC SA and did not function as a reinforcer when substituted for NIC. Interestingly, MECA functioned as a reinforcer in monkeys with a history of NIC SA. These results emphasize when evaluating novel pharmacotherapies, the importance of assessing how reinforcing effects can vary depending on the drug history of an individual. DA012460

## 26

**Reduction of PGE2-induced mechanical allodynia in the rat hindpaw by delta opioid receptor (DOR) agonists, SNC80 and DPDPE**

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A unique regulatory difference exists between opioid receptor systems located in the central versus the peripheral nervous systems. We have found that receptors in the periphery are functionally quiescent with respect to antinociception under normal (e.g. uninflamed, undamaged) conditions. However, after brief exposure to an inflammatory mediator (e.g. bradykinin [BK] or arachidonic acid [AA]), peripheral opioid systems become functionally competent for reducing PGE2-induced thermal allodynia in the rat hindpaw. In this study, we determined whether DOR agonists are effective in reducing mechanical allodynia and if exposure to an inflammatory mediator is also required. We utilized an electronic Von Frey anesthesiometer to measure the effect of the agonists SNC80 and DPDPE on PGE2-induced mechanical allodynia. Following baseline measurements of paw withdrawal threshold (PWT), rats were given an intraplantar (i.pl.) injection (50µl) of an inflammatory mediator (i.e. BK, 25µg or AA, 0.3µg) followed by a second i.pl. injection 15 minutes later of PGE2 (0.5µg) with or without SNC80 (5ug) or DPDPE (20ug). Injection of BK alone produced a long-lasting reduction in PWT (mechanical allodynia) that extended past 60 minutes. In contrast, injection of AA alone induced a transient mechanical allodynia, which reversed within 10 minutes. Following AA pretreatment, injection of vehicle (i.pl.) did not change baseline PWT, however, injection of PGE2 (i.pl.) produced a significant mechanical allodynia (73% decrease in PWT). We then determined the effect of the DOR agonists on PGE2-induced mechanical allodynia in the presence and absence of pretreatment with AA. Following AA pretreatment, SNC80 and DPDPE attenuated PGE2-induced mechanical allodynia by 35% and 56%, respectively. However, in the absence of AA pretreatment, neither had an effect. Consistent with our findings for the reduction in PGE2-induced thermal allodynia, DOR agonists are effective at reducing PGE2-induced mechanical allodynia and require exposure to an inflammatory mediator.

Support provided by DA024865 and T32DA031115.

## 27

**Effects of morphine and hydrocodone on delay discounting of food in rhesus monkeys**

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Opioid-dependent individuals tend to discount the value of delayed reinforcers more rapidly than non-dependent individuals, suggesting that drug use is associated with increases in this aspect of impulsivity (delay discounting). However, it is not known whether increased discounting is the consequence of direct effects of the drug or other factors related to drug use (e.g., withdrawal). In this study, a delay discounting procedure was established in rhesus monkeys in order to study the effects of acute and chronic treatment with drugs of abuse as well as discontinuation of chronic treatment. Two monkeys responded under a concurrent fixed-ratio 30 schedule in which responses on one lever delivered one food pellet immediately and responses on another lever delivered two food pellets either immediately or after a delay (30, 60, or 120 sec). The delay to the larger reinforcer increased across blocks allowing for determination of a delay function within session. With no delay, monkeys responded exclusively for the larger reinforcer and, as the delay increased, responded progressively more for the smaller, immediately available reinforcer. Acute administration of morphine (0.032-5.6 mg/kg, s.c., 15 min) impacted delay-discounting in a bi-phasic fashion similarly for both monkeys. Smaller doses (0.1-0.32 mg/kg) decreased, whereas larger doses (1.0-5.6 mg/kg) increased, choice of the larger, delayed reinforcer. Hydrocodone (0.1-1.78 mg/kg, s.c., 15 min) did not substantially impact delay functions in either monkey up to doses that significantly reduced response rates. Responding under this procedure is sensitive to reinforcer delay and amount, and reliable delay functions can be generated daily that allow for assessment of delay functions both at particular time points (e.g., acute drug administration) and changes in discounting across time (e.g., during chronic drug treatment). Supported by USPHS Grants R01DA029254, K05DA017918 (CPF), and T32DA031115 (DRM).

## 28

**The role of Neuromedin U in control of food seeking and reinforcement**

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In the US alone, almost $400 billion dollars are spent annually to treat a wide variety of reinforcement disorders, ranging from abuse of illicit drugs to the overconsumption of obesogenic foods. A novel target for the treatment of these conditions is neuromedin U (NMU), a neuropeptide shown to affect both food intake and weight gain. Infusions of NMU into the paraventricular nucleus of the hypothalamus (PVN) markedly decreases food consumption, and knockouts of the NMU gene in mice induce hyperphagia and obesity. We hypothesize that NMU is capable of regulating habitual reinforcement behaviors involving natural rewards (e.g. palatable food). Our findings indicate that RNAi knockdown of neuromedin receptor 2 (NMUR2) in the PVN increases weight gain and consumption of palatable, high-fat food. Furthermore, NMUR2 knockdown increases preference for higher-fat containing food and potentiates binge eating. We predicted that intraperitoneal injections of NMU would conversely decrease operant responding for a palatable food reinforcer on a progressive-ratio schedule of reinforcement. Our initial testing supports this hypothesis, with NMU-treated rats responding less on the progressive ratio schedule compared to vehicle control animals. Furthermore, we examined NMU's effects on food-induced reinstatement of operant response after extinction training. Peripheral injection of NMU failed to suppress noncontingent food-induced lever pressing compared to vehicle control. These results indicate that NMUR2 signaling is capable of specifically regulating consumption of high-fat foods and preference for dietary fat. Peripheral delivery of NMU may be effective at decreasing reinforcement efficacy for normally habit-forming rewards.

# Poster Communications

## 29

**Kappa opioid receptor-mediated antinociception involves activation of GIRK but not cAMP in peripheral sensory neurons**

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The kappa opioid receptor (KOR), a G protein coupled receptor, has been shown to couple to a variety of intracellular signaling cascades, including opening of inward rectifying K+ channels (GIRK), closing of calcium channels, and inhibition of adenylyl cyclase (AC). Although all of these signaling cascades may potentially play a role in antinociceptive mechanisms of KOR agonists in peripheral sensory neurons, to date, definitive cellular-signaling mediator(s) have yet to be determined. Here we sought to determine the signaling mechanism(s) that mediate anti-thermal allodynia in rat hindpaw by the KOR agonist, U50488. To test if inhibition of cAMP production is responsible for KOR-mediated anti-allodynia rats were injected intraplantarly (i.pl. 50µl) with either PGE2 (0.3µg) or the cAMP analogue, 8-bromo-cAMP (0.3µg) with or without U50488 (0.1µg) and paw withdrawal latencies (PWL) to a thermal stimulus determined. Both PGE2 and 8-bromo-cAMP produced a similar magnitude of allodynia. Treatment with U50488 completely reduced the thermal allodynia produced by PGE2 and 8-bromo-cAMP in a similar manner. These data suggest that changes in cellular cAMP levels do not mediate KOR anti- thermal allodynia. To determine if activation of GIRK mediated the antinociceptive response to U50488, we measured PWL in the presence of the K+ channel blocker tertiapin-Q (TPNQ). The U50488-mediated antinociceptive response was blocked completely when PGE2 was used to produce the thermal allodynia, whereas, in contrast, TPNQ had no effect on the U50488-mediated antinociceptive response when 8-bromo-cAMP was used to produce allodynia. Moreover, the U50488-mediated antinociceptive response was significantly greater for reducing 8-bromo-cAMP-induced thermal allodynia in the presence of TPNQ. Taken together, these results suggest that KOR mediated anti-thermal allodynia may involve multiple signaling pathways including activation of GIRK, but is independent of changes in cellular cAMP levels. Supported by DA024865 and AG013319.

## 30

**The Potential Abuse Liability of Synthetic Cathinones**

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The increased use and abuse of synthetic cathinones signifies a need more for information concerning the rewarding effects and abuse liability of these drugs. Using the conditioned place preference paradigm, this study will determine which synthetic cathinones induce a place preference and therefore have the potential to become mainstream drugs of abuse. 3,4-Methylenedioxypyrovalerone (MDPV), methylone, mephedrone, naphyrone, flephedrone, butylone, and pentylone were assessed for rewarding effects in the conditioned place preference behavioral assay. MDPV (3mg/kg), butylone (10mg/kg), and pentylone (30 mg/kg) increased the amount of time spent on the drug paired floor. Mephedrone (10 mg/kg), methylone (5mg/kg), naphyrone (5mg/kg), and flephedrone (10mg/kg) did not increase the time spent on the drug paired floor. At this time more doses of the synthetic cathinones need to be tested using the conditioned place preference paradigm. Many of the cathinones tested are currently in use implying the presence of rewarding effects. Increasing the doses of the few compounds that did not induce a place preference may uncover the actual rewarding effects reported to be induced by all of the synthetic cathinones.

## 31

**The differential expression of MDPV-induced conditioned taste aversions, thermoregulation and brain amine levels in adolescent and adult rats: A behavioral and neurochemical assessment of "Bath Salts."**

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As with all drugs of abuse, MDPV, a primary constituent in "bath salts," is rewarding in rats. However, little is known of its aversive effects, those which might limit drug intake. Recent reports have shown that adolescents are generally less sensitive to the aversive properties of drugs which may contribute to an increased vulnerability to use and abuse in this population. The present study used the conditioned taste aversion procedure to determine if MDPV induces aversions in rats and if those aversions are age-dependent. Specifically, subjects of both ages were given access to a novel saccharin solution followed by various doses of MDPV. This procedure was repeated for a total of four conditioning trials followed by a two-bottle test of the aversion. Additionally, core body temperatures and monoamine levels (and their metabolites) were quantified to determine if MDPV administration produces hyper/hypothermia and/or long-lasting changes in select neurotransmitter levels. Adolescent rats displayed less robust MDPV-induced taste aversions than adult rats during acquisition and on the two-bottle assessment. Core body temperature measurements revealed that adults exhibited hyperthermia, while adolescents exhibited hypothermia following acute exposure to MDPV. In general, neurotransmitter levels differed as a function of age (and not drug), although MDPV induced minor changes in dopaminergic levels in adult subjects. Given that drug use and abuse is a function of the relative balance between the drug's rewarding and aversive effects, the fact that the aversive effects are weaker in adolescents suggests that this population may be more vulnerable to MDPV use and abuse. Research supported by a Robyn Rafferty Mathias scholarship to APM, AU Artists and Scholars Fellowship to APM and a grant from the Mellon Foundation to ALR.

## 32

**PPARγ as a Therapeutic Target in Drug Abuse**

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Psychostimulant abuse, addiction, and relapse during abstinence remains a confounding public health issue in the United States and safe, effective pharmacotherapies are still needed for treatment. Here we explore a novel therapeutic target, peroxisome proliferator-activated receptor (PPAR), using a preclinical model of addiction in vivo. This ligand activated transcription factor belongs to the nuclear receptor family and its gamma isoform (PPARγ) plays a vital role as a primary lipid sensor and regulator of lipid metabolism. Thus, there are several FDA approved ligands that are clinically used for the treatment of diseases such as type 2 diabetes. However PPARγ is also widely distributed in the CNS and is highly expressed in neurons. Our lab has already demonstrated that PPARγ rescues hippocampal cognitive impairment in an animal model of Alzheimer's. This rescue partly involves the recruitment of hippocampal ERK MAPK activity to the nucleus (Rodriguez et al., 2010). Given the important role for learning and memory in the process for which drug abuse transitions into addiction, and our recent evidence that neuronal PPARγ is involved in restoring cognitive deficits through ERK MAPK, we hypothesize that neuronal PPARγ represents a potential therapeutic target for maintaining drug abstinence during stimulant withdrawal.

# Poster Communications

## 33

**Unraveling mechanisms contributing to lack of antidepressant efficacy in juveniles and adolescents**

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Depression is a major health problem for which most patients are not effectively treated. This problem is further compounded in children and adolescents where only two antidepressants [both selective serotonin reuptake inhibitors (SSRIs)] are currently approved for clinical use. Mouse models provide tools to identify mechanisms that might account for poor treatment response to antidepressants. However, until now the use of such models has been limited to studies in adult mice. Here we show that the tail suspension test can be used to assay antidepressant-like effects of reference drugs in mice aged 21 (juvenile) and 28 (adolescent) days post-partum, and that the antidepressant-like activity of these drugs relates positively to expression levels of serotonin- and norepinephrine transporters. Importantly, we found that juvenile mice had markedly greater expression levels of plasma-membrane monoamine transporter (PMAT) than adult mice. PMAT clears serotonin from extracellular fluid, and therefore may limit the therapeutic efficacy of SSRIs, providing a mechanistic basis for poor treatment response to SSRIs, particularly in juveniles and adolescents.

## 34

**Discriminative stimulus effects of a novel epibatidine analog RTI-102**

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Smoking cessation therapy with low efficacy nicotinic acetylcholine receptor agonist, such as varenicline, decreases the health risks posed by cigarette smoking. RTI-102 is a low efficacy analog of the nicotinic acetylcholine receptor agonist epibatidine. Drug discrimination was used to compare the effects of nicotine, epibatidine, and RTI-102. Male C57BL/6J mice (n=8) discriminated nicotine (1 mg/kg, s.c.) from saline while responding under a fixed ratio 10 schedule of food presentation. Nicotine, epibatidine, and RTI-102 were studied alone, and RTI-102 was studied in combination with nicotine. Nicotine and epibatidine dose-dependently increased nicotine-appropriate responses to a maximum of 99% and 91%, respectively. The ED50 values (95% confidence limits) were 0.64 (0.27-1.52) mg/kg for nicotine and 0.0019 (0.0011-0.0032) mg/kg for epibatidine. In contrast, RTI-102 only produced a maximum of 44% nicotine-appropriate responses up to a dose that disrupted responding. When combined with the training dose (1 mg/kg) of nicotine, RTI-102 dose-dependently attenuated the discriminative stimulus effects of nicotine to 31%. These results demonstrate that epibatidine and nicotine have qualitatively similar effects. The markedly greater potency of epibatidine as compared with nicotine is consistent with their different binding affinities at nicotinic acetylcholine receptors. The low efficacy of RTI-102 in vivo, evidenced by antagonism of the training dose of nicotine to the level of effect produced by RTI-102 alone, provides a basis for further developing this or related compounds as smoking cessation aids.

## 35

**Enhanced rewarding effects of nicotine as assessed by place preference procedures in a rodent model of diabetes**

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Ongoing work in our laboratory has shown that diabetic rats display an increase in nicotine self-administration and suppressed dopamine systems as compared to healthy controls. These findings have lead to the question of whether enhanced nicotine intake in diabetic rats is related to an overcompensation for suppressed dopamine systems or enhanced rewarding effects of nicotine. To address this question, we compared the rewarding effects of nicotine in diabetic and healthy control rats using place preference procedures. Separate groups of rats received a systemic injection of streptozotocin (STZ; 45 mg/kg) or vehicle. STZ is toxic to insulin-producing cells in the pancreas and produces high glucose levels of approximately 500 mg/dl. Fourteen days after diabetes induction, all rats were tested for their initial preference for 2 distinct compartments of a conditioning apparatus. The rats were conditioned 5 days later during which time the rats received an injection of saline or nicotine (0.1 or 0.2 mg/kg) and were placed into their initially non-preferred side. On alternate days, they received saline and were placed into the alternate side. After 8 days of conditioning, the rats were tested for their preference for 5 consecutive days. The results revealed that nicotine produced a shift in place preference for the compartment where the rats received nicotine as compared to rats that received saline. Diabetic rats displayed a larger shift in preference to the nicotine-paired compartment versus controls. Although preference behavior decreased over time in both groups, the greater preference behavior in diabetic rats persisted across the 5 test days. Taken together with our self-administration data, our results suggest that the rewarding effects of nicotine are enhanced in diabetic rats. Thus, diabetic patients may experience strong rewarding effects of nicotine that confer enhanced vulnerability to tobacco use.

## 36

**A behavioral assessment of the aversive properties of delta-9-THC in Fischer-Lewis rats**

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Although Lewis (LEW) and Fischer (F344) rats differ in their sensitivity to the rewarding effects of THC, no data have been reported on differences in their sensitivity to the drug's aversive effects, a limiting factor in drug use and abuse. Examining the degree of differences (if any) in such effects in these strains may help further characterize possible genetic factors important to abuse vulnerability. Accordingly, the aversive effects of THC were examined in 32 F344 and 32 LEW subjects using the conditioned taste aversion procedure. In this procedure, animals of both strains were given access to saccharin followed by vehicle or various doses of THC (1, 3.2 and 5.6 mg/kg). Three water recovery days followed conditioning. This procedure was repeated for four conditioning cycles. Two weeks after the final conditioning cycle, core body temperatures were examined following injections of the conditioning doses of THC. Subjects in both strains displayed dose-dependent THC-induced taste aversions, with no significant strain difference. Core body temperatures of F344 subjects were significantly higher than LEW rats, although these differences were independent of THC (which itself induced hypothermia in both strains). These results suggest that the reported differences between the strains in THC self-administration reflect differences in the drug's rewarding (and not aversive) effects and that such aversions are not due to drug-induced hypothermia.

This work was supported by grants from the Mellon Foundation to AGP and ALR.

# Poster Communications

## 37

**Role of extrasynaptic GABAA receptors in the discriminative stimulus effects of ethanol in rats**

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Behavioral effects of ethanol, including discriminative stimulus effects, are mediated at least in part by positive modulation of GABAA receptors. Unlike some positive GABAA modulators (e.g. benzodiazepines), ethanol has actions at both synaptic and extrasynaptic GABAA receptors, and in vitro studies suggest that it is most potent at extrasynaptic GABAA receptors. The goal of this study was to determine whether extrasynaptic GABAA receptors contribute to the discriminative stimulus effects of ethanol. Eight rats discriminated 0.75 g/kg ethanol while responding under a fixed ratio 10 schedule of food presentation. Given the greater potency of ethanol at extrasynaptic GABAA receptors, this relatively small training dose of ethanol was predicted to be selective for those receptors. Under these conditions, ethanol produced ≥ 80% responding on the ethanol lever in all rats with the benzodiazepine midazolam producing ≥ 80% ethanol-lever responding in 7 of 8 rats. In contrast, the μ opioid receptor agonist morphine was studied up to doses that markedly decreased response rates, and rats responded predominantly on the saline lever. Drugs with actions at extrasynaptic GABAA receptors include gaboxadol, which is an agonist selective for extrasynaptic GABAA receptors, and neuroactive steroids, which are positive modulators acting at both synaptic and extrasynaptic GABAA receptors; gaboxadol and the neuroactive steroids allopregnanolone and pregnanolone produced ≥ 80% responding on the ethanol lever in some but not all rats. Because benzodiazepines do not act at extrasynaptic GABAA receptors, the effects of midazolam suggest that the role of these in the ethanol discriminative stimulus is limited. That other drugs acting at extrasynaptic GABAA receptors produce ethanol-lever responding only in some rats further supports this view. Thus, despite in vitro data indicating that ethanol is selective for extrasynaptic GABAA receptors, behavioral data suggests a limited, if any, role of these receptors in the discriminative stimulus effects of ethanol. Supported by USPHS grant DA017240.

## 38

**Assessment of Dopaminergic Actions in the Discriminative Stimulus Effects of Modafinil in Male Sprague-Dawley Rats**

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Modafinil is a novel wake-promoting drug with FDA approval for the treatment of daytime sleepiness. It has also been prescribed for ADHD and has recently been assessed as a potential treatment for psychostimulant dependence. Previous research indicates that modafinil modestly increases locomotor activity and produces similar discriminative stimulus effects to psychostimulants in rodents, although the subjective effects of modafinil are reportedly distinct from those of amphetamine in humans with a history of psychostimulant abuse. The current study employed drug discrimination procedures to assess the combined effects of modafinil and damphetamine and to determine the pharmacological actions contributing to modafinil's discriminative stimulus effects. Eight male Sprague-Dawley rats were trained to discriminate oral administration of 256 mg/kg modafinil from vehicle (5% arabic gum) under a FR 20 schedule of food reinforcement. Substitution tests were conducted with d-amphetamine (0.03-3.0 mg/kg), the D2 agonist PNU-91356A (0.03-0.3 mg/kg), and the DAT inhibitor GBR-12909 (5-20 mg/kg). Antagonist tests were conducted with the D1/D5 antagonist Sch 39166 (0.03-0.3 mg/kg) and the D2 antagonist haloperidol (0.1-0.5 mg/kg). Amphetamine (1.0 mg/kg) was also tested in combination with modafinil. Results indicate d-amphetamine produced nearly full substitution at a dose that completely suppressed responding in half the animals tested. Amphetamine pretreatment shifted the modafinil dose response curve to the left, indicating possible additive effects of these drugs. Full substitution was obtained with both PNU-91356A and GBR-12909 and preliminary results indicate both Sch 39166 and haloperidol block modafinil discrimination. The current preclinical findings are particularly relevant to elucidating the pharmacological actions of modafinil and its potential interactions with other psychostimulants.

## 39

**Effects of acute food-restriction and light cycle on dopamine neuron firing in the substantia nigra**

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Feeding state and drug use exhibit a complex interaction and eating disorders are often co-morbid with drug abuse. While decreasing food intake increases the reinforcing effects of abused drugs, the neurophysiological mechanisms responsible for this phenomenon are still being investigated. Dopamine (DA) neurons of the substantia nigra project to the striatum and have established roles in addiction, reward, and voluntary movement. Here we used cell-attached patch clamp electrophysiology to investigate the effects of feeding state and light-cycle on the excitability of dopamine neurons in the substantia nigra of the ventral midbrain. Male DBA mice were split into four cohorts: light-cycle/ad lib, light-cycle/food-restricted, dark-cycle/ad lib, dark-cycle/food-restricted. Food-restricted animals were fed ad libitum until 24 hours prior to recording, at which time access to food was removed. Mice that had been in their dark-cycle or acutely food-restricted exhibited higher neuronal firing rates than light-cycle and ad libitum-fed controls. A two-way analysis of variance indicated that there were significant main effects of light/dark cycle ($P=0.0209$) and food-restriction ($P=0.0122$). The data suggest that feeding state and time of day can affect the parameters responsible for basal firing of dopamine neurons in the substantia nigra. Further, these effects could contribute to the behavioral effects observed in mice when these variables are manipulated. Funding provided through the South Texas Advanced Research Training, Undergraduate Program (NIH grant NS80684).

## 40

**Action of △FosB is regulated by cocaine and psychological stress and the response to environmental enrichment.**

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Previous studies indicated that both psychological stress and drugs such as cocaine and amphetamine can cause the induction of △FosB. In addition, △FosB protein accumulates in neurons with chronic drug exposure or repeated stress. However, action of △FosB in different brain regions and the subsequent effect of △FosB accumulation are still not fully understood. This project investigates regulation of △FosB and △FosB target genes after acute and repeated cocaine and restraint stress with the environmental enrichment paradigm using quantitative PCR, western blot, immunohistochemistry, proteomic technologies and next generation RNA sequencing in rat brain. The results indicate that △FosB is induced by acute stimulation in prefrontal cortex, nucleus accumbens and dorsal striatum of rat brain. However, the induction is attenuated with repeated stimulation. Additionally, enriched rats show similar response of △FosB to rats exposed to repeated stress and cocaine, as a result, the transcriptional response of some △FosB target genes is repressed. Our ongoing studies are exploring more △FosB target genes and their effects on neuronal activity . In conclusion, the results of this study suggest that the molecular response of △FosB and its target genes plays a significant role in drug addiction and psychological stress behavior subsequent to environmental enrichment.

# Poster Communications

## 41

**Discriminative stimulus and hypothermic effects of the synthetic cannabinoid JWH-018 in rhesus monkeys**

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Many synthetic cannabinoids (e.g. JWH-018) are reported to have higher CB1 receptor agonist efficacy than Δ9-tetrahydrocannabinol (Δ9-THC). To examine relationships between efficacy and effects in primates, rhesus monkeys (n=5) discriminated a relatively large dose of JWH-018 (0.1 mg/kg i.v.); rectal temperature was measured in the same monkeys. Monkeys were able to discriminate JWH-018 after 60, 61, 71, 105, and 134 training sessions per monkey. The potency (ED50 value) of JWH-018 to produce discriminative stimulus effects and to decrease rate of responding was 0.01 mg/kg and 0.06 mg/kg, respectively. Cannabinoids substituted for the JWH-018 discriminative stimulus in the following rank order potency: CP-55940 (ED50 = 0.005 mg/kg) = JWH-018 > Δ9-THC (ED50 = 0.04 mg/kg) = WIN-55212-2 (ED50 = 0.04 mg/kg) = JWH-073 (ED50 = 0.07 mg/kg). JWH-018 and Δ9-THC decreased temperature by a maximum of 2.2 and 2.8 °C, respectively, and potency (i.e., dose decreasing temperature by 2 °C) was 0.21 and 1.14 mg/kg, respectively. The duration of action of JWH-018 for discriminative stimulus and hypothermic effects was 4-5 h. The apparent affinity (pA2 or pKB) values of the CB1 receptor-selective antagonist rimonabant were 6.6 for JWH-018 and Δ9-THC in the discrimination assay, and 6.8 for JWH-018 in the hypothermia assay. These results strongly suggest that the same (CB1) receptors mediate the discriminative stimulus and hypothermic effects of JWH-018. The difference in efficacy between JWH-018 and Δ9-THC reported in vitro does not appear to result in greater maximum effects in vivo, even under conditions that presumably require high efficacy.

## 42

**Restricted access to high fat or standard chow impacts sensitivity of rats to drugs acting on serotonin 2A or dopamine D3/D2 receptors**

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Type and quantity of food can impact sensitivity to drugs acting on dopamine (DA) systems; much less is known about the impact of different feeding conditions on drugs acting on serotonin (5-HT) systems. Male Sprague-Dawley rats had free access (10 weeks) followed by restricted access (6 weeks) to high fat (34.3% fat; n = 8) or standard (5.7% fat; n = 7) chow. Rats eating high fat chow developed insulin resistance within 2 weeks and gained more weight than rats eating standard chow. Eating high fat chow did not impact head twitching or effects on body temperature produced by the 5-HT2A receptor agonist 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM; 0.1-3.2 mg/kg). Eating high fat chow increased sensitivity to quinpirole-induced (DA receptor agonist; 0.0032-0.32 mg/kg) yawning, but not hypothermia. Restricting access to either chow decreased sensitivity to DOM-induced head twitching and decreased quinpirole-induced yawning, without altering drug-induced changes in body temperature. That is, sensitivity to DOM and quinpirole was impacted by quantity of food, but eating high fat chow only impacted sensitivity to quinpirole. Drugs of abuse (e.g. cocaine) as well as therapeutic compounds (e.g. antidepressants) act on 5-HT and DA systems. These results suggest that food restriction decreases while eating high fat food increases sensitivity to drugs acting on these systems, thereby possibly increasing vulnerability to abuse. CPF is supported by the NIDA Senior Scientist Award (K05 DA017918).

## 43

**Melanocortin receptor agonist injected into the nucleus accumbens decreases food intake but does not increase metabolic rate in mice**

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Obesity is a major health problem facing society. Understanding the factors driving body weight homeostasis, both feeding behavior and metabolism, is key to the development of pharmaceuticals to decrease body weight. Proopiomelanocortin (POMC), the melanocortin peptide precursor, is essential in the regulation of body weight with effects on both ingestive behaviors and metabolism. Deletion of POMC or impairment of melanocortin signaling in the brain results in obesity due to hyperphagia and decreased energy expenditure. Neurons in the hypothalamic arcuate nucleus produce POMC and project to many areas including the nucleus accumbens (NAcc). Previous studies in our lab have shown that injection of the melanocortin receptor agonist MT-II into the NAcc acutely decreases feeding. These studies were conducted to test the hypothesis that MT-II injected in the NAcc does not also affect metabolic rate. Using a repeated measures design, male, C57BL/6J mice were microinjected bilaterally into the NAcc (100 nl/side) with the melanocortin receptor 3/4 agonist MT-II (0, 0.1, and 0.3 nmol/side). To determine any changes in the metabolic measures of oxygen consumption (V02) and respiratory exchange ratio (RER) indirect calorimeter chambers were utilized (OxyMax; Columbus Instruments). For test sessions, baseline measures were obtained, the mice were then microinjected with saline or MT-II, and returned to the OxyMax chamber for at least four hours. While MT-II in the NAcc significantly inhibits food consumption for four hours after microinjection, there was no change in RER or VO2 over that same time period. These results suggest that although melanocortin receptors in the NAcc mediate feeding behaviors, they do not increase metabolic parameters. In addition, these results support the localization of our injection to the NAcc since this dose would be expected to increase metabolic rate if delivered into the ventricles.

## 44

**EFFECTS OF "UPTAKE 2" BLOCKADE AND/OR RISPERIDONE ON MURINE 5-HT UPTAKE, SOCIAL AND REPETITIVE BEHAVIOR**

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Uptake 2 mechanisms in the brain such as organic cation transporters (OCTs) may play a major role in the modulation of monoamine neurotransmission. OCTs have affinity for and/or transport many endogenous and xenobiotic compounds, including neurotransmitters. Their blockade produces similar effects to selective serotonin (5-HT) reuptake inhibitors to promote excitatory neurotransmission. We hypothesized that D-22 produces its effects on social behavior by blocking OCTs or other uptake-2 sites in the mouse brain. It is of interest that in vivo clearance of high concentrations (> 4 μM) of 5-HT in the CA3 region of hippocampus is faster in BTBR mice than in C57BL/6 or wild-type SERT mice. However, in vitro uptake 2 mechanisms may not fully account for the behavioral effects we observe in vivo with systemic D-22 administration. Through high performance liquid chromatography (HPLC) measurements and quantitative autoradiography we found that D-22 was detectable in the brain when administered by intraperitoneal (i.p.) injection at 10 mg/kg, but not at lower doses. D-22 has a serum clearance half-life of approximately 30 min in BTBR mice. Nonetheless, OCT3 blockade appears to be a promising therapeutic strategy for social interaction deficiencies.

# Poster Communications

## 45

**Differential effects of bradykinin and arachidonic acid on delta opioid receptor (DOR) function in a rodent behavioral model of pain**

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A major drawback associated with systemically administered opioid analgesics is side effects due to off-target opioid receptor activity. Therefore, peripherally-restricted opioid analgesics represent an attractive alternative; however, peripheral opioid analgesia remains unreliable. We have established that consistent analgesic effects can be produced by peripherally-restricted delta opioid receptor (DOR) agonists following brief (15 min) pre-treatment with inflammatory mediators such as bradykinin (BK) or arachidonic acid (AA). In both primary cultures of rat peripheral sensory neurons (ex vivo model) and a rodent model of pain, the DOR agonist, DPDPE, does not elicit a response unless cells or tissue are pre-treated (15 min) with BK or AA. However, responsiveness of the DOR system is transient with a return to baseline levels by 60 min. Thus, we examined if DOR antinociception could be re-induced by subsequent BK and/or AA treatments in a rodent model of thermal allodynia. Rats received initial intraplantar (i.pl.) injections of either vehicle, BK (25 µg), or AA (3 µg), followed by a second injection with BK (25 µg). Then (45 min later) PGE2 (0.3 µg)-mediated thermal allodynia was measured in the presence and absence of DPDPE (20 µg). We found DOR-mediated responses could be re-established after initial BK, but not AA intraplantar injections suggesting that the DOR system becomes “refractory” following treatment with AA. Pre-treatment with a lipoxygenase (LOX) inhibitor, NGDA, allowed for re-induction of DOR functional competence by BK after initial AA treatment indicating that a LOX-dependent AA metabolite is involved in the loss of DOR responsiveness. Overall, these studies demonstrate that distinct AA metabolic pathways differentially regulate DOR function. We propose that inhibition of LOX, combined with a competence-inducing stimulus may promote and sustain peripheral DOR-mediated analgesia.

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## 46

**A Within-Subjects Comparison of Psychostimulant and Opiate Self-administration in a Model of Compulsive Drug Taking: Preliminary Data**

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Recent studies suggest that a sub-population of rats choose cocaine over food reward, regardless of cocaine dose, food-deprivation status, etc. (for reviews, see Ahmed, 2010; 2012). Psychostimulants (e.g., cocaine) and opiates (e.g., heroin) differ in many important aspects with regards to their effects upon behavior (for a review, see Badiani, Belin, Epstein, Calu & Shaham, 2011). Furthermore, it has previously been demonstrated that the effects of self-administered cocaine and heroin are mediated by dissociable neurobiological substrates (Ettenberg, Pettit, Bloom & Koob, 1982). The goal of the present study was to compare choice between heroin and food and choice between cocaine and food in the same rats. Adult male Long-Evans rats were trained to choose between either cocaine (1.0 mg/kg, I.V.) or heroin (0.02mg/kg, I.V.) and a single 45-mg food pellet in separate phases with the order of drug vs. food choice phases counterbalanced across animals. Rats chose cocaine on average 30% of free-choice trials, while they chose heroin on average 15% of free-choice trials. Three out of eight rats (37.5%) reliably chose cocaine over food, while one out of eight (12.5%) reliably chose heroin over food. There was a significant rank-order correlation between percentage of choices for the drug lever during the cocaine phase and during the heroin phase. This preliminary research is a first step towards fully characterizing the cocaine- and heroin-preferring phenotypes and determining the extent to which these two sub-populations overlap.

## 47

**Neural systems modified by repeated cocaine exposure: a cytochrome oxidase study**

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Addiction has been considered an aberrant form of learning that incorporates synaptic plasticity. When changes in neuronal activity occur throughout the brain, the energy demands of a cell also fluctuate. Cytochrome oxidase (CO) is a mitochondrial membrane protein that helps supply energy demand by generating ATP via oxidative phosphorilation. Here we wish to characterize which neural systems modify their CO activity as a result of cocaine sensitization. Rats were injected with 15mg/kg cocaine i.p. or isovolumic saline for five days. One hour after last injection brains were removed and slices were stained for CO activity. Subjects injected with cocaine had developed an increased locomotor activity when compared to day one CO activity was significantly decreased in cocaine-treated animals in the superficial layers of the dorsal and lateral frontal cortex regions when compared to saline-treated animals Inter-regional correlations of CO activity showed that noradrenergic paths between the locus coeruleus and deep layers of the infralimbic cortex were positively correlated in animals treated with cocaine but not in control rats. In dopaminergic pathways, significant positive correlations were observed between the substantia nigra compacta and the superficial layer of the medial frontal cortex, the deep layer of the lateral frontal cortex and the superficial layer of the lateral orbital cortex only in cocaine treated animals. In cholinergic pathways, CO activity in the interpeduncular nucleus was negatively correlated with the activities of the deep layer of the dorsal frontal cortex, the superficial and deep layers of the anterior insular cortex the superficial and deep layers of the lateral orbital cortex in saline treated animals but not in rats that received cocaine. Taken together our data suggest that prefrontal networks change from inhibitory cholinergic influences to networks driven by noradrenergic and dopaminergic pathways after cocaine exposure. Sensitization to cocaine may release behaviors that normally are inhibited by the prefrontal cortex. When prefrontal networks for inhibitory control are impaired, impulsive behaviors may arise.

## 48

**Chronic Maternal Nutrient Restriction Reduces Expression of 5-HT Related Genes in Baboon Fetuses**

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In human offspring, low birth weight (<2500g) indicates intrauterine growth restriction (IUGR) and is associated with increased risks for numerous mental problems. Chronic maternal nutrient restriction (MNR) is commonly used in animal studies for creating IUGR-like offspring. Prenatally protein restricted adult rats display abnormal function of the central serotonin (5-HT) system. However, our knowledge on the impacts of prenatal malnutrition on the development of the central 5-HT system is still largely limited. To fill the knowledge gap, brains from fetal baboons whose mothers were exposed to 30% nutrient restriction were examined by immunohistochemistry at gestational day 165 (0.9 gestation). These studies revealed that the protein levels of multiple serotonergic markers in the pons and frontal cortex were significantly reduced in MNR baboon fetuses, and also indicated a trend of global reduction. Here, we examined whether there is the same trend in the mRNA levels. To do this, we performed qRT-PCR to quantify the fold difference in mRNA expression between MNR and well-nourished control fetuses at 0.9 gestation. MNR fetuses have lower levels of mRNAs of all the genes tested, including 5-HT1a receptor, serotonin reuptake transporter (SERT) and the rate limiting 5-HT synthesis enzyme (tryptophan hydroxylase 1 and 2, TPH1/2). This result suggests that there is a global and paralleling reduction at serotonergic proteins and mRNAs in MNR fetuses. In the future, we will exam whether this global reduction results from serotonergic neuronal morphological losses.

# Poster Communications

## 49

**Chronic wheel running affects cocaine-induced c-Fos expression in brain reward areas in female rats**

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Emerging evidence from humans and animal suggests that exercise is a highly effective treatment for drug addiction. However, most work has been done in behavioral models, and the effects of exercise on the neurobiological substrates of addiction have not been identified. Specifically, it is unknown whether prior exercise exposure alters neuronal activation of brain reward circuitry in response to drugs of abuse. To investigate this hypothesis, rats were given 30 days of daily access to voluntary wheel running in a locked or unlocked running wheel. Subsequently, they were challenged with a saline or cocaine (15 mg/kg, ip) injection and sacrificed for c-Fos immunohistochemistry. The c-Fos transcription factor is a measure of cellular activity and was used to quantify cocaine-induced activation of brain reward areas such as the nucleus accumbens (NAc), caudate putamen (CPu), and prefrontal cortex (PFC). Results showed that cocaine elicited more c-Fos expression than saline in the core and shell of the NAc and the dorsolateral CPu regardless of exercise exposure, and overall c-Fos-reactive cell counts were lower in the core and shell of the NAc; the dorsomedial and dorsolateral CPu; and the prelimbic, infralimbic, and orbitofrontal cortex regions of the PFC in exercising rats compared to sedentary rats. However, the mean fold change in cocaine-induced c-Fos cell counts over saline-induced c-Fos cell counts was significantly higher in exercising vs. sedentary rats in the NAc core, dorsomedial and dorsolateral CPu, the prelimbic area, and the orbitofrontal cortex, indicating differential cocaine-specific cellular activation of brain reward circuitry between exercising and sedentary animals. These results may shed light on the neurobiological mechanism by which voluntary wheel running decreases cocaine-seeking behavior and provide support for exercise as a treatment for drug addiction.

## 50

**Delta-9-tetrahydrocannabinol enhances the discriminative stimulus effects of quinpirole in rats**

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Dopamine (DA) systems play a critical role in mediating the rewarding effects of various drugs of abuse. Cannabis use often precedes the initiation of other drug abuse, and prior cannabis use might change dopamine systems in a manner that alters the rewarding effects of other drugs. The current study examined the effects of delta-9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, on sensitivity to the discriminate stimulus effects of a direct-acting dopamine receptor agonist. Eight male Sprague Dawley rats were trained to discriminate 0.032 mg/kg quinpirole (i.e. D2/D3 receptor agonist) from saline while responding under an FR10 schedule of food presentation. On the day of administration, 0.32 and 1.0 mg/kg of THC did not occasion quinpirole-lever responding and had no effect on response rate; neither dose of THC affected sensitivity to the discriminative stimulus effects of quinpirole on the day of administration or 24 hours later. In contrast, 3.2 mg/kg of THC eliminated responding throughout the 6-cycle session on the day of administration; 24 hours later the quinpirole discrimination dose-response curve was shifted 28.4-fold leftward. A dose of the benzodiazepine midazolam (5.0 mg/kg) that eliminated responding had no effect on the discriminative stimulus effects of quinpirole 24 hours later indicating that the suppression of responding was not sufficient to alter the effect of quinpirole the next day. These results indicate a pharmacologically selective role of THC in enhancing sensitivity to a DA receptor agonist and further suggest that cannabis use might impact propensity to abuse other drugs.

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## 51

**Using drug discrimination to investigate potential actions of fluoxetine at GABAA receptors in rhesus monkeys**

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Selective serotonin uptake inhibitors (SSRI) are frequently prescribed for anxiety and depression. The mechanisms underlying the therapeutic effects of SSRIs involve the serotoninergic system, although other systems, known to be involved in anxiety, have also been implicated in their effects. For example, the SSRI fluoxetine has been reported to increase endogenous levels of the neuroactive steroid allopregnanolone and therefore to indirectly activate GABAA receptors. The aim of this study is to explore the effects of fluoxetine in an assay capable of capturing behaviorally relevant activity at GABAA receptors. Five rhesus monkeys discriminated between the benzodiazepine midazolam (0.178 mg/kg, s.c.) and vehicle while responding under a fixed-ratio 10 schedule of stimulus-shock termination. Because of the long duration of action of fluoxetine, midazolam dose-effect curves were determined 5 min or 22 hours after fluoxetine administration (10-17.8 mg/kg, s.c.). Midazolam dose dependently increased drug-lever responding. Fluoxetine alone did not produce drug-lever responding or shift midazolam dose-effect curves; larger doses were not studied because rate-decreasing effects were evident following administration of 17.8 mg/kg. These data indicate that even large doses of fluoxetine do not mimic or alter the discriminative stimulus effects of midazolam. Therefore, any increase in allopregnanalone levels produced by fluoxetine is not large enough to be behaviorally relevant. That effects mediated by GABAA receptors are not altered by fluoxetine suggest that GABAA receptors do not contribute to the behavioral effects of SSRIs.

Supported by USPHS grants R01DA09157 and K05DA017918 (CPF).

## 52

**Serotonin 5-HT2A receptor (5-HT2AR) and 5-HT2CR Assemble into Heteromers in Living Cells**

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Serotonin 2A receptors (5-HT2AR) and 2C receptors (5-HT2CR) share structural homology and intracellular signaling cascades, but exhibit intriguing oppositional effects in vivo which may be mediated in the same neuron or within neuronal circuitry. We first demonstrate that the 5-HT2AR and 5-HT2CR colocalize to single neurons, and in the present study, we tested the hypothesis that the 5-HT2AR and 5-HT2CR assemble into a heteromer (5-HT2AR:5-HT2CR) in living cells. To this end, we developed a split luciferase complementation assay (LCA) to investigate the interaction of 5-HT2AR to 5-HT2CR in vitro. The inactive complementary C- and N-terminus fragments of firefly luciferase were fused to the 5-HT2AR (5-HT2AR-CLuc) and 5-HT2CR (5-HT2CR-NLuc), respectively, and transiently transfected into HEK 293 cells. In the presence of the substrate D-luciferin, association of the two proteins brings the luciferase fragments into close proximity to reconstitute the enzyme activity. Dramatic increases in luminescence upon D-luciferin administration (~50-fold) were observed in cells co-expressing 5-HT2AR-CLuc plus 5-HT2CR-NLuc suggesting the formation of 5-HT2AR:5-HT2CR heteromers. Serotonin itself evoked a predicted increase in intracellular calcium release indicating that retention of functionality of the constructs in these transiently transfected cells. The close proximity (<45 μm) of these two receptors was also confirmed in these transiently transfected cells by a proximity ligation assay (PLA; Duolink®). Studies examining the unique signaling cascades and physiological functions of the 5-HT2AR:5-HT2CR heteromer are currently underway. Thus, we present exciting data in support of the assembly of 5-HT2AR:5-HT2CR heteromers in live cells and propose that this newly-discovered heteromer may diversify and expand the repertoire of signaling and be a unique target to explore the oppositional 5-HT2AR and 5-HT2CR control of function in vivo. Supported by: ITS/CTSA pilot grant, K05 DA020087 (KAC), P20 DA024157 (KAC), R01 DA006511 (KAC), R01 DA030977 (KAC/SRG), F30 DA034488 (LHF), Klarman Family Foundation

**Preparing Effective Oral Presentation Slides**

**Adapted from 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 |
|---|---|---|---|---|
| ABSTRACT | **Text:** Logical? Clear? Well-organized? Complete? Sufficiently succinct? | | | |
| PRESENATION CONTENT | **Introduction:** Objectives/background clear? Appropriate rationale? | | | |
| | **Methods and Results:** Appropriate design? Appropriate detail? Clearly explained? | | | |
| | **Conclusions:** More than summary? Supported by the data? | | | |
| STYLE/ORGANIZATION/VISUALS | **Style:** Clear voice? Volume? Appropriate inflection? Eye contact? Pace? Energy? | | | |
| | **Organization/Timing:** Logical sequence? Appropriate time for different sections? | | | |
| | **Visuals/Graphs:** Visible? Clear? Not cluttered? Used appropriately? See guidelines | | | |

**OVERALL SCORE (CIRCLE ONE):** **POINT TOTAL**

| | | | | | |
|---|---|---|---|---|---|
| **5 Outstanding** | **4 Excellent** | **3 Very good** | **2 Good** | **1 Fair** | |

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