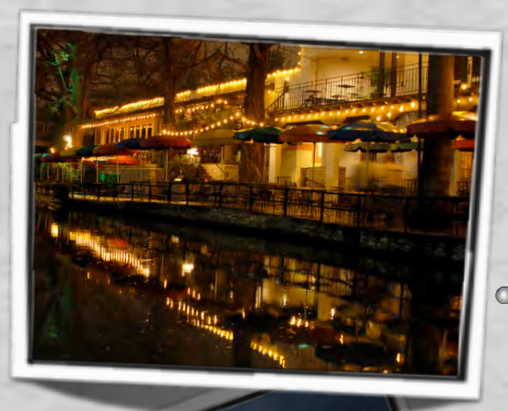
Behavior, Biology, and Chemistry:
Translational Research in Addiction

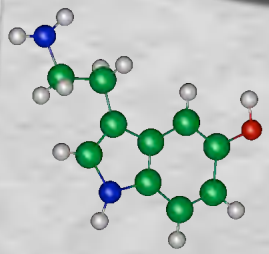
March 15-16, 2014

La Quinta Inn & Suites

Medical Center

San Antonio, TX





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Wanda Williams

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Program Overview

Friday March 14, 2014

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

Saturday March 15, 2014

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: "Non-classical pharmacology of the dopamine transporter and addiction" Speakers: Maarten Reith, Bruce E. Blough, Jonathan L. Katz, Charles O'Brien (Chairs: Maarten Reith and Wouter Koek)
10:25 am - 10:40 am	Coffee Break
10:40 am - 12:00 pm	Open Oral Communications 1 (Chair: Christopher Cunningham)
12:00 pm - 1:15 pm	**Lunch**
1:15 pm - 2:55 pm	Open Oral Communications 2 (Chair: Gregory Collins)
2:55 pm - 3:10 pm	Coffee Break
3:10 pm - 4:10 pm	Special Lecture: Kenner C. Rice "Medicinal chemistry in opioid research at NIH. Looking back" (Chair: James Woods)
4:10 pm - 4:30 pm	Poster Set-up
4:30 pm - 7:00 pm	Poster Session
7:00 pm - 9:00 pm	**Dinner** After Dinner Speaker: James Barrett; "Pharmacological plasticity: Black swans, tipping points and creative destruction" (Chair: Michael Nader)
9:00 pm - 11:00 pm	Hospitality and Entertainment

Sunday March 16, 2014

8:00 am - 9:40 am	Open Oral Communications 3 (Chair: Jonathan Pinkston)
9:40 am - 9:55 am	Coffee Break
9:55 am - 11:15 am	Open Oral Communications 4 (Chair: Rajeev Desai)
11:15 am - 11:30 am	Coffee Break
11:30 am - 12:30 pm	Special Lecture: A. Thomas McLellan; "What it really means to treat addiction as a chronic illness: Implications for treatment, evaluation, insurance and policy" (Chair: Barbara Turner)
12:30 pm - 12:40 pm	Presentation of travel awards and awards for oral and poster presentations
12:40 pm - 1:30 pm	**Adjournment and Lunch**

See you at BBC 2015!

Program Details

Friday March 14, 2014 (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 15, 2014

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

Plenary Symposium (Chairs: Maarten Reith and Wouter Koek)

Non-classical pharmacology of the dopamine transporter and addiction

The dopamine transporter is the main target for addictive drugs in the psychostimulant class, and therefore a logical target for the search for medicines to treat stimulant addiction. The earliest research on discovery of such treatments focused on the possibility of a compound that blocked cocaine but allowed dopamine uptake. As the potential for finding such a compound appeared to vanish, new evidence suggested novel drug actions and interactions, with the dopamine transporter having a dynamic role, and new opportunities for anti-addictive effects, increasing interest in a host of new DAT compounds. This symposium will cover the pharmacology, chemistry, and behavioral activity of non-classical DAT modulators including partial inhibitors and releasers, and atypical DAT blockers with a preference for the inward-facing conformation of the DAT. One such compound in the latter group is already on the market: modafinil – this compound will be discussed from both basic and human clinical perspectives.

8:05 am - 8:40 am	***Maarten Reith***; New York University How non-classical can interaction be between DAT and novel lead compounds for addiction treatment?
8:40 am - 9:15 am	***Bruce E. Blough***; RTI International Dopamine partial releasers: therapeutic potential at the boundary of uptake inhibition and translocation
9:15 am - 9:50 am	***Jonathan L. Katz***; NIDA/NIH Atypical dopamine uptake inhibitors and pharmacological class warfare
9:50 am - 10:25 am	***Charles O'Brien***; University of Pennsylvania/VAMC Effects of modafinil in patients with cocaine use disorder

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

Saturday March 15, 2014 (continued)

Open Oral Communications 1 (Chair: Christopher Cunningham)

10:40 am -11:00 am	***Leah Mayo,*** University of Chicago The effect of methamphetamine on behavioral motivation
11:00 am- 11:20 am	***Brendan Tunstall,*** American University Cocaine cues become more powerful reinstaters of reinforcer seeking than food cues
11:20 am - 11:40 am	***Christopher Wild,*** University of Texas Medical Branch Allosteric modulation of the 5-HT2C receptor (5-HT2CR): A novel strategy toward the treatment of cocaine use disorder
11:40 am - 12:00 pm	***Alfredo Oliveros,*** Mayo Clinic ENT1-mediated adenosine signaling regulates learning and reward seeking behaviors

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

Open Oral Communications 2 (Chair: Gregory Collins)

1:15 pm - 1:35 pm	***Vivek Kumar,*** NIDA Novel and high affinity fluorescent ligands for the serotonin transporter based on (S)-citalopram.
1:35 pm - 1:55 pm	***David Thorn,*** University at Buffalo Anti-hyperalgesic effects of imidazoline I2 receptor agonists and their interactions with opioids in a rat model of inflammatory pain
1:55 pm - 2:15 pm	***Comfort Boateng,*** NIDA Developing highly selective and potent D3 receptor antagonists and partial agonists using a synthon approach
2:15 pm - 2:35 pm	***Sarah Kromrey,*** Wake Forest University School of Medicine Relationship of social rank to hormone levels, cognitive performance, and homecage activity in female cynomolgus monkeys
2:35 pm - 2:55 pm	***Oluyomi Okunola-Bakare,*** NIDA Novel modafinil analogs define a role for transmembrane helix 10 (TM10) in DAT versus SERT selectivity.

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

Special Lecture 3:10 pm - 4:10 pm (Chair: James Woods)

Kenner C. Rice, NIDA/NIH: "Medicinal chemistry in opioid research at NIH. Looking back"

Saturday March 15, 2014 (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. 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: Michael Nader)

James Barrett, Drexel University College of Medicine: "Pharmacological plasticity: Black swans, tipping points and creative destruction"

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

Come and enjoy the fun in the ballroom!

Sunday March 16, 2014

Open Oral Communications 3 (Chair: Jonathan Pinkston)

8:00 am - 8:20 am	***Amanda Quisenberry,*** Virginia Tech Carilion Research Institute Dopamine uptake inhibitors produce complete stimulus generalization in rats trained to discriminate 256 mg/kg modafinil
8:20 am - 8:40 am	***Meenakshi Sabina Subbaraman,*** Alcohol Research Group, Emeryville Cannabis use among individuals in recovery from alcohol use disorders
8:40 am - 9:00 am	***Christopher Cunningham,*** Concordia University Wisconsin School of Pharmacy Functional characterization of piperazine- and tropane-based CB1R allosteric modulators
9:00 am - 9:20 am	***Jun-Xu Li,*** University at Buffalo Discriminative stimulus effects of the analgesics clonidine and CR4056 in rats with or without chronic pain
9:20 am - 9:40 am	***Thomas Keck,*** NIDA Novel analogues of sumanirole provide clues to biased agonism at the dopamine D2 receptor

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

Open Oral Communications 4 (Chair: Rajeev Desai)

9:55 am - 10:15 am	***Susan Schenk,*** Victoria University of Wellington MDMA self-administration in rats: It's all about dopamine
10:15 am - 10:35 am	***David Kearns,*** American University Cocaine cues and deepened extinction
10:35 am - 10:55 am	***Erik Oleson,*** University of Colorado Denver Endocannabinoid-dopamine interactions in negative reinforcement: Implications for conditioned withdrawal
10:55 am - 11:15 am	***Gregory Collins,*** University of Texas Health Science Center at San Antonio Dopaminergic regulation of conditioned reinforcement: Impact of drug-taking history

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

Special Lecture 11:30 am - 12:30 pm (Chair: Barbara Turner)

A. Thomas McLellan, University of Pennsylvania: "What it really means to treat addiction as a chronic illness: Implications for treatment, evaluation, insurance and policy"

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

Adjournment and Lunch (12:40 pm - 1:30 pm)

Abstracts

Oral Communications

1

The effect of methamphetamine on behavioral motivation

Mayo, Leah M.[1,2]; DeArcangelis, Jessica[2]; and de Wit, Harriet[2]

[1]Committee on Neurobiology and [2]Department of Psychiatry and Behavioral Neuroscience; University of Chicago; Chicago, IL, USA

Behavioral motivation relies upon the desire to both approach positive, rewarding outcomes and to avoid negative, aversive outcomes. In this study, we used a modified version of the Monetary Incentive Delay (MID) task to assess behavioral motivation in response to potential monetary gains and avoidance of monetary losses in healthy, human subjects. We then explored the effect of a prototypic stimulant drug (20 mg methamphetamine; MA) on these incentivized processes. Healthy, non-dependent human participants (N = 75) came in for 2 placebo sessions and 2 drug administration sessions (20mg methamphetamine), completed in alternating order under double-blind conditions. At peak drug effect (30min post-drug administration), participants completed a modified version the MID task. This version of the MID task included trails in which subjects could earn money (GAIN trials), prevent losing money (LOSS trials), or have no monetary consequence (NONE trials). In each trial, a cue denoting trial type was displayed and participants then had to respond to presentation of a target by clicking a button as quickly as possible. Although participants were aware that there was no monetary consequence to some trials (NONE trials), they were told to still respond as quickly as possible for *all* trials. Participants were given feedback after each trial and were able to take home any money earned. Under placebo conditions, participants had the fastest reaction times (RTs) in LOSS trials, and RTs were slowest in GAIN trials. Under methamphetamine, RTs in GAIN and LOSS trials were significantly decreased, but RTs are unaffected in trails with no monetary consequence (NONE trials). This suggests that a typical stimulant drug has the ability to enhance behavioral motivation in response to potential gains and aversion of losses, and that this effect is not simply a result of enhanced psychomotor ability.

2

Cocaine Cues Become More Powerful Reinstaters of Reinforcer Seeking Than Food Cues

Tunstall, Brendan J. and Kearns, David N.

Department of Psychology, American University, Washington, DC.

Several theories of drug addiction posit that maladaptive learning can cause cocaine cues to gain a disproportionate amount of control over behavior. The present study aimed to directly test this hypothesis. In Experiment 1, rats were trained on a choice procedure where pressing one lever resulted in cocaine and pressing the other lever resulted in food delivery. Delivery of each reinforcer was paired with a distinct audiovisual cue. On average, rats chose food on approximately 80% of trials. After an extinction phase, a cue-induced reinstatement test was administered where pressing a lever resulted in presentation of the associated audiovisual cue but not food or cocaine. Surprisingly, despite the fact that rats preferred food over cocaine when these primary reinforcers were available, rats displayed significantly greater cocaine-cue-induced responding than food-cue-induced responding during the test. This effect was maintained on subsequent cue-induced reinstatement tests conducted at 3 and 8 weeks post-extinction. In Experiment 2, we tested the notion that this phenomenon of disproportionate conditioned reinforcer strength is unique to drugs of abuse. This was achieved by systematically replicating the procedure of Experiment 1, but with sucrose and grain pellets as the primary reinforcers. Rats preferred sucrose over grain when they could choose between them. In contrast to the outcome of Experiment 1, the cue associated with the preferred reinforcer (sucrose) produced significantly more reinstatement than the cue associated with the non-preferred, grain reinforcer (i.e., primary and conditioned reinforcement were in alignment). This pattern of results suggests that cocaine-based conditioned reinforcers are qualitatively different from conditioned reinforcers based on natural rewards. It appears that cocaine-paired cues become unusually strong conditioned reinforcers and are more able to influence extinguished reward-seeking behavior than food cues. This finding may be of particular interest for understanding the maladaptive choices made by drug-addicted humans.
Supported by R01DA008651 from NIDA

3

Allosteric Modulation of the 5-HT_{2C} Receptor (5-HT_{2C}R): A Novel Strategy Toward the Treatment of Cocaine Use Disorder.

Wild, Christopher; Ding, Chunyong; Zhang, Gongliang; Hartley, Rachel M.; Anastasio, Noelle; Moncrief, J. Scott; Carbonaro, Theresa M.; Fox, Robert G.; Stutz, Sonja J.; Smith, Thressa D.; Cunningham, Kathryn A.;* Zhou, Jia.*

Center for Addiction Research, and Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX 77555. Email: jizhou@utmb.edu; kcunning@utmb.edu

Cocaine use disorder remains without an FDA-approved pharmacotherapy. Accumulating preclinical evidence suggests that enhancing the 5-HT_{2C} receptor function as a strategy to treat cocaine use disorder has promise. The development of potent agonists that can selectively target one of the fourteen serotonin receptors is an exciting prospect (Lorcaserin being a primary example) but also presents a challenge due to the highly conserved residues at the orthosteric binding site that accommodate the endogenous ligand. On the other hand, positive allosteric modulators (PAMs) present a unique approach to augment serotonin signaling with receptor subtype selectivity and even complete specificity. Moreover, other therapeutic advantages can be envisioned such as a reduced side effect profile, capacity for probe dependence, and ability to induce signaling bias. Our efforts to develop selective 5-HT_{2C}R PAMs began with the synthesis and pharmacological validation of PNU-69176E, the only reported 5-HT_{2C}R PAM. Subsequent structural analogs have been rationally designed, synthesized and evaluated using live cell assays and *in vivo* behavioral studies, affording several new lead compounds. The structures of the most recent PAMs of 5-HT_{2C}R will be disclosed and the results of molecular docking as a tool to design potential bitopic allosteric/orthosteric ligands will be discussed. CYD-1-79 has been identified to possess a favorable pharmacokinetic profile and suppress impulsivity and cocaine cue reactivity in rats, indicating efficacy in primary animal models pertinent to relapse in cocaine use disorder. (Supported by P30 DA028821, K05 DA020087, R21 MH093844, a training fellowship from the Keck Center for Interdisciplinary Bioscience Training of the Gulf Coast Consortia (T32 GM089657-03), and the UTMB Center for Addiction Research.)

4

ENT1-mediated Adenosine Signaling Regulates Learning and Reward Seeking Behaviors.

Alfredo Oliveros[1]; Hyung W. Nam[1]; Gamze, B. Camsari[2]; Maria P. Noterman[1]; Carrie Jo Heppelman[4]; Sun Choi[1]; David J. Hinton[2]; Chelsea Vadnie[2] and Doo-Sup Choi[1, 2, 3]

[1]Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN, USA; [2]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA; [3]Neurobiology of Disease Program, Mayo Clinic, Rochester, MN, USA;[4]Proteomics Research Center, Mayo Clinic, Rochester, MN, USA

Although adenosine plays an essential role in hippocampal function, it remains unclear if deletion of the equilibrative nucleoside transporter 1 ($ENT1^{-/-}$), which regulates adenosine signaling in the hippocampus, can play an essential role in addictive behaviors. Adenosine signaling has been implicated in altering the nucleus accumbens neuroproteome and ethanol-seeking behaviors in mice lacking ENT1. In this study, we examined the dorsal hippocampus (dHPC) of $ENT1^{-/-}$ mice using label-free quantitative proteomics. We identified 1,866 proteins in the dHPC, with 125 significantly decreased and 58 significantly increased in expression. Ingenuity Pathway Analysis (IPA) associated significant changes in biological processes and canonical pathways derived from focus and reference protein data sets. Notably, we found significantly altered proteins involving enhanced synaptic long-term potentiation, neuronal cytoskeleton reorganization through the ARP2/3 complex, and mitochondrial dysfunction. Interestingly, the protein profile in the dHPC showed reduced expression of the adenosine A_{2A} receptor, deficits in glutamate degradation and GABA receptor signaling. We then examined learning behavior in $ENT1^{-/-}$ mice with a Pavlovian learning task and an operant second-order schedule discrimination task. Our results showed that $ENT1^{-/-}$ mice had significant enhancements in Pavlovian learning, and displayed shorter response latencies upon onset of a visual-cue signaling reinforcement in the discrimination task. This suggests that $ENT1^{-/-}$ mice learn faster than wild-type littermates. Furthermore, $ENT1^{-/-}$ mice had significantly more responses during extinction of a previously reinforced response for a natural reward. Our findings suggest that deletion of ENT1 increase glutamate signaling and lead to enhanced learning and compulsive responding in reward seeking behaviors.

Oral Communications

5

Novel and High Affinity Fluorescent Ligands for the Serotonin Transporter based on (*S*)-Citalopram.

Vivek Kumar,[a] Troels Rahbek-Clemmensen,[b] Christian B. Billesbølle,[b] Trine Nygaard Jorgensen, [b] Ulrik Gether, [b] Amy Hauck Newman [a]

[a]Medicinal Chemistry Section, NIDA-IRP, NIH and [b]Molecular Neuropharmacology Laboratory and Center for Pharmacogenomics, Department of Neuroscience and Pharmacology, The Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.

The selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants, which are prescribed for the treatment of anxiety and major depressive disorders, work through inhibition of serotonin reuptake via the serotonin transporter (SERT). Despite clinical success, drug-protein interactions at the molecular and cellular levels that result in inhibition of serotonin reuptake have not been characterized fully. We have previously synthesized a highly useful tropane-based fluorescent probe, JHC 1-064 that binds to all three monoamine transporters and has primarily been used to visualize the dopamine transporter (DAT). Herein we describe the synthesis of novel rhodamine-labeled ligands, based on the SSRI (*S*)-citalopram. This series of N- and 5-subsituted-(*S*)-citalopram analogues was evaluated for uptake inhibition at the SERT, DAT and norepinephrine transporter (NET) and for binding at SERT, in transiently transfected COS7 cells. All four fluorescent analogues demonstrated moderate to high binding affinity at SERT and none of the analogues were active at DAT or NET, at a concentration of 10 μM. VK 02-83 demonstrated the highest affinity and selectivity for SERT (K_i = 3 nM), which is comparable to the parent compound. VK 02-83 also binds highly specifically to cells transiently transfected with EGFP-SERT as observed by confocal microscopy in HEK293 cells. Visualization and transporter trafficking studies with VK 02-83 are underway in raphe neurons.

6

Anti-hyperalgesic effects of imidazoline I2 receptor agonists and their interactions with opioids in a rat model of inflammatory pain

David A. Thorn[1], Yanan Zhang[2], Jun-Xu Li[1]:

[1]Department of Pharmacology and Toxicology, University at Buffalo, Buffalo, NY, [2]Research Triangle Institute, Research Triangle Park, NC

Pain affects > 30% of the US population and currently available analgesics are not adequate to meet the clinical needs, leaving a big population with undertreated pain. Opioids are effective for treating moderate to severe pain; however, their use is limited due to the unwanted effects, particularly in the treatment of chronic pain. We recently found that imidazoline I2 receptor agonists produce antinociceptive effects in rat models of chronic pain (complete Freund's adjuvant [CFA]-induced inflammatory pain and chronic constriction injury [CCI]-induced neuropathic pain), and also enhance the antinociceptive effects of morphine. However, little is known of the duration of action of I2 receptor agonists on chronic pain as well as their interaction with other opioids. This study examined the anti-hyperalgesic effects of selective I2 receptor agonists (2-BFI, phenyzoline, CR4056 and RS45041) alone and in combination with oxycodone in rats using the von Frey filament test. In rats with CFA-induced inflammatory pain, 2-BFI (1-10 mg/kg, i.p.; 0.32-3.2 mg/kg, i.v.), phenyzoline (17.8-56 mg/kg, i.p.), CR4056 (3.2-32 mg/kg, i.p.; 10-56 mg/kg, p.o.) and RS45041 (10-32 mg/kg, i.p.) all dose-dependently produced significant antinociceptive effects of varied duration. When studied as combinations, 2-BFI and oxycodone as well as phenyzoline and oxycodone produced additive interactions for their effects against mechanical hyperalgesia in CFA-treated rats. Taken together, these studies suggest that imidazoline I2 receptor agonists alone have anti-hyperalgesic effects and also enhance the effects of opioids in a rat model of chronic pain. Therefore, drugs acting on the imidazoline I2 receptor may represent a novel class of pharmacotherapy for the management of chronic pain.

7

Developing highly selective and potent D3 receptor antagonists and partial agonists using a synthon approach

Comfort A. Boateng,[a] Oluyomi M. Okunola-Bakare,[a] Ashwini K. Banala,[a] Thomas M. Keck,[a] Prashant Donthamsetti,[b] Jonathan A. Javitch,[b] Lei Shi,[c] and Amy H. Newman[a]

[a]Med. Chem. Section , NIDA–IRP, NIH, [b]Columbia U., [c]Weill Med. Coll. of Cornell U.

The dopamine D3 receptor (D3R) is involved in brain rewarding pathways and is a promising therapeutic target for drug abuse. Several highly selective D3R antagonists and partial agonists based on the 4-phenylpiperazine (PP) scaffold have been discovered, using small molecule structure-activity relationships (SAR). Computational studies using R-PG648 and the D3R crystal structure have shown that the PP binds to the orthosteric binding site (OBS) in which the known D2/D3 antagonist eticlopride binds, whereas the arylamide terminus binds in a second binding pocket (SBP) that is divergent between D3R and D2R. Using a synthon approach, we have discovered that substitution of the PP can influence the binding modes of the arylamide terminus within the SBP that not only determines D3R binding affinity and selectivity, but also efficacy. In the present study, we have modified both substitutions on the PP ring as well as the arylamide. Using PG648 as our lead compound, we have replaced the 2,3-diCl-substitution of the PP with a 2-OMe, 3-Cl- or a 2,3-naphthyl-substituent. In addition, bioisosteric replacement of the indole- was also explored using quinoline-amides. These novel ligands were synthesized and their binding affinities were determined using [^{3}H]NMS radioligand binding in HEK293 cells expressing dopamine D2-like receptors. We found several ligands display high affinity D3R (Ki<1 nM) and (> 100-fold) selectivity profiles at the D3R versus the D2 and D4 receptors. Preliminary data indicate that in the full-length ligands, functional efficacies increased in the presence of the 3-OH-substituted linker with the quinoline-amide secondary pharmacophore. We also synthesized and evaluated the synthons that make up these novel ligands in both binding and the BRET1-based G_{oA} activation functional assays and compared these to the full-length molecules. These studies will extend our understanding of ligand-receptor interactions and the relationship between the OBS and SBP that lead to both affinity and efficacy at the D3R.

8

Relationship of social rank to hormone levels, cognitive performance, and homecage activity in female cynomolgus monkeys

Kromrey, Sarah A[1], Czoty, Paul W[1], Rowe, Michael C[1], and Nader, Michael A[1]
[1]Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, NC.

Nonhuman primate social groups, which represent a continuum of experiences from environmental enrichment in dominant monkeys to chronic social stress in subordinates, have been used to study susceptibility and resilience to human diseases. We have shown that social rank influences sensitivity to cocaine and other dopaminergic drugs and that there are sex differences in these outcomes. In both males and females, it is not clear what biological and environmental factors determine what rank an individual monkey will attain, or how variables are modified after rank is established. In females, novel object reactivity and CSF concentrations of 5-HIAA were related to social rank; these factors did not change after hierarchies stabilized. The present studies examined whether other variables, assessed in individually housed monkeys, including hormone levels of total testosterone and cortisol, cognitive function (using CANTAB touchscreen software) and activity (using Actical monitors), predict eventual social rank and change after social hierarchies stabilized. Prior to social housing 4 monkeys per pen, performance on a cognitive task was not different in eventual dominant and subordinate monkeys. After stable hierarchies were formed, subordinate monkeys demonstrated cognitive impairments. Furthermore, future subordinates had higher activity during the day which remained higher after hierarchies stabilized, and preliminary results suggest social rank differences in nighttime activity. The relationship between cognitive behavior, activity and hormone concentrations and cocaine reinforcement are currently being investigated. Understanding behavioral phenotypes and individual differences in response to environmental manipulations, such as attainment and occupation of social ranks, and the relationship to cocaine self-administration will aid in the development of behavioral and pharmacological treatment strategies for drug addiction. DA017763, DA10584

Oral Communications

9

Novel Modafinil Analogs Define A Role for Transmembrane Helix 10 (TM10) in DAT versus SERT Selectivity.

Okunola-Bakare, Oluyomi M[1]; Cao, Jianjing[1]; Kopajtic, Theresa[1]; Tanda, Gianluigi[1]; Katz, Jonathan L[1]; Loland, Claus J[2]; Shi, Lei[3]; Newman, Amy H[1]
[1]Molecular Targets and Medications Discovery Branch, NIDA–IRP, NIH, MD USA; [2]Copenhagen University, Copenhagen, Denmark; [3]Weill Medical College of Cornell University, NY USA.

Inhibition of dopamine (DA) reuptake via the dopamine transporter (DAT) is the primary mechanism underlying the reinforcing effects of abused drugs such as cocaine. However, modafinil (2-[(diphenylmethyl)sulfinyl]acetamide, (±)-**1**) has been described as a unique DA uptake inhibitor that binds the DAT differently from cocaine and may have therapeutic potential for the treatment of psychostimulant abuse. To further investigate structural requirements for this divergent binding mode, novel thio- and sulfinyl-acetamide and ethanamine analogs of (±)-**1** were synthesized, wherein substituents were added to 1) the diphenyl rings and/or 2) the terminal amide/amine nitrogen. In general, these modifications gave analogs with higher binding affinities at DAT compared to (±)-**1** (K_i = 2600 nM). Halogen substitution of the diphenyl rings of (±)-**1** gave several amide analogs with improved binding affinity at DAT and robust selectivity over the serotonin transporter (SERT), whereas affinity improved at SERT over DAT for the amine analogs. Overall, we identified one highly DAT-selective amide analog (>2900-fold over SERT) and two highly SERT-selective amine analogs (K_i < 30 nM). Molecular docking studies, using a subset of analogs with DAT and SERT homology models, and functional data obtained with DAT (A480T) and SERT (T497A) mutants defined a role for transmembrane helix 10 in the substrate/inhibitor S1 binding site of DAT and SERT. Additionally, in preliminary *in vitro* and *in vivo* studies, the amine analog **JJC 8-016** readily crossed the blood brain barrier, displayed good microsomal stability and pharmacokinetic profile, and did not increase locomotor activity as compared to cocaine. These novel analogs may prove useful for elucidating mechanisms underlying therapeutic effects of (±)-**1**, and efforts are underway in our labs to further develop these compounds as potential medications to treat psychostimulant abuse.

10

Dopamine uptake inhibitors produce complete stimulus generalization in rats trained to discriminate 256 mg/kg modafinil

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The wake-promoting drug, modafinil, is a mild stimulant that has a lower affinity for the dopamine transporter and fewer side effects when compared to traditional psychostimulants, thus it is a promising candidate for agonist replacement therapy in stimulant dependent individuals. The subjective effects of modafinil are reportedly distinct from those of amphetamine in humans with a history of psychostimulant abuse although previous research indicates that modafinil modestly increases locomotor activity and produces similar discriminative stimulus effects to psychostimulants in rodents. The current study employed drug discrimination, a well-established preclinical screening assay, to assess the neurochemical mechanism of modafinil by examining psychoactive substances for substitution 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 solution) under a FR 20 schedule of food reinforcement. Following the completion of substitution tests with a range of modafinil (16 - 384 mg/kg) and d-amphetamine (0.03 - 3.0 mg/kg) doses, generalization tests were conducted with the dopamine uptake inhibitors, cocaine (1.25 - 10 mg/kg), GBR 12909 (5 - 20 mg/kg), and methylphenidate (1.25 - 10 mg/kg). Results indicate that all compounds produced a dose-dependent increase in modafinil-lever responding with near full substitution at the highest doses tested. Response rate was also significantly reduced at the highest doses tested for all compounds with the exception of modafinil and methylphenidate. Response rate remained steady for all doses of modafinil and methylphenidate tested. This is the first study to establish discrimination with modafinil in rodents and to evaluate modafinil's mechanism utilizing modafinil as the training drug in the drug discrimination paradigm. Results suggest modafinil's discriminative stimulus effects are mediated by its actions on the dopamine transporter, although the lack of a dose-dependent decrease in response rate during modafinil tests indicates modafinil has motor effects that are distinguishable from traditional dopamine uptake inhibitors.

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Cannabis use among individuals in recovery from alcohol use disorders

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Background: Cannabis is the most commonly used drug among alcohol-dependent individuals, perhaps due to the similar behavioral, subjective, and physiologic effects of these substances. Some individuals recovering from alcohol use disorders (AUD) attribute their reductions in alcohol use and related problems to cannabis. Other studies report that cannabis increases the risk of post-treatment drinking, and can lead to more alcohol-related problems. These mixed findings demonstrate that existing research lacks rigorous epidemiologic documentation of the differences in alcohol-related problems between cannabis users and non-users in recovery from AUD. Furthermore, the rates of cannabis use could increase as a consequence of cannabis decriminalization. Thus, AUD treatment providers need to understand who is likely to increase cannabis use during AUD recovery affects alcohol-related outcomes. Aims: The current study uses secondary data from the 2005 and 2010 National Alcohol Surveys (N=811) to examine the differences in alcohol problem severity, drunk driving, alcohol-related consequences and general health between past-year cannabis users and non-users who self-report as in recovery from AUD. Methods: Chi-square tests and multivariate regressions. Results: Bivariate chi-square tests showed that cannabis users had significantly more problems and were more likely to drive drunk than cannabis non-users. General health did not differ. Multivariate regressions controlling for age, sex, race, education, employment, and DSM-IV lifetime alcohol severity showed that cannabis users were still more likely to meet current DSM-IV alcohol abuse criteria (OR=2.60, P<.001), current DSM-IV alcohol dependence criteria (OR=1.98, P<.001), and drive drunk (OR=3.02, *P*<.003) than non-users. Conclusions: Cannabis appears to hinder alcohol-related outcomes among individuals in recovery from AUD. Cannabis users who are attempting to quit or reduce drinking should be encouraged to cease cannabis use simultaneously.

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Functional characterization of piperazine- and tropane-based CB1R allosteric modulators.

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Allosteric modulators of the cannabinoid CB1 receptor (CB1R-AMs) represent a novel approach to the treatment of disorders of stress, anxiety, and pain that may have limited psychotropic ancillary effects compared to orthosteric CB1R agonists. CB1R-AM effects were previously observed when GBR 12909 and JHW-007 were co-incubated with CB1R orthosteric agonist, CP55,940 in CB1R-transfected Chinese hamster ovary (CHO) cells overexpressing $G_{\alpha16}$. The goal of the present study is to evaluate the ability of these agents to activate G protein-mediated signaling in *ex-vivo* mouse brain membranes. We tested the ability of GBR 12909, JHW-007, and close analogue GBR 12935, to modulate CP-55,940 binding and efficacy in inducing GDP/GTP exchange. GBR 12909 dose-dependently enhanced the Bmax for [^{3}H]CP55,940 at concentrations up to 10 μM; Bmax was not significantly affected by other compounds. Concentration-response relationships with GBR 12909 and JHW-007 were found that both decreased [^{3}H]CP55,940 specific binding with pKB values of 5.746 and 5.203, respectively. None of the compounds tested were capable of enhancing CP55,940 (10 μM)-mediated stimulation of [^{35}S]GTPγS binding over 5 log unit concentration-effect curve, with JHW-007 diminishing activity at approximately 0.01 μM. In the [^{35}S]GTPγS functional assay, GBR 12909 (1 μM) produced an insignificant enhancement of CP55,940 activity. The previous study demonstrated significant enhancement of Emax for both GBR 12909 and JHW-007 in a calcium mobilization assay; to determine whether our observations are indicative of a biased agonist effect, further pathway-specific evaluation of these and other CB1R-AM chemotypes is currently in progress.

This work was supported by a New Investigator Award (American Association of Colleges of Pharmacy, CWC), and by the Research Component of the Healthier Wisconsin Endowment of the Medical College of Wisconsin (CJH).

Oral Communications

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Discriminative stimulus effects of the analgesics clonidine and CR4056 in rats with or without chronic pain

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Pain is an integral subjective experience but current preclinical pain studies rely heavily on the measures of reflex-based sensory pain. Drug discrimination procedure measures the interceptive stimulus properties of drugs and may offer an approach to detect analgesic-induced subjective experience of pain relief when pain is present. This study trained different groups of rats to discriminate the established analgesic clonidine or novel imidazoline I2 receptor ligand and analgesic CR4056. For each training drug, two groups of rats were used with one group receiving single saline administration in the right hind paw and the other group receiving single 50 µl complete Freund's adjuvant (CFA) administration (a model of chronic inflammatory pain). All rats acquired the discriminative stimulus of clonidine or CR4056 after similar training sessions and the sessions to criteria were not different in rats with or without pain. In rats discriminating 0.032 mg/kg clonidine, CR4056, u opioid analgesic morphine and NMDA receptor antagonist ketamine all predominantly occasioned vehicle-associated lever responding while clonidine produced nearly 100% clonidine-associated lever responding. In rats discriminating 10 mg/kg CR4056, clonidine, morphine and ketamine all predominantly occasioned vehicle-associated lever responding while CR4056 produced near maximal CR4056-associated lever responding. The substitution potencies of the training drugs were not different in rats with or without chronic pain in both discrimination groups. At the completion of the studies, CFA-treated rats remained hypersensitive to a mechanical stimulus, suggesting the presence of pain. In summary, this study found that the presence of pain did not facilitate the acquisition of clonidine or CR4056 discrimination and that pain suppression did not contribute significantly to the discriminative stimulus effects of clonidine or CR4056 in rats with chronic inflammatory pain. These results suggest that pain does not alter the pharmacological specificity of drug discrimination. (Supported by a NIH grant DA034806)

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Novel analogues of sumanirole provide clues to biased agonism at the dopamine D2 receptor

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The dopamine (DA) D2 receptor (D2R) is a $G_{i/o/z}$-coupled GPCR and key component of brain reward circuitry. D2R is a pharmacotherapeutic target for schizophrenia, Parkinson's, and psychostimulant addiction. DA binding to D2R induces signaling via multiple pathways, including suppression of cAMP production and β-arrestin-mediated signaling. Recent studies suggest D2R agonists biased toward β-arrestin signaling may have greater antipsychotic efficacy, fewer motoric side effects, and may represent a new mechanistic target for pharmacological manipulation. In the present study, we synthesized novel analogues of the purported D2R-preferential full agonist sumanirole to evaluate the molecular determinants of D2R receptor selectivity (versus homolog D3R) and agonist efficacy. Compound binding was analyzed using agonist ([^{3}H]7-OH-DPAT) and antagonist ([^{3}H]N-methylspiperone) radioligands; receptor signaling was evaluated using mitogenesis, β-arrestin coupling, cyclic AMP, and G_o activation assays in hD2R- or hD3R-transfected cells. Modification of sumanirole's N-methylamino function to a tertiary amine with one or two n-propyl groups biased the signaling profile toward β-arrestin. Surprisingly, addition of N-n-butylarylamide functions found in D3R-selective antagonists such as NGB2904 afforded analogues with equal or higher D2R affinity than sumanirole. Addition of n-propyl and n-butyl groups at the cyclic amide nitrogen enhanced D3R binding affinity and reduced efficacy to partial agonist or antagonist levels in D2R and D3R β-arrestin assays. Overall, this set of novel sumanirole analogs revealed several trends that may be exploitable in future SAR studies for the discovery of functionally biased pharmacotherapies.

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MDMA self-administration in rats: It's all about dopamine

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MDMA is the principle psychoactive ingredient of the popular street drug, "ecstasy". Most users consume the drug infrequently but there are a number who progress to more frequent use of higher doses and some meet criteria for dependence. MDMA is self-administered by laboratory animals but the profile of self-administration differs from other drugs of abuse. Latency to acquisition of self-administration is relatively long and only about 50% of the rats meet acquisition criteria. Once self-administration is acquired, however, there is an escalation of responding over days and pronounced drug seeking is produced by exposure to either stimuli that were associated with self-administered infusions or to certain drug primes. Initially, MDMA preferentially stimulates the release of serotonin but following extensive exposure, serotonin neurotransmission becomes compromised and dopamine responses increase. I will present data from a large cohort of rats to show the profile of acquisition and maintenance of MDMA self-administration. Additionally, I will present data that indicate the role of both serotonin and dopamine n MDMA self-administration.

16

Cocaine Cues and Deepened Extinction.

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Drug cues can trigger relapse after periods of abstinence. Extinction has been used in attempts to reduce the power of drug cues, but success with such cue-exposure treatments has been limited. This has led to a search for improved extinction-based treatments for drug cues. We previously showed in rats that briefly compounding (i.e., simultaneously presenting) two cocaine cues during their extinction attenuated subsequent spontaneous recovery of cocaine seeking. The present study was performed to determine whether a cue previously associated with a non-drug appetitive reinforcer could be used to deepen the extinction of a cocaine cue. Tone and click were each first established as discriminative stimuli for rats' cocaine-reinforced responding and light was a cue for food-reinforced responding. In an initial extinction phase, all stimuli were extinguished individually. Then, light and one of the cocaine cues (counterbalanced over subjects) were presented simultaneously for an additional compound extinction session. The other cocaine cue was presented by itself during this session. Surprisingly, the cocaine cue compounded with the food cue during extinction controlled greater cocaine seeking on a subsequent spontaneous recovery test than did the cocaine cue always presented alone. In a comparison group of rats, compounding two food cues during extinction resulted in the expected deepened extinction effect. These results suggest that deepened extinction depends on the compound presentation of cues that were previously associated with the same reinforcer and that the co-presentation of non-drug cues could even interfere with the extinction of drug cues. Care should be taken in the design of potential treatments incorporating deepened extinction procedures. This research was supported by NIDA grant DA008651.

Oral Communications

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Endocannabinoid-Dopamine Interactions in Negative Reinforcement: Implications for Conditioned Withdrawal.

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Negative reinforcement plays a prominent role in drug addiction. Through Pavlovian conditioning, exteroceptive cues can become associated with negative stimuli and exert powerful influences over behavior in their own right. We recently demonstrated that subsecond dopamine release in the nucleus accumbens encodes conditioned predictors of negative reinforcement and believe these data provide novel insight into how the brain processes conditioned withdrawal. Dampening dopaminergic encoding of conditioned predictors of negative reinforcement may lead to novel pharmacotherapies that are particularly suited for attenuating the effects of conditioned withdrawal. The endocannabinoid system modulates dopamine release and cue-motivated behavior. Thus, we hypothesized that disrupting endocannabinoid signaling would decrease dopaminergic encoding of conditioned cues during conditioned avoidance. In this task, a stimulus light is presented as a warning signal for 2s prior to the delivery of recurring foot shocks. During the 2s warning period, a response lever extends into the testing chamber which, if pressed at any time during the session, produced a 20s safety period signaled by a tone. Rats can initiate an avoidance response by pressing the lever within the 2s warning period, entirely preventing shock. Alternatively, once shocks commenced, animals can initiate an escape response by pressing the lever, thereby terminating shock. Pretreatment with the cannabinoid CB1 antagonist/inverse agonist rimonabant dose-dependently (0.3-1 mg/kg IV) decreased cue-evoked dopamine release and shifted the behavioral outcome from avoidance to escape. These data reveal that disrupting endocannabinoid signaling reduces the power that dopaminergic representations of cues exert over negative reinforcement, suggesting that targeting the endocannabinoid system might be conducive to treating the effects of conditioned withdrawal.

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Dopaminergic regulation of conditioned reinforcement: Impact of drug-taking history

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Environmental stimuli that have been associated with drug use (e.g., paraphernalia, drug-taking environment, etc.) are known to take on conditioned properties capable of eliciting physiologic changes and drug craving in abstinent drug abusers. These studies used a modified version of the cue-induced reinstatement model of relapse in which responding for cocaine-paired stimuli is maintained under a progressive ratio (PR) schedule of reinforcement during periods of cocaine unavailability. In order to determine if the involvement of dopamine D2-like (D_2, D_3, and D_4) receptors in controlling the conditioned reinforcing effects of cocaine-paired stimuli differed as a function of drug-taking history, the effectiveness of pramipexole, a dopamine D2-like receptor agonist, to stimulate responding for cocaine-paired stimuli was evaluated in rats trained to self-administer either 0.1 mg/kg/inj or 1.0 mg/kg/inj cocaine. Although pramipexole resulted in dose-dependent increases in PR responding for stimuli that were paired with either the small or large dose of cocaine, pramipexole was both more effective and more potent at stimulating responding in rats with a history of responding for the 1.0 mg/kg/inj, as compared to 0.1 mg/kg/inj dose of cocaine. Together with the results of previous studies, these findings suggest that differences in reinforcement history can alter not only the strength of relapse-related responding, but also the relative contribution of D_2 and D_3 receptors in mediating these effects. These findings highlight how individual differences can impact vulnerability to relapse and provide insight into the development of individualized treatment strategies targeting dopamine D_2 and D_3 receptors to help people remain abstinent.

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Poster Communications

1

The sigma-1 receptor modules activity of the dopamine transporter mediated by methamphetamine.

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The principle mechanism for terminating dopaminergic signaling is the reuptake of dopamine via the dopamine transporter (DAT). The activity of this Na^+/Cl^- symporter determines the intensity and duration of dopamine neurotransmission in the brain. The transporter is implicated in a variety of neurological disorders and is one of the primary targets for psychostimulants such as cocaine and methamphetamine (METH). METH is a highly addictive drug that competes with dopamine at the transporter and induces dopamine efflux via DAT. Past studies indicate that self-administration of METH causes up-regulation of the σ_1 receptor, an endoplasmic reticulum chaperone protein, in midbrain regions. Upon activation, this receptor translocates to the plasma membrane where it has been shown to modulate the activity of various receptors and channels. Using co-immunoprecipitation and fluorescence resonance energy transfer (FRET) we have found that the DAT and σ_1 receptor interact at the plasma membrane, and that this interaction is potentiated by treatment with METH. In this study, we investigated the functional consequence of the DAT/σ_1 receptor interaction on the activity of the transporter. These results suggest that the upregulation or activation of the σ_1 receptor can modulate the activity of the transporter when exposed to METH. Because METH self-administration increases σ_1 receptor levels in brain regions with the highest number of DAT positive terminals, understanding the mechanism of σ_1 receptor regulation of DAT activity may reveal novel therapeutic approaches for the treatment of METH addiction.

2

Precipitated withdrawal from high efficacy synthetic cannabinoid JWH-018 in mice: neutral antagonist versus inverse agonist effects

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Cannabinoid withdrawal (CW) has largely been characterized with Δ^9-THC, a low efficacy CB1R agonist. However, many abused synthetic cannabinoids (SCBs) are full agonists, suggesting that discontinuation of SCB use could elicit greater withdrawal than that observed after cessation of Δ^9-THC. Still, one complication with studying CW in animals is distinguishing true withdrawal effects from direct effects of an antagonist or inverse agonist, such as rimonabant (a CB1R antagonist/inverse agonist). In these studies, two putative neutral CB1R antagonists, TV-6-41 and TV-5-249, were compared with rimonabant in behavioral assays relevant to CW. First, conditioned taste aversion was used to assess direct aversive effects. Rimonabant and TV-5-249 induced aversive effects but TV-6-41 did not. Next, Δ^9-THC- or JWH-018-exposed mice were treated with rimonabant or TV-6-41 and observed for CW signs, including paw tremor, face rubbing, scratching and ptosis. Finally, precipitated withdrawal-induced suppression of response rates was assessed following cumulative doses of rimonabant or TV-6-41 in mice previously treated with JWH-018 or saline. Rimonabant dose-dependently suppressed response rates in both pretreatment groups, but TV-6-41 more potently suppressed response rates in JWH-018-treated mice as compared to mice without a cannabinoid history. Collectively, these findings suggest that there are behaviorally-relevant differences between rimonabant and TV-6-41, both in terms of their direct effects and in their capacity to precipitate CW, which should be further explored and exploited in future drug design. Importantly, these differences may be attributed to negative efficacy versus neutral antagonism at CB1Rs. Research support: RR029884, RR020146 and UAMS Department of Pharmacology and Toxicology.

3

Daily self-administered methamphetamine impairs learning-to-learn but not cognitive flexibility in the squirrel monkey

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Long-term chronic exposure to methamphetamine (MA) has been related to profound neural impact including, but not limited to, damage to monoamine nerve terminals. In turn, neural changes following repeated MA administration may be related to adverse effects on learning and other cognitive performance. However, the characterization of such neurobehavioral deficits remains incomplete. The present study assessed the effects of ongoing MA self-administration on touchscreen-based discrimination learning and reversal performance in nonhuman primates. Prior to daily sessions of MA self-administration (i.e., 20-hr after the previous day's session), monkeys engaged in a repeated acquisition task in which changes in the rate of discrimination learning for a stimulus pair were assessed over the successive presentation of novel stimulus pairs. Subsequently, discrimination reversal tests were also conducted requiring the subject to inhibit the previously reinforced response to obtain reinforcement. Results indicate that ongoing MA self-administration produced markedly deleterious effects on the development of learning sets in discrimination learning. Importantly, the magnitude of adverse effects on learning correlated well with the level of daily MA intake among individual subjects. However, cognitive flexibility measured via discrimination reversal was largely unaffected in all subjects. Roles of both behavioral and drug history will be discussed.

4

The role of calcium on dopamine D2 autoreceptor-mediated currents in substantia nigra dopamine neurons

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This work investigated the calcium dependence of dopamine-mediated outward currents in the substantia nigra. Dopamine neurons in the substantia nigra are involved in the initiation of voluntary movement and reward-related processes. D2-type autoreceptors on these neurons powerfully inhibit cell firing and have been associated with psychostimulant use. Previous work from our lab suggests that intracellular calcium inhibits maximal autoreceptor-mediated outward currents in dopamine neurons from mouse brain slices. Further, we have also observed that methamphetamine self-administration decreases maximal D2 autoreceptor-mediated outward currents in a calcium-dependent manner. However, since under physiological conditions only some of the autoreceptors are activated at any given time it is important to determine the effects of calcium on outward currents induced by lower concentrations of agonist. To address this, we performed patch clamp electrophysiology of dopamine neurons in brain slices from DBA/2J mice, and applied the neurotransmitter dopamine by iontophoresis and bath perfusion. The internal solution of the recording pipette contained either 10 mM BAPTA (high calcium chelation) or 0.025 mM EGTA (control conditions, low calcium chelation). Dopamine iontophoresis was used to determine the maximal D2 receptor mediated outward current that could be obtained from each cell, and bath perfusion of 3, 10, and 30 μM dopamine was used to investigate the effect of increasing dose on amplitude of outward currents. The outward currents from dopamine bath perfusion were then taken as percent of the pre-perfusion iontophoresis. The results will test the hypothesis that calcium chelation produces a leftward shift in the dopamine concentration-response curve at D2 autoreceptors. This would suggest that, in addition to altering efficacy, agonist potency is influenced by calcium and would have implications for the effects of psychostimulants on dopaminergic synaptic transmission.

Poster Communications

5

Tolerance to repeated 5-HT_{2C}R agonist administration in vivo: Implications for clinical therapeutics.

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The serotonin 5-HT_{2C} receptor (5-HT_{2C}R) is known to play a role in several psychiatric disorders and has been targeted for the development of novel therapies in treating disorders such as schizophrenia, obesity, Parkinson's disease, and addiction. However, chronic treatment with 5-HT_{2C}R agonists may induce tolerance by altering receptor responsiveness. Lorcaserin (Belviq®) is a first-in-class selective 5-HT_{2C}R agonist approved by the FDA for obesity. Studies in rodents have reported that lorcaserin produces a transient decrease in food intake, which returns to baseline after seven days. The observation that the same dose of lorcaserin loses efficacy over time indicates the development of tolerance to lorcaserin. We are interested in the mechanisms of such tolerance and the prospects for sustaining therapeutic efficacy. To this end, male Sprague-Dawley rats were treated daily for seven days with saline or lorcaserin (10 mg/kg, SC). Daily lorcaserin treatment reduced body weight, and altered some behavioral responses such as decreased general motor activity and increased oral movement. To compare acute and repeated treatment of lorcaserin, a 30-min locomotor activity session with a lorcaserin challenge (10 mg/kg, SC) was assessed 24-hrs following the 7-day regimen. Administration of lorcaserin induced hypomotility in saline treated rats, which was blunted following repeated lorcaserin treatment, suggesting tolerance developed to the 5-HT_{2C}R agonist. The influence of acute and repeated lorcaserin treatment on 5-HT_{2C}R expression, subcellular localization and trafficking will be assessed. Determining the mechanisms of tolerance found in this study will be informative for managing sustained efficacy of 5-HT_{2C}R agonists in clinical use.

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6

Subjective effects of minor tobacco alkaloids in nonhuman primates.

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Smoking behavior and relapse to smoking are mediated in part by the interoceptive stimulus effects of nicotine–the primary psychoactive substance responsible for the maintenance of tobacco consumption. Preclinical studies in rats have suggested that other non-nicotine tobacco constituents may also exhibit pharmacological properties relevant to the maintenance of tobacco consumption. We will present data from drug discrimination studies in which the nicotine-like subjective (discriminative-stimulus) effects of minor tobacco alkaloids (nornicotine, anabasine, cotinine, myosmine, anabaseine, anatabine) was examined in nonhuman primates. The effectiveness with which such minor tobacco alkaloids engender nicotine-like discriminative-stimulus effects in monkeys, may serve as a preclinical indicator of their pharmacological actions in smoking behavior. These studies were conducted in stimulant (0.1 mg/kg methamphetamine)- or 0.001 mg/kg (+)-epibatidine-trained squirrel monkeys that responded under a 10-response fixed-ratio schedule of stimulus termination (n=4/group). Results show that in stimulant-trained monkeys, the minor tobacco alkaloids anabasine and anabaseine partially reproduced methamphetamine-like DS effects, and in (+)-epibatidine-trained monkeys, they engendered full (nornicotine, anabasine, myosmine, anatabine), or no (cotinine) substitution for (+)-epibatidine. In additional experiments, ED_{50} doses of nicotine that produced 0.001 mg/kg (+)-epibatidine discrimination were combined with ED_{50} doses of minor tobacco alkaloids. Results, to date, indicate that ED_{50} doses of nicotine in combination with nornicotine or anatabine engender full 0.001 mg/kg (+)-epibatidine-like discriminative-stimulus effects. In conjunction, these findings suggest that: a) some minor tobacco alkaloids (nornicotine, anabasine, anabaseine, myosmine, anatabine) exhibit nicotine-like pharmacological properties that may contribute towards maintaining tobacco consumption; and b) minor tobacco alkaloids may augment the abuse-related behavioral effects of nicotine.

7

Substantial enantiomer-specific differences in the neurochemical and behavioral actions of the synthetic cathinone mephedrone

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Synthetic cathinones are an emerging group of amphetamine-derived compounds gaining popularity in abuse both in the United States and worldwide. Mephedrone (MEPH) is one of the most commonly abused of the synthetic cathinones. MEPH is a non-specific monoamine transporter substrate that produces psychostimulant effects similar to both amphetamine and MDMA. Similar those amphetamines and other cathinones, mephedrone has a chiral center and exists stably as two enantiomers, R-mephedrone (R-MEPH) and S-mephedrone (S-MEPH). We provide the first investigation into the neurochemical and behavioral differences of R-MEPH and S-MEPH. R-MEPH and S-MEPH were found to have similar effects on dopamine transporter reuptake inhibition and release in rat brain synaptosomes, while S-MEPH was more potent in serotonin transporter reuptake inhibition and release. Locomotor activity was evaluated in acute and repeated, intermittent paradigms, with R-MEPH producing significantly greater ambulation and stereotypy than S-MEPH across multiple doses and only R-MEPH produced sensitization of repetitive movements. Conditioned place preference assays determined R-MEPH, but not S-MEPH, produces place preference. Finally, following observations of serotonin's involvement in S-MEPH action, the effects of 5-HT_{2C} receptor antagonism with S-MEPH administration were determined. Pretreatment with the 5-HT_{2C} antagonist SB242084 potentiated S-MEPH acute locomotor response, as well as potentiating the development of CPP. Taken together, this data illustrates stereospecific mechanisms for mephedrone on specific monoamine systems and warrants further study.

8

Oxytocin receptor gene variation predicts subjective responses to MDMA

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3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") is used recreationally to enhance mood and sociability. Evidence from human laboratory studies indicate that MDMA produces several prosocial effects, including increased desire to socialize, heightened feelings of empathy, and enhanced recognition of positive emotions. Evidence from rodents and humans suggests that MDMA may exert its prosocial effects by increasing oxytocin levels in the brain. Here we examined the influence of a single nucleotide polymorphism (SNP) in the oxytocin receptor gene (OXTR) on subjective responses to MDMA in humans. Previous studies have shown that the GG genotype at rs53576 is associated with increased empathic concern and enhanced sensitivity to social cues. We therefore hypothesized that GG individuals would show greater MDMA-induced sociability. Healthy volunteers with past MDMA experience (N=67) completed this 3-session, double blind, within-subjects study during which they received single doses of oral MDMA (0, 0.75mg/kg and 1.5mg/kg). Before the first session, participants provided blood samples to be used for genotyping. Following drug administration, participants completed self-report questionnaires assessing feelings of sociability, anxiety, and positive mood. Individuals with the GG genotype experienced significantly stronger feelings of MDMA-related sociability at the 1.5mg/kg dose than individuals possessing the AG genotype, but the groups did not differ in cardiovascular responses to the drug or subjective reports of drug-related euphoria. Such genetic differences may cause individuals to be differentially sensitive to MDMA-induced oxytocin changes in the brain. These results provide further evidence for the role of oxytocin in generating the prosocial effects of MDMA.

Poster Communications

9

Effects of TAAR1 agonist RO5263397 on cocaine self-administration in rats: reinstatement procedure and behavioral economic analysis.

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Cocaine addiction remains a major public health problem. Although cocaine's mechanism of action is well established, no effective pharmacotherapy for cocaine addiction exists. The trace amine-associated receptor 1 (TAAR1), activated by endogenous trace amines, has proven to be an important modulator of the dopaminergic system and is considered a promising target for the treatment of neuropsychiatric disorders. However, little is known regarding the impact of TAAR1 agonists on abuse-related effects of cocaine. The aim of the present study was to determine if a TAAR1 agonist RO5263397 could attenuate the reinstatement of cocaine-seeking behavior after extinction and to examine the effect of RO5263397 on the reinforcing strength of cocaine using behavioral economic analysis. In experiment 1, rats were trained to self-administer 0.75 mg/kg cocaine infusion (fixed ratio 5) in 2-h daily sessions for 14 days. After the lever-pressing behavior was extinguished, rats were administered RO5263397 (1.0, 3.2 or 5.6 mg/kg) prior to re-exposure to cues associated with cocaine infusion or 10 mg/kg i.p. cocaine priming injections. In experiment 2, rats were trained to self-administer cocaine (0.75 mg/kg/infusion) during daily 2-h sessions. The response requirement was progressively increased across sessions according to the following orders: 3, 10, 18, 32, 56, 100, 178, until the subject failed to earn one reinforcer for two consecutive sessions. If the number of reinforcers earned was stable at a particular ratio, saline or RO5263397 5.6 mg/kg were administered as a pretreatment on the following day. RO5263397 significantly attenuated both cue-induced and cocaine-primed reinstatement of cocaine seeking. RO5263397 also reduced cocaine self-administration behavior, shifted the demand curve downward, and significantly decreased the reinforcing strength of cocaine. Taken together, TAAR1 agonists can attenuate some abuse-related effects of cocaine and that drugs targeting TAAR1 receptors may represent a viable target for the development of novel pharmacotherapy against cocaine abuse.

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Effects of buspirone and the dopamine D2/D3 receptor antagonist PG01037 on food-drug choice in rhesus monkeys.

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Within the dopaminergic system, the dopamine D3 receptor (D3R) has been shown to mediate many of the behavioral effects of psychostimulants associated with high abuse potential. Recent preclinical studies have shown that buspirone (Buspar®), a D3/D2R antagonist, was able to decrease cocaine self-administration in rhesus monkeys responding under multiple schedules of cocaine and food reinforcement. Thus, the present study sought to extend the assessment of buspirone on cocaine and methamphetamine (MA) self-administration and reinstatement to include a food-drug choice procedure. These effects were compared with the non-selective D2-like receptor antagonist eticlopride and the highly selective D3R antagonist PG01037. Seven male rhesus monkeys served as subjects in which complete cocaine and MA dose-response curves were determined daily in each session. Buspirone (0.01-0.3 mg/kg, i.m.) and eticlopride (0.001-0.01 mg/kg, i.v.) were administered chronically (5 days) to monkeys self-administering cocaine and MA (n=3-4/group) while PG01037 (1.0-5.6 mg/kg, i.v.) was administered acutely. The ability of buspirone (1.0-1.7 mg/kg, p.o.) to block reinstatement was examined using the choice procedure in which saline was substituted for the self-administered drug (n=3/group). Neither buspirone nor eticlopride decreased drug choice or intake while buspirone significantly increased the choice of low drug doses. However, buspirone attenuated both cocaine- and MA-induced reinstatement. Acute administration of PG01037 was effective in reallocating choice behavior from cocaine to food responding in 3 of 4 monkeys but not in monkeys self-administering MA. These data support a potential use for buspirone in the drug abuse treatment of relapse and support the continued examination of D3 compounds for novel therapeutic agents.

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The effects of eating a high fat diet on sensitivity of adolescent female rats to the rewarding effects of cocaine.

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Feeding condition (e.g., type and amount of food consumed) can impact sensitivity to some of the behavioral effects of drugs acting on dopamine systems. For example, eating a high fat diet increases sensitivity of rats to the locomotor-stimulating effects of cocaine, which are often used to predict changes in sensitivity to some of the abuse-related (e.g., rewarding) effects of cocaine. The conditioned place preference procedure allows for a more direct assessment of the impact of diet on sensitivity to the rewarding effects of cocaine. Adolescent female rats ate standard laboratory chow (5.7% fat by weight) or a high fat laboratory chow (34.3% fat by weight) for four weeks, after which twice daily conditioning sessions were performed over three consecutive days. Saline was administered in the morning and paired with one floor texture, and cocaine was administered in the afternoon, and paired with the alternate floor texture (counterbalanced among subjects in each group). Different doses of cocaine (1.0-5.6 mg/kg) were administered to different groups of rats. The day after the last conditioning day, all subjects were placed in a chamber that had both floor textures in a preference test. Rats eating high fat chow gained more weight than rats eating standard chow. The largest dose of cocaine (5.6 mg/kg) induced a significant place preference in rats eating standard chow. Eating high fat chow did not increase sensitivity of rats to conditioned place preference induced by this dose of cocaine. These results indicate that while diet can increase sensitivity to some of the behavioral effects of cocaine (e.g., locomotor stimulation) other effects of cocaine (e.g., conditioned place preference) are not increased. This work was supported by T32DA031115; K05DA17918.

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Effects of Chronic Nicotine Administration and Nicotine Withdrawal on the Episodic Memory and Dopaminergic Deficits Caused by Methamphetamine

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Methamphetamine (METH) abuse is a serious problem in our society that, among other neurotoxic effects, leads to persistent episodic memory and dopaminergic deficits. Furthermore, the majority of METH abusers also smoke cigarettes and thus self-administer nicotine (NIC). However, few studies have evaluated the impact of NIC administration and NIC withdrawal on the episodic memory and dopaminergic deficits caused by METH. Accordingly, rats were given oral NIC administration via their drinking water or regular water from adolescence (post-natal day (PND) 40) to adulthood (up to PND 89, PND 90, or PND 97) at doses known to produce plasma NIC levels resembling those found in moderate tobacco smokers. METH was administered at PND 90 (4 x 7.5 mg/kg/injection or saline 4 x 1ml/kg, 2-h intervals, s.c.). Episodic memory assessment via novel object recognition was performed on PND 96. Somatic withdrawal signs and core body temperature were monitored. Striatal dopamine transporter function was assessed on PND 97. Results revealed that removing NIC from NIC-treated rats caused significant higher somatic signs in comparison to controls. Furthermore, a similar degree of METH-induced hyperthermia was observed among all of the four groups of METH-treated rats. Lastly, all of the three NIC administration protocols, i.e., from PND 40 to 89, PND 40 to 90 and PND 40 to 97, attenuated METH-induced episodic memory and striatal dopaminergic deficits. These data indicate that long-term pre-treatment with NIC is sufficient to afford protection, which is not mediated by reduction in hyperthermia, and these neuroprotective effects remain for at least 24 h after the final NIC exposure. Acknowledgment: NIDA DA 033097

Poster Communications

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Redox modulation of cocaine-conditioned locomotor behavior

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The objective of this study was to investigate the modulatory effect of cellular redox state on neural plasticity events mediating associations of context with psychostimulant exposure. Three compounds with different antioxidant actions were evaluated for their ability to affect the acquisition and expression of context-dependent increases in locomotion produced by a single exposure to cocaine. Cocaine (40 mg/kg, i.p.) was administered to different groups of Swiss-Webster mice, in either a locomotor activity testing apparatus or the home cage, 2 hours following an activity test under saline. Mice placed in the testing chambers were given 30 minutes to explore freely and locomotion was monitored using a Digiscan photocell apparatus. A conditioned effect of cocaine was inferred by an increase in horizontal activity counts relative to home cage cocaine controls during a test in the same apparatus on the following day. N-acetylcysteine (25, 50, 100 mg/kg), dimethylthiourea (5, 10, 25, 50 mg/kg), L-ascorbic acid (25-500 mg/kg), or vehicle was administered prior to placement into the activity chambers on the test day and prior to the acquisition day in a separate set of studies. N-acetylcysteine (100 mg/kg) and dimethylthiourea (25 and 50 mg/kg) inhibited the expression and the acquisition of cocaine-conditioned locomotion, though L-ascorbic acid (100 mg/kg) increased the acquisition of the conditioned locomotor effect and did not affect its expression. Additionally, L-ascorbic acid was found to facilitate the acute motor stimulant effect of cocaine, whereas N-acetylcysteine and dimethylthiourea did not affect the locomotor response to cocaine. The ability of these compounds to inhibit or exacerbate the conditioned behavior suggests that alteration of redox state may indeed influence neural plasticity dependent alterations in brain mediating addiction and relapse. Therefore, compounds producing alterations in cellular redox state may be viable targets for addiction treatment medications.

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Pharmacokinetic analysis of a PEGylated high-affinity anti-methamphetamine antibody fragment

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Methamphetamine (METH) is considered one of the top drug problems in the United States today, yet there are no FDA approved pharmacological treatments available for METH abuse. To this end, we have designed and produced an anti-METH single chain antibody fragment (scFv7F9Cys) as an anti-METH pharmacological treatment. However, scFv7F9Cys has a short half-life in its native state, limiting its potential clinical use. Thus, the aim of this study was to examine the pharmacokinetic effects of conjugating scFv7F9Cys to poly(ethylene) glycol (PEG). A 20kDa PEG was conjugated to scFv7F9Cys generating scFv7F9Cys-PEG. Binding analysis of both purified scFv7F9Cys-PEG and native scFv7F9Cys suggested PEGylation did not alter METH binding affinity. Pharmacokinetic parameters of scFv7F9Cys and scFv7F9Cys-PEG were then tested in an *in vivo* rat model. Rats were administered METH (3.2 mg/kg/day, s.c.) and scFv7F9Cys, scFv7F9Cys-PEG, or saline (30 mg/kg, i.v.) containing a radiolabeled tracer. Blood samples were taken at multiple time points after therapeutic protein administration and analyzed for therapeutic protein (scintillation counting) and METH concentrations (LC-MS/MS). Our results indicate PEGylation resulted in a several-fold increase both in the serum half-life of scFv7F9Cys and its ability to alter METH disposition. Funding: NIDA R01 DA026423, NIDA T32 DA022981

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Neurotensin induces presynaptic long-term depression of dopamine D2 autoreceptor-mediated neurotransmission in midbrain dopamine neurons.

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Increased dopaminergic signaling gives rise to severe mesencephalic pathologies, including psychostimulant abuse and schizophrenia. While innervation of the modulatory peptide neurotensin to midbrain dopamine neurons transiently increases activity by decreasing D2 autoreceptor function, little is known about the mechanisms that underlie important long-lasting effects. Here we show that neurotensin produces long-term depression (LTD) of D2 autoreceptor-mediated inhibitory postsynaptic currents (D2-IPSCs) through a calcineurin-dependent mechanism. Application of exogenous neurotensin was sufficient to induce LTD, and decreased presynaptic dopamine release. Finally, we show that neurotensin also induces postsynaptic depression of D2-IPSCs that does not persist over time. These results indicate that neurotensin acts as a retrograde messenger to decrease presynaptic dopamine release while transiently decreasing postsynaptic autoreceptor signaling.

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Neuromedin U in the nucleus accumbens shell modifies behavioral responses to cocaine.

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Neuromedin U (NMU) is a neuropeptide expressed in reward-associated areas of the brain. While NMU has been studied for its ability to regulate food reward, NMU has not been studied in the context of drugs of abuse (e.g., cocaine). Therefore, we evaluated the effects of NMU on behavioral sensitization to cocaine, a behavior that is dependent on neural plasticity in the nucleus accumbens shell (NAcSh). In this study, NMU was microinjected directly to the NAcSh of cocaine sensitized and non-sensitized rats shortly before a cocaine challenge. NMU was found to decrease acute, but not sensitized, cocaine-induced locomotion when administered directly to the NAcSh. This suggests that NMU signaling regulates the acute locomotor response to cocaine.

The neural pathways that might underlie the change in locomotor activity were investigated using confocal microscopy with immunofluorescence. The primary receptor for NMU in the brain, NMU receptor 2 (NMUR2) was found in the NAcSh and colocalizes with GAD67 a marker of GABAergic neurons. Furthermore, anterograde viral tracers injected into the dorsal raphe nucleus, but not the amygdala, caudate putamen, or globus pallidus colocalized with NMUR2. This work suggests a novel NMU pathway from the dorsal raphe to the nucleus accumbens which is capable of regulating behavioral responses to cocaine.

Poster Communications

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Age-related changes in the sensitivity to inflammatory mediators and opioid agonists.

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Effective and safe pain management in the elderly is a major medical challenge. Furthermore, little is known regarding the effect of aging on nociceptor (pain-sensing neuron) responsiveness or the function of opioid receptors expressed on nociceptors. Here, we compared the effects of the sensitizing agent, bradykinin (BK), and delta and kappa opioid receptor (DOR, KOR) agonists on nociceptors in young (4-months-old) and aged (26-months-old) Fisher x Brown Norway rats. Behavioral responses to noxious heat, cold, or mechanical stimulation were determined following intraplantar injections of BK. For all three stimuli, aged rats had a greater allodynic response to BK. In primary cultures, activation of phospholipase C in nociceptors from aged rats was more sensitive to BK than those from young rats. In addition, both opioid agonists, SNC80 (DOR) and Salvinorin A (KOR), produced greater antinociceptive effects in aged rats compared to young rats. Similarly, opioid receptor-mediated inhibition of adenylyl cyclase activity was greater in nociceptors from aged rats. Overall, our results indicate that aging enhances allodynic effects of the inflammatory mediator, BK, as well as increases antinociceptive effects of opioid agonists. We propose that peripherally-restricted opioids may be a valuable analgesic strategy for treating pain in the elderly.

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Behavioral and neurochemical effects of repeated 96-hour methamphetamine self-administration sessions in male and female rats

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A unique aspect of human methamphetamine (MA) use is that it is typically used in binges. However, there is no animal model of MA self-administration that appears to represent a human MA self-administration binge. Recently we have developed a binge and crash model of MA self-administration. Male and female rats were trained to self-administer MA for 96 consecutive hours for 5 weeks. Responding by female and male rats tended to escalate to binge-like behavior, as the animals responded continuously during their normal periods of activity as well during their inactive periods for up to 72 hours, followed by a crash of 6 or more hours. Behaviorally this model seems to be relevant to human MA use; however, the effects of self-administered binge and crash MA on brain neurochemistry have yet to be characterized. Therefore, male and female (n=4/group) rats were implanted with jugular catheters and trained to self-administer MA freely on an FR1 schedule of reinforcement over a period of 96 hours (Monday-Friday) for a total of five weeks. Control rats were paired with MA treated rats in a yoked-saline paradigm. On the fifth week, rats were sacrificed immediately following the last self-administration session on Friday, and the brain tissue was harvested, collected in punches and analyzed for dopamine, serotonin and norepinephrine via HPLC. Blood was also collected throughout the 96-hour sessions to monitor levels of MA. Female rats showed an increase in nucleus accumbens dopamine compared to saline-treated rats. These results suggest that our 96-hour paradigm is both behaviorally and neurochemically relevant to human MA use. This model could lead to more translatable research involving MA abuse and treatment.

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Treatment needs of driving while intoxicated offenders: A multi-component treatment model

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Driving while intoxicated (DWI) is a major source of mortality; in 2012, Texas had the largest increase in crash fatalities involving alcohol impaired drivers. In addition, Texas ranked 2nd in the US in terms of the number of alcohol related driving arrests (DWI, DUI, etc). The majority of alcohol related driving fatalities have been attributed to repeat DWI offenders and it is estimated that approximately 1/3 of all convicted drivers are repeat offenders. In the course of developing a novel intervention aimed at reducing DWI recidivism we first conducted an assessment in order to identify the treatment needs of this population. We conducted interviews with 60 adults recruited from the community and 59 adults recruited from a forensic residential substance abuse treatment facility for adults on probation, all of whom had at least one DWI arrest. Analyses demonstrated overall high rates of alcohol use disorder (AUD) diagnoses and an increased likelihood of multiple substance use disorder diagnoses within the residential sample. Variations between the two samples in terms of motivation for treatment, drinking related locus of control, negative alcohol expectancies and consequences of alcohol use will be presented. Components of a treatment model aiming to address the varying needs and stages of adjudication will be discussed.

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Characterization of an intravenous nicotine discriminative stimulus in rhesus monkeys

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In general, the discriminative stimulus effects of drugs are examined following subcutaneous, intramuscular, or intragastric administration. These procedures may not be completely predictive of the effects of drugs that are abused by other means; nicotine, for example, is primarily inhaled in the form of cigarette smoke. In the present study, drug discrimination was used to examine the effects of nicotine administered intravenously at a training dose of 0.032 mg/kg in rhesus monkeys (n=4) responding under a fixed ratio 5 schedule of stimulus-shock termination. The ED_{50} value (95% confidence limits) of nicotine to produce discriminative stimulus effects was 0.0067 (0.0052-0.0087) mg/kg. Time to peak effect of the training dose (0.032 mg/kg) was less than 1 min and the duration of action was less than 10 min. Subcutaneously administered nicotine (1.78-5.6 mg/kg) did not mimic the effects of nicotine discriminated intravenously. The non-competitive nicotinic acetylcholine receptor antagonist mecamylamine (1 mg/kg) produced a minimum 15-fold shift in the nicotine dose-effect function. When combined with the training dose (0.032 mg/kg) of nicotine, mecamylamine dose-dependently decreased discriminative stimulus effects; the ED_{50} value (95% confidence limits) of mecamylamine to attenuate the effects of nicotine was 0.13 (0.07-0.23) mg/kg. Collectively, these results both suggest that the discriminative stimulus effects of intravenous nicotine are mediated by nicotinic acetylcholine receptors, and demonstrate that the effects of nicotine vary qualitatively as a function of the route of administration. Route of administration should be considered in evaluating the predictive validity of nicotine discriminations for the effects of cigarette smoking.

Poster Communications

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Activation of stress systems in the nucleus accumbens promote anxiety-like behavior produced by nicotine withdrawal in female rats

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Pre-clinical studies in our laboratory have revealed that female rats display more anxiety-like behavior than males during nicotine withdrawal. Female rats also displayed a larger up-regulation of stress-associated genes in the nucleus accumbens (NAcc), a brain region that modulates nicotine reward and withdrawal. The present study examined the functional significance of these sex differences in corticotropin releasing factor (CRF) gene expression in the NAcc during withdrawal. To address this issue, we compared anxiety-like behavior following intra-NAcc infusions of CRF in female and male rats experiencing nicotine withdrawal. Rats were surgically implanted with bilateral guide cannula in the NAcc and an osmotic pump that delivered nicotine for 14 days. On the test day, separate groups of rats received intra-NAcc administration of CRF (0, 0.5 or 1.0 μg) and systemic administration of the nicotine receptor antagonist mecamylamine (1.5 mg/kg) to precipitate withdrawal. Rats were then assessed for anxiety-like behavior on the elevated plus maze and light/dark transfer tests. The results revealed that intra-NAcc infusions of CRF increased anxiety-like behavior produced by nicotine withdrawal, and this effect was larger in females as compared to males. Taken together, our findings suggest that CRF systems in the NAcc play an important role in promoting anxiety-like behavior produced by nicotine withdrawal in females.

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Adult male mice pretreated with fluoxetine during adolescence exhibit an enhanced behavioral response to cocaine.

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Pediatric depression was not well recognized until relatively recently. Now we know that major depressive disorder (MDD) exists in children and adolescents, that it is also a common condition, and that it can have negative consequences that often extend into adulthood. It is estimated that children and adolescents who suffer from MDD are likely to develop conduct and anxiety disorders, and that 20-25% eventually develop substance abuse disorder. Consequently, this has resulted in a disproportionate increase in the prevalence of antidepressants prescribed to populations below 20 years of age. Despite the heightened rates in antidepressant use, little is known about the long-term clinical and neurobiological adaptations resulting from antidepressant treatment during periods prior to adulthood. To address this issue at the preclinical level, we examined whether Fluoxetine (Prozac) exposure during adolescence results in long-lasting changes in sensitivity to the rewarding effects of cocaine. To do this, male C57BL/6 mice were exposed to Prozac (20 mg/kg) during adolescence (postnatal days [PD] 35-49) and were later assessed in adulthood (PD 70+) on behavioral responsivity to cocaine (0, 2.5, 5, 10, or 20 mg/kg) place conditioning (CPP). Our results show that adult mice pre-treated with Fluoxetine during adolescence (PD35-49) displayed enhanced preference for environments previously paired with moderately low doses of cocaine (5 or 10 mg/kg), when compared to saline pre-treated controls.

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Levo-tetrahyrdopalamtine (l-THP) and low dose naltrexone (LDN): A novel combination therapy for the prevention of cocaine relapse.

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Abstract: **Background:** It has been established that long term use of cocaine induces alterations in the mesolimbic dopaminergic pathway which can lead to development of addiction; however evidence suggests that the alterations to the endogenous opioids also could play a role in the pathophysiology of cocaine addiction. Taken together this suggests that a combination relapse prevention medication, targeting both the dopaminergic and endogenous opioid systems, would be more efficacious at preventing relapse. The combination of l-THP and LDN is intended as a therapeutic agent for cocaine addiction, primarily targeting both dopamine and opioid receptors. **Methods:** C57-BJ6 mice and Wistar rats were used in the conditioned place preference and self-administration paradigms, respectively, to assess the combination of l-THP and LDN in preventing drug seeking behavior during cocaine reinstatement. Mice were used to determine l-THP and LDN effect on locomotion and in naltrexone induced withdrawal. **Results:** We found that combination of l-THP and LDN attenuates cocaine self-administration in rats as well as attenuates cocaine seeking behavior in conditioned place preference mice. The combination of l-THP and LDN also decrease the sedative effect caused by l-THP. **Conclusion:** We conclude that the combination of l-THP and LDN could be a more effective and safe medication for cocaine relapse prevention with high potential for translation to the clinical setting.

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The behavioral economics of effort: The unspecified role of the sub-criterion response.

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Although response effort is considered a dimension of the cost to obtain reinforcement, little research has examined the economic impact of effort on demand for food. The goal of the present study was to explore the relationship between effort and demand. Three Sprague Dawley rats were trained to press a force transducer under a series of fixed-ratio schedules (1, 10, 18, 32, 56, 100, 180, 320, and 560) under different force requirements (5.6 g, 18 g, and 56 g). Thus, we maintained a constant nominal unit price (responses / food) but varied the minimal response force. Using a force transducer allowed us to measure responses failing to meet the minimal force requirement (i.e. "sub-criterion responses"), an advantage over prior approaches using weighted levers to manipulate effort. Results showed that demand assessments were reliable at each force requirement. Consistent with prior research, increasing the unit price decreased food consumption, and raising minimum force requirements further reduced demand for food. Additionally, increasing the force requirement increased the number of sub-criterion responses. The increase in sub-criterion responses raises the question of whether previous reports of force-related decreases in food demand result from the force manipulation or from incidental changes in the sub-criterion class.

Poster Communications

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Effects of repeated intermittent restraint stress followed by amphetamine exposure on the development and expression of locomotor sensitization in adult male rats

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Locomotor sensitization often results from repeated intermittent exposure to psychostimulants, and previous research has shown that prior exposure to stress induces cross-sensitization to psychostimulants. Few preclinical studies have explored the effects of simultaneous exposure to stress and a psychostimulant during the development of sensitization. The purpose of the present study was to implement both of these conditions during the induction period to evaluate the effects on the development and expression of locomotor sensitization to amphetamine (AMPH). Adult male rats were divided into non-restraint (NR) and restraint stress (RS) groups: NR+saline (SAL); RS+SAL; NR+AMPH; and RS+AMPH. Intermittent restraint stress was implemented twice a day under a variable interval schedule (days 1, 2, 4, 7, and 8). Injections of AMPH (1.5mg/kg) or SAL were administered following the second stress session of each day. Animals in all groups were challenged with 0.5mg/kg AMPH after a 2-day and 2-week wash out period. Locomotor activity was monitored following dosing on day 1 and 8 and after each challenge dose. Horizontal activity and stereotypy were significantly greater on day 8 compared to day 1 in the NR+AMPH group, whereas vertical activity was significantly greater in the RS+AMPH group. Findings following the challenge doses were limited to significant differences in vertical activity following the 21-day washout period with greater activity in those animals in the NR+AMPH group followed by RS+AMPH group compared to the NR +SAL group. Additionally, animals that were previously exposed to restraint stress (RS+SAL) exhibited less vertical activity following a challenge dose compared to animals previously exposed to AMPH (NR+AMPH). These results suggest that during the development of sensitization to AMPH, various measures of behavior may be differentially affected under conditions of stress. Findings revealed that repeated intermittent stress exposure prior to an AMPH challenge produced a diminished locomotor response compared to repeated intermittent AMPH exposure, and a combination of the two conditions does not necessarily procedure an additive effect on the expression of sensitization.

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The rewarding effects of nicotine and the aversive effects of withdrawal from this drug are enhanced in hypoinsulinemic rats.

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Tobacco use is maintained by a balance between the rewarding effects of nicotine and avoiding the aversive effects of withdrawal. It is presently unclear how nicotine reward and withdrawal contribute to nicotine dependence in patients with metabolic disorders, such as diabetes. To address this issue, the present study employed a rodent model of diabetes involving streptozotocin (STZ) administration. STZ destroys insulin-producing cells in the pancreas and produces high glucose levels (above 500 mg/dL). Fourteen days after STZ or vehicle administration, we compared nicotine reward and withdrawal using place conditioning procedures. Rats were first tested for their initial preference for either of 2-distinct compartments. Conditioning was conducted over 8 days. In the reward study, rats received nicotine and were confined to their initially non-preferred compartment. On alternate days, they received saline in their initially preferred side. In the aversion study, the rats were first implanted with subcutaneous pumps that delivered nicotine for 14 days. Once the rats were dependent on nicotine following 7 days of exposure, the rats received repeated administration of the nicotinic receptor antagonist mecamylamine to precipitate withdrawal in their initially preferred compartment. On alternate days, they received saline in their non-preferred side. Following conditioning, rats were re-tested for preference behavior. The results revealed that STZ-treated rats displayed a dose-dependent enhancement of nicotine reward versus controls. Also, STZ-treated rats displayed greater aversive effects of withdrawal versus controls. Taken together, our findings of greater nicotine reward and withdrawal provide a basis for greater vulnerability to tobacco use in patients with metabolic disorders, such as diabetes.

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D4 receptor antagonist L-745,870 improves performance in executive functioning task after repeated amphetamine exposure.

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The attentional set shifting task (ASST) is a rodent analog of the Wisconsin Card Sorting Task (WCST) which measures executive functioning. The ASST tests for reversal of stimulus-response learning and the formation and maintenance of attentional sets. Depletion of dopamine has been show to improve performance on attentional shifts. The study presented here questioned if a D4-specific antagonist, L-745,870, could have a similar effect on animals treated with repeated doses of amphetamine. Three groups of rats (N=8 each) were given either 10 saline injections, 10 amphetamine injections (2 mg/kg), and 10 amphetamine injections plus one pretreatment injection of L-745,870 (.2 mg/kg) twenty minutes prior to testing. The rats were tested in a series of trials where they must dig to obtain food in a flower pot. Each pot has a specific scent or a digging medium but only one perceptual dimension signals reward. In each stage, the rule is either reversed from the previous stage or switches to a previously irrelevant perceptual dimension. Each stage is completed when the animal gets six correct responses in a row. The number of trials needed to reach completion is analyzed for overall performance. One-way ANOVA results showed that amphetamine only rats were significantly impaired in all three reversals compared to the control and L-745,870 treated rats (all $p<.01$). Amphetamine only rats required more trials to reach criterion in each reversal (M=19, 16.4, 17.1) compared to L-745,870 treated rats (M=9.8, 10.9, 9.6) and controls (M=8.6, 9.6, 9.3). The results imply that dopamine depletion, or specifically blocking of D4 receptors, can improve performance in reversals even after being affected by chronic drug exposure.

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Differential generalization among nicotinic acetylcholine receptor agonists in nicotine, varenicline, and epibatidine drug discriminations in mice.

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In addition to a nicotine discrimination assay, two novel nicotinic acetylcholine receptor (nAChR) agonist discriminations were established to examine the relative contribution of nAChR agonist efficacy to behavioral effects. Male C57Bl/6J mice were trained to discriminate nicotine (1 mg/kg), the low efficacy nAChR agonist varenicline (3.2 mg/kg), or the high efficacy nAChR agonist epibatidine (0.0056 mg/kg) from saline. Nicotine produced a maximum effect of 86% and 82% drug-appropriate responding in the nicotine and varenicline discriminations, respectively. In mice trained to discriminate epibatidine, nicotine produced 84% drug-appropriate responding, but at a dose that reduced the rate of responding to 19% of control. Varenicline produced 95% drug-appropriate responding in the varenicline discrimination, but only a maximum of 46% and 70% drug-appropriate responding in the nicotine and epibatidine discriminations, respectively. A t-test showed that the maximum effect for varenicline was significantly lower ($p<0.05$) in the nicotine discrimination than in the varenicline discrimination. Epibatidine produced no less than 90% drug-appropriate responding in all three discriminations. These data suggest that the discriminative stimulus effects of nAChR agonists vary as a function of the efficacy of the training drug. That nicotine only substituted for epibatidine at a dose of nicotine that markedly decreased response rate might suggest that epibatidine and nicotine have overlapping, but not identical, in vivo effects.

Poster Communications

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Effects of consuming diets high in fat and/or sugar on the locomotor-stimulatory effects of acute and repeated cocaine in male and female C57BL/6J mice.

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There is a growing body of evidence that shows diets high in sugar or fat alter behavioral effects of drugs acting on dopamine systems. It is thought that the neurobiological mechanisms underlying locomotor sensitization to stimulant drugs are also involved in the potential of these drugs for abuse, and as such diet-induced increases in locomotor sensitization might predict an increased vulnerability to abuse these drugs. This study examined whether mice (n=8 per group) maintained under one of four dietary conditions [(1) standard diet (5.8% fat by weight) + water; (2) standard diet + 10% sucrose solution; (3) high-fat diet (34.3% fat by weight) + water; or (4) high-fat diet + 10% sucrose solution) differed with respect to their locomotor responses to acute cocaine (week 4) or to the development of locomotor sensitization across three additional weekly cocaine tests (weeks 5-7). During the acute cocaine tests (week 4), the minimal effective dose of cocaine to increase locomotor activity was smaller for mice maintained under the high-fat diet + sucrose or standard diet + sucrose conditions than those maintained under the standard diet. These diet-induced increases in sensitivity to cocaine persisted with repeated testing, and area under the curve analysis revealed significant effects of diet and a significant interaction between diet and sex on total cocaine-induced activity. In males, the diet-induced enhancement of the effects of cocaine appeared to be primarily due to the consumption of the high-fat diet, whereas in females the consumption of the high-fat diet or the sucrose solution resulted in an enhancement of the effects of cocaine. These results suggest that diet alters the locomotor effects of cocaine in mice in a sex dependent manner.

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Chronoamperometry Study of the Sparing of Motor and Cognitive Function in the Hemiparkinsonian Rat by Amphetamine Sensitization

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Methodological advances in electrochemical analysis have granted researchers a powerful tool allowing previously unattainable temporal and spatial precision in neurotransmitter detection. Chronoamperometry is one such technique that allows for the measurement of dopamine (DA) on a sub-second timescale. Our lab is currently in the beginning stages of the fabrication of chronoamp electrodes and is determining optimal specifications for DA detection. Performance of electrodes depend on delicate care during construction and vary via city climate, as a result of this we are in the process of 1) Mastering the general skills involved in electrode fabrication and 2) Establishing a set procedure for consistent reliable DA detection. This has involved manipulations in carbon fiber electrode length and electrode coating, which improves selectivity for DA but also reduces detection response time. Once we have met our preliminary goals of exceptional electrochemical DA detection we will implement this tool to investigate the neural plasticity produced by the enduring effects of amphetamine sensitization as potential mechanism(s) to strengthen the weakened dopaminergic circuits in a Parkinsonian animal model. We predict that insights from our planned research will serve to improve motor and cognitive function in human Parkinson's patients.

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The effect of a high fat diet on the sensitizing response to methamphetamine during adolescence in male and female rats.

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Evidence suggests that diet can modulate the effects of drugs of abuse. For example, adult rats given access to a high fat diet are more sensitive to the locomotor stimulating effects of methamphetamine (METH). In addition, adolescent and adult female rats given access to a high fat diet are more sensitive to the locomotor stimulating effects of cocaine. Despite these efforts, little research has examined the effect of a high fat diet on the locomotor sensitizing response to drugs of abuse in adolescent rats. In the present study, male and female rats were fed a standard or high fat diet beginning on postnatal day (PD) 21 and for the remainder of the study. Behavioral testing began on PD 31, during which rats received daily intraperitoneal (IP) injections of either saline or METH (1.0 or 3.0 mg/kg) for 10 consecutive days (PD 31-40) immediately before locomotor activity was assessed for 30 min. Following two abstinence days (PD 43), all rats then received a challenge injection of METH (1.0 mg/kg, IP) to assess for behavioral sensitization. Results show that male and female adolescent rats chronically treated with METH showed an elevated behavioral response compared to controls, however the locomotor activity did not increase across pretreatment days nor was it modulated by a high fat diet. During testing, rats chronically treated with METH exhibited behavioral sensitization compared to rats given an acute injection of METH. Contrary to our expectations, rats given a high fat diet were not more responsive to the behavioral sensitizing effects of METH. These data suggest that high fat diet given for only two weeks does not influence the development of METH behavioral sensitization in adolescent rats.

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The impact of methylphenidate on the reinforcing effects of methamphetamine and dopamine transporter activity.

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Psychostimulants, such as methylphenidate (MPD), are clinically effective in treating attention-deficit/hyperactivity disorder. However, the increase in MPD prescription rates and availability has raised public health concerns for misuse and recreational abuse among adults in general, and college students in particular. The majority of preclinical studies investigate whether therapeutically relevant doses of MPD alter sensitivity to the reinforcing effects of other drugs, but it remains unclear whether doses of MPD exceeding therapeutic relevance impact the reinforcing effects of drugs. Thus, the current study trained male, Sprague-Dawley rats to self-administer MPD (0.56 mg/kg/infusion for 7 days) and examined the subsequent (i.e. 2 weeks after last MPD administration) impact on the reinforcing effects of methamphetamine (METH) and striatal dopamine transporter (DAT) function. In order to test the specificity of these effects, it was also determined whether MPD alters subsequent responding for a non-drug reinforcer (i.e. food). For comparison, the impact of a therapeutically relevant dose of MPD (2 mg/kg/injection/day for 7 days) on the reinforcing effects of METH was evaluated. Results indicate that only a history of self-administering MPD increased sensitivity to the reinforcing effects of METH. Furthermore, and regardless of drug history, MPD did not alter food-maintained responding or striatal DAT function. Taken together, these data suggest that the non-medical use of MPD increases the abuse liability, and perhaps for an extended period, of other related drugs.

Poster Communications

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Interactions between diet and exercise on the locomotor effects of acute and repeated cocaine administration in mice.

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Mice consuming a diet high in fat have been shown to develop insulin resistance and exhibit enhanced locomotor responses to acute and repeated cocaine administrations. The current study investigated the effectiveness of voluntary exercise (wheel running) to modify insulin sensitivity and the development of sensitization to the locomotor-stimulating effects of cocaine in adult male CJ57BL/6J mice consuming either a standard laboratory diet (17% kcal from fat), or a high-fat diet (60% kcal from fat). Eight mice were assigned to each dietary condition; four mice from each group provided 24-hr/day access to a running wheel whereas the other four mice were never provided access to a running wheel. Mice that consumed the high-fat diet gained more weight and had higher fasting blood glucose levels than mice that consumed the standard diet. Allowing mice to run on a wheel reduced the rate of weight gain in mice that consumed the high-fat, but not the standard diet, and lowered fasting blood glucose levels, regardless of dietary condition. Although the dose-response curves for acute cocaine (3.2-32.0 mg/kg) did not differ as a function of diet or wheel running, differences among the groups began to emerge with repeated testing. Most notably, wheel running reduced the rate at which sensitization to the locomotor effects of cocaine developed in mice that ate the standard diet; however, wheel running did not alter the development of sensitization in mice consuming the high-fat diet. Results of these studies provide additional evidence that wheel running reduces the abuse-related effects of cocaine in animals maintained under standard laboratory conditions, however, they also suggest that wheel running does not prevent the development of a sensitized locomotor response to cocaine in mice consuming a high-fat diet.

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Oxycodone Induces an Array of Xenobiotic Receptors, Transporters and Drug Metabolizing Enzymes in Brain and Liver Tissues of Rats

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Perturbations of the expression of transporters and drug-metabolizing enzymes (DMEs) by opioids can be the locus of deleterious drug-drug interactions (DDIs). Many transporters and DMEs are regulated by xenobiotic receptors (XRs) [e.g., Pregnane X receptor (PXR), Constitutive androstane receptor (CAR) and Aryl hydrocarbon receptor (AhR)]; however, there is a paucity of information regarding the influence of opioids on XRs. The objective of this study was to determine the influence of oxycodone administration (15 mg/kg i.p. b.i.d/8 days) on brain and liver expression of XRs, transporters and DMEs in rats. Microarray, quantitative RT-PCR and immunoblotting analyses were used to identify significantly regulated genes. Many XRs (e.g. PXR, CAR and AhR), transporters (e.g., Abcb1, Slc22a8) and DMEs (e.g., Cyp2b2, Cyp3a1) were regulated ($p<0.05$) with fold changes (FC) ranging from -46.3 to 17.1. Using MetaCore™ (computational platform), we identified a unique gene-network of transporters and DMEs assembled around PXR, CAR, and AhR. Taken together, these findings identify signature gene-networks associated with repeated oxycodone administration in rats and demonstrate that oxycodone regulates the expression of many transporters and DMEs which could lead to undesirable DDIs upon co-administration of substrates of these transporters/ DMEs with oxycodone.

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The transcriptomic study of environmental enrichment and cocaine-taking behavior in rat.

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Environmental enrichment produces a protective addiction phenotype in rats. Previous study suggests that rats reared in enriched condition (EC) have less cocaine taking behavior compared to rats reared in an isolated condition (IC). However, the mechanism of the protective effect is still not fully understood. Hence, the goal of this study is to investigate differentially regulated mRNA in rat nucleus accumbens (NAcc) under the effect of environmental enrichment and cocaine using next generation high-throughput RNA sequencing. After primary data processing, over 14,000 transcripts were quantified in this experiment. In addition to Ingenuity Pathway Analysis (IPA), Gene Set Enrichment Analysis (GSEA) was applied to studying the transcription factors, and comparing our gene list with Gene Ontology (GO) and curated lists from publications. We found that under the effect of environmental enrichment, transcription factors, mitochondrial function and Akt pathways are significantly regulated in NAcc. On the other hand, a number of functions and pathways were regulated by cocaine, such as AP-1 pathway, translation initiation, oxidative stress response, etc. In conclusion, the result suggests that the protective phenotype of environmental enrichment is involved in regulation of many important molecular pathways in nucleus accumbens.

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Unique regulation of peripheral kappa opioid receptor (KOR) function by the protean ligand, norBNI.

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KOR is known to regulate cellular signaling cascades including c-Jun N-terminal Kinase (JNK). We have found that norBNI, a prototypical KOR “antagonist”, has “agonist” activity towards JNK, leading to long-term reduction in some aspects of KOR function in peripheral pain-sensing neurons. Using a rodent behavioral model of nociception, we have found that KOR-mediated peripheral antinociception is abolished 2 and 7 days following a single intraplantar injection of norBNI. This effect was blocked by pre-injection of a selective JNK inhibitor, SP600125. Treatment of pain-sensing neurons in culture with norBNI for 1h, followed by washing, eliminated KOR-mediated inhibition of adenylyl cyclase, measured 24h later, which was blocked by SP600125. However, KOR-mediated activation of extracellular signal-regulated kinase (ERK) was unaffected by norBNI treatment.

Since JNK is a well-known activator of transcription factors, ultimately leading to protein synthesis, we sought to determine if protein synthesis is required for the long-term effects of norBNI. Prior treatment with the protein synthesis inhibitor, cycloheximide, eliminated effects of norBNI, suggesting that increased synthesis of an unknown protein leads to prolonged reduction in some KOR-mediated responses. These data provide strong evidence that norBNI is a protean ligand which has powerful capacity to regulate peripheral KOR function.

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Poster Communications

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Design and Synthesis of Small Molecule Haptens and Development of Nanofiber-Based Vaccines Against Cocaine Addiction

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Cocaine abuse and dependence remain one of the greatest challenges on the public health agenda in the USA and there are ~1.4 million current users aged 12 or older in 2011. Cocaine is also cited as the most common cause of drug-related medical emergencies and costs a staggering 500 billion dollars annually. There are currently no FDA-approved medications for cocaine addiction and therapies that would reduce the amount and rate of its entry into the brain, and interrupt its rewarding effects are urgently needed. Early clinical studies suggest a role for active vaccination to prevent relapse to drug use in abstinent users who voluntarily enter treatment. However, a primary limiting factor to their success appears to be the degree of immunity evoked by the cocaine antigen and lack of efficient delivery vehicles. Higher than average titers that those currently produced, are essential for vaccines to become a viable treatment option. The chemical positioning of a linker to the target antigen is crucial for proper immune stimulation both in terms of amount of antibody elicited and antibody specificity. Here, we will present design and chemical synthesis of novel cocaine-based small molecule haptens tethered with unique functionalities that could be conjugated with a peptide nanofiber-based delivery platform for efficient induction of anti-cocaine antibodies. In preliminary studies we synthesized a synthetic cocaine analog carboxylated at the P3 site and conjugated it to the self-assembling peptide KFE8. The cocaine-KFE8 fusion assembled into nanofibers in physiological buffers and, when injected into mice, raised cocaine-specific antibodies. The efficacy of these novel synthetic vaccines to blunt the effects of cocaine in behavioral animal models of addiction is under the assessment. Thus, this interdisciplinary project coupling new chemistry and vaccine delivery strategies has the potential to achieve the goal to maintain abstinence and promote relapse prevention in cocaine addicts. (Supported by R21 DA036663 and Center for Addiction Research, UTMB).

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Drinking sucrose enhances sensitivity of rats to the behavioral effects of the dopamine D_2/D_3 receptor agonist quinpirole.

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Increased consumption of foods high in fat and sugar contribute to the current worldwide obesity epidemic. Sensitivity to the behavioral effects of drugs acting on dopamine systems is increased in rats eating a high fat diet or drinking sucrose solution. The current studies were designed to test whether continuous access to sucrose is necessary to increase sensitivity to drugs acting on dopamine receptors, or if intermittent access is sufficient. These studies also tested whether sensitivity to behavioral effects of quinpirole increases in rats drinking the non-caloric sweetener saccharin. Quinpirole-induced yawning dose-response curves (0.0032-0.32 mg/kg) were determined once weekly in rats drinking water, 10% sucrose solution or 0.1% saccharin solution. Rats either had continuous access to water, sucrose or saccharin, or had access to sucrose or saccharin for 2/7 days per week (with access to water on the other 5/7 days). Rats had free access to standard laboratory chow for the duration of the experiment. With increasing doses, quinpirole increased then decreased yawning resulting in an inverted U-shaped dose-response curve. Pretreatment with the selective D_3 antagonist PG01037 shifted the ascending limb of the quinpirole dose-response curve to the right, while pretreatment with the selective D_2 antagonist L741626 shifted the descending limb to the right. Continuous access to sucrose enhanced sensitivity to quinpirole-induced yawning. Specifically, the ascending (D_3 receptor-mediated) limb of the quinpirole dose-response curve was shifted to the left. That drinking sucrose solution increased sensitivity of rats to a dopamine receptor agonist might indicate that sensitivity to, and therefore vulnerability to abuse, drugs that act indirectly on dopamine receptors (e.g., cocaine) might also be increased by consumption of a high sugar diet. This work was supported by T32DA031115 and K05DA17918.

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Selective enhancement of cue-induced motivation in obesity prone vs. resistant rats is accompanied by sensitization to cocaine and increased striatal AMPA receptor expression.

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In humans, exposure to cues associated with food can increase ratings of desire to eat, and the amount of food consumed. Similarly, in rodents food-cues can elicit approach, reinforce operant responding, and increase food consumption. Recent studies suggest that obesity prone people are more susceptible to these motivational effects of food-cues. In addition, exposure to food-cues activates the striatum more strongly in obese vs. non-obese people, even prior to weight gain. This differential activation may be driven in part by differences in AMPAR levels as they provide the main source of excitation in the striatum, play a role in behavioral responses to food-cues, and are increased after exposure to sugar. In addition, exposure to sucrose and the development of obesity produce cross-sensitization to psychostimulant drugs, consistent with enhanced sensitivity of mesolimbic systems.

Here, we examined interactions between susceptibility to obesity and 1) motivation for cues paired with sugar, 2) cross-sensitization to cocaine, and 3) enhanced expression of AMPARs in the striatum. We found that both obese "junk-food" diet fed and selectively bred obesity-prone rats were more willing to work for a presentation of a cue paired with sucrose compared to non-obese "junk-food" diet fed and obesity-resistant rats. In addition, obese and obesity-prone rats were sensitized to cocaine compared to non-obese and obesity-resistant rats. In outbred obese rats, sensitization was seen after "junk-food" diet was removed and rats were given ad lib access to standard lab chow for 2 weeks, whereas sensitization was evident in selectively bred obesity prone vs. resistant rats without any diet manipulation. Surface expression of the AMPAR subunit GluA1 was increased in the nucleus accumbens (NAc) of obese vs. non-obese outbred rats, while GluA2 protein expression remained unchanged. These data are discussed in light of potential overlaps between drug abuse and obesity.

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Effects of 2,5-dimethoxy-4-methylamphetamine (DOM) on two different measures of impulsivity in rats

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The serotonin (5-HT) system has been implicated in modulation of impulsive behavior. For example, 5-HT_{2A} receptor antagonists decrease premature responding in the 5-choice serial reaction time task (5-CSRTT), an effect thought to reflect a decrease in impulsive action. If antagonism at 5-HT_{2A} receptors decreases impulsive behavior, then increasing activity at 5-HT_{2A} receptors (e.g. by administering an agonist) should increase impulsive behavior. However, little is known about the effects of 5-HT_{2A} receptor agonists on impulsivity. The current experiment examined the effects of the 5-HT_{2A} receptor agonist 2,5-dimethoxy-4-methylamphetamine (DOM) on two types of impulsivity: impulsive action, quantified by premature responses in the 5-CSRTT, and impulsive choice, quantified by the preference for smaller, immediate reinforcers over larger, delayed reinforcers in a delay discounting procedure. In one group of rats responding under the 5-CSRTT, DOM (0.1-1.0 mg/kg) had no effect on premature responses up to doses that increased omissions, suggesting no change in impulsive action. In another group responding under a delay discounting procedure, DOM dose-dependently increased choice for the smaller, immediately available reinforcer and increased omissions at the highest dose, suggesting an increase in impulsive choice. Differing results in these paradigms suggest that DOM selectively modulates impulsive choice (delay discounting), possibly by increasing activity at 5-HT_{2A} receptors but has no impact on impulsive action. Supported by NIH grants T32DA031115, F32DA035605, and K05DA017918.

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Sex, chronic drug exposure, cognition and the dopamine D3 receptor

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Chronic cocaine (COC) and methamphetamine (MA) exposure can cause neuroadaptations in the dopamine system, especially the D2-like superfamily, including the D_3 receptor (DRD3), a subtype of the D2-like family. However, most studies have utilized male subjects. Recently, we found sex differences in the relationship between D2-like receptors and vulnerability to cocaine self-administration (SA). One aim of the present study was to determine the effects of quinpirole (QNP), a preferential DRD3 agonist, in drug-naïve male and female rhesus monkeys. QNP-elicited yawning was characterized as an inverted U-shaped function of dose; significant sex differences were noted with QNP being less potent and eliciting fewer yawns at lower doses in females. Next, we examined the effects of chronic COC (n=3) and MA (n=3) exposure on sensitivity to QNP in male monkeys. Monkeys with a MA SA history were more sensitive to the behavioral effects of low doses of QNP vs. controls, whereas COC SA monkeys were not significantly different than controls. Finally, using PET imaging with the radioligand [^{11}C]PHNO ([^{11}C]-(+)-propyl-hexahydro-naphtho-oxazin), we examined the relationship between DRD3 availability and (1) QNP-elicited yawning and (2) simple discrimination and reversal performance – a measure of cognitive flexibility. Analyses revealed significant correlations between DRD3 availability and both QNP-elicited yawning and acquisition of discrimination in several regions of the brain. These findings suggest that QNP-elicited yawning is an excellent tool for examining DRD3 activity, that this receptor is critical in discrimination learning, and that both sex and drug history influence individual sensitivity to the behavioral effects of DRD3 preferring compounds. Such information will be critical in developing sex-specific treatments for drug abuse. Supported by DA012460

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Central corticosterone: A potential target for treating addiction.

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We have previously demonstrated that a combination of drugs (i.e., metyrapone and oxazepam) known to attenuate HPA-axis activity effectively decreases cocaine self-administration and cue reactivity in rats. However, we did not find changes in plasma corticosterone (CORT) that matched the behavioral effects we observed, indicating that a different mechanism of action must be involved in the effects of this drug combination. In addition to activating the HPA axis, cocaine increases local CORT concentrations in discrete brain regions, including the medial prefrontal cortex (MPC). Therefore, we *hypothesized* that the combination of metyrapone and oxazepam attenuates cocaine taking and seeking by decreasing cocaine-induced increases in CORT in the MPC. Male rats were implanted with guide cannulae targeting the MPC. After the rats recovered from surgery, the microdialysis session was conducted. Rats were housed in the experimental chamber and the dialysis probes inserted into the guide cannulae the night before the session. The following day, dialysate samples were collected over a five-hour session. Baseline samples were collected for the first two hours, every 20 minutes. Samples were then collected following administration of cocaine (15 mg/kg, ip). Before injections of cocaine, rats were pretreated with either vehicle or the combination of metyrapone (50 mg/kg, ip) and oxazepam (10 mg/kg, ip). The administration of cocaine resulted in an increase in CORT in the MPC following vehicle pretreatment. This cocaine-induced increase in CORT was attenuated by the administration of the combination of metyrapone and oxazepam. Reducing cocaine-induced increases in CORT in the medial prefrontal cortex might represent a novel mechanism through which the combination of metyrapone and oxazepam produces its effects.

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Effects of a "Priming" Dose of Alcohol on Behavioral Impulsivity and Ad Lib Drinking Using a Taste Test Paradigm

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Loss of behavioral control is hypothesized to occur in biologically vulnerable individuals, and "priming" doses of alcohol are hypothesized to lead to increased alcohol consumption in binge drinkers. The purpose of the current study was to determine if an initial "priming" dose of alcohol would affect laboratory tasks of behavioral impulsivity and subsequent choices for consuming additional alcohol. Thirty-three participants (n = 19 binge drinkers, n = 14 non-binge drinkers) completed laboratory measures of behavioral impulsivity before and immediately after drinking a "priming" dose of 0.3g/kg of alcohol. Participants were then asked to complete a taste test of five 12oz beers and rate each beer. After the 90-minute tasting period, participants completed behavioral impulsivity measures one last time. A repeated measures 3 (Time) X 2 (Binge-status) ANOVA showed participants became increasingly impulsive on response initiation (IMT) and response inhibition (GoStop) impulsivity, but there were no significant binge-status effects or interactions. Examination of total within-subjects effects shows significant differences between all three IMT tasks, indicating the priming dose affected response initiation impulsivity differences. There were no significant correlations between milliliters consumed in the taste test compared to response initiation (IMT ratio) or response inhibition (GoStop ratio), but there was a significant negative correlation between volume consumed and SKIP Latency, indicating participants who drank more during the taste test had more trouble delaying rewards. Overall, we demonstrated that behavioral impulsivity increases with a "priming" dose of alcohol for response initiation, and increases with alcohol self-administration for response initiation, inhibition, and delay discounting.

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Neuromedin U Receptor 2 as a regulator of motivation for food

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Motivation for food is thought to underlie excess food intake in obese individuals. A novel regulator of motivation for food may be Neuromedin U receptor 2 (NMUR2), a highly-conserved neuropeptide receptor which influences food intake. Infusing the endogenous NMUR2 agonist, Neuromedin U, into the paraventricular nucleus of the hypothalamus (PVN) significantly decreases food consumption, while NMUR2 knockout phenotypes display hyperphagia. We hypothesize that NMUR2 signaling regulates motivation for highly reinforcing foods (e.g. high-fat diet). Previous data from our laboratory indicate that RNAi knockdown of NMUR2 in the PVN increases preference for higher-fat foods and potentiates binge eating. Progressive-ratio (PR) operant responding, a classic test of motivation, allows for an analysis of the strength of reinforcement. Successively greater numbers of lever-press responses are required in order to gain consecutive reinforcers, providing insight into the degree of motivation to gain a reinforcer, as well as the breakpoint at which animals will no longer work for the reinforcer. New studies demonstrate that the knockdown potentiates progressive-ratio (PR) operant responding for a high-fat diet, following abstinence. Treatment of wild-type rats with an intraperitoneal dose of NMU causes a decrease in PR responding; the effect is also found in NMUR2-knockdown animals, however, indicating that a PVN-specific knockdown was insufficient to abolish the phenotype. These results indicate that NMU-NMUR2 signaling can regulate the motivation for highly reinforcing foods.

Poster Communications

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Optimizing the Synthesis of UMB 425: A Novel Opioid Analgesic with Reduced Tolerance

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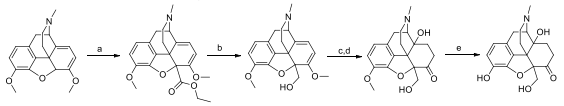
Opioid analgesics such as morphine are used for the treatment of moderate-to-severe chronic pain. The side effects associated with these drugs include respiratory depression, tolerance, physical dependence, constipation, and nausea. UMB 425 has emerged as a novel potent analgesic with less side effects than morphine. UMB 425 showed maximal antinociceptive response at comparable doses to morphine with reduced development of tolerance in mice after administration of an ED_{90} dose (2×day) for 5 days. The aim of the current project is to develop a robust process for the scale up synthesis of UMB 425 to allow pharmacological assays in other species. Temperature was found to be a critical factor in each step of synthesis. The gram scale synthesis was achieved via thebaine deprotonation using *n*-BuLi and tetarmethylethylenediamine (TMEDA) in excess (2-3 equiv.). When the reaction was quenched with NH_4Cl at -70°C the yield was optimized to 75% (step a). For the reduction of the ester (step b), LAH was used in excess and the reaction mixture was quenched with saturated Na_2SO_4 with cooling (-5°C), followed by oxidation with H_2O_2/HCO_2H (4°C) and subsequent catalytic hydrogenation (steps c,d). BBr_3 was used for 3-O-demethylation, and quenching at -40°C, furnished UMB 425 in 22% overall yield (29% based on recovered thebaine).



Reaction conditions: (a) *n*-BuLi/TMEDA, ethylchloroformate, THF, -78°C, 4h, sat. NH_4Cl, -70°C, 1h, 75% (b) LAH, THF, 0°C-rt, -5°C, sat. Na_2SO_4, 85% (c) H_2SO_4, H_2O_2, HCOOH, 4°C, 72h, 74% (d) 10% Pd/C, 1:1 ethanol/glac. acetic acid, 4h, 70% (d) BBr_3, -40°C, 3h, 66%.

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Membrane Voltage-Dependent Regulation of Dopamine Transporter Trafficking

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The dopaminergic system is essential for the function of the brain's reward, motor coordination, attention and cognitive processes whereas aberrations in dopamine (DA) neurotransmission contributes to neuropsychiatric disorders; including addiction, attention deficit/hyperactivity disorder (ADHD), Schizophrenia, and Parkinson's. DA neurotransmission timing and magnitude is dependent on how DAT regulates extracellular DA levels, but membrane surface expression of DAT is plastic. Regulation of DAT trafficking to and from the cell surface is sensitive to changes in multiple protein-protein interactions and substrate binding. However, many of the substrates and DA-related disease states linked to altered DAT trafficking also effect neural excitability. Since some cell signaling mechanisms known to alter DAT trafficking are also sensitive to changes in membrane conductance or excitability (e.g. CaMKII) themselves, their voltage-dependent activation/inhibition may change the cytosolic/membrane distribution of proteins like DAT.

Using Total Internal Reflection Fluorescence (TIRF), confocal microscopy, whole-cell patch-clamp and cell surface biotinylation, we examined the effect of changes in the membrane voltage on the density of cell surface YFP-DAT and internalization of DAT in CHO and HEK293 cells. It was found that depolarization of the cell's RMP reduces membrane surface TIRF YFP-DAT signal and increases DAT and DAT-JHC1-064 complex internalization in HEK cells and DAergic neurons. Conversely, membrane potential hyperpolarization increases membrane surface TIRF YFP-DAT density. These voltage-dependent changes in membrane surface DAT were also sensitive to CaMKII inhibition. Results indicate the sensitivity of protein trafficking to cellular electrophysiological state; providing a new mechanism dynamically regulating protein function through changes in cell surface density.

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Environmental enrichment and the role of NR4A1 (Nur77) and NR4A3 (NOR-1) in rat nucleus accumbens.

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Environmental enrichment produces a robust protective addiction phenotype. Enriched rats are exposed to novelty, social contact, and exercise and will self-administer less cocaine and amphetamine than isolated rats. We are investigating the role of NR4A1 (Nur77) and NR4A3 (NOR-1) in the nucleus accumbens in contributing to the protective addiction phenotype of environmental enrichment. It was found through Next Generation RNA sequencing that NR4A1 and NR4A3 mRNA are more highly expressed in isolated rats under basal conditions. NR4A3 mRNA is induced by cocaine in isolated and enriched rats while NR4A1 is induced by cocaine only in isolated rats. These mRNA changes were some of the most robust found with Next Generation sequencing. Using quantitative PCR analysis, we found NR4A1 mRNA peaked thirty minutes after an acute injection of cocaine while NR4A3 mRNA peaks at 60 minutes following a cocaine injection. NR4A1 and NR4A3 mRNA is induced faster and NR4A3 mRNA is induced more with repeated injections of cocaine. NR4A1 and NR4A3 are immediate early genes induced by cocaine and altered with environmental enrichment. These nuclear receptors in the nucleus accumbens may be important for the protective addiction phenotype of environmental enrichment and further work is exploring this hypothesis.

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Dose-response pattern of reward of three substituted cathinones

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Synthetic cathinones, sold online and in head shops as "bath salts," have seen a tremendous increase in popularity since 2007. Consequently, the number of cathinone-related hospitalizations has increased, hitting a peak in 2011. Although cathinone usage and hospitalization has decreased since the Synthetic Drug Prevention Act was passed in 2012, the drugs remain popular amongst young people and dance club frequenters. While the literature on synthetic cathinones has been steadily accumulating, behavioral data still remains sparse, especially in regards to abuse liability. The current study examined the dose-dependent rewarding effects of three substituted cathinones: MDAI (1, 3, 10 mg/kg), flephedrone (4-FMC, 3, 10, 30 mg/kg), and butylone (1, 3, 10 mg/kg). A biased conditioned place preference model of drug reward was utilized. For each drug, three doses between 1-30 mg/kg were administered to generate a dose-response curve. MDAI resulted in increased time on the drug-paired floor at all three doses, with 3 mg/kg yielding the largest increase. Flephedrone produced an inverted U-shaped dose-response curve with 10 mg/kg resulting in an increase in drug-paired floor time, but not 3 or 30 mg/kg. Butylone produced a dose-dependent increase in drug-paired floor time from 1 to 10 mg/kg. These results suggest that MDAI, flephedrone, and butylone produce rewarding effects. Given earlier findings that these compounds produced cocaine- and methamphetamine-like discriminative stimulus effects, they have a strong potential to be abused. Potency, efficacy, and dose-response pattern differed among the three drugs, with MDAI being the most potent, followed by butylone, then flephedrone.

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Increased risk to methamphetamine abuse after juvenile exposure to methylphenidate in late adolescent female but not male rats.

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Methylphenidate is the most prescribed psychiatric medication in children. Yet, the effects of the early and extended use of this drug, particularly when it is prescribed to preschool age children remain relatively unknown. Previous studies have demonstrated that the early exposure to methylphenidate alters the rewarding effects of drugs when animals are tested as adults. However, the effects of early methylphenidate exposure on the sensitivity to methamphetamine (METH) reward during adolescence have not been investigated. Thus, we examined the effects of early exposure to methylphenidate on the rewarding effects of METH in adolescent rats using conditioned place preference (CPP). Male and female rats were treated twice daily with methylphenidate (0, 2, or 4 mg/kg) from postnatal days 11-20, a period of development comparable to preschool age children. Rats were then assessed for METH-induced CPP, beginning on postnatal (PD) 27 (early adolescence) or PD 39 (late adolescence) using a 10-day CPP procedure. During days 1 and 10 of the CPP procedure, rats were tested for their preconditioning and postconditioning place preference, respectively, in 15-minute sessions. During days 3-8, rats were conditioned 30-minutes a day with either METH (0.1 or 0.05 mg/kg) or saline on alternating days. Days 2 and 9 were rest days. Our main findings suggest that exposure to methylphenidate alters the rewarding effects of METH across adolescence, but in a sex and age dependent manner. Late adolescent males pretreated with methylphenidate (2 mg/kg and 4 mg/kg) showed an attenuated METH-induced CPP, as only saline-pretreated rats showed CPP. In contrast, late adolescent female rats pretreated MPH (4.0 mg/kg) showed increased rewarding effects of METH, as only this group exhibited METH-induced CPP. Altogether, these results add to a growing body of literature showing that methylphenidate alters the rewarding effects of drugs of abuse. As such, the use of methylphenidate in pediatric populations should be carefully considered.

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Effect of levo-Tetrahydropalmatine on Nicotine Self-Administration in Sprague Dawley Rats

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Nicotine addiction via tobacco smoking is the leading cause of lung disease and cancer in the U.S. Though the negative consequences of nicotine use are known and documented, abstaining from nicotine use and remaining nicotine free remains a challenge for the vast majority of nicotine abusers. *l*-Tetrahydropalmatine (l-THP), a novel Chinese compound, displays utility in treatment of cocaine and heroin addiction via reduction of self-administration (SA) and reinstatement; the present study sought to extend this utility to nicotine addiction. Animals were trained to self-administer 0.03mg/kg nicotine under fixed ratio of 5. Once animals displayed consistent responding for nicotine, they were pretreated with l-THP or saline and allowed to self-administer nicotine in 2hr sessions. l-THP (5mg/kg, i.p.) significantly reduced responding for nicotine [$F_{1, 10} = 35.74$, $p<0.0001$, n=6] in comparison to saline pretreatment. After SA, extinction began; nicotine and external cues were removed. Once animals responded consistently at 25% of baseline nicotine SA, reinstatement began. Animals were pretreated with l-THP or saline, challenged with 0.3mg/kg (s.c.) nicotine, and reintroduced to pre-extinction conditions. l-THP (3mg/kg, i.p.) blocked reinstatement of nicotine responding ($p<0.01$, n=6) while pretreatment with saline did not (n=6). These results are the first to suggest utility of l-THP in treatment of nicotine addiction.

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Estimating standard alcohol units consumed using transdermal alcohol concentration readings.

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Alcohol consumption can be characterized in several ways including breath and blood alcohol concentrations and self-reports of the number of drinks consumed. However, self-reports of alcohol consumption tend to be unreliable and blood and breath alcohol concentrations only capture intoxication at one point in time. Beyond the level of intoxication, the number of drinks consumed is relevant to a person's immediate risk and long-term health consequences. Transdermal alcohol monitoring allows for objective, continuous measurements of alcohol consumption. In the current study, 46 participants each consumed 1, 2, 3, 4 and 5 beers in the laboratory on separate days while wearing transdermal alcohol monitoring devices; drinks were consumed within 2 hours. The data obtained from the transdermal alcohol monitoring devices was used to reliably estimate the number of standardized alcohol drinks consumed. After considering potentially relevant variables in statistical models, three variables were found to be critical in developing a model that could accurately estimate the number of drinks consumed. These variables include: time-to-peak transdermal alcohol concentration (or TAC), area under the TAC curve, and sex. These statistical models not only accurately predicted the number of alcohol drinks consumed in this study, but when they were applied to data collected in a separate study (Dougherty et al., 2012), we found that the number of drinks could be reliably estimated. In summary, when considered in conjunction with another study estimating breath alcohol concentrations (Hill-Kapturczak et al., submitted), transdermal alcohol monitoring devices can be used to characterize drinking in terms of intoxication level and the number of drinks consumed. Objective methods characterizing both intoxication and number of drinks consumed could be useful in research and treatment settings.

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Differential effects of the benzodiazepines alprazolam and oxazepam on methamphetamine-related behaviors in rats

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Drug users often combine benzodiazepines with psychostimulants, such as methamphetamine (METH). Previous research has shown that not all benzodiazepines have the same potential for abuse. While alprazolam (ALP) is highly preferred by drug users, oxazepam (OX) has a far lower abuse potential. We hypothesized that METH would induce conditioned place preference (CPP), while OX and ALP would block the METH-induced CPP. We hypothesized that OX and ALP would attenuate METH discrimination. CPP was conducted to study the reward potential of the benzodiazepines OX and ALP when combined with METH to simulate polydrug abuse in rats (n=8/group). To determine if ALP and/or OX would alter the subjective effects of METH, we also investigated the effects of these drugs on the discriminative stimulus effects of METH in rats (n=7/group). Rats were trained to discriminate METH (1.0 mg/kg, ip) from saline using a two-lever operant, food-reinforced, drug discrimination design. The effects of ALP (2 and 4 mg/kg, ip) and OX (5, 10, and 20 mg/kg, ip) on METH discrimination were determined by administering these drugs prior to various doses of METH (0, 0.125, 0.25, 0.5, 1, or 2 mg/kg, ip) and then measuring whether the rat pressed the METH- or saline-associated lever. Data were analyzed using one-way ANOVA. METH produced a CPP, and OX blocked this METH-induced CPP. However, ALP did not block the METH-induced CPP. OX significantly attenuated METH discrimination in rats. However, we found that the high dose of ALP augmented the subjective effects of lower doses of METH. The results of these experiments suggest that OX and ALP can differentially affect meth-related behaviors. OX attenuates the rewarding properties as well as the subjective effects of METH, while ALP may actually increase the rewarding properties of lower doses of METH. Future research will aim to identify the underlying mechanisms mediating the divergent effects of these benzodiazepines.

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Procedure-dependent effects of antagonism of nicotinic acetylcholine receptors on conditioned nicotine-seeking behavior in rat models of smoking relapse.

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Our previous studies *(Liu et al., 2007)* have demonstrated that blockade of nAChRs attenuated cue-induced reinstatement of nicotine seeking, extending the role of nAChRs in mediating nicotine primary reinforcement to nicotine-associated conditioned reinforcement. This study examined effects of pharmacological antagonism of the two major nAChR subtypes, α4β2 and α7 nAChRs, on cued nicotine seeking with an emphasis on comparison between an abstinence-only and an extinction-reinstatement procedures. 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. A nicotine-conditioned cue was established via association of a sensory stimulus (5-s tone/20-s lever light on) with each nicotine infusion. In the abstinence-only procedure, rats remained in their home cages for two weeks, whereas in the extinction-reinstatement procedure, lever responding was extinguished in ten daily sessions over a two-week period. Then, lever responses with contingent re-presentations of the nicotine cue without availability of nicotine were examined after pretreatment with antagonists at the nAChRs. In the abstinence-only rats, neither dihydro-β-erythroidine (DHβE, α4β2-selective antagonist) nor methyllycaconitine (MLA, α7-selective antagonist) altered the cue-maintained lever responses. In the extinction-reinstatement rats, however, MLA but not DHβE significantly suppressed the cue-reinstated lever responses. These results demonstrated the conditioned incentive properties of nicotine cues independent of testing procedures. Interestingly, the sensitivity of cued nicotine seeking to pharmacological blockade of nAChRs, the α7 but not α4β2 subtype, was observed in the extinction-reinstatement but not the abstinence-only procedure. The findings suggest that neurobiological changes involving α7 nAChRs may have accrued during the extinction of nicotine-reinforced responses. Further examination of the procedural differences between abstinence-only and extinction is warranted.

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Greater Exposure to Stressful Life Events During Childhood Predicts the Onset of Substance Use During Early Adolescence

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Adolescents with a family history of substance use disorders (FH+) are at increased risk for initiating substance during early adolescence (i.e., prior to age 15), relative to those without such family histories (FH-). Substance use initiation during early adolescence is associated with particularly negative outcomes, including an increased risk for later substance use disorders. Increased exposure to childhood stressors among FH+ youth may relate to their increased risk for early substance use. However, previous research in this area has not comprehensively assessed exposure to childhood stressors in FH+ youth and related it to their subsequent substance use. Participants in the present study were 305 FH+ and 81 FH- adolescents enrolled in a longitudinal study of adolescent development and substance use. Exposure to childhood stressors was assessed at age 10-12, when participants entered the longitudinal study. During the follow-up period, 60 FH+ adolescents initiated substance use prior to age 15, most commonly alcohol and marijuana. A comparison of exposure to childhood stressors at study entry indicated participants who initiated substance use before age 15 reported significantly greater exposure to childhood stressors. These results suggest FH+ youth with high exposure to childhood stressors are most at risk for initiating substance use during early adolescence. Interventions targeting this group aimed at reducing the impact of stressors may decrease substance use initiation during early adolescence.

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Positive allosteric modulators (PAMs) of the serotonin (5-HT) 2C receptor (5-HT_{2C}R) as novel therapeutics for cocaine use disorder.

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The cycling course of cocaine use disorder and relapse is tied to a multitude of cognitive processes with impulsivity (rapid unplanned reactions to stimuli without regard for the consequences) and cue reactivity (attentional bias toward cocaine-associated cues) cited as two key phenotypes that set up vulnerability to relapse even years into recovery. We recently reported that rats with the highest levels of impulsivity displayed the lowest levels of 5-HT_{2C}R protein expression in the medial prefrontal cortex (mPFC); using viral vectors to knockdown 5-HT_{2C}R expression, we confirmed that 5-HT_{2C}R loss in the mPFC leads to an aggregate increase in impulsivity and cocaine cue reactivity. These data suggest that dampened 5-HT_{2C}R signaling may play a key role in phenotypic vulnerability to relapse and that normalization of 5-HT_{2C}R function is a promising pharmacological target to promote recovery in cocaine use disorder. Here, we synthesized new chemical entities to develop 5-HT_{2C}R PAMS as a novel strategy to augment 5-HT_{2C}R signaling and suppress impulsivity and cocaine cue reactivity. Our lead compound CYD-1-79 potentiated 5-HT_{2C}R-induced Ca_i^{++} release ($p < 0.05$) and $ERK_{1/2}$ activation ($p < 0.05$), but did not alter Ca_i^{++} release when tested alone in stably-transfected 5-HT_{2C}R-CHO cells. In the 1-CSRT task, CYD-1-79 significantly decreased impulsive action ($p<0.05$). CYD-1-79 also significantly suppressed both context-induced ($p<0.05$) and cue-reinforced ($p<0.05$) cocaine-seeking. We have synthesized new chemical entities with the profile of 5-HT_{2C}R PAMs, one of which (CYD-1-79) suppressed both impulsive behavior and cocaine cue-reactivity *in vivo*. Optimization of our newly-identified 5-HT_{2C}R PAMs and further evaluation of these molecules in preclinical models will allow us to develop novel pharmacotherapies for cocaine use disorder.

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Antidepressant potential of organic cation transporter blockade: the role of norepinephrine.

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Depression is a major health problem for which most patients are not effectively treated. This underscores a need to identify new targets for the development of antidepressants with improved efficacy. Our previous studies have shown that blockade of organic cation transporters (OCTs) and the plasma membrane monoamine transporter (PMAT) with decynium-22 (D-22) can produce antidepressant-like effects, which are correlated with the ability of D-22 to inhibit serotonin (5-HT) clearance in brain, when the 5-HT transporter (SERT) is pharmacologically or genetically compromised. *In vitro* studies show that OCT3 takes up norepinephrine (NE) more efficiently than 5-HT, which raises the possibility that D-22 might enhance the antidepressant-like actions of drugs that block NE uptake via the NE transporter (NET). Using *in vivo* chronoamperometry, an electrochemical technique which allows second by second recording of extracellular biogenic amine concentrations, we show D-22 increases time to clear NE from the extracellular space, and show D-22 potentiates the effects of NET blockers venlafaxine (VEN) and desipramine (DMI) to increase clearance time of NE in the dentate gyrus and CA3 of the hippocampus. We next investigated if D-22 can enhance the antidepressant-like effects of VEN/DMI. Both VEN and DMI reduced immobility on the tail suspension test (TST), a test commonly used to assay antidepressant-like activity of drugs in mice. Unlike the enhancing effect of D-22 on increasing clearance time of NE, D-22 did not enhance the antidepressant-like effect of VEN/DMI in wild-type mice. Ongoing studies are investigating the antidepressant-like effect of D22 in SERT KO and heterozygous mice.

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Intracellular methamphetamine prevents the dopamine-induced enhancement of neuronal firing

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Dysregulation of dopaminergic system has been implicated in pathological conditions like drug addiction. Dopamine transporter (DAT) regulates dopaminergic neurotransmission in brain. Structurally similar psychostimulants, amphetamine (AMPH) & methamphetamine (METH), which are DAT substrates, compete with dopamine (DA) uptake & differentially induce DA reverse transport via DAT resulting in differential extracellular DA levels albeit by poorly understood mechanism. Here we tested the possibility that METH vs. AMPH differentially alter DAT-mediated current, firing of midbrain DA neurons and plasma-membrane microdomain distribution of DAT. We found that compared to METH or DA, extracellular AMPH caused higher increase in DAT-dependent firing of midbrain DA neurons, larger DAT-dependent inward current, that is largely sensitive to extracellular Cl^- ions. While isosmotic substitution of extracellular Na^+ ions equally decreased METH- and AMPH-mediated inward currents, isosmotic substitution of extracellular Cl^- ions caused a greater inhibition of the AMPH-induced inward current. We also examined if simultaneous or stepwise drug access to the internally accessible binding site, in addition to an externally accessible DAT binding site, is required for maximum response. We observed that upon direct dialysis into the neurons via patch-pipette, METH prevented extracellular DA-induced increase in neuronal firing and DAT current. To further understand the differences in mechanisms, we investigated the effects of AMPH and METH on membrane microdomain distribution of DAT. Compared to AMPH, we found METH increased DAT localization in the lipid-rafts and decreased the mobility of DAT. Our ongoing studies will investigate if changes in the microdomain distribution of DAT affects the neuronal excitability and DAT-mediated currents. The results potentially reveal new therapeutic approaches for the treatment of drug addiction and novel research tool to study DA neurotransmission in the brain.

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Discriminative stimulus effects of the selective imidazoline(2) receptor ligand CR4056 in rats

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ImidazolineI(2) receptors are widely distributed in the central nervous system (CNS) and have been related to pain, neuroprotection and multiple brain disorders. Recent evidence has suggested that CR4056, a novel imidazoline-2 receptor ligand, exerts a significant analgesic effect in rat models of inflammatory and neuropathic pain. However, it is unclear whether CR4056 has similar pharmacological effects with other reported I2 receptor ligands. Given the high pharmacological specificity of drug discrimination procedure, the current study attempted to train rats to discriminate CR4056 as a discriminative stimulus and conduct a preliminary pharmacological characterization of this stimulus control. Eight male Sprague-Dawley rats were trained to discriminate 10.0 mg/kg CR4056 (i.p.) from vehicle in a two-lever food-reinforced drug discrimination procedure. All rats acquired CR4056 stimulus control after 26.25±16.10 training sessions. Increasing doses of CR4056 increased responding on the drug-associated lever. Several I(2) receptor ligands (2-BFI, phenyzoline, tracizoline, RS45041, idazoxan, 3.2-75 mg·kg(-1), i.p.) all occasioned > 80% CR4056-associated lever responding. Other drugs that only occasioned partial or no CR4056-associated lever responding included the endogenous imidazoline receptor ligand agmatine (10-100 mg·kg(-1), the μ-opioid receptor agonist morphine (0.32-10 mg·kg(-1), i.p.) and methadone (1-5.6 mg·kg(-1), i.p.), the selective I(2) receptor ligand BU224 (3.2-17.8 mg·kg(-1), i.p.), the α(2)-adrenoceptor agonist clonidine (0.01-0.1 mg·kg(-1), i.p.), the monoamine oxidase (MAO) inhibitor harmane (3.2-10 mg·kg(-1), i.p.), the NMDA receptor antagonist ketamine (1-17.8 mg·kg(-1), i.p.) and the indirect dopamine receptor agonist methamphetamine (0.032-5.6 mg·kg(-1), i.p.). The α(2)-adrenoceptor antagonist yohimbine (2 mg·kg(-1), i.p.), μ-opioid receptor antagonist naltrexone (0.32 mg·kg(-1), i.p.), D2 receptor antagonist haloperidol (0.1 mg/kg(-1), i.p.) and 5-HT(2) receptor antagonist MDL100907 (0.1 mg/kg(-1), i.p.) failed to alter the stimulus effects of CR4056. Collectively, these results show that CR4056 can serve as a discriminative stimulus in rats, which demonstrated high pharmacological specificity and appears to be mediated by imidazoline I2 receptors.

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Dopamine Regulation of Disengagement in the Basal Ganglia Circuitry

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Drug dependence is the transition from recreational drug use to compulsive behaviors that eventually become habit. This idea suggests that drug addicts have problems "terminating" compulsive behaviors once they are turned into addictive habits. It has been suggested that parallel Basal Ganglia loops in prefrontal cortex influence executive control and modulate transitions in drug users from recreational and sporadic patterns to relentlessly habitual patterns. We speculate that disengagement behavior is aberrant in striatal function during drug addiction. Interestingly, one study has suggested that dopamine in the Basal Ganglia, specifically the nigrostriatal pathway, regulates engagement ("starting") and disengagement ("stopping") of movement in rats. To test this hypothesis we are training rats to walk on a treadmill in a continuous and discontinuous fashion. During treadmill walking, *in vivo* intracerebral microdialysis sampling for dopamine and its metabolites (DOPAC, HVA) are collected. Dialysate is subsequently assayed using high pressure liquid chromatography (HPLC) coupled with electrochemical detection. We predict that dopamine utilization will be greater during discontinuous treadmill walking that involves repetitive engage/disengage behavior. Such findings will provide a rationale for future studies investigating the disruption of executive control by dopamine during the relentless motor habits of drug addiction.

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Evaluation of Lisdexamfetamine ± Modafinil for Cocaine Use Disorder.

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Modafinil and sustained release amphetamine have each shown efficacy for cocaine use disorder, albeit with equivocal results. We hypothesize that a combination medications approach may be more efficacious for cocaine use disorder. The specific aim of this study is to determine the effects of treatment with lisdexamfetamine alone, and lisdexamfetamine + modafinil, versus placebo, on the subjective and reinforcing effects produced by cocaine in non-treatment-seeking individuals with cocaine use disorder. In this ongoing study, participants are being recruited from the Houston metropolitan area, meet DSM-IV criteria for cocaine use disorder, and are not seeking treatment. Participants are randomized to placebo, lisdexamfetamine (30 mg/day), or modafinil (200 mg/day) + lisdexamfetamine (30 mg/day) for 4 days. On day 4, participants complete two self-administration sessions involving 5 choices for either cocaine (20 mg/infusion) or saline. Primary outcome measures include number of choices made for cocaine/saline, and changes in subjective effects and cardiovascular measures. To date, the majority of enrolled participants (N=18) are African American males who smoke cocaine. The majority of individuals also smoke cigarettes, and use alcohol and marijuana. In comparison to saline, exposure to cocaine resulted in significantly greater choices for an infusion, increased heart rate and blood pressure, and greater self-reports of positive subjective responses (e.g., "High", "Any Drug Effect") (all p's < 0.001). To date, no medication effects have been observed among treatment groups as compared to placebo. The preliminary analyses did not reveal any significant effects produced by the test compounds; however, the group sizes are small (N~ 6/group) and data collection is ongoing (final N=20/group).

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Cholinergic transmission during nicotine withdrawal is influenced by age and pre-exposure to nicotine: Implications for teenage smoking

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Adolescence is a period characterized by enhanced tobacco use and long-term vulnerability to neurochemical changes produced by nicotine exposure. To understand the mechanisms that contribute to developmental differences in tobacco use, this study compared changes in cholinergic transmission produced by nicotine exposure and withdrawal in rats of different ages. The first study compared levels of acetylcholine (ACh) in the nucleus accumbens (NAcc) during nicotine withdrawal in adolescent, adult and adult rats exposed to nicotine during adolescence (pre-exposed adults). Following 13 days of nicotine exposure via osmotic pumps, rats were implanted with microdialysis probes in the NAcc. Dialysis samples were collected during baseline and after administration of the nicotine antagonist mecamylamine (1.5 and 3.0 mg/kg, IP). A second study examined metabolic differences in cholinergic transmission in adolescent, adult and pre-exposed adult rats. After 14 days of nicotine exposure, NAcc was dissected and acetylcholinesterase (AChE) activity compared. To examine group differences in nicotine metabolism, plasma levels of cotinine (a nicotine metabolite) were compared. Results revealed that baseline ACh was highest in the NAcc of adolescents vs. both groups of adults. During withdrawal, ACh levels in the NAcc were increased in a similar manner in adolescent and naïve adult rats, but were absent in pre-exposed adult rats. Differences do not appear to be related to nicotine metabolism, as plasma cotinine levels were similar across groups. The second study revealed that AChE activity in the NAcc was highest in adolescents vs. both groups of adult rats. In conclusion, results suggest that nicotine exposure during adolescence enhances baseline ACh in the NAcc, and that exposure to nicotine during adolescence suppresses increases in cholinergic responses during withdrawal, evidencing short- and long-term changes within cholinergic systems that may contribute to the enhanced susceptibility to tobacco use during adolescence.

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Sex differences in the reinforcing effects of morphine as a function of paclitaxel-induced chronic peripheral neuropathic pain in mice.

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Clinical management of chronic pain with prescription opioids remains a challenge due to concerns about opioid-induced dependence and addiction. Sex differences in pain sensitivity, opioid analgesia, and reinforcing effects of opioids are observed in rodents. The purpose of our study is to test the hypothesis that the presence of paclitaxel-induced chronic peripheral neuropathy will differentially alter the sensitivities of male and female mice to morphine-induced reinforcing effects. Male and female C57Bl/6 mice were trained to intravenously self-administer morphine under a progressive ratio (PR) schedule of reinforcement. Following stable responding, mice were treated with saline or paclitaxel (PAC) to determine the reinforcing effects of morphine (0.01-0.1 mg/kg/inf) as a function of chronic pain under the PR schedule. The breakpoints for morphine increased with the development of allodynia and a significant upward shift in the dose-effect curve for morphine was observed in the presence of PAC-induced chronic pain in male mice. In contrast, increases in the PR responding for morphine were observed in both the saline- and PAC-treated female groups suggesting a general increase in sensitivity to the reinforcing effects of morphine regardless of the PAC-induced pain state. The cumulative records from the self-administration sessions displayed altered pattern of drug taking behavior in the PAC-treated versus control male mice. Further, PAC-treated male mice displayed increased intake of morphine in the state of chronic pain compared to their saline-treated counterparts. These results suggest that the reinforcing effects and the motivational salience of morphine are altered by the presence of chronic pain with male mice displaying greater sensitivity to these effects compared to female mice. Overall, these results may have implications for the understanding of potential sex differences in the clinical management of pain and the gender-dependent abuse liability of prescription opioids in humans. (Supported by R01 CA129092).

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The effects of adolescent drug pre-exposure on adult use and abuse: Overview and implications.

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Data from our laboratory has demonstrated that adolescent exposure to drugs of abuse impacts the affective properties of those drugs in adulthood (as evidenced by reduced conditioned taste avoidance; CTA and increased conditioned place preferences; CPP). For example, adolescent ethanol exposure attenuates cocaine-induced CTAs in adulthood while increasing cocaine's ability to induce place preferences. Given that drug use and abuse is a function of the balance of its rewarding and aversive effects, changes in either of these affective properties are likely to increase subsequent use and abuse vulnerability. Currently, we are investigating if adolescent pre-exposure to THC affects THC-induced aversions and/or preferences in adulthood, using a combined CTA/CPP procedure that allows assessments of reward and aversion in the same animal (at the same dose, route of administration and temporal patterning of the drug). Given that THC is largely aversive in most place and taste conditioning research, we are assessing if adolescent THC exposure weakens aversions, potentiates preferences, or changes both effects. We are also interested in examining the biological mechanisms that may be underlying these effects. The kappa opioid system's suspected role in the aversive effects of THC and the CB1 receptor's probable role in preferences induced by THC may provide us with information regarding if and how both of these receptor systems may be altered by adolescent pre-exposure. Furthermore, an exploration of sex differences may further elucidate whether these effects are sex dependent, as well as describing any differences of magnitude between aversions or preferences induced by THC after adolescent exposure. This research will be discussed regarding future projects that will seek to determine sex differences in adolescence pre-exposure as well as the biological mechanisms underlying these effects and how such effect may be related to abuse vulnerability.

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Electrical Stimulation uses Sodium Channel Dependent Depolarization to Produce Exocytotic–like Dopamine release and Turning Behavior

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Rat studies have shown that with repeated cocaine exposure, neutral stimuli paired with the drug (conditioned stimuli) start to increase dopamine by themselves. This increase in dopamine is a conditioned response, which could underlie drug-seeking behavior. We predict that presynaptic mechanisms that modulate dopamine release (exocytosis) undergo plasticity with repeated drug exposure to produce this conditioned response. This current study is intended to validate that electrical stimulation can be utilized to investigate presynaptic plasticity by its ability to evoke dopamine release similar to conditioned stimuli-induced release by mimicking exocytosis. It is hypothesized that electrical stimulation evokes action potentials and thus is dependent upon sodium-channels to produce dopamine release concomitantly with turning behavior. To test this, rats received electrode and cannulae implants along the nigrostriatal pathway, and then underwent *in vivo* intracerebral microdialysis testing. Preliminary data indicate that lidocaine, a sodium channel blocker: decreased both basal and electrically stimulated dopamine release, and induced ipsiversive turning. The current data support that electrical stimulation requires exocytotic mechanisms to induce dopamine release. As a result, electrical stimulation can be used to investigate presynaptic plasticity that occurs in drug addiction.

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The microtubule-targeting agent, paclitaxel, differentially affects B_2 bradykinin receptor-expressing nociceptors

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Paclitaxel (TAX) produces debilitating peripheral neuropathy accompanied by pain. Interestingly, patients complain more frequently of increased sensitivity to cold but not hot temperatures. Thus, we hypothesize that TAX differentially damages functional subpopulations of peripheral pain-sensing neurons (i.e., nociceptors). Here, we evaluated TAX effects on bradykinin (BK) receptor-expressing nociceptors. Paw withdrawal latency (PWL) to a heat or cold stimulus was determined following TAX treatment. PWL of TAX rats to cold was decreased, whereas PWL to heat was increased, suggesting that TAX differentially affected cold- and heat-responsive nociceptors. We then evaluated PWL to cold and heat following i.pl. BK injections. As expected, BK produced a transient cold and heat allodynia in vehicle rats. By contrast, TAX treatment reduced heat, but prolonged cold allodynia. Treatment of primary nociceptor cultures with TAX produced a time-dependent, tri-phasic effect on BK-stimulated phospholipase C activity that was blocked by a B_2, but not B_1, antagonist. Taken together, these data suggest that nociceptor subpopulations are differentially sensitive to TAX. Understanding why some nociceptors are resistant to effects by TAX could reveal novel treatment/preventative strategies for chemotherapy-induced peripheral neuropathy.

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Evaluation of a mathematical model for P-gp substrates: Application to opioid receptor ligands.

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The xenobiotic efflux transporter, P-glycoprotein (P-gp) plays a role in limiting the central availability of opioid analgesics. Our overall goal is to identify and develop small molecule opioid analgesics that are not substrates of P-gp. Previous studies in our laboratories and others describe differential P-gp recognition of opioids as a function of chemical structure. Efficient development of novel, non-P-gp substrate opioid analgesics would benefit from use of a computational modeling approach. Numerous models currently exist that purport to predict P-gp substrate activity as a function of chemical structure. One such model (*PLoS One*, 2011, *6* (10), e25815) claims enhanced predictive accuracy over other methods by combining molecular physiochemical properties with automated docking (AutoDock Vina). The goal of the current project is to compare model prediction against experimentally-determined P-gp activity. The model correctly predicted P-gp substrate activity with 58% accuracy (23/40). Of those predicted incorrectly, 6 (35%) were false positives, and 11 (65%) were false negatives. No correlations were observed between incorrect prediction and cLogP or Interacting Surface Area (ISA). We conclude that this model does not accurately predict P-gp substrate activity of opioids. Future modeling studies will focus on improving accuracy of this model as it pertains to opioid receptor chemotypes.

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Evaluation of MDPV and mephedrone in rats trained to discriminate MDMA or a MDMA-amphetamine mixture.

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Reports by physicians and law enforcement agencies indicate a recent dramatic rise in the abuse of novel synthetic cathinone substances, colloquially known as “bath salts”. To date, no published studies have explored the use of drug mixtures to evaluate the behavioral effects of these substances. Drug discrimination methodology utilizing drug mixtures offers a novel approach to characterizing drugs as complex stimuli. The present study assessed the discriminative stimulus effects of the bath salt constituents 4-methylmethcathinone (mephedrone) and methylenedioxypyrovalerone (MDPV) in animals trained to discriminate 3,4-methylenedioxymethamphetamine (MDMA) or a mixture of MDMA and d-amphetamine (AMPH). Adult male Sprague-Dawley rats were trained to discriminate 1.5 mg/kg MDMA (n = 7) or a mixture of 1.5 mg/kg MDMA+ 0.5 mg/kg AMPH (n = 8) from saline. A range of doses of the training drugs, both alone and in various mixtures were tested for substitution in both groups. Additionally, MDPV (0.25-2.0 mg/kg) and mephedrone (0.25-2.0 mg/kg) were evaluated for substitution in each training group. MDMA produced dose-dependent increases in drug-lever responding with full substitution in both groups at 1.5 mg/kg. Whereas AMPH produced only partial substitution in animals trained to discriminate MDMA, AMPH appeared to overshadow the stimulus effects of MDMA in animals trained to discriminate the MDMA +AMPH mixture. Interestingly, MDPV produced differential effects between the two training conditions, with only partial substitution in the MDMA-trained rats and full substitution in the MDMA+AMPH-trained rats. However, mephedrone produced equivalent effects and overlapping dose response curves in the two training groups. These preliminary findings indicate that MDPV’s effects may be more similar to those of AMPH, whereas mephedrone may be more similar to MDMA. Further substitution tests with other psychostimulants and receptor antagonists are currently in progress to further elucidate specific receptor mechanisms mediating the discriminative stimulus effects of MDPV and mephedrone.

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Chronoamperometry Study of the Sparing of Motor and Cognitive Function in the Hemiparkinsonian Rat by Amphetamine Sensitization

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Methodological advances in electrochemical analysis have granted researchers a powerful tool allowing previously unattainable temporal and spatial precision in neurotransmitter detection. Chronoamperometry is one such technique that allows for the measurement of dopamine (DA) on a sub-second timescale. Our lab is currently in the beginning stages of the fabrication of chronoamp electrodes and is determining optimal specifications for DA detection. Performance of electrodes depend on delicate care during construction and vary via city climate, as a result of this we are in the process of 1) Mastering the general skills involved in electrode fabrication and 2) Establishing a set procedure for consistent reliable DA detection. This has involved manipulations in carbon fiber electrode length and electrode coating, which improves selectivity for DA but also reduces detection response time. Once we have met our preliminary goals of exceptional electrochemical DA detection we will implement this tool to investigate the neural plasticity produced by the enduring effects of amphetamine sensitization as potential mechanism(s) to strengthen the weakened dopaminergic circuits in a Parkinsonian animal model. We predict that insights from our planned research will serve to improve motor and cognitive function in human Parkinson’s patients.

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An assessment of the effects of norbinaltorphimine, a potent kappa opioid receptor antagonist, on Δ^9-tetrahydrocannabinol (THC)-induced conditioned taste avoidance in adolescent rats.

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Studying the mechanisms that modulate cannabinoid abuse potential in adolescents is important, given that chronic adolescent cannabis exposure has been reported to cause irreversible cognitive impairments in adulthood. Although a drug's abuse potential is thought to be mediated by the balance between its rewarding and aversive effects, little is known about the aversive effects of Δ^9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, and how these effects might vary with specific experiential and subject factors. The aversive effects of THC are mediated by the kappa-opioid receptor (KOR) system in adults; however, it is not clear whether these effects are mediated similarly in adolescents. To address this, the present study assessed the effects of the KOR antagonist, norbinaltorphimine (norBNI), on THC-induced conditioned taste avoidance in adolescent Sprague-Dawley rats. Specifically, adolescent rats were given 45-min access to a novel saccharin solution on four separate conditioning trials and were injected with either vehicle or one of four doses of THC (0.56, 1.0, 1.8 or 3.2 mg/kg) on each trial. These injections were preceded by norBNI (15 mg/kg) or equivolume vehicle. THC induced a dose-dependent taste avoidance, but norBNI had no effect on this avoidance at any dose of THC. Thus, although THC is aversive in both adolescents and adults, the mechanisms mediating this effect appear to differ between the two age groups.

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Title: Investigation into the relationship between performance on the fixed-consecutive number task and measures of cocaine addiction-like behaviors; Preliminary results.

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The goal of the present study is to determine whether performance on the fixed-consecutive number (FCN) task predicts cocaine taking and seeking behavior. Rats (n=12) were first trained on the FCN task. Briefly, rats were simultaneously presented with a "reward" lever and "chain" lever. Subjects had to first emit 8 responses on the chain lever prior to transitioning to the reward lever. A response on the reward lever prior to completion of a full response chain was punished with a time-out period. Such premature responses on the reward lever are considered impulsive behavior. The FCN task also permits assessment of perseverative responding. This occurs when rats respond in excess of the FCN requirement on the chain lever. The FCN procedure is a relatively understudied impulsivity task, and how FCN performance relates to various measures of addiction is currently unknown.

After training rats on the FCN task, jugular vein catheters were implanted and rats were allowed to self-administer cocaine. FCN task performance was compared to cocaine vs. food reward preference, reactivity to a cue previously paired with cocaine infusions, and severity of cocaine escalation during extended (6 hours) self-administration sessions. Preliminary results so far appear to suggest that FCN performance is not related to cocaine preference, but increased impulsivity on the FCN task may be associated with heightened reactivity to cocaine cues.

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The effects of Δ^9-tetrahydrocannabinol on the discriminative stimulus effects of agonists varying in efficacy at the mu opioid receptor

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Cannabinoid receptor agonists such as Δ^9-tetrahydrocannabinol (THC) can attenuate the discriminative stimulus effects of mu opioid receptor agonists (e.g., morphine); however, the mechanisms underlying this effect are unclear. One possibility is that administration of one drug interferes with the ability to detect another drug, a phenomenon referred to as "masking". If masking plays a role, then the discriminative stimulus effects of low efficacy agonists might be more easily attenuated than those of higher efficacy agonists. This study examined whether THC differentially affects the discriminative stimulus effects of agonists varying in efficacy at the mu opioid receptor in monkeys discriminating 0.01 mg/kg of fentanyl from saline. The mu opioid receptor agonists etorphine, fentanyl, and nalbuphine dose-dependently increased fentanyl-lever responding. Pretreatment with THC (0.032-1.0 mg/kg) shifted the nalbuphine dose-effect curve rightward up to 11-fold and shifted the etorphine and fentanyl dose-effect curves rightward a maximum of 2-fold. In contrast, the mu opioid receptor antagonist naltrexone (0.032 mg/kg) was equally effective in attenuating the discriminative stimulus effects of all three mu opioid receptor agonists, shifting the dose-effect curves rightward 8- to 11 -fold. These data suggest the discriminative stimulus effects of low efficacy drugs are more easily disrupted, possibly masked, than those of higher efficacy drugs in so far as doses of THC that attenuated the effects of nalbuphine were less effective in altering the effects of etorphine or fentanyl. Moreover, naltrexone was equally effective in attenuating the discriminative stimulus effects of all three opioid agonists, confirming that those agonists act at the same receptor. That the discriminative stimulus effects of some drugs are more susceptible to attenuation than others might have implications for assessing abuse liability of drug combinations, especially if combinations (e.g., of cannabinoids and opioids) have therapeutic potential (e.g., analgesia). Supported by NIH grants R01DA05018, T32DA031115, F32DA035605, and K05DA017918.

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Reinforcing, locomotor, and thermoregulatory effects of orally administered "bath salt" constituent 3,4-methylenedioxypyrovalerone (MDPV) in mice

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Recently, 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 previous studies in our lab have demonstrated hyperthermic and locomotor stimulant effects of this compound after intraperitoneal administration in the mouse. In the present studies, adult male NIH Swiss mice were used to further assess the behavioral effects of MDPV after oral administration. Reinforcing effects of MDPV were assessed using two-bottle choice oral self-administration, and the effects of voluntary consumption of MDPV solutions on core temperature and motor activity were studies using biotelemetry. MDPV concentrations sufficient to produce locomotor stimulation and self-injury (0.1 and 0.3 mg/ml) were preferentially consumed when the alternative fluid was 0.1 mg/ml quinine – a concentration which did not reduce baseline total fluid consumption when quinine was the only available fluid. However, when water was available as an alternative to MDPV, very little MDPV consumption occurred at the concentrations which previously elicited biological effects. In biotelemetry studies, mice were provided with only MDPV solutions to drink (0.03, 0.1, 0.3, and 1 mg/ml). Stimulation of locomotor activity and hyperthermia was observed following consumption of the highest concentration of MDPV (1 mg/kg), similar to the effects documented in our previous studies. These results demonstrate that oral MDPV has abuse-related reinforcing effects in the mouse. Additionally, orally self-administered MDPV elicits biological effects consistent with those of other psychostimulants. Future studies will determine the mechanism mediating the reinforcing, thermoregulatory, and locomotor stimulant effects of MDPV. These studies supported by UAMS TRI [RR029884], CTN [RR020146], and Department of Pharmacology & Toxicology.

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Chronic treatment of (+)-methamphetamine-induced psychomotor effects in rats using two high affinity anti-(+)-methamphetamine monoclonal antibodies.

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Monoclonal antibody mAb7F9 has a greater in vitro affinity for METH than mAb4G9 (KD = 9 and 16 nM, respectively), but mAb4G9 has a greater affinity for (+)-amphetamine (a pharmacologically active metabolite of METH). Since each antibody has unique advantages (affinity vs. specificity), we wanted to know if one antibody or a combination of the two mAbs would produce greater *in vivo* efficacy. Thus, we hypothesized that treatment with mAb7F9 alone would be more effective in reducing METH-induced effects than treatment with a 50:50 mixture of mAb7F9:mAb4G9. To test this hypothesis in male Sprague-Dawley rats (n=6-8/group), we compared the in vivo efficacy of mAb7F9 and the combination therapy to matched saline controls in their ability to suppress METH-induced hyperlocomotion. The rats were first subjected to repeated METH administrations (0.56 mg/kg iv) until locomotor responses stabilized. We then administered saline or an equimolar loading dose of mAb7F9 or mAb7F9:mAb4G9. The next doses of saline or antibody therapies (141 mg/kg) occurred on days 7 and 14 (once/half-life). METH challenge doses (0.56 mg/kg iv) were administered at 4 hrs and 3 days after each saline or mAb administration, and on day 21. Results showed METH serum concentrations 5 hrs after METH were significantly ($P<0.05$) increased in mAb7F9-treated rats after all 7 METH challenges, and in the first 6 METH challenges in combination-treated rats. MAb7F9 significantly decreased METH-induced distance traveled from 60-120 min after all 7 METH challenges and significantly decreased METH-induced rearing after the first 6 challenges. Combination therapy only decreased METH-induced distance traveled after 5 of the METH challenges and had no significant effect on rearing. In conclusion, the higher affinity, more specific mAb7F9 therapy reduced METH-induced pharmacological effects more than the combination therapy. Funded by NIDA U01DA023900, T32DA022981 and NCATS UL1TR000039.

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Ongoing Stress Moderates Pituitary-adrenal Reactivity in Predicting Post-Treatment Drinking

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Stress and alterations in HPA activity have both been implicated in increasing relapse risk. However, the shared contribution of HPA dysfunction and stress upon post-treatment drinking severity has yet to be explored. This study assessed the impact of pre-discharge basal and provoked HPA activity upon post-discharge drinking severity as well as the moderating effects of stress. Between 2-4 weeks of abstinence, basal and provoked ACTH and cortisol were obtained during the Trier Social Stress Test (TSST) and two pharmacological provocations (oCRH and cosyntropin). Following discharge, stress was assessed with the UCLA Life Stress Interview and drinking with the Timeline Followback (TLFB). Stress alone predicted increased drinking severity in all models ($p<0.03$). Stress moderated low oCRH-induced ACTH ($p= .0006$), increased TSST basal cortisol ($p=.01$), and increased adrenocortical reactivity [pharmacological cortisol:ACTH provocation ($p=.0005$) and basal TSST cortisol:ACTH ($p<.0001$)] in predicting drinking severity. Lower TSST basal ACTH ($p=.004$) predicted drinking severity despite ongoing stress. To our knowledge, this is the first study to exhibit that ongoing stress increases post-treatment drinking severity. This suggests that focused efforts to address both heightened stress and cortisol reactivity may be important in lessening relapse severity.

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Adult male mice pretreated with fluoxetine during adolescence exhibit an enhanced behavioral response to cocaine.

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Pediatric depression was not well recognized until relatively recently. Now we know that major depressive disorder (MDD) exists in children and adolescents, that it is also a common condition, and that it can have negative consequences that often extend into adulthood. It is estimated that children and adolescents who suffer from MDD are likely to develop conduct and anxiety disorders, and that 20-25% eventually develop substance abuse disorder. Consequently, this has resulted in a disproportionate increase in the prevalence of antidepressants prescribed to populations below 20 years of age. Despite the heightened rates in antidepressant use, little is known about the long-term clinical and neurobiological adaptations resulting from antidepressant treatment during periods prior to adulthood. To address this issue at the preclinical level, we examined whether Fluoxetine (Prozac) exposure during adolescence results in long-lasting changes in sensitivity to the rewarding effects of cocaine. To do this, male C57BL/6 mice were exposed to Prozac (20 mg/kg/day) during adolescence (postnatal days [PD] 35-49) and were later assessed in adulthood (PD 70+) on behavioral responsivity to cocaine (0, 2.5, 5, 10, or 20 mg/kg) place conditioning (CPP). Our results show that adult mice pre-treated with Fluoxetine during adolescence (PD 35-49) displayed enhanced preference for environments previously paired with moderately low doses of cocaine (5 or 10 mg/kg), when compared to saline pre-treated controls.

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Validation of an *in-vitro* system to study pharmacological inhibition of the plasma membrane transporter (PMAT)

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Dopamine (DA), serotonin (5-HT), and norepinephrine (NE) mediate an array of brain behaviors and physiological functions. Extracellular levels of these neurotransmitters are tightly regulated by reuptake mechanisms via transporters of two varieties – a high-affinity, low-capacity (uptake-1) and low-affinity, high-capacity (uptake-2). Increased extracellular neurotransmitter levels are achieved from the inhibition of uptake-1 transporters, either by abused psychostimulants (e.g. cocaine) or therapeutic agents (e.g. antidepressant reuptake blockers). The uptake-2 system in brain is less studied; however, it is rapidly gaining recognition for its contribution to neurotransmitter clearance mechanisms that can negatively impact drug abuse liability and therapeutic benefits. Investigations of uptake-2 transporters, which include the plasma membrane monoamine transporter (PMAT) and organic cation transporters, are limited by lack of selective ligands. To date, the only commercially available uptake-2 inhibitor is decynium-22 (D-22), a non-selective antagonist. In efforts to overcome this limitation, we have partnered with chemists to evaluate the pharmacological properties of novel D-22 analogs with the goal of finding ligands selective for each of these uptake-2 transporters. These analogs display a wide range of potencies to inhibit MPP^+ uptake into synaptosomal preparations, with some having greater potency in comparison to the parent D-22 compound. Here, we utilize *in vitro* overexpression of PMAT, a member the uptake-2 transporter family, in human embryonic kidney (HEK) and mouse neuronal (N2a) cells. We employ transient transfection procedures to exogenously express PMAT or knockdown endogenous PMAT levels. This cell based approach will allow us to parse out the role of particular uptake-2 transporter subtypes in neurotransmitter uptake and characterize the inhibition profile of novel compounds.

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The effects of pioglitazone, a PPARγ receptor agonist, on the abuse liability of oxycodone

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Activation of glial cells by opioids is thought to play an important role in opioid-induced reward, tolerance, and dependence. Preclinical research has shown that pioglitazone (PIO) is capable of preventing the acquisition of heroin self-administration, and reducing stress-induced reinstatement of heroin seeking. The ability of PIO to alter the effects of opioids in humans has not been characterized in a controlled, laboratory setting. Accordingly, the proposed investigation seeks to examine the effects of PIO on the subjective effects of oxycodone. During this 7-9-week investigation, prescription opioid abusers who were not physically dependent on opioids were maintained on ascending daily doses of PIO (2-3 weeks on placebo, followed by 2-3 weeks on 15 mg, followed by 2-3 weeks on 45 mg). Following at least 14 days of maintenance on each PIO dose, a laboratory session occurred during which the subjective effects of oxycodone were characterized using a cumulative dosing procedure (oxycodone: 0, 10, and 20 mg, cumulative dose = 30 mg). An acute dose of the maintenance PIO dose was also given immediately prior to the lab session, in order to maximize our ability to detect a medication effect. Data from 15 participants who completed the study were available at the time of this analysis (14M, 1F; 7 African-Americans, 4 Latinos; 2 Caucasians, 2 Multiracial, mean age: 33.4 years). Oxycodone produced dose-dependent increases in positive subjective responses. Overall, ratings such as: drug "liking," "high," and "good drug effect," were not significantly altered as a function of PIO maintenance dose. PIO also did not affect oxycodone-induced ratings of "Bad" drug effect, which were generally minimal (<10 mm on a visual analog scale that ranged between 0 and 100 mm). On its own, PIO appeared to have no positive or negative subjective effects. These data suggest that PIO does not alter the positive or aversive effects of moderate doses of oxycodone, and therefore has little impact on the drug's abuse liability. Study supported by: NIDA grant R01DA031022 to SDC and K01DA030446 to JDJ

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PPARγ as a Therapeutic Target in Cocaine Relapse

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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) (Jahrling et al., 2014) 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.

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Localized and Functionally Connected Neural Predictors of Relapse in Cocaine Dependence

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Background: Multiple areas of brain disruption have been identified in addicted disorders. Nevertheless, there is little evidence to suggest that these alterations are relevant to the high relapse rates that are apparent after treatment. This study was designed to assess whether resting measures of regional cerebral blood flow (rCBF) and related resting state functional connectivity (rsFC) prospectively predict the likelihood of early relapse in cocaine-addicted patients. Methods: 39 2- to 4-week abstinent cocaine-dependent patients in residential treatment and 20 healthy control participants were assessed. rCBF, using arterial spin labeling (ASL), and rsFC were obtained shortly prior to treatment discharge. Cocaine-dependent participants were assessed twice-weekly for substance use following discharge. "Relapsed" identified participants using stimulants within 30 days following treatment discharge; "early remission" were participants who had not relapsed by 30 days post-discharge. *Results:* 21 cocaine-addicted participants relapsed within 30 days following discharge and 18 did not. Differences ($p<0.05$, corrected) between relapsed, early remission, and control groups were identified in left posterior hippocampus (pHp) rCBF as well as in a functionally-connected region to left pHp seed. Increased pHp rCBF and strengthened pHp-PCC FC independently contributed to a survival analyses predicting days to relapse ($\chi^2 = 6.27$, df=1, $p=.01$). *Conclusion:* Increased pHp rCBF in cocaine-dependent patients at risk of early relapse may reflect the persistence of contextual cue-related memories, even in a neutral environment. Increased FC between the pHp and PCC in this group may separately reflect heightened self-referential processing of autobiographical narratives associated with cocaine use. Mechanisms to delink pathologically connected neural circuits, and strengthen protective neural circuits, may prove useful in the treatment of addicted patients at high risk of relapse

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Blood levels do not predict behavioral or physiological effects of Δ9-tetrahydrocannabinol in rhesus monkeys with different patterns of exposure

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Recent changes in the legality of cannabis have prompted evaluation of whether blood levels of Δ [9]-tetrahydrocannabinol (THC) or its metabolites could be used to substantiate impairment, particularly related to behavioral tasks such as driving. However, because marked tolerance develops to behavioral effects of THC, the applicability of a particular threshold of blood THC as an index of impairment in people with different patterns of use remains unclear. Studies relevant to this issue are difficult to accomplish in humans, as prior drug exposure is difficult to control. Here, effects of THC to decrease rectal temperature and operant response rate compared to levels of THC and its metabolites were studied in blood in two groups of monkeys: one received intermittent treatment with THC (0.1 mg/kg i.v.) and another received chronic THC (1 mg/kg/12 h s.c.) for several years. In monkeys with intermittent THC exposure, a single dose of THC (3.2 mg/kg s.c.) decreased rectal temperature and response rate. The same dose did not affect response rate or rectal temperature in chronically exposed monkeys, indicative of greater tolerance. In both groups, blood levels of THC peaked 20-60 min post-injection and had a similar half life of elimination, indicating no tolerance to the pharmacokinetics of THC. Notably, in both groups, the behavioral effects of THC were not apparent when blood levels were maximal (20-min post-administration). These data indicate that thresholds for blood levels of THC do not provide a consistent index of behavioral impairment across individuals with different patterns of THC exposure.

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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Maharaj ("Raj") Ticku, PhD

Dr Maharaj ("Raj") Ticku was born in India. In 1970, after graduating with Honors in Pharmacy from the Birla Institute of Technology and Science in Pilani, he moved to the United States, subsequently receiving an MS in Pharmacology from the University of Oklahoma and a PhD in Biochemical Pharmacology from the State University of New York, Buffalo. Raj then joined the laboratory of Dr Richard Olsen at the University of California Los Angeles where he began his pioneering work on γ-aminobutyric acid (GABA) and *N*-methyl-D-aspartic acid (NMDA) receptors. In 1978 he joined the Department of Pharmacology at the University of Texas Health Science Center at San Antonio where he rapidly rose through the ranks to professor (Pharmacology and Psychiatry).

Raj was truly a pioneer in pharmacology and alcohol abuse research. He was always on the cutting edge of research on GABA and NMDA receptor expression, trafficking, and phosphorylation and his work continues to have a major impact on our understanding of receptor signaling and the neuropharmacology of alcohol. In 1980 he published a paper entitled "*The effects of acute and chronic ethanol administration and its withdrawal on gamma-aminobutyric acid receptor binding in rat brain*" which laid the groundwork for the next several decades of research on the mechanisms of action of alcohol. Another seminal contribution was a 1981 paper on "*Histidine modification with diethyl pyrocarbonate shows heterogeneity of benzodiazepine receptors,*" in which he predicted what receptor cloning and sequencing would require another decade to unravel, that the α-subunits of the GABA-A receptor vary in a critical histidine that determines their drug sensitivity. Raj continued to expand his interests and expertise throughout his career. When it became a popular drug of abuse in the early 2000s, he characterized the mechanism of action of γ-hydroxybutyric acid and shortly before his passing he was awarded a new grant to use state-of-the-art epigenetic approaches to study the heritability of alcoholism.

Raj served on numerous National Institutes of Health (NIH) study sections and as a referee for many prestigious national and international scientific journals. Throughout his career he was exceptionally well supported by the NIH including a prestigious MERIT award from the National Institute on Alcohol Abuse and Alcoholism. Raj's research was of the highest quality and he was very prolific, publishing more than 180 original manuscripts and 24 invited book chapters.

Raj was known for his enthusiasm, his distinct laugh, his love for and extensive knowledge of different foods and cuisines, and above all his inquisitiveness of science and respect for his fellow scientists. In memory of Raj's many significant contributions to addiction research, each year an investigator who is not more than 4 years beyond postdoctoral training is awarded the ***Maharaj Ticku Memorial Travel Fellowship for New Investigators*** to attend and make an oral presentation at the annual meeting of ***Behavior, Biology and Chemistry: Translational Research in Addiction***.