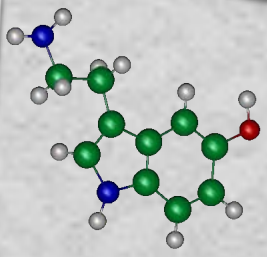
Behavior, Biology, and Chemistry:
Translational Research in Addiction

March 5-6, 2016

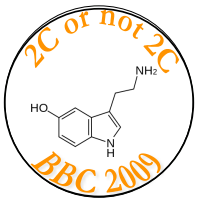
La Quinta Inn & Suites

Medical Center

San Antonio, TX



BBC Publications



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Acknowledgements

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Program Overview

Friday March 4, 2016

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

Saturday March 5, 2016

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: "Glial and neuroinflammatory targets for treating substance use disorders" Speakers:Ryan K. Bachtell, Patrick M. Beardsley, Keith G. Heinzerling, Sandra D. Comer (Chairs: Sandra D. Comer and Patrick M. Beardsley)
10:25 am - 10:40 am	Coffee Break
10:40 am - 12:00 pm	Open Oral Communications 1 (Chair: Lisa Baker)
12:00 pm - 1:15 pm	**Lunch**
1:15 pm - 2:55 pm	Open Oral Communications 2 (Chair: Clinton Canal) 
2:55 pm - 3:10 pm	Coffee Break
3:10 pm - 4:10 pm	Special Lecture: Thomas E. Prisinzano "Beyond morphine: Salvia divinorum and the quest for novel opioids" (Chair: Andy Coop)
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: Robert Balster; "How can you soar like an eagle when reviewers want you to walk like a duck?" (Chair: Ellen Walker)
9:00 pm - 11:00 pm	Hospitality and Entertainment

Sunday March 6, 2016

8:00 am - 9:40 am	Open Oral Communications 3 (Chair: Michael Gatch)
9:40 am - 9:55 am	Coffee Break
9:55 am - 11:15 am	Open Oral Communications 4 (Chair: Thomas Keck)
11:15 am - 11:30 am	Coffee Break
11:30 am - 12:30 pm	Special Lecture: David J. Nutt; "The acid test, can psychedelic drugs help us understand how the brain works?" (Chair: Alan Frazer)
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 2017!

 Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee

Program Details

Friday March 4, 2016 (6:00 pm - 9:00 pm)

Opening Reception

La Vista Terrace on the Riverwalk

6:00 pm	Buses depart from La Quinta
6:30 pm - 9:00 pm	Reception at La Vista Terrace
9:00 pm	Buses depart for La Quinta

Come and enjoy the beautiful San Antonio Riverwalk. Buses will depart from La Quinta at 6:00 pm to take you to La Vista Terrace on the Riverwalk where there will be a fajita station for dinner and drinks. Buses will return to La Quinta at 9:00 pm. You will need your badge to board the bus and for dinner. Additional tickets can be purchased in advance or at the registration desk for $40.00.

Saturday March 5, 2016

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

Plenary Symposium (Chairs: Sandra D. Comer and Patrick M. Beardsley)

Glial and neuroinflammatory targets for treating substance use disorders

Glia (including astrocytes, microglia, and oligodendrocytes) have many of the same receptors as neurons, secrete neurotransmitters and neurotrophic and neuroinflammatory factors, control clearance of neurotransmitters from synaptic clefts, and are intimately involved in synaptic plasticity. Drugs of abuse can affect glial activity, including their neuroinflammatory processes, and glial activity in turn, has been found to modulate the effects of some drugs of abuse. Consequentially, glia and neuroinflammatory processes have become potential targets for pharmacotherapeutics for treating substance use disorders. This symposium will present preclinical and clinical data illustrating the range of effects some glial and neuroinflammatory modulators can have on the abuse-related effects of psychostimulants and opioids, and how drugs of abuse can affect these cells and processes, within the context of targeting pharmacotherapeutics for treating substance use disorders.

8:05 am - 8:40 am	***Ryan K. Bachtell***, University of Colorado at Boulder Role of microglia and toll-like receptor 4 in cocaine seeking
8:40 am - 9:15 am	***Patrick M. Beardsley***, Virginia Commonwealth University Preclinical effectiveness of glial and neuroinflammatory modulators for attenuating some abuse-related effects of drugs
9:15 am - 9:50 am	***Keith G. Heinzerling***, UCLA Medical Center Targeting microglia in stimulant use disorders: initial clinical studies with ibudilast and methamphetamine
9:50 am - 10:25 am	***Sandra D. Comer***, Columbia University and NYSPI Clinical studies of ibudilast, minocycline, and pioglitazone as potential treatments for opioid use disorder

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

Saturday March 5, 2016 (continued)

Open Oral Communications 1 (Chair: Lisa Baker)

10:40 am -11:00 am — ***Edward Townsend,*** University of Mississippi Medical Center
Effects of the atypical kappa opioid receptor agonist, nalfurafine, on the thermal antinociceptive and reinforcing effects of oxycodone in male rats

11:00 am- 11:20 am — ***Alyssa Fournett,*** Louisiana State University Health Sciences Center
Mephedrone: An abused synthetic cathinone with stimulant-like discriminative stimulus effects

11:20 am - 11:40 am — ***Justin Siemian,*** University at Buffalo
Anti-hyperalgesic effects of the imidazoline I2 receptor agonist 2-BFI in a rat model of inflammatory pain: interactions with μ-opioids of varying efficacies

11:40 am - 12:00 pm — ***Jennifer Martin,*** University at Buffalo
The essential role of Drebrin in mediating opiate-induced plasticity in the nucleus accumbens

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

Open Oral Communications 2 (Chair: Clinton Canal)

1:15 pm - 1:35 pm — ***Laura Ferguson,*** University of Texas at Austin
Old drugs for new diseases: Drug repurposing for alcoholism.

1:35 pm - 1:55 pm — ***Megan Moerke,*** University of Texas Health Science Center at San Antonio
Antagonism of and acute tolerance to the discriminative stimulus effects of nicotine and varenicline in rhesus monkeys

1:55 pm - 2:15 pm — ***Erik Garcia,*** Kansas State University
The effects of novelty choice on preference for ethanol oral self-administration

2:15 pm - 2:35 pm — ***Nicholas Griggs,*** University of Michigan
Biochemical and behavioral evaluation of mu opioid receptor agonist/delta opioid receptor antagonists as potential analgesics with reduced adverse effects

2:35 pm - 2:55 pm — ***Bryan Cruz,*** University of Texas at El Paso
Insulin normalizes the strong rewarding effects of nicotine observed in hypoinsulinemic rats

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

Special Lecture 3:10 pm - 4:10 pm (Chair: Andy Coop)

Thomas E. Prisinzano, University of Kansas: "Beyond morphine: Salvia divinorum and the quest for novel opioids"

Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee

Travel Awardee

Saturday March 5, 2016 (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 minute 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)

Additional tickets can be purchased in advance or at the registration desk for $60.00.

After Dinner Lecture (Chair: Ellen Walker)

Robert Balster, Virginia Commonwealth University: "How can you soar like an eagle when reviewers want you to walk like a duck?"

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

Come and enjoy the fun in the ballroom!

Sunday March 6, 2016

Open Oral Communications 3 (Chair: Michael Gatch)

8:00 am - 8:20 am  ***Michael Salling,*** Columbia University
Binge alcohol consumption during adolescence in mice alters prefrontal neuronal excitability and causes deficits on a prefrontal dependent working memory task

8:20 am - 8:40 am  ***John Harkness,*** Washington State University, Vancouver
Cocaine preference acquisition disrupted by knockdown of perineuronal net cartilage link protein-1 within the medial prefrontal cortex

8:40 am - 9:00 am ***Brenda Gannon,*** University of Texas Health Science Center at San Antonio
Relative reinforcing effects of 3,4-methylenedioxypyrovalerone (MDPV) under a progressive ratio schedule of reinforcement in rats

9:00 am - 9:20 am  ***Priscilla Martinez,*** University of California, Berkeley
Immune activation is associated with symptoms of depression and psychological distress among people with alcohol and substance abuse disorders

9:20 am - 9:40 am  ***Sherrica Tai,*** University of Arkansas for Medical Sciences
Cannabinoid effects on learning and memory in mice

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

Open Oral Communications 4 (Chair: Thomas Keck)

9:55 am - 10:15 am  ***Todd Hillhouse,*** University of Michigan
The mixed efficacy opioid ligand BU10119 attenuates cocaine seeking behavior in mice

10:15 am - 10:35 am  ***Steven Graves,*** Northwestern University
Methamphetamine, mitochondrial stress, and dopamine toxicity: mechanism leading to increased risk for Parkinson's disease

10:35 am - 10:55 am ***Juan Dominguez,*** The University of Texas at Austin
The medial preoptic area modulates cocaine-induced neural and behavioral activity

10:55 am - 11:15 am  ***Clinton Canal,*** Northeastern University
A novel phenylaminotetralin-chemotype 5-HT_{2C} agonist, 5-HT_{2A} and 5-HT_{2B} neutral antagonist and an extension of a 5-HT_{2C} receptor activation mechanism for treating addiction

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

Special Lecture 11:30 am - 12:30 pm (Chair: Alan Frazer)

David J. Nutt, Imperial College London: "The acid test, can psychedelic drugs help us understand how the brain works? "

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

Effects of the atypical kappa opioid receptor agonist, nalfurafine, on the thermal antinociceptive and reinforcing effects of oxycodone in male rats.

Townsend, Edward A[1]; Naylor, Jennifer E[2]; Kapanda, Coco N[3]; McCurdy, Christopher R[3]; Sufka, Kenneth J[4]; Husbands, Stephen M[5] and Freeman, Kevin B[1]

[1]Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS USA; [2]Division of Neurotoxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR USA; [3]Department of Medicinal Chemistry, University of Mississippi, University, MS USA; [4]Department of Psychology, University of Mississippi, University, MS USA; [5]Department of Pharmacy and Pharmacology, University of Bath, Somerset, UK.

Prescription opioids (e.g., oxycodone) are the most commonly abused class of medications, and strategies to reduce their misuse are critically needed. One approach to reduce the abuse liability of prescription opioids includes compounding a deterring agent within the medication such that escalation of use would result in an unpleasant state. We have previously reported that combining the kappa opioid agonist, salvinorin A, with a mu opioid agonist can reduce the reinforcing effects of the latter. The aim of the current study was to extend these findings with an atypical kappa opioid agonist (i.e., nalfurafine) that does not produce the psychotomimetic effects that are typical of other kappa opioid agonists. Specifically, we assessed the effect of adding nalfurafine to oxycodone in measures of self-administration and thermal antinociception in male rats. Three dose proportions of oxycodone and nalfurafine were tested for thermal antinociception using the hot-plate assay. Isobolographic analysis indicated an additive analgesic effect with one of the tested dose proportions and infra-additive effects with the other proportions. The additive dose proportion was subsequently tested in self-administration under a fixed-ratio schedule of reinforcement. Rates of self-administration of the oxycodone / nalfurafine mixture were significantly lower than oxycodone alone. The present findings suggest that the addition of nalfurafine to oxycodone can decrease oxycodone's reinforcing effect while supplementing its antinociceptive effect.

2

Mephedrone: An abused synthetic cathinone with stimulant-like discriminative stimulus effects

A.F. DeLarge[1], P.J. Winsauer[1]
1LSUHSC-NO Department of Pharmacology and Experimental Therapeutics

Mephedrone (4-methylmethcathinone) is one of the major constituents of the recreational substances known as "bath salts". It is a synthetic cathinone and psychostimulant that has been reported to cause auditory and visual hallucinations, as well as problematic cardiovascular effects. This study compared the discriminative stimulus effects of mephedrone (0.32-10 mg/kg) alone with other drugs, such as cocaine (0.56-32 mg/kg), delta-9-tetrahydrocannabinol (THC, 0.56-10 mg/kg), ketamine (1.8-18 mg/kg), phencyclidine (PCP, 1-5.6 mg/kg), 2,5-dimethoxy-4-iodoamphetamine (R-DOI, 0.1-1 mg/kg), heroin (1-10 mg/kg), methylenedioxypyrovalerone (MDPV, 0.56-5.6mg/kg), and d-amphetamine (0.18-3.2 mg/kg). The discriminative stimulus effects of mephedrone were also examined after the administration of rimcazole (0.32-10 mg/kg), a sigma receptor antagonist, desipramine (1.8-18 mg/kg), a tricyclic antidepressant with relatively selective affinity for norepinephrine transporters (NET), and fluoxetine (1.8-18 mg/kg), an antidepressant with selective affinity for serotonin transporters (SERT). Rats were trained to discriminate an intraperitoneal injection of mephedrone from saline under a fixed-ratio 20 schedule of food presentation. The training dose of mephedrone (3.2 mg/kg) was reliably discriminated from saline by all subjects. Following training, substitution of varying doses of mephedrone produced dose-dependent increases in mephedrone-lever responding, with full substitution considered to be greater than 80% responding on this lever. Of the drugs tested, only cocaine and THC fully substituted for mephedrone. However, full substitution of THC only occurred at a dose that substantially decreased response rate. Both THC and R-DOI produced dose-dependent rate-decreasing effects ($\geq$ 20% decrease in response rate compared to vehicle). In addition, although rimcazole and desipramine did not substitute for mephedrone, both drugs potentiated mephedrone's discriminative stimulus effects by producing leftward shifts of the dose-effect curve. In summary, the discriminative stimulus effects of mephedrone most closely approximate those for the stimulant, cocaine, and these effects may be mediated by multiple receptors and/or transporters.

3

Anti-hyperalgesic effects of the imidazoline I2 receptor agonist 2-BFI in a rat model of inflammatory pain: interactions with μ-opioids of varying efficacies

Justin Siemian[1], Yanan Zhang[2], Yan Zhang[3], Jun-Xu Li[1]

[1]Department of Pharmacology and Toxicology, School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY.
[2] Research Triangle Institute, Research Triangle Park, NC.
[3]Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, VA.

Chronic pain is the single largest health care challenge facing the United States and currently available analgesics including μ-opioids are not adequate for long-term chronic pain management. Preclinical studies have established the imidazoline I2 receptor (I2R) as a target to treat chronic pain, both as monotherapy and when combined with μ-opioids. This study systematically examined the anti-hyperalgesic effects of the selective I2R agonist 2-BFI alone and in combination with opioids of varied efficacies using the von Frey and Hargreaves tests in adult male and female rats with complete Freund's adjuvant (CFA)-induced inflammatory pain. Isobolographic and dose-addition analyses were used to characterize the interactions. 2-BFI with fentanyl, a high efficacy μ-opioid receptor agonist, produced additive interactions in the von Frey test and infra-additive interactions in the Hargreaves test. 2-BFI with buprenorphine, a medium-low efficacy μ-opioid receptor agonist, produced supra-additive interactions in the von Frey test and infra-additive interactions in the Hargreaves test. 2-BFI with NAQ, a very low efficacy μ-opioid receptor agonist, produced supra-additive interactions in both the von Frey and Hargreaves tests. The interactions of the same dose combinations on food-maintained operant responding were found to be generally additive. In females, pretreatments of buprenorphine or NAQ produced greater leftward shifts than fentanyl on the dose-effect curve of 2-BFI in the von Frey test. Collectively, these data suggest that the nature of I2 and μ-opioid receptor interactions may be related to the efficacy of the μ-opioids. Using low-efficacy μ-opioids in combination therapies likely represents an improvement over existing treatment strategies.

4

The essential role of Drebrin in mediating opiate-induced plasticity in the nucleus accumbens

Jennifer A. Martin[1], Zi-Jun Wang[1], Monica Humby[1], Aaron Caccamise[1], Lauren E. Mueller[1], Rachael L. Neve[2], Amy M. Gancarz[1], David M. Dietz[1]

[1]University at Buffalo Department of Pharmacology and Neuroscience, [2]Massachuessetts Institute of Technology

Opiate addiction has dramatically increased, becoming a worldwide epidemic with great societal and financial burdens. Drug addiction, defined as a chronic relapsing disease, involves the 'rewiring' of the brain through long-term changes, such as structural plasticity, in several key regions of the mesolimbic dopaminergic pathway. There is a great deal of evidence demonstrating that chronic psychostimulant exposure increases the number of dendritic spines on medium spiny neurons in the nucleus accumbens (NAc). In contrast, exposure to opiates, such as morphine and heroin, which similarly induce behavioral sensitization, leads to a decrease in dendritic spine density. However, there are minimal data regarding the cellular neurobiology that regulates this opiate-induced plasticity. Following both morphine sensitization and heroin self-administration there is a decreased expression of the actin binding protein drebrin in the NAc. This decrease in drebrin results from an increase in HDAC2 expression and binding at the promoter of the transcriptional start site, accompanied by a decrease in pan-H3 acetylation.

Overexpression of drebrin, using viral-mediated gene therapy, during morphine-induced locomotion (5 mg/kg, i.p.) blunted the expression of morphine sensitization (challenge dose: 2.5 mg/kg, i.p.) compared to HSV-GFP controls. In order to determine the role of drebrin in drug relapse, animals were trained to self-administer heroin (0.02 mg/kg/inf). Interestingly, following heroin self-administration, overexpression of drebrin in the NAc significantly decreased responding during heroin-primed reinstatement (0.25 mg/kg, s.c.), but not cue-induced reinstatement. Finally, overexpression of HDAC2 leads to a potentiation of behavioral response to low doses of morphine. Taken together, these data suggest that epigenetic regulation of drebrin is functionally regulated following exposure to opiates and may be a key molecular mechanism underlying opiate-induced behavioral plasticity.

Oral Communications

5

Old drugs for new diseases: Drug repurposing for alcoholism.

Ferguson, LB, Ponomarev, I, Mayfield, RD and Harris, RA

Waggoner Center for Alcohol and Addiction Research, Institute for Neuroscience, University of Texas at Austin, Austin, TX USA.

Using genomic data to repurpose compounds for novel indications (i.e., diseases) is an active area of investigation. Computational approaches that integrate gene expression signatures of drugs and diseases have successfully repurposed drugs for several complex disorders, e.g., obesity [1] and inflammatory bowel disease [2]. However, these approaches have not yet been applied to psychiatric illnesses. Alcoholism is a complex psychiatric disorder with strong genetic as well as environmental risk factors. The genetic risk factors can cause changes in gene expression that may underlie their deleterious alcohol drinking patterns. Therefore, we focused our analysis on the transcriptome and used gene expression data from alcoholics and preclinical models of excessive alcohol consumption, LINCS (Library of Integrated Cellular Signatures) and other publicly available databases to predict drugs that will decrease alcohol consumption. Our analysis identified compounds that have previously demonstrated effects on alcohol consumption, thus validating our approach. Therefore, the novel compounds suggested by our investigation might have therapeutic potential for alcoholism.

1. Liu, J., et al., *Treatment of obesity with celastrol.* Cell, 2015. **161**(5): p. 999-1011.

2. Dudley, J.T., et al., *Computational repositioning of the anticonvulsant topiramate for inflammatory bowel disease.* Sci Transl Med, 2011. **3**(96): p. 96ra76.

6

Antagonism of and acute tolerance to the discriminative stimulus effects of nicotine and varenicline in rhesus monkeys

Moerke, MJ[1] and McMahon, LR[1]

[1]Department of Pharmacology, University of Texas Health Science Center, San Antonio, TX

Current pharmacotherapies for tobacco dependence include nicotine replacement and the low efficacy agonist varenicline (Chantix®). However, the rate of relapse among cigarette smokers remains high; as such, a better understanding of these therapies is crucial to improvements in treating tobacco dependence. In the current study, antagonism and tolerance/cross-tolerance were used in drug discrimination to determine the extent to which the discriminative stimulus effects of nicotine and varenicline are mediated by the same receptor mechanism. Rhesus monkeys (n=5) discriminated 0.032 mg/kg nicotine base under an FR5 schedule of stimulus-shock termination. Nicotine dose-dependently increased drug-lever responding; the ED_{50} value (95% confidence limits) of nicotine to produce discriminative stimulus effects was 0.013 (0.0033-0.050) mg/kg. Varenicline fully substituted for the nicotine discriminative stimulus: the ED_{50} value of varenicline was 0.021 (0.0067–0.068). The β2-selective nicotinic acetylcholine receptor (nAChR) antagonist dihydro-β-erythroidine produced a 4-fold rightward shift in the nicotine dose-response function, and a 4.2-fold rightward shift in the varenicline dose-response function. Methyllycaconitine, an α7-selective nAChR antagonist, up to 10 mg/kg did not antagonize the nicotine discriminative stimulus. Pretreatment with nicotine (0.032 mg/kg) 45 and again 30 min before re-determination of sensitivity to the effects of nicotine resulted in a 5.5-fold rightward shift in the dose-response function. These results provide evidence for acute tolerance to the discriminative stimulus effects of nicotine and suggest that the nicotine discriminative stimulus is mediated by β2-containing, not α7-containing, nAChRs. Furthermore, there was no apparent difference in efficacy between nicotine and varenicline in this assay. Collectively, these results demonstrate that tolerance to the discriminative stimulus effects of nicotine can be produced by acute exposure to nicotine and suggest that the mechanism underlying acute tolerance may be related to rapid desensitization of β2-containing nAChRs. Supported by USPHS grant DA25267

7

The effects of novelty choice on preference for ethanol oral self-administration

Garcia, Erik J[1]; Jorgensen, Emily T[1]., Sprick, Lukas S[1]., and Cain, Mary E[1]

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High novelty and sensation seeking (NSS) is positively correlated with earlier ethanol (ETOH) consumption, and sustained drinking into early adulthood. However, rodent behavioral data measuring NSS suggests that NSS is complex and manifests in multiple behaviors. It appears that the inescapable novelty response is important for drug acquisition, while choice novelty is important for the transition to compulsive drug taking. The present study aimed to determine whether forced or choice novelty was more important for developing a preference to drink ETOH. Thirty-eight male Long Evans rats were tested for their response to NSS using two different rodent NSS tests aimed at measuring forced and choice NSS responses. The rats were first tested with the inescapable novelty (IEN) test. Then rats were tested for their choice to engage a novel environment using the novelty place preference (NPP) test. Using the intermittent two bottle paradigm, rats were then gradually exposed to increasing concentrations of ETOH over 2 weeks. For the final 6 weeks, they had access to 20% ETOH (w/v). The 8 control rats only had water access. The dependent measure of interest was consumption on the bottle that contained ETOH or water on alternating days. A simple mixed effects model was used to analyze the data to determine if either forced or choice novelty response predicts preference to consume ETOH over water across the 8 week drinking period. Correlational results indicate that the forced and choice novelty responses are not correlated and they are separate behavioral measures. Mixed effects model results determined that the choice to engage novelty (NPP) can uniquely predict the preference to consume ETOH. The NPP response predicted the preference to consume ETOH over water, such that higher NPP responders showed a higher preference for ETOH across time that lower NPP responders did not. IEN did not show any predictive relationship with preference for ETOH consumption. These results indicate that the choice to engage novel environments in adolescence is an important variable that promotes the preference for ETOH consumption into adulthood.

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Biochemical and behavioral evaluation of mu opioid receptor agonist/delta opioid receptor antagonists as potential analgesics with reduced adverse effects.

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Drug discovery and development of opioid ligands has largely favored highly selective agonists/antagonists for a single opioid receptor (OPr); opioid analgesics, such as morphine, are primarily selective for and activate the mu opioid receptor (MOPr). However, evidence suggests that modulation of other opioid receptors may be beneficial in MOPr-mediated analgesia. In particular, there is evidence that simultaneous activation of MOPr with inhibition of the delta opioid receptor (DOPr) can reduce the development of morphine tolerance and dependence. Thus one strategy is to design single compounds that target both mu and delta opioid receptors (activate MOPr and inhibit DOPr) to use as potential therapeutics for the improved clinical management of pain. The compounds we have synthesized are peptides and peptidomimetics, which maintain key elements of opioid peptides vital for activity but that have small molecule-like features to provide for bioavailability, blood brain barrier permeability and duration of action. Our compounds have been characterized *in vitro* by radioligand binding to provide affinity (K_i) values and for potency and relative efficacy (EC_{50}, % stimulation compared to standard agonist) using the degree of incorporation of $GTP\gamma^{35}S$ into G proteins in membranes from cells expressing MOPr or DOPr. Certain compounds have been evaluated for antinociceptive activity *in vivo* by the mouse warm water tail withdrawal assay, as well as for development of tolerance and dependence after 5-day escalating drug treatment. Lead compounds display maximal antinociceptive activity with a long duration of action and also with a marked reduction in tolerance, dependence and conditioned place preference. Our preclinical research provides a strong foundation for the development of novel opioid analgesics with fewer adverse effects such as reduced abuse liability. Funded by DA-03910 and the Pharmacological Sciences Training Program (NIGMS-GM007767).

Oral Communications

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Insulin normalizes the strong rewarding effects of nicotine observed in hypoinsulinemic rats

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Introduction: Previous research has demonstrated that hypoinsulinemic rats display enhanced rewarding effects of nicotine. However, it is unclear whether the strong rewarding effects of nicotine observed in these rats are modulated via insulin. To address this issue, the present study examined whether insulin replacement in streptozotocin (STZ)-treated rats would 1) normalize the rewarding effects of nicotine and 2) reverse the alterations in insulin-signaling proteins observed in the brains of STZ-treated rats. **Methods**: A rodent model of hypoinsulinemia was used involving STZ administration, which is a drug that is toxic to the insulin-producing cells of the pancreas. Male rats received STZ (45 mg/kg, sc) or vehicle. Half of the animals were then implanted with an insulin pellet or received a sham surgery. The rats were then given 23-hour access to nicotine self-administration using an escalating dose regimen (0.03, 0.06 and 0.09 mg/kg/0.1 ml infusion). In a follow up study, western blot analyses were performed in a separate cohort of STZ-treated rats that received insulin replacement. Brain tissue was collected 2 weeks after STZ administration, in order to examine alterations in insulin-signaling proteins at a corresponding time point to our behavioral studies. Tissue was collected from the nucleus accumbens (NAc) for the analysis of the insulin-signaling proteins, IRS-2 and IGF-1Rβ. **Results**: Our behavioral results revealed that insulin replacement normalized the rewarding effects of nicotine in STZ-treated rats. Our protein analysis revealed that the levels of IRS-2 and IGF-1Rβ were increased in STZ-treated rats, and this effect was normalized to control levels in the NAc of rats that received insulin treatment. **Conclusion**: These observations indicate that insulin systems play an important role in modulating the strong rewarding effects of nicotine in hypoinsulinemic rats. Taken together, these results have implications for the development of tobacco intervention approaches in patients with metabolic disorders such as diabetes that suppress insulin signaling.

10

Binge alcohol consumption during adolescence in mice alters prefrontal neuronal excitability and causes deficits on a prefrontal dependent working memory task

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Alcohol abuse during adolescence has been associated with deficits in learning and memory. This relationship may be partly explained by the effects of alcohol on the developing prefrontal cortex (PFC). The PFC is critical to working memory and undergoes significant maturational change during adolescence. Importantly, the PFC is known to be especially vulnerable to the effects of alcohol; for example, binge drinking has been associated with decreased PFC function and imaging studies suggest that this dysfunction persists in chronic alcohol abusers. To better understand the effects of adolescent drinking on the PFC function and neurophysiology, we used an animal model of binge drinking, where C57BL/6J mice voluntarily consumed high levels of alcohol (blood alcohol levels > 80 mg/dl) during their adolescent period (postnatal day 30 to 60). Behavioral testing following this exposure revealed that binge drinking mice showed deficits in the acquisition and performance on a delayed non-match to sample T-maze task. Using ex vivo whole-cell patch clamp electrophysiology, we measured passive and active membrane properties of layer 5 pyramidal neurons (PNs) following adolescent binge drinking. We found that the resting membrane potential (RMP) of mPFC PNs from binge-drinking mice is hyperpolarized by ~5 mV, due to a significant reduction of the hyperpolarized-activated cation current (I_h), a conductance important for setting RMP and controlling persistent firing. Importantly, this form of persistent activity is present in PFC PNs, can be induced by cholinergic activation and has been shown to mediate specific aspects of working memory. We demonstrate that along with a reduction in I_h, persistent firing is significantly reduced in layer 5 PNs in adolescent binge drinking mice and that it can be restored by resetting the RMP. In summary, our recent work demonstrates that a reduction in I_h and persistent firing are consequences of binge-like alcohol drinking during adolescence that may contribute to long-term working memory deficits in adulthood.

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Cocaine preference acquisition disrupted by knockdown of perineuronal net cartilage link protein-1 within the medial prefrontal cortex.

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Acquisition and extinction of cocaine-induce conditioned place preference (CPP) in rodents can be impaired by disruption of extracellular matrix aggregations called perineuronal nets (PNNs). Targeted disruption of PNNs may be useful in future therapeutic approaches for the treatment of human cocaine use disorder. PNNs surrounding synaptic connections of fast-spiking, parvalbumin-containing GABAergic interneurons are likely important for stabilization of synapses following learning, and for limiting plasticity after the critical period. We have previously demonstrated that administration of the bacterial enzyme chondroitinase-ABC in the prelimbic medial prefrontal cortex (PL mPFC) of rats results in degradation of extracellular matrices. However, this enzyme is not specific to PNNs, and may eliminate chondroitin-sulfate proteoglycan containing structures other than just PNNs. The presence of cartilage link protein-1 (Crtl-1) differentiates PNNs from other extracellular matrices. A vivo-morpholino [1:5] knockdown of Crtl-1 in the PL mPFC of adult rats resulted in degradation specific to PNNs. We have shown functional and behavioral results of Crtl-1 knockdown that are similar to those of chondroitinase-ABC. In the present work, we tested a higher concentration [1:2.5] of vivo-morpholino to knockdown Crtl-1, administered prior to acquisition of cocaine-induced CPP. Additionally, disruption of PNN formations were measured by immunohistochemistry and staining with *Wisteria floribunda* agglutinin. In combination with previous results, these results indicate that knockdown of Crtl-1 using a morpholino can specifically degrade PNNs, and disrupt acquisition of cocaine CPP.

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Relative reinforcing effects of 3,4-methylenedioxypyrovalerone (MDPV) under a progressive ratio schedule of reinforcement in rats

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The abuse of designer drugs such as *bath salts* over the past 10 years has reached epidemic proportions. 3,4-Methylenedioxypyrovalerone (MDPV) is a synthetic derivative of cathinone commonly found in *bath salt* products and has a cocaine-like mechanism of action. The present study aimed to directly compare the reinforcing effectiveness of MDPV to cocaine, methamphetamine, and methylone (a *bath salt* constituent with an amphetamine-like mechanism of action) in male Sprague-Dawley rats. Rats were initially trained to self-administer MDPV under a progressive ratio (PR) schedule, with dose-response curves for each drug generated by dose substitution. Differences were observed with regard to both the potency [MDPV > methamphetamine > cocaine > methylone] and effectiveness [MDPV > methamphetamine = cocaine > methylone] of the drugs to maintain responding under the PR schedule, with MDPV maintaining very high levels of responding (~29 infusions, and final ratios in excess of 1500 responses). Because MDPV is a chiral molecule, we next sought to determine whether the reinforcing effects of its enantiomers differed from those of the racemic mixture (i.e., MDPV). Again, differences were observed with regard to both potency [S(+)-MDPV > MDPV >> R(-)-MDPV] and effectiveness [S(+)-MDPV = MDPV > R(-)-MDPV] to maintain responding. Taken together, these findings suggest that MDPV is a more effective reinforcer in rats than the widely abused psychostimulants cocaine and methamphetamine. Future studies will be aimed at identifying the neuropharmacologic mechanism(s) that account for the powerful reinforcing effects of MDPV, as well as the degree to which these properties are shared by other synthetic cathinones.

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Oral Communications

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Immune activation is associated with symptoms of depression and psychological distress among people with alcohol and substance abuse disorders

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The associations between immune activation, depression, and psychological distress (PD) among people with substance use disorders (SUD) remain little explored. This study aimed to examine the association between depression, PD, and cytokine levels among people in treatment for a substance use disorder. We collected cross-sectional data from inpatients at 5 substance abuse treatment centers in South Eastern Norway via structured questionnaires, medical chart review, and laboratory testing of blood samples. We assessed depression with the depression subscale of the Symptom Checklist-90-Revised version, and PD with the full version. Cytokines assessed included IL-6, IL-10, TNF-α, and INF-γ. We used Spearman rank tests to observe associations between depression, PD, and cytokine levels, and fitted linear regressions to examine the effect of cytokine level on depression and PD controlling for covariates. A total of 80 participants were included, where the mean age was 42 years and 71% were male. In bivariate analysis, significantly and positively associated with depression were IL-6 (ρ=0.27, p=0.02) and TNF- α (ρ =0.23, p=0.04). For PD, only IL-6 (ρ=0.28, p=0.01), was significantly and positively associated. In multivariate analysis, all cytokines were significantly and positively associated with depression, and only IL-6 (β=0.53, p=0.04) was associated with PD. Findings suggest elevated cytokine levels among patients in treatment for a substance abuse disorder are associated with symptoms of depression and PD. Results also suggest cytokine profiles may differ between symptoms of depression and symptoms of psychological distress. Immune function among people with alcohol and substance abuse disorders may be affected by symptoms of depression and psychological distress above and beyond the impact of the alcohol or drug use disorder.

14

Cannabinoid effects on learning and memory in mice.

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Marijuana abuse is associated with psychosocial and health-related consequences, including decrements in various measures of neurocognition. Recreational and medicinal use of marijuana has historically been considered controversial, but more recently social acceptance has risen across the US with some states and municipalities embracing legalization. At the same time, use of synthetic cannabinoid products containing drugs with higher efficacy than the phytocannabinoid Δ^9-tetrahydrocannabinol (Δ^9-THC) is also spreading particularly among young people. In these studies, we examined the effects of cannabinoids on learning and memory in mice after acute or chronic exposure to Δ^9-THC or synthetic cannabinoid JWH-018, using a passive avoidance conditioning paradigm. This paradigm assesses learning and memory based on the association between an electrical stimulus and an environmental context (dark chamber). In control (drug-naïve) subjects, the latency to crossover from the light chamber into the dark chamber was assessed every 24 hrs after receiving the stimulus in the dark chamber. In experimental groups, single injections or five daily injections of Δ^9-THC and JWH-018 were administered pre- and post-conditioning to determine effects on learning and memory. We found that chronic exposure to JWH-018 before conditioning greatly reduced crossover latency compared to mice that had no drug history (control), but that Δ^9-THC had only minor effects. CB1R selective antagonist rimonabant was administered to determine if these effects were CB1R mediated. Cannabinoids administered after conditioning did not have any systematic effects on crossover latency compared to controls. These findings suggest that cannabinoids induce strong deficits in learning which may be related to either dose or intrinsic efficacy, while the effects on memory should be further explored (e.g., short-term vs long-term memory). This work was supported by RR029884, RR020146 and UAMS Department of Pharmacology and Toxicology.

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The mixed efficacy opioid ligand BU10119 attenuates cocaine seeking behavior in mice.

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Cocaine and opioid pain relievers are among the top three most abuse illicit drugs. Moreover, ~78% of cocaine users and ~71% of opiate users also abuse other substances (poly-drug abuse). Current treatments for addiction leave much to be desired as the majority of drug users relapse within the first year of treatment. The opioid system has emerged as a viable target for drug relapse prevention in drug addicts. For example, the mixed efficacy opioid burprenorphine effectively decreases the number of positive drug tests in poly-drug users. However, there are concerns surrounding prolonged buprenorphine treatment due to physical dependence and addiction liability associated with mu opioid receptor (MOPr) agonists. To combat this issue, we developed BU10119 which has similar pharmacological properties to buprenorphine, but lacks agonist action at MOPr *in vitro* and has improved activity at nociceptin receptors (NOPr). Here, we confirm the *in vitro* pharmacological profile of BU10119 using *in vivo* behavioral assays in mice. BU10119 completely blocked the antinociceptive effects of the MOPr agonist morphine and kappa opioid receptor agonist EKC in the warm water tail withdrawal assay, attenuated the antinociceptive effects of the delta opioid receptor agonist SNC80 in acid-stimulated stretching and caused a hyperalgesic response consistent with its NOPr agonism. When tested in a conditioned placed preference (CPP), BU10119 attenuated cocaine-primed reinstatement. Taken together, BU10119 is a mixed efficacy opioid ligand that decreases cocaine seeking behavior in mice and may be a safer alternative to buprenorphine.

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Methamphetamine, mitochondrial stress, and dopamine toxicity: mechanism leading to increased risk for Parkinson's disease

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Methamphetamine (meth) is a potent and addictive psychostimulant abused by ~33 million people (UNODC, 2007) and increases the risk for developing Parkinson's disease (PD) by 2-3 fold (Callaghan *et al*., 2012, *Drug Alcohol Depend* p.35; Curtin *et al*., 2015 *Drug Alcohol Depend* p.30). PD is the second most common neurodegenerative disease, characterized by the degeneration of dopamine neurons in the substantia nigra pars compacta (SNc). One of the earliest hypotheses of PD pathogenesis was that dopamine itself is neurotoxic due to auto-oxidation or monoamine oxidase (MAO) metabolism leading to cytosolic stress. Ex *vivo* slices expressing a redox sensitive probe targeted to SNc dopamine neuron cytosol or mitochondria were assayed to determine the effect of meth on cellular stress. Meth had no effect on cytosolic but increased mitochondrial stress selectively terminals and dendrites. MAO inhibition attenuated meth-induced mitochondrial stress but increased cytosolic stress. To determine whether inhibiting MAO enzymes was beneficial or detrimental to SNc dopamine neurons, mice were administered 5mg/kg meth for 2 weeks with a 30min pretreatment of 1mg/kg rasagiline (MAO inhibitor) or saline, sacrificed after 2 weeks withdrawal and tyrosine hydroxylase positive (TH^+) cells in the SNc counted. Chronic meth decreased TH^+ cells in the SNc and rasagiline pretreatment prevented toxicity. These results challenge the current view of dopamine toxicity by demonstrating that MAO-dependent dopamine metabolism selectively increased mitochondrial stress and that this mitochondrial stress contributed to the loss of SNc dopamine neurons. Supported by USPHSG NS047085, JPB and Northwestern Memorial Foundations.

Oral Communications

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The medial preoptic area modulates cocaine-induced neural and behavioral activity.

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Cocaine exerts its effects by exploiting natural neurobiological reward mechanisms, especially the mesolimbic dopamine system. However, the mesolimbic system does not operate in isolation, and input from other reward-relevant structures may play a role in cocaine's effects. Here, using a combination of chemical, anatomical, and behavioral assays we determined whether the medial preoptic area (mPOA), a region in the hypothalamus that regulates natural reward and makes strong anatomical connections with limbic system, is modulating response to cocaine. Results show that the mPOA innervates the VTA in a region-specific manner, that lesions of the mPOA augment cocaine-induced Fos expression in the nucleus accumbens and cocaine-induced conditioned place preference. We also show that approximately 68% of mPOA-VTA efferents release γ-aminobutyric acid (GABA), over 75% are sensitive to dopamine as evidenced by co-localization with dopamine receptors, and nearly 60% of these contain both dopamine receptors and GABA, which suggests a novel key role for the mPOA in the inhibition of the mesolimbic DA circuit. Additionally, we show that lesions of the mPOA or microinjections of estradiol directly into the mPOA increased cocaine-induced release of dopamine in the nucleus accumbens. Immunohistochemical analyses revealed that the mPOA modulates cocaine responsiveness via projections to both dopaminergic and GABAergic neurons in the VTA, and that these projections are sensitive to estrogenic stimulation. Together, our findings point to a novel estradiol-dependent pathway that modulates cocaine-induced neural, neurochemical, and behavioral activity.

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A novel phenylaminotetralin-chemotype 5-HT2C agonist, 5-HT2A and 5-HT2B neutral antagonist and an extension of a 5-HT2C receptor activation mechanism for treating addiction.

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The serotonin 5-HT2A and 5-HT2C G protein-coupled receptors (GPCRs) have emerged as novel medication targets for the treatment of drug addiction. Results from numerous, independent laboratories provide evidence that reduction of 5-HT2A signaling as well as activation of 5-HT2C signaling modulate dopamine signaling in reward circuits, and behavioral studies show that these effects translate to impact many indices of addiction. Recently, we reported novel 2-aminotetralin (AT) chemotypes, including (2*S*,4*R*)- 4-phenyl-AT (PAT) and meta-bromo-PAT (MBP), that possess unique, combined 5-HT2A (and 5-HT2B) antagonist and 5-HT2C agonist polypharmacology properties. *In vivo*, PAT and MBP are effective at blocking psychomotor effects of many addictive drugs, including amphetamine, cocaine, and oxycodone. Though MBP, PAT, and other 2-AT analogues that we have developed do not affect locomotor activity on their own, they do possess high affinity antagonist/inverse agonist activity at histamine H1 GPCRs. Herein, we report on results to optimize 2-AT-type ligands to enhance selectivity at 5-HT2 over H1 GPCRs. The 4-meta-chlorophenyl-6-methoxyl-AT analog (CMAT) maintains <40 nM affinity at 5-HT2 receptors, but displays >80 nM affinity at H1. Furthermore, CMAT maintains potent 5-HT2C agonist activity (EC50 = 34 nM), without activating 5-HT2A, 5-HT2B, or H1 receptors (neutral antagonism), determined by *in vitro* Gq-phosphoinositide hydrolysis. *In vivo* assessment of CMAT in several addiction assays are in progress. Results will be presented in the framework of a mechanistic hypothesis wherein 5-HT2C receptor activation can regulate intrinsic neuronal activity in the nucleus accumbens shell to counteract effects of addictive drugs. Future studies will test this hypothesis employing our 2-AT drug candidates and commercially available, selective 5-HT2C agonist probes. Support: R01-DA023928, DA030989, MH081193.

Poster Communications

1

Additive Effects of Spiradoline and CP55940 in Rats: Potential of Drug Mixtures for Treating Pain

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Chronic pain is experienced by approximately 100 million Americans, and currently available pharmacotherapies for treating pain are not effective in some patients and have adverse effects that preclude their use in others. By combining drugs it might be possible to use smaller doses thereby reducing the likelihood of adverse effects. CP55940 (cannabinoid receptor agonist) and spiradoline (kappa opioid receptor agonist) both produce antinociceptive effects, and a mixture of small doses of these drugs have antinociceptive effects that are equal to larger doses of either drug given alone. The current experiment compared the antinociceptive and hypothermic effects of spiradoline and CP55940 alone and in mixtures. Cumulative dose-effect functions (30-min inter-injection intervals) were determined for spiradoline (0.32 – 32.0 mg/kg, i.p.) and CP55940 (0.01 – 1.0 mg/kg, i.p.) in 8 male Sprague Dawley rats for warm water tail withdrawal latency and rectal body temperature. Both drugs increased tail withdrawal latency from 50°C water to 20 s (maximum) and decreased body temperature by approximately 4°C. ED_{50} values for antinociception were used to determine the doses for mixtures in ratios of 3:1, 1:1, and 1:3. The interaction between spiradoline and CP55940 in mixtures was at least additive for antinociception and hypothermia. Thus, CP55940 enhanced both a potentially useful effect of spiradoline (antinociception) and an adverse effect (hypothermia). It remains to be determined whether selective enhancement of antinociception occurs with other drugs, as the interaction between opioids and cannabinoids under other conditions vary markedly depending on the drugs in the mixtures. Support: NIDA K05DA017918 and T32DA031115.

2

Kappa opioid receptor targeted drug abuse therapy through the development of salvinorin A analogs.

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Over 23 million Americans require treatment for drug or alcohol addiction each year. Limited medication options are currently available for the treatment of opioid and alcohol abuse, but no FDA approved medications for stimulant abuse exist. Kappa opioid receptor (KOR) agonists have shown success in treating abuse related behaviors in several animal models of drug abuse.

The potent and selective KOR agonist salvinorin A (SVA) is a structurally-unique natural product, lacking a basic nitrogen. It is a structurally complex molecule, with a variety of sensitive functional groups and stereocenters. While SVA has interesting and desirable pharmacological activity, it still possesses some undesirable pharmacokinetic properties such as poor water solubility and bioavailability. By probing the structure-activity relationships (SAR) at KORs, we hope to identify a point on the molecule that can be modified to address these pharmacokinetic shortfalls without loss of KOR activity.

Previous investigation of the SVA structure indicated the lactone as being tolerant to modifications. Development of synthetic strategies to further derivatize this lactone position (C17) now allow for semisynthetic modification of salvinorin A. Evaluation of these analogs for KOR activity indicate that while C17 substitutions are tolerated, they are not required. Additionally, substituents capable of hydrogen-bonding as well as sterically small groups are preferred. The lactone moiety of SVA has been validated as a point on the natural product where structural changes affecting water solubility are tolerated without activity loss.

3

Prolonged functional competence of Delta opioid- Kappa opioid (DOR-KOR) heteromers in the rat carrageenan model of inflammatory pain.

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Opioid receptor systems expressed by peripheral pain-sensing neurons (nociceptors) are under dual regulatory control by cyclooxygenase (COX) and lipoxygenase (LOX) dependent arachidonic acid (AA) metabolites. We have found that for both DOR and KOR, COX metabolites enhance opioid receptor-mediated antinociceptive signaling whereas LOX metabolites inhibit antinociceptive signaling in vivo and ex vivo. In addition, we have found that in nociceptors, DOR and KOR form heteromers that when activated, produce profound antinociception. In this study, we examined the actions of the DOR agonist, DPDPE, the KOR agonist, U50488 and the DOR-KOR heteromer agonist, 6'-GNTI, to inhibit carrageenan induced thermal allodynia in the rat. When tested 15 min after intraplantar (i.pl) injection of carrageenan (500 ug), all agonists were effective at reducing carrageenan-induced thermal allodynia. When tested either at 3h or 24h post-injection of carrageenan, neither DPDPE nor U50488 reduced thermal allodynia. However, responsiveness to both agonists was restored following i.pl injection of the selective 12/15 LOX inhibitors, luteolin and baicalein. By contrast, the heteromer agonist, 6'-GNTI, inhibited thermal allodynia when tested at both 3h and 24h post-injection of carrageenan. Further, following injection of the LOX inhibitors, antinociception to 6'-GNTI was unaltered suggesting that DOR-KOR heteromer signaling is not regulated by LOX. These data suggest that in striking contrast to DOR and KOR, DOR-KOR heteromers remain functionally competent for a prolonged period of time under carrageenan induced inflammatory conditions. We propose that DOR-KOR heteromers may be good targets for development of peripherally-restricted opioid medications for treatment of inflammatory pain.
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4

The ovarian hormone estradiol promotes the rewarding effects of nicotine in female rats

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Introduction: Epidemiological studies have revealed that females are more susceptible to tobacco use than males. However, it is presently unclear whether sex differences in the rewarding effects of nicotine are modulated via the presence of ovarian hormones, such as β-estradiol (E2) in females. To address this question, the present study utilized a rodent model of intravenous self-administration (IVSA) to compare the rewarding effects of nicotine in intact females, males and ovariectomized (OVX) female rats. A follow up study also compared nicotine IVSA in OVX rats that received either vehicle or E2 supplementation. **Methods**: Rats received OVX or sham procedures (intact) at post-natal day 45. A separate group of female rats received OVX procedures and then immediately began an E2 supplementation regimen (25 or 250 μg) or repeated injections of a peanut oil vehicle. The E2 supplementation procedure involved E2 administration for 2 consecutive days followed by 2 days of vehicle injections throughout the study. The rats were trained to operant respond for food and water for 5 days in the operant chambers. Then, they were implanted with a jugular catheter for IVSA procedures. Following a 4-day recovery period, the rats were then given 23-hour access to nicotine IVSA using an escalating dose regimen (0.015, 0.03, and 0.06 mg/kg). Each dose was self-administered for 4 days with 3 intervening days of drug abstinence. **Results**: With regard to sex differences, our results revealed that intact females displayed significantly higher levels of nicotine intake as compared to males. With regard to the role of ovarian hormones, we found that intact females also displayed higher levels of nicotine intake as compared to OVX females. Furthermore, our results revealed that the latter effects are E2-mediated given that OVX rats that received E2 supplementation displayed significantly higher levels of nicotine intake as vehicle controls. **Conclusion**: Taken together, our data suggest that the rewarding effects of nicotine are enhanced in female versus male rats. Also, our findings imply that the strong rewarding effects of nicotine are modulated via the presence of the ovarian hormone, E2.

Poster Communications

5

The medial preoptic area modulates cocaine-induced locomotion in male rats.

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Cocaine-induced locomotion is modulated by dopamine in the nucleus accumbens (NAc). Recent evidence suggests that the medial preoptic area (mPOA), a region in the rostral hypothalamus, modulates cocaine-induced increased dopamine in the NAc. Whether the mPOA similarly influences cocaine-induced locomotion is not known. To answer this question, we examined whether radiofrequency or neurotoxic lesions of the mPOA in male rats influence changes in locomotion that follow cocaine administration. Locomotion was measured following cocaine administration in male rats with neurotoxic, radiofrequency, or sham lesions of the mPOA. Results indicate that bilateral lesions of the mPOA facilitated cocaine-induced locomotion. This facilitation was independent of lesion type, as increased locomotion was observed with either approach. These findings support a role for the mPOA as an integral region in the processing of cocaine-induced behavioral response, in this case locomotor activity.

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Atypical Dopamine Transporter Inhibitors R-Modafinil and JHW007 Differentially Alter D2 Autoreceptor Currents and Firing Rate in Midbrain Dopamine Neurons

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Psychostimulants increase attention and induce euphoria, are commonly abused, and can damage human health up to and including death. Currently, there are no FDA approved clinical treatments for psychostimulant abuse. A common target of psychostimulants is the DA transporter (DAT), which is expressed on midbrain DA neurons and is responsible for reuptake of DA from the extracellular space. D2 autoreceptors on these neurons powerfully inhibit cell firing and have been inversely associated with psychostimulant use. Cocaine, a highly abused psychostimulant, is a typical DAT inhibitor that produces hyperlocomotion and reinforcement in rodents. Recently, a separate class of compounds termed atypical DAT inhibitors have been shown to bind DAT with high affinity and block reuptake, but are less likely to induce cocaine-like behavioral effects. Evidence from behavioral studies supports that atypical DAT inhibitors can decrease cocaine self-administration in rodents, which suggests potential therapeutic benefits for human cocaine users. However, the cellular actions of atypical compounds are unknown. Therefore, we are investigating the effects of atypical DAT inhibitors R-Modafinil and JHW007 on D2 autoreceptor-mediated currents and DA neuron excitability by performing patch-clamp electrophysiology of midbrain DA neurons in brain slices from DBA/2J mice. R-Modafinil increased D2 autoreceptor current amplitude and width and decreased DA neuron firing rate in a D2 autoreceptor dependent manner. Conversely, JHW007 primarily decreased D2 autoreceptor current amplitude and had little effect on width and DA neuron firing rate. These findings suggest that, despite both being atypical DAT inhibitors, these two compounds exhibit profoundly different effects on DA neuron excitability.

7

Interactions between vulnerability phenotypes and 3,4-Methylenedioxypyrovalerone (MDPV) self-administration in rats.

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The use of designer stimulants (*bath salts*) is associated with high rates of abuse and toxicity. 3,4-Methylenedioxypyrovalerone (MDPV) is a synthetic cathinone and common constituent of *bath salt* preparations. Early studies in rats suggest that MDPV has powerful reinforcing effects and that a subset of rats exhibit high rates of drug intake (~3-fold greater) and high levels of responding during timeouts (TOs). The goal of the current study was to determine if behavioral phenotypes associated with high levels of cocaine self-administration (e.g., response to novelty, saccharin preference, and sign-tracking) would also predict exaggerated MDPV self-administration. Accordingly, male Sprague Dawley rats (n=16) were first assessed in a battery of tests (90-min open field test, 24-hr two-bottle saccharin preference test, and a Pavlovian conditioned approach procedure) prior to the acquisition of responding for 0.032 mg/kg/inf MDPV under a fixed ratio (FR) 1:TO 5-sec schedule of reinforcement. Following the initial 10-day acquisition period, the response requirement was increased and rats were allowed to respond for MDPV under an FR5:TO 5-sec for an additional 10 sessions. Forty percent of rats were characterized as *high-responders* (operationally defined as making >20% of total responses during TOs), with the remaining 60% characterized as *low-responders* (<20% of total responses during TOs). Despite a 6-fold greater level of MDPV self-administration, *high-responders* did not differ from *low-responders* with regard to the amount of activity during the open field test, saccharin preference, or the development of a sign-tracking phenotype during the conditioned approach procedure. These findings suggest that the factors that underlie high levels of MDPV intake differ from those that predispose animals to high levels of cocaine intake, and that these factors might contribute to the high rates of abuse among *bath salts* users.

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"Binge-like" toluene exposure produces sub-region and layer specific alterations in the excitability of mPFC pyramidal neurons projecting to NAc core of adolescent but not adult rats.

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Inhalants are often one of the first drugs of abuse tried among adolescents and young adults and abuse rates among adolescents are greater than those of adults. Similar to other drugs of abuse, inhalants such as toluene have a high abuse potential and are capable of modifying brain reward circuitry such as the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc). However, it remains unclear whether the higher incidence of inhalant abuse among adolescents reflects a heightened sensitivity of reward circuitry to solvents such as toluene. In this study, we hypothesized that "binge-like" toluene exposure would alter the activity of mPFC neurons in a projection specific manner. To address this question, we used whole-cell electrophysiology to assess the intrinsic excitability of prelimbic (PRL) and infralimbic (IL) pyramidal neurons in both adolescent and adult rats previously exposed to air or toluene (5700 PPM). Prior to vapor exposure, fluorescent retrobeads were injected into the NAc core sub-region in order to identify projection specific mPFC neurons. In toluene treated adolescent rats. PRL layer 5 (PRL5) neurons exhibited suppressed firing rates that were associated with increased rheobase, increased ½ spike duration, increased inward rectification, a reduction in membrane resistance, and a reduced IH current. These alterations were not observed in PRL layer 2/3 (PRL2/3) neurons. In contrast to PL neurons, IL layer 5 (IL5) and layer 2/3 (IL2/3) exhibited enhanced firing in toluene-exposed animals. Enhanced firing of IL5 neurons was associated with a reduction in rheobase. "Binge-like" exposure to toluene in adult rats did not produce sub-region or layer-specific alterations of mPFC neurons projecting to the NAc core. These findings suggest that specific projections of the reward circuitry are more susceptible to the effects of toluene abuse during adolescence. Supported by grants R01 DA013951 and T32 DA007288.

Poster Communications

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Behavioral effects of novel $GABA_A$ receptor positive allosteric modulators in rats.

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Chronic pain remains a clinical challenge. While opioids are commonly prescribed for treatment, their use is limited due to undesired effects. Consequently, the development of novel effective analgesics is a critical need. Positive allosteric modulators (PAMs) of the $GABA_A$ receptors selective for α2/3 subunits, have received increasing attention as potential analgesics. Unlike classical benzodiazepines (nonselective to all $GABA_A$ receptor subunits), these PAMs could potentially produce analgesia (an α2/3 subunit-mediated effect) without producing other pharmacological effects. This study examined the behavioral effects of 3 novel subunit-selective $GABA_A$ receptor PAMs, HZ166, KRM II 18B, and KRM II 81, in rats. In two pain assays (mechanical and thermal hyperalgesia as measured by von Frey and plantar tests) using a rat model of complete Freund's adjuvant-induced inflammatory pain, all 3 PAMs and the benzodiazepine (BZD) midazolam dose-dependently attenuated mechanical and thermal hyperalgesia. In the procedure of food-maintained operant responding, all PAMs did not significantly alter the response rate at doses that produced analgesia. However, midazolam significantly reduced the response rate at the dose that significantly reduced hyperalgesia. In a horizontal wire test designed to measure muscle relaxation, within the dose range that produced antihyperalgesic activity only midazolam dose-dependently increased the score of wire test, suggestive of muscle-relaxant activity. All behavioral effects can be attenuated by the BZD receptor antagonist flumazenil, confirming behavioral effects of these subunit-selective PAMs are mediated through the BZD binding site of $GABA_A$ receptors. Collectively, unlike midazolam which produced antihyperalgesic, rate-suppressing and muscle-relaxant activity at similar doses, the subunit-selective $GABA_A$ receptor PAMs seem to selectively produce antihyperalgesic effect, although at significantly larger doses other behavioral effects were evident. These data support the further study of α2/3 subunit-selective $GABA_A$ receptor PAMs as potential analgesics against chronic pain.

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Investigation of ligands targeting the Nociceptin opioid receptor as non-addictive anti-nociceptive agents in a mouse model of inflammatory pain

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A substantial body of evidence has indicated that the Nociceptin receptor (NOPr) may be a viable alternative target for pain treatment without the risk of addiction and dependence present with traditional painkillers acting through the mu opioid receptor. This work investigates the actions of agonists and antagonists acting at NOPr both in wild type mice with inflammatory injuries, and in mice with genetic modifications involving signaling molecules downstream of NOPr activation.

λ-carrageenan is a seaweed derived protein which causes a local inflammatory reaction when applied to tissue. When administered to the hind paw this protein produces a behavioral hypersensitivity reaction to noxious mechanical stimuli (e.g. Von Frey test). Here we show that the NOPr antagonist J-113397 (J11) can significantly reverse this hypersensitivity reaction, while the systemically active NOPr agonist Ro64-6198 can mimic this hypersensitivity (in a J11 reversible manner) when administered to healthy mice.

Signaling downstream of NOPr, like other opioid receptors, is negatively modulated by Regulator of G protein Signaling (RGS) proteins, a family of intracellular accessory proteins. To further test the role of NOPr in these behaviors we studied mice that have a genetic mutation such that they lack RGS regulation of the NOPr. These mice showed a baseline hypersensitivity in the Von Frey test that was reversed by the NOPr antagonist J11.

Together the results suggest that NOPr is involved in inflammatory hypersensitivity to mechanical stimuli, and suggests that NOPr antagonists should be investigated as non-addictive analgesics for the treatment of inflammatory pain.

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Examination of Phosphatidylethanol in Light vs. Heavy Drinkers Before and After 0.4 and 0.8 g/kg Ethanol Consumption

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The purpose of this study was to examine baseline levels, half-life, and area under the curve (AUC) of phosphatidylethanol (PEth) in uncoagulated, whole blood samples taken from light vs. heavy drinkers before and after consumption of 0.4 and 0.8 g/kg doses of ethanol. Heavy (n = 24) and light (n = 24) drinkers received either 0.4 (n = 25) or 0.8 g/kg (n = 23) oral doses of ethanol during a 15 min period. Blood samples were collected prior to and during the next 6 hrs after each ethanol dose, and every 3 days during the next 14 days. Breath alcohol concentrations were measured concurrently and a transdermal alcohol monitor was worn throughout the 22 days of participation to verify abstinence 7 days prior and 14 days after the ethanol consumption. PEth levels were quantified using HPLC/MS/MS and are reported as PEth 16:0/18:1, PEth 16:0/18:2, and combined PEth (PEth 16:0/18:1 + PEth 16:0/18:2). Results revealed that there are large inter-individual differences among participants for baseline level, half-life, and AUC of PEth 16:0/18:1, PEth 16:0/18:2, and combined PEth). Though heavy drinkers tended to have higher baseline levels of combined PEth than light drinkers, no significant differences at $p < 0.05$ were identified. Also, only tendencies for participants who consumed heavy dose to have a larger AUC, longer half-life, and high final combined PEth measurements (end of the 14 days post-ethanol consumption) were evident. The variability of these results is likely due to different absorption rates of ethanol and synthesis and elimination rates of PEth among participants. The mean half-life of combined PEth determined using blood samples collected during the 14 days post-ethanol consumption (combined PEth 16:0/18:1 and PEth 16:0/18:2) was 6.0 ± 3.7 (SD) days (range 1.48 to 15.4 days). Future research should more thoroughly examine how PEth levels may vary among types of drinkers, given their differential patterns of drinking (e.g., binge drinkers vs. social drinkers). This research was funded by a grant from NIAAA.

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Design of Sterol Carrier Protein-2 (SCP-2) Inhibitors as Endocannabinoid Transport Modulators

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Agents capable of augmenting endocannabinoid (eCB) signaling have potential in treating disorders of stress, anxiety, and pain, absent adverse behavioral effects. The presence of a putative uptake transporter for anandamide (AEA) remains controversial; though several probes are capable of inhibiting AEA uptake *in vitro* and producing antinociceptive actions *in vivo*, the protein or proteins responsible for this activity are unknown. We recently identified sterol carrier protein-2 (SCP-2) as a cytoplasmic binding and transport protein for eCBs [*Mol. Neurobiol.*, 2014, 50, 149-158]. To delineate the role of SCP-2 in eCB pharmacology *in vivo*, high-potency SCP-2-selective probes must be developed. We applied computational docking (AutoDock 4.2) to predict binding modes of endogenous SCP2 cargo (cholesterol; AEA; 2-arachidonoyl glycerol, 2-AG), known AEA uptake inhibitors (AM-404), and a series of five SCP-2 inhibitors (SCPI1-5). We also discovered novel potential lead compounds within our in-house library using high-throughput screening *in silico*. Our finding that AM-404 inhibits SCP-2 *in silico* and *in vitro* supports the hypothesis that SCP-2 plays a role in AEA transport. The results of this study provide a rationale for developing SCP-2-selective inhibitor probes as novel anxiolytics and analgesics.

This work was supported by a New Investigator Award given by the American Association of Colleges of Pharmacy (AACP, CWC) and a Concordia Intramural Research Grant (CIRG, CWC).

Poster Communications

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Discovery of 4-Undecylpiperidine-2-Carboxamides as Selective Serotonin (5-HT) 5-HT$_{2C}$ Receptor Positive Allosteric Modulators for Potential Neurotherapeutics

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Abstract: Augmentation of serotonergic tone, specifically at the serotonin (5-HT) 5-HT$_{2C}$ receptor (5-HT$_{2C}$R), has been identified as a promising therapeutic strategy in response to pathologically diminished signaling capability, as seen in multiple neurological disorders, such as depression, schizophrenia, and impulsive disorders including cocaine addiction. Positive allosteric modulators (PAMs) of the 5-HT$_{2C}$R present a novel and favorable strategy to fine-tune binding and/or signaling in response to endogenous 5-HT in a site- and event-specific manner. PNU-69176E is currently the only reported selective PAM of 5-HT$_{2C}$R. While biological characterization via intracellular calcium (Ca_i^{2+}) release assay suggests efficacy and potency at 5-HT$_{2C}$R with no intrinsic agonist activity, PNU-69176E has sub-optimal drug-like properties and poor bioavailability. Therefore, lead optimization of PNU-69176E is of high importance to promote translational therapeutic development with new simplified small molecules. Novel analogues (e.g., CYD-1-79) have been achieved through the modification of the lipophilic long alkyl chain (undecyl) and polar moiety that flank the piperidine-2-carboxamide core scaffold. Excitingly, these efforts have yielded a selective and efficacious 5-HT$_{2C}$R PAM that exhibits favorable pharmacokinetic characteristics and modulates 5-HT$_{2C}$R-associated behaviors *in vivo* in a dose-dependent manner. Such PAMs for the 5-HT$_{2C}$R are capable of functioning as unique tools to elucidate neuropathological serotonergic function, and further medicinal chemistry optimization will yield promising therapeutic candidates with a potential for a first-in-class neurotherapeutic.

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Self-Compassion and Substance Use

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Self-compassion, extending compassion to one's self in instances of perceived inadequacy or failure, is associated with improved health outcomes. It may also be a valuable construct when considering interventions for substance use disorders. This pilot study examines the association between drug risk and self-compassion. Bivariate statistics indicated that age, males, and low education level were significantly associated with drug risk. A linear regression was used to explore the association of self-compassion and sex on drug risk. This study suggests levels of self-compassion may potentially be predictive of drug risk, especially when considering sex.

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CXCR4 antagonist Plerixafor attenuates cue and drug Induced relapse to cocaine seeking and expression and development of cocaine-induced conditioned place Preference.

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Evidences suggest that chemokines have neuromodulatory functions. The chemokine receptor CXCR4 is a plasma membrane G-protein coupled receptor (GPCR) expressed on astroglia and neurons in CNS. Studies have shown that CXCR4 activation by the endogenous ligand CXCL12, also identified as stromal cell-derived factor-1α (SDF1-α), increases astrocytic glutamate release. In addition, intranigral injection of SDF1-α increased striatal extracellular dopamine, an effect that was blocked by administration of a selective CXCR4 antagonist. We have previously shown that CXCR4 antagonist, Plerixafor, attenuates cocaine induced locomotor activity and decreases cocaine taking behavior under the FR-1 schedule of reinforcement of self-administration. In this study, we assessed the effect of Plerixafor, a selective CXCR4 antagonist, on cue- and cue/drug- induced reinstatement to cocaine, on expression and development of cocaine induced conditioned place preference and identify a role for the CXCR4 system in cocaine reinforcement. Our results show that AMD3100 attenuated cue-induced and cue and drug-induced reinstatement to cocaine seeking. AMD3100 also decreased preference score in both expression and development of cocaine-induced conditioned place preference.

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Validation of an Electronic Cigarette (E-Cig) Rodent Dosing System.

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Aims: Despite dramatic increases in use of electronic cigarettes (e-cigs) for both intended and unintended purposes (drug abuse), most preclinical research continues to use parenteral administration to investigate biological and behavioral mechanisms underlying their use. These routes of administration do not allow for investigation of the effects of aerosol products to which humans are actually exposed. The purpose of this study was to validate an e-cig aerosol delivery system for rodents using nicotine and cannabinoids and to compare aerosol effects to injected drug.
Method: A commercially available e-cig device was modified to deliver generated aerosol to a mouse enclosed in a vapor chamber. Adult ICR mice were administered vehicle or drug, either via aerosol (5 min exposure) or injection, and subsequent effects on body temperature, analgesia and motor activity were assessed. Three concentrations/doses of nicotine, CP55,940, AB-CHMINACA, XLR-11 and JWH-018 were tested.
Results: All the drugs tested produced concentration/dose-dependent decreases in temperature and locomotor activity for both routes of administration. The cannabinoids, but not nicotine, produced concentration/dose-dependent effects on analgesia as well.
Conclusion: The e-cig rodent dosing system was successful in generating aerosol from a liquid containing nicotine or cannabinoids. Aerosol or parenteral administration of nicotine and cannabinoids produced a similar profile of effects in mice, although there were some differences in time course. These results validate use of the aerosol method to deliver pharmacologically active concentrations of nicotine and cannabinoids. One limitation of the procedure was that aerosol required a longer exposure time than is ideal, representing an area for future research. Future research with this system will also focus on delineation of pharmacokinetic differences between aerosol and other routes of administration as well as modifications to allow for self-administration of aerosol.
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Poster Communications

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Abuse-related effects $GABA_A$ receptor positive allosteric modulators in an assay of intracranial self-stimulation in rats

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$GABA_A$ receptor positive allosteric modulators ($GABA_A$ PAMs), such as the benzodiazepine diazepam, are used clinically to treat disorders that include insomnia and anxiety; however, therapeutic use of these compounds is limited in part by abuse liability. In an effort to improve therapeutic efficacy and safety, novel $GABA_A$ PAMs have been developed that vary in efficacy at, and selectively for, $GABA_A$ receptor subtypes that contain α1, α2 or α3 subunits. Intracranial self-stimulation (ICSS) is one preclinical procedure that has been used to evaluate abuse potential of drugs, and this study compared effects on ICSS produced by diazepam (high-efficacy and relatively non-selective), zolpidem (high-efficacy and selective for $GABA_A$ receptors containing an α1 subunit), and the compounds JY-XHe-053, XHe-II-053 and HZ-166 (intermediate-efficacy with putative selectivity for $GABA_A$ receptors that contain α2/α3 subunits). Adult, male Sprague-Dawley rats (n=17), implanted with a bipolar electrode in the medial forebrain bundle, were trained to respond under a fixed-ratio 1 schedule for brain stimulation delivered at 10 different frequencies (56-158 Hz in 0.05 log increments). Under baseline conditions, brain stimulation maintained a frequency-dependent increase in response rates. Diazepam (0.1-10 mg/kg) and zolpidem (0.032-3.2 mg/kg) produced a transient and abuse-related facilitation of ICSS at low doses but primarily depressed ICSS at higher doses. JY-XHe-053 (3.2-32 mg/kg) and HZ-166 (3.2-32 mg/kg) produced significant but weaker and less reliable ICSS facilitation, and XHe-II-053 (3.2-32 mg/kg) had no effect on ICSS. These results are consistent with other clinical and preclinical evidence for abuse potential of diazepam and zolpidem and also suggest that high efficacy and/or selectivity at α1 $GABA_A$ receptor subtypes contributes to abuse-related effects of $GABA_A$ PAMs in this ICSS procedure.

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A rational drug design strategy for novel dopamine D4 receptor agonists.

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The dopamine D4 receptor (D4R) is enriched in the prefrontal cortex where it is believed to play an important role in modulating executive function. Previous studies using D4R ligands of varying efficacies indicate the D4R signaling may have important consequences in drug addiction and cognition. Developing novel D4R-selective ligands will allow more detailed investigations into the biological roles of D4R signaling in the brain and may lead to pharmacotherapies for a variety of neuropsychiatric conditions.

Herein, we describe preliminary results from a rational drug design strategy—using combined techniques in medicinal chemistry, pharmacology and molecular modeling—in the design of novel D4R agonists. A library of novel ligands structurally related to the selective D4R agonist A-412997 was synthesized and evaluated for binding affinity and *in vitro* efficacy in D4R-expressing HEK293 cells. A homology model of D4R was created using the high-resolution X-ray structure of D3R in complex with a ligand (3PBL). Using affinity values determined experimentally or from literature, the best docking score function was selected and subsequently used to make predictions on the binding affinities of the novel library. We found a good correlation (R^2=0.633) between predicted binding energies of the novel ligands and experimentally derived affinity values. Using this validated model, we are designing, synthesizing and testing a second generation of ligands with the goal of developing new research tools and potential pharmacotherapeutics.

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The role of impulsivity in the accumulation of stress across adolescence

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Impulsivity is a complex construct that may impact how stress is accumulated across time. Early life stress exposure may occur, at least in part, because of the actions or behaviors of highly impulsive parents (i.e. behavior-independent stress). Additionally, impulsive youth create their own stress (i.e. behavior-dependent stress) and it has been suggested that emerging studies of stress exposure consider and test direct relationships between familial impulsivity (i.e. youth and parent) and the accumulation of early life stressors. The current study sought to explore the effects of youth and parent impulsivity on the accumulation of stressful life events (i.e. overall stress, behavior-independent stress, and behavior-dependent stress) in adolescence.

Three-hundred thirty-one youth (52.3% girls) and their biological mothers participated in semi-structured diagnostic interviews and self-report measures both at study entry and biannual follow-ups.

Linear mixed-effects models examined relations between youth and maternal impulsivity and the accumulation of youth stressful life events over time while controlling for gender, family history status, and history of maternal substance use. No significant three-way interactions between youth impulsivity, mother impulsivity and time were found. Reduced models showed that unlike mother's impulsivity, youth's impulsivity at study entry was associated with an increased rate of accumulation of overall ($t(1850) = 3.33$, $p = 0.001$), behavior-independent ($t(1850) = 3.02$, $p = 0.003$), and behavior-dependent stressful life events across time ($t(1850) = 2.72$, $p = 0.007$). Girls and youth with family histories of substance use disorder reported faster rates of overall, behavior-independent, and behavior-dependent stress.

This novel study extends the limited research on the role of impulsivity in the accumulation of adolescent stress exposure. We continue to follow this cohort prospectively and future research will explore the factors contributing to stress exposure in adolescence.

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Evaluation of 3,4-methylenedioxypyrovalerone (MDPV) and 4-methylmethcathinone (4-MMC) in rats trained to discriminate d-amphetamine.

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Recent reports on the abuse of novel synthetic cathinone derivatives (i.e. "bath salts") call attention to serious public health risks of these chemicals. In response to this concern, a growing body of preclinical research has characterized the psychopharmacology and abuse liability of these substances, particularly that of two of the most common constituents, methylenedioxypyrovalerone (MDPV) and 4-methylmethcathinone (4-MMC). The present study assessed the discriminative stimulus effects and pharmacodynamics of MDPV and 4-MMC in animals trained to discriminate d-amphetamine. Eight adult male Sprague-Dawley rats were trained to discriminate 0.5 mg/kg d-amphetamine (AMPH) from saline. Dose response curves were determined with AMPH (0.125 – 1.0 mg/kg), MDPV (0.125 – 2.0 mg/kg), and 4-MMC (0.25 – 2.0 mg/kg). Additionally, a range of selected doses of MDPV and 4-MMC were tested in combination with the D_1 receptor antagonist SCH 39166 (0.3 mg/kg) to assess D_1 receptor mediation in producing the interoceptive stimuli of these drugs. MDPV and 4-MMC both produced dose-dependent increases in drug-lever responding with full substitution for AMPH at 0.5 mg/kg MDPV and 2.0 mg/kg 4-MMC. SCH 39166 produced a marked downward shift in the MDPV dose response curve at all doses tested. Preliminary results indicate a similar downward shift with SCH 39166 in combination with 4-MMC. A comparison of the MDPV dose-response curve with that of 4-MMC suggests that MDPV has considerably more potent psychostimulant effects than 4-MMC. This is line with our previous findings indicating that MDPV and 4-MMC produce amphetamine-like and MDMA-like discriminative stimuli respectively. The downward shift in the MDPV and 4-MMC dose response curves produced by SCH 39166 implicates the involvement of D_1 receptors in the discriminative stimulus effects of these synthetic cathinones. Additional receptor antagonist tests are currently in progress to further elucidate specific receptor mechanisms mediating the discriminative stimulus effects of MDPV and 4-MMC.

Poster Communications

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A Comparison of the Antinociceptive Effects of ZZ204G, an α9α10 nAChRs Antagonist and Morphine in a Rodent Model

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Treatment of multimodal chronic pain remains a problem because of differential sensitivity of different types of pain to a given treatment and side effects of existing analgesics (opioids, NSAIDs, etc.). Although the real target remains elusive, some selective α9α10 nicotinic acetylcholine receptor (nAChR) antagonists (α-conotoxins and small non-peptide molecules) were identified as promising and well-tolerated pharmaceutical tools for pain treatment. In this study, we determined the antinociceptive effects of acute and chronic treatment with one such small molecule (ZZ204G). Morphine (MOR) was used as a reference standard. Experiments were conducted in male Sprague-Dawley rats. ZZ204G and MOR were administered intraperitoneally, acutely or chronically (9-day daily treatment). The antinociceptive effects of treatments were measured by hot water tail flick latency (TFL), hind limb paw withdrawal hot plate threshold (HPT), paw pinprick sensitivity threshold (PST) and paw pressure threshold (PPT) tests. In acute treatment experiments, ZZ204G dose-dependently increased TFL, HPT and PST (ED_{50}=190±19, 26±9 and 168±80 μg/kg respectively), but had little effect on PPT. MOR produced antinociceptive effects in TFL, HPT and PPT tests, but not in the PST test. When tested at the highest safe doses in the TFL test, antinociceptive effects of ZZ204G (1.8mg/kg) and MOR (5.6mg/kg) peaked at 15 and 60 minutes, but the action of ZZ204G outlasted that of MOR by approximately 4 hours. Co-administration of ZZ204G and MOR at their ED_{50} dose produced additive antinociception (HPT). In chronic treatment experiments, complete tolerance to MOR was developed within 7-9 days in all pain assays, while antinociceptive efficacy of ZZ204G toward PST, HPT and TFL remained preserved over 9-day treatment. ZZ204G appears to be a suitable alternative to MOR for treatment of acute and chronic superficial burning and pricking pain.

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Differential antagonism and nicotine-induced tolerance/cross-tolerance among nAChR agonists in mice

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This study examined the extent to which nAChR agonists act at the same receptors to produce in vivo effects. Various nAChR agonists were studied alone, in combination with mecamylamine and the β2* nAChR antagonist dihydro-β-erythroidine (DHβE), and during daily nicotine treatment consisting of 3 doses per day, 1.78 mg/kg per dose, 90 min apart. Male C57BL/6J mice (n=7) responded under an FR20 schedule of food delivery; rectal temperature was assessed. Nicotine, epibatidine, varenicline, and cytisine dose-dependently decreased rate of responding. Nicotine, epibatidine, and varenicline also dose-dependently decreased rectal temperature, whereas cytisine did not up to a dose of 5.6 mg/kg. Mecamylamine (1 mg/kg) significantly antagonized the rate-decreasing and hypothermic effects of each agonist ($p<0.05$). DHβE (3.2 mg/kg) antagonized the rate-decreasing and hypothermic effects of nicotine and epibatidine, but not those of varenicline and cytisine. Daily nicotine treatment produced significant rightward shifts in the nicotine dose-response functions (i.e., tolerance) of 4.7-fold for rate-decreasing effects and 5.1-fold for hypothermic effects. Daily nicotine treatment produced significant cross-tolerance to epibatidine (i.e., 2.2-fold for rate-decreasing effects and 2.9-fold for hypothermic effects) and varenicline (i.e., 2.0- and 1.7-fold, respectively). Daily nicotine treatment did not significantly modify the potency of cytisine. These results suggest that β2* nAChRs mediate the rate-decreasing and hypothermic effects of nicotine and epibatidine, whereas non-β2 nAChRs mediate the effects of varenicline and cytisine. However, cross-tolerance that develops from nicotine appears to be due to desensitization of both β2* and non-β2 nAChRs.

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Synthesis and evaluation of haptenic heroin surrogates in the development of a heroin vaccine.

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Heroin abuse has emerged as an important public health issue. There has been a 6-fold increase in the number of deaths due to heroin overdose and the number of habitual heroin users has more than doubled (119,000 to 289,000) over the past 14 years. Current treatments for addiction are expensive, potentially abusable, and require significant patient compliance, leading to low long-term success rates. Our goal is to develop a heroin vaccine as an alternative to opiate replacement therapy. Vaccines to drugs of abuse function by eliciting the production of antibodies that then sequester the drug before it crosses the blood brain barrier. Developing a vaccine against heroin is particularly challenging due to the rapid sequential metabolism of heroin into active metabolites 6-acetylmorphine (6-AM) and morphine. We report the synthesis and biological evaluation of novel haptens, 6-AcMorHap and 6-PrOxyHap, which induce high titer and high affinity antibodies for heroin and its metabolites 6-AM and morphine.

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Neurotensin Enhances GABA(A) and Depresses GABA(B) Receptor-Mediated Neurotransmission in the Substantia Nigra through Pre- and Post-synaptic Mechanisms

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Midbrain dopamine neurons play physiological roles in many processes including reward learning and motivated behavior. Midbrain dopamine neurons are tonically inhibited by γ-Aminobutyric acid (GABA)ergic inputs from multiple brain regions. Neurotensin (NT) is a neuropeptide which modulates midbrain dopamine neuron excitability through multiple mechanisms, including a decrease of GABA(B) receptor-mediated inhibition of dopamine neurons. However, it is not known if NT acts post-synaptically on GABA(B) receptor signaling, pre-synaptically at GABA terminals to alter GABA release, or through a combination of synaptic mechanisms. Furthermore, it is not known if NT alters GABA(A) receptor-mediated signaling. Here we utilize whole cell patch-clamp electrophysiology of dopamine neurons in brain slices to investigate NT-induced changes in GABA(A) and GABA(B) receptor-mediated currents in the substantia nigra in mice. Bath perfusion of NT produced a sustained depression of GABA(B) receptor-mediated currents when GABA was released endogenously (due to electrical stimulation) and when GABA was directly applied to the cell (via iontophoresis). Furthermore, NT did not alter GABA(B) receptor-mediated current paired pulse ratios. Together, these data suggest that NT acts post-synaptically to decrease GABA(B) receptor-mediated signaling. Conversely, bath application of NT resulted in an increase in GABA(A) receptor-mediated signaling when currents were elicited via electrical stimulation but not when GABA was applied directly to the cell. These data suggest that NT is acting pre-synaptically to enhance GABA(A) receptor-mediated signaling. As NT is an endogenous peptide present at high levels in the midbrain, determining the mechanism of action by which NT alters midbrain dopamine neuron excitability is a crucial step in understanding the importance of NT in dopamine mediated behavior.

Poster Communications

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The ovarian hormone estradiol promotes the rewarding effects of nicotine in female rats

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Introduction: Epidemiological studies have revealed that females are more susceptible to tobacco use than males. However, it is presently unclear whether sex differences in the rewarding effects of nicotine are modulated via the presence of ovarian hormones, such as β-estradiol (E2) in females. To address this question, the present study utilized a rodent model of intravenous self-administration (IVSA) to compare the rewarding effects of nicotine in intact females, males and ovariectomized (OVX) female rats. A follow up study also compared nicotine IVSA in OVX rats that received either vehicle or E2 supplementation. **Methods**: Rats received OVX or sham procedures (intact) at post-natal day 45. A separate group of female rats received OVX procedures and then immediately began an E2 supplementation regimen (25 or 250 μg) or repeated injections of a peanut oil vehicle. The E2 supplementation procedure involved E2 administration for 2 consecutive days followed by 2 days of vehicle injections throughout the study. The rats were trained to operant respond for food and water for 5 days in the operant chambers. Then, they were implanted with a jugular catheter for IVSA procedures. Following a 4-day recovery period, the rats were then given 23-hour access to nicotine IVSA using an escalating dose regimen (0.015, 0.03, and 0.06 mg/kg). Each dose was self-administered for 4 days with 3 intervening days of drug abstinence. **Results**: With regard to sex differences, our results revealed that intact females displayed significantly higher levels of nicotine intake as compared to males. With regard to the role of ovarian hormones, we found that intact females also displayed higher levels of nicotine intake as compared to OVX females. Furthermore, our results revealed that the latter effects are E2-mediated given that OVX rats that received E2 supplementation displayed significantly higher levels of nicotine intake as vehicle controls. **Conclusion**: Taken together, our data suggest that the rewarding effects of nicotine are enhanced in female versus male rats. Also, our findings imply that the strong rewarding effects of nicotine are modulated via the presence of the ovarian hormone, E2.

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UMB 426: A pyaranomorphinan as a rearrangement product of UMB425

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Even with astonishing advances in the treatment of diseases, there is a continuing need for new drugs to treat moderate-severe pain, especially for chronic pain. 5-(hydroxymethyl)oxymorphone (UMB425) was recently reported as a unique opioid with a dual profile of mu agonism and delta antagonism. This specific polypharmacological profile of UMB425 led to an agent active as an antinociceptive agent in mice, but lacking the undesired effect of tolerance [1]. As part of our continuing studies to optimize and scale-up the synthesis of UMB425 for further development, we discovered an unusual rearrangement of the 3-methylether of UMB425 to give a pyranomorphinan UMB426 as an unusual product during treatment with BBr_3.

Modeling studies predicted UMB426 to possess the desired profile of mu agonism/delta antagonism, confirmed through *in vitro*evaluation. UMB426 has a closer delta/mu affinity ratio than UMB425 (4 vs. 65, respectively), but with a 10-fold lower mu agonist affinity and potency. Accordingly, it represents a strong lead compound to study the optimal ratio for minimal tolerance and dependence *in vivo.*

References: Healy et al., ACS Chemical Neuroscience, 2013, 4 (9), pp 1256-1266

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D1 and D2 receptors in the infralimbic and medial orbitofrontal cortices differentially mediate the reinstatement of cocaine seeking in rats

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Recent work has examined the role of the ventral medial prefrontal cortex (vmPFC) in the regulation of cocaine-seeking behaviors. In particular, evidence suggests that the infralimbic cortex (IL) within the vmPFC suppresses cocaine-seeking behaviors, whereas the more anterior subregion, the medial orbitofrontal cortex (mOFC), has received very little attention in this regard. Despite the established dopaminergic innervation of the vMPFC, whether activation of dopamine receptors in each subregion influences the reinstatement of cocaine seeking is unclear. To address this issue, male Sprague-Dawley rats underwent cocaine self-administration followed by extinction training and reinstatement testing. Immediately prior to reinstatement, rats received microinjections of the D1 antagonist SCH 23390, the D2 antagonist sulpiride, or their respective vehicles. D1 receptor blockade in the IL reduced cued reinstatement but had no effect on cocaine-prime and cue + cocaine-prime reinstatement, whereas D2 receptors blockade in the IL had no effect except to reduce cue + cocaine-prime reinstatement. For the mOFC, however, D1 receptor blockade in the mOFC reduced cocaine seeking in all types of reinstatement, whereas blocking D2 receptors in the mOFC had no effect on any form of cocaine seeking. These findings suggest differential roles for D1 vs. D2 receptors in the IL and the mOFC in regulating cocaine-seeking behavior. Moreover, even as previous work indicates that IL inactivation does not affect reinstatement but, in fact, induces cocaine seeking, the present findings suggest that D1 and D2 receptor activation in the IL promotes cocaine seeking.

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Synthesis of 9-oxophenylmorphans: Potential Biased 5-HT_{2A} Receptor Agonists.

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Alcohol abuse and alcoholism are serious public health concerns. In 2014, over 16 million adults in the USA had an alcohol-use disorder (AUD). Of these 16 million, nearly 1.5 million adults sought treatment for their AUD. Additionally, nearly 88,000 people suffer alcohol-related fatalities every year. These grim statistics show the need for an effective treatment for alcohol abuse. A sizable amount of literature from the 1960's and exciting recent studies indicate that treatment with hallucinogenic drugs as an adjunct to psychotherapy may promote abstinence in those suffering from an AUD. Unfortunately, their hallucinogenic properties limit their clinical utility. Hallucinogens, such as 2,5-dimethoxy-4-iodoamphetamine (DOI), act as agonists of serotonin 2A (5-HT_{2A}) receptors. However, agonists of 5-HT_{2A} receptors that are not hallucinogenic are also known. We have developed a computational chemistry method of predicting non-hallucinogenic 5-HT_{2A} receptor agonists. This model has been validated using the β-blocker carvedilol, which we have determined acts as a 5-HT_{2A} receptor agonist, shows no hallucinogen-like activity *in vivo*, and blocks the hallucinogen-like effects of DOI. This lends promise to the idea that new non-hallucinogenic 5-HT_{2A} agonists can be developed and that these compounds may be useful for the treatment of AUD. We have found an appreciable molecular overlay between our computational model of non-hallucinogenic 5-HT_{2A} agonists and *N*-methyl-9-oxophenylmorphan (PM), and we have begun the synthesis of PM derivatives. In this poster, we will discuss the synthesis and chiral resolution of PM derivatives.

Poster Communications

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Behavioral sensitization to a low dose of cocaine and cross sensitization to mephedrone in male Sprague-Dawley rats.

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The recreational use of synthetic cathinones has increased recently in the United States. For a number of reasons, users often take these drugs in combination with other drugs of abuse, such as cocaine. Prior use of psychostimulant drugs may influence an individual's sensitivity to the addictive properties of synthetic cathinones. As such, preclinical models can provide an essential tool for examining the impact of previous drug exposure on the behavioral effects of these drugs. Toward this aim, the current study implemented a behavioral sensitization paradigm to evaluate the effects of prior cocaine exposure on sensitivity to the locomotor stimulant effects of 4-methylmethcathinone (4MMC). Seventy-two male Sprague-Dawley rats were administered subcutaneous injections of either saline or 5 mg/kg cocaine once per day for five consecutive days. Locomotor activity was monitored on day 1 and day 5 one hour immediately before and one hour immediately after drug injections. After a ten-day drug washout period, rats were administered either saline or 4-MMC (1, 5, 10 mg/kg, S.C.) and locomotor activity was monitored in the same manner as on days 1 and 5 to assess cross-sensitization to 4-MMC. As expected, cocaine induced behavioral sensitization, as evidenced by significantly greater cocaine-induced activity on day 5 compared to day 1. Compared to rats pretreated with saline, those pretreated with cocaine displayed a nonsignificant trend toward cross-sensitization to 1 and 5 mg/kg 4-MMC. Experiments with 10 mg/kg 4-MMC are still in progress and are expected to produce significant evidence for cocaine-induced cross-sensitization to 4-MMC. Such findings are indicative of a heightened abuse liability of the synthetic cathinones in individuals with a prior history of cocaine abuse.

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Paternal alcohol exposure alters the behavior of adult male and female offspring.

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The heritability of alcoholism is estimated to be ~50%, yet the genetic basis for the disease is still poorly understood. A growing body of evidence suggests that paternal exposure to drugs of abuse influences druginduced behaviors and drug consumption in offspring, possibly as a result of epigenetic modifications inherited through the male germ line. Given this information, we hypothesized that paternal alcohol exposure may induce phenotypic alterations in the subsequent generation. To test this hypothesis, male Wistar rats underwent a chronic intermittent ethanol (EtOH) exposure regimen (CIE), where they were exposed to either alcohol (8 h/day over 5 consecutive days/week for 6 weeks) or served as a nonexposed control. Eight weeks after the last day of CIE, rats were mated with EtOHnaive female and adult offspring were tested in early adulthood on a range of EtOHinduced behaviors. Separate groups of offspring were intragastrically administered EtOH (1.5 g/kg) or water 30 min prior to testing for anxietylike behaviors (elevated plus maze [EPM]), general locomotor activity, and motor coordination (rotorod). We found that female, but not male, offspring of paternalalcohol exposed sires show less anxiety behaviors at baseline (EPM) or after alcohol administration (times in center of locomotor apparatus). Male, but not female, offspring of paternalalcohol exposed sires show less sensitivity to decreases in locomotor activity after alcohol administration. Paternalalcohol offspring of both sexes exhibit deficits in basal motor coordination that is not impaired further by alcohol administration. Overall, these results indicate that paternal alcohol exposure alters functional responsiveness in adult offspring which in some cases occur in a sexdependent manner.

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Behavioral sensitization following concurrent exposure to 4-methylmethcathinone (4-MMC) and 3,4-methylenedioxymethamphetamine (MDMA) in male Sprague-Dawley rats

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Recreational use of a new class of stimulant drugs known as synthetic cathinones is a recent health concern. Although the Drug Enforcement Administration placed several of the most common of these substances permanently on schedule 1, their use is still prevalent as they remain low cost, easily procurable, and potent. In humans, the concomitant use of cathinone derivatives and other drugs is commonly reported, especially other psychostimulants. Despite the prevalence of synthetic cathinone abuse, there is currently a paucity of scientific research regarding the behavioral and neurochemical effects of these drugs when combined with other drugs of abuse. The behavioral sensitization paradigm is a preclinical tool that can be used to assess the influence of prior drug exposure on sensitivity to the behavioral effects of another drug. Utilizing this paradigm, the present study assessed the combined effects of methylenedioxymethamphetamine (MDMA) and a common bath salt constituent, 4methylmethcathinone (4-MMC). Male Sprague-Dawley rats (N=120) were randomly assigned to one of 15 treatment groups (N=8) and administered intraperitoneal injections of one of the following treatments once per day for seven consecutive days: saline, 3 mg/kg MDMA, 4MMC (1 or 5 mg/kg), 3 mg/kg MDMA+4-MMC (1.0 or 5.0 mg/kg). A 10 day drug-free incubation period followed, after which rats were challenged with a single I.P. injection of either saline, 4-MMC (1.0 or 5.0 mg/kg), or 3 mg/kg MDMA. Some groups of animals received the same drug they had received on days 1-7, while other groups received the opposite drug. On days 1 and 7, and on the post-incubation challenge day, locomotor activity was monitored for one hour immediately before and one hour immediately after injections. Preliminary results indicate 4-MMC alone failed to induce behavioral sensitization, but when combined with MDMA, the induction of sensitization was greater than that produced by MDMA alone. These findings suggest the possibility of increased abuse liability of 4-MMC when used concurrently with MDMA or following prior MDMA use.

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Characterization of the Pharmacokinetics of Phosphatidylethanol 16:0/18:1 and 16:0/18:2 in Human Whole Blood After Alcohol Consumption in a Clinical Lab Study.

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Background. The purpose of this study was to characterize the pharmacokinetics of two homologues of phosphatidylethanol (PEth) and their combined total in uncoagulated, whole blood samples taken from participants in a human clinical lab study after consumption of low doses of ethanol. **Methods.** As part of a larger study, male and female participants received either 0.25 or 0.50 g/kg oral doses of ethanol during a 15 min period. Blood samples were collected before and throughout 6 h after each ethanol dose on the day of consumption, and then every 3 days during the next 14 days. PEth 16:0/18:1 and PEth 16:0/18:2 levels were quantified in blood samples by HPLC/MS/MS and reported separately or as their combined total (combined PEth). Breath ethanol concentrations (BrAC) were measured concurrently with each blood collection. Transdermal ethanol concentrations (TAC) were measured every 30 min during the entire 22 day study to confirm abstinence during a 7 day period before and the 14 day period after ethanol consumption. **Results.** (1) Single doses of 0.25 and 0.50 g ethanol/kg produced proportional increases in BrAC and combined PEth levels of all participants; (2) the areas under the curve (AUC) for each participant's BrAC levels during the 6 h period after ethanol administration were correlated with AUCs of cPEth (calculated as the AUC of the increase above baseline for combined PEth); (3) the mean rates of formation and elimination of PEth 16:0/18:1 were lower than those of PEth 16:0/18:2 after ethanol administration and during the subsequent 14 day period of abstinence; (4) the mean half-life of combined PEth, determined during the 14 day period after ethanol consumption, was 5.5 ± 2.3 (SD) days (range: 2.1 to 11 days). **Conclusions.** Combined PEth is a sensitive biomarker for the identification of relatively low levels of ethanol consumption. The measurement of these two homologues may provide additional sensitivity to identify low levels of drinking. Funding Sources: NIDA and NIAAA.

Poster Communications

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Using Vagus Nerve Stimulation to Enhance Extinction of Drug-Seeking Behavior: Effects on Plasticity in the Prefrontal Cortex-Amygdala Pathway and pCREB Expression

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Cocaine addiction can cause maladaptive neuroplasticity that persists long after cessation of drug taking. The relative permanence of cue associations formed during drug taking contributes to the difficulties in treating addiction. Re-exposure to these cues can trigger relapse to drug use. Extinction learning can break the cue-drug associations and help prevent relapse. Vagus nerve stimulation (VNS) has previously been used to enhance extinction of conditioned fear. Under these conditions VNS reduced both the expression of conditioned fear and altered synaptic plasticity in fronto-limbic circuits. Here we trained animals to self-administer cocaine and extinguished the drug seeking response in the presence or absence of VNS. VNS-treated animals had increased rates of extinction and showed reductions in cue-induced reinstatement.

After reinstatement, we performed extracellular recordings in the basolateral amygdala (BLA) and stimulated the infralimibic prefrontal cortex (IL) to measure how VNS paired with extinction learning affected the plasticity in this pathway. We used 1 Hz stimulation designed to induce long term depression (LTD) and measured changes in the amplitude of the evoked response. While LTD was reliably induced in naive and sham-stimulated animals, VNS-treated animals were resistant to the induction of LTD. Thus VNS may facilitate extinction and reduce reinstatement by modulating the projection from the IL to the BLA.

This modulation of circuitry associated with drug-seeking and extinction learning was further studied by quantifying expression of activated cAMP response element-binding protein (pCREB) in the mPFC and the BLA of sham- and VNS-treated animals. We observed a selective reduction in the levels of pCREB in the BLA of VNS-treated animals, without similar changes in the IL.

These findings provide systems-level information about neural plasticity during extinction and suggest a novel approach for the treatment of drug addiction.

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Pharmacological Characterization of the Discriminative-Stimulus Effects of the Nicotinic Agonist (+)-Epibatidine in Squirrel Monkeys

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The present studies were undertaken to characterize the discriminative-stimulus effects of (+)-epibatidine (EPI), a α4β2-selective nicotinic agonist that is pharmacologically similar and structurally distinct from nicotine (NIC). Using a standard two-lever drug discrimination procedure, squirrel monkeys (n=4) were trained to discriminate i.m. injections of 0.001 mg/kg (+)-EPI from saline on a 10-response fixed-ratio schedule of stimulus-termination. Results show that high efficacy nicotinic agonists [(-)-EPI, NIC] substituted fully for (+)-EPI, whereas the highest doses of other nicotinic agonists produced intermediate levels of (+)-EPI-like discriminative-stimulus effects [varenicline (VAR), cytisine (CYT), isoarecolone (ISO)] or did not substitute for (+)-EPI (lobeline). Drugs from other pharmacological classes (methamphetamine, atropine, citalopram, arecoline) did not generalize for (+)-EPI's stimulus effects. Pretreatment studies with nicotinic antagonists show that: a) mecamylamine (non-selective) insurmountably antagonized (+)-EPI's effects; b) dihydro-β-erthroidine (α4β2-selective) surmountably (>3-fold rightward shift) blocked (+)-EPI's effects; and c) methyllycaconitine (α7-selective) failed to modify the discriminative-stimulus effects of (+)-EPI. Interestingly, the peripherally-restricted nicotinic antagonist hexamethonium also appeared to produce some attenuation of (+)-EPI's discriminative-stimulus effects (approximately 3-fold rightward shift) suggesting that a peripheral component may also play a role in (+)-EPI's discriminative-stimulus effects. In further studies, pretreatment with the partial nicotinic agonists VAR, CYT, and ISO did not block the discriminative-stimulus effects of (+)-EPI, and in fact, CYT and VAR pretreatment shifted the (+)-EPI dose-effect curve to the left (>3-10-fold). These results suggest that multiple nicotinic receptor subtypes may mediate the behavioral effects of nicotinic agonists (supported by NIH DA031231).

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Targeting glutamate homeostasis for potential treatment of nicotine dependence.

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Several studies demonstrated that impairment in glutamatergic neurotransmission is linked to drug dependence and drug-seeking behavior. Increased extracellular glutamate concentration in mesocorticolimbic regions has been observed in animals developing nicotine dependence. Changes in glutamate release might be associated with stimulatory effect of nicotinic acetylcholine receptors (nAChRs) via nicotine exposure. We and others have shown increased extracellular glutamate concentration, which was associated with downregulation of the major glutamate transporter, glutamate transporter 1 (GLT-1), in brain reward regions of animals exposed to drug abuse, including nicotine and ethanol. Importantly, studies from our laboratory and others showed that upregulation of GLT-1 expression in the mesocorticolimbic brain regions may have potential therapeutic effects in drug dependence. In this review article, we discussed the effect of antagonizing presynaptic nAChRs in glutamate release, the upregulatory effect in GLT-1 expression and the role of glutamate receptors antagonists in the treatment of nicotine dependence.

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Binge alcohol effects on prefrontal cortex neurons

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Approximately 92% of U.S. adults who drink excessively report binge drinking in the past 30 days. Increased alcohol marketing in recent years has particularly targeted women, causing a 36% increase in the last 10 years in the number of women who are engaging in binge alcohol consumption. Since women appear to be more vulnerable to the harmful neurological effects of alcohol, this increase is of particular concern. In studies performed on rats using a model of binge drinking, female rats were found to have an enduring loss of neurons in the hippocampus and also manifested spatial navigation impairments on the Morris water maze task following alcohol exposure, yet no significant deficiencies were detected in male rats. Aside from the hippocampus, one of the brain regions most affected by binge alcohol consumption is the frontal cortex, an area important for many functions and decision making of daily life. Loss of prefrontal grey matter resulting from heavy alcohol consumption has been documented, however this volume loss does not appear to be caused by a decrease in the number of prefrontal cortex neurons. This study aimed to determine whether the medial prefrontal cortex (mPFC) in female rats is more vulnerable to alcohol induced damage, by examining neuronal volume and quantity following binge alcohol exposure. To assess this, adult male and female Long-Evans rats (N=27) were assigned to binge or control groups and exposed to ethanol using a well-established 4-day model of alcohol-induced neurodegeneration. NeuN + cells in the mPFC were quantified using stereology. Both male and female binged animals had significantly smaller average neuronal volumes than their respective control groups, however no differences were found between binged male and binged female rats. There were no significant differences in estimated mPFC neuronal population between groups. Our results support prior research indicating that frontal regions are vulnerable to binge alcohol damage.

Poster Communications

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Munc 13-1 regulates ethanol self-administration in mice.

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The role of the *munc 13-1* pre-synaptic protein in alcohol-related behaviors has been little-studied, but holds promise for researchers modeling alcohol addiction. *Munc 13-1* is an active zone protein that is vital for vesicle fusion with the membrane wall and the release of glutamate at the synapse. Mice who are heterozygous for the gene regulating *munc 13-1* produce synapses that, while structurally sound, show a drastic decrease in glutamate transmission. When ethanol binds to *munc 13-1*, it further decreases neuronal signal and antagonizes glutamatergic targets. In a previous study that partially knocked out the fly homolog *dunc 13-1*, changes to ethanol-related behaviors were observed. Compared to wildtype, flies that lacked *dunc 13-1* consumed more alcohol and were more attracted to alcoholic substances. However, introduction of the rat *munc 13-1* gene *in vivo* suppressed the affinity for, and decreased the consumption of alcohol, suggesting that *munc 13-1* acts as a powerful mediator of ethanol self-administration behavior. In the current study, baseline behavioral tests were administered in order to identify possible phenotypes in these *munc 13-1* deficient mice. Adult C57BL/6J mice (N = 27) were first analyzed for baseline behavioral differences using the open field task, accelerating rotarod, and a novel object recognition paradigm. No significant differences were found between genotypes in these three tasks; thus, mutant mice behave similarly to wildtype mice in measures of anxiety, motor coordination, and object memory. To examine the role of *munc 13-1* knockdown in alcohol self-administration behavior, wildtypes (n = 14) and heterozygotes (n = 13) were exposed to 20% ethanol using the 4-day Drinking in the Dark (DID) paradigm. Mutant mice drank more ethanol solution than wildtype mice did. This effect appears to be moderated by sex, with females drinking significantly more than males (regardless of genotype). This study extends previous *Drosophila melanogaster* findings to a mammalian model, and supports further investigation into *munc 13-1* as a genetic target for alcohol addiction research.

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Treatment response profiles of at-risk drinkers during a 12-week contingency management intervention.

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Contingency management (CM) interventions for reducing alcohol use are generally effective, however, studies have typically relied on group based analyses, which conceals variability in individual response to treatment. Determining subgroups of individuals who have similar response profiles over time during treatment and the predictors of such response profiles will offer opportunities to improve treatment outcomes. In the current study, 66 non-treatment seeking at- risk drinkers completed 4 study phases: (Phase 1) 5 days of behavioral impulsivity testing; (Phase 2) 28 days of naturalistic drinking measured by transdermal alcohol monitors; (Phase 3), 12 weeks of CM treatment where participants were paid $50 weekly for not exceeding a low level drinking criterion as measured by transdermal alcohol monitoring; and (Phase 4) monthly assessments of self-reported drinking for 3 months after the contingencies were removed. Cluster analyses based on whether the contingency criteria was met during each week demonstrated three treatment response profiles; Optimal Responders (n=10), Responders (n=30) and Non- Responders (n=26). Response profile was not significantly predicted by, demographic characteristics (age, sex, race, ethnicity, marriage status, and IQ), pre-CM drinking patterns (objectively measured during Phase 2), or impulsive performance (response initiation, response inhibition and consequence sensitivity impulsivity either under placebo, alcohol, tryptophan depletion and a combination of both). Low levels of non-planning impulsivity as measured by the Barratt Impulsiveness scale did, however, predict membership in the Optimal Responders cluster. Drinking patterns during the 3-month follow-up did not differ between the clusters. The results show that there is significant heterogeneity in response to CM but that the majority of at-risk drinkers responded positively. Further research will be required to replicate these findings in a clinical sample and further assess potential predictors of such response profiles.

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Methamphetamine self-administration in mice results in both pre and postsynaptic changes in dendritic dopamine neurotransmission in midbrain dopaminergic neurons.

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Dopaminergic neurons of the ventral midbrain are key mediators of substance abuse and addiction-related behaviors. In the midbrain, dopamine release activates inhibitory postsynaptic currents through D2 autoreceptors (D2-IPSCs) and G protein-coupled potassium (GIRK) channels. Methamphetamine is a highly addictive psychomotor stimulant that acutely enhances D2-IPSCs by decreasing uptake of dopamine. Chronic methamphetamine exposure can induce neurophysiological adaptations in midbrain dopaminergic neurons, but data regarding specific synaptic adaptations following self-administration of methamphetamine is limited.
In this study we investigated the effects of methamphetamine self-administration in mice on synaptic determinants of dopamine neuron excitability. Adult mice were trained to nose-poke under a fixed ratio 3 (FR3) schedule for intravenous infusions of methamphetamine (0.05 mg/kg/infusion) in daily 2 h sessions for 8 to 12 days. Their average intake of methamphetamine was 1.3 mg/kg/day. Subsequently, patch clamp electrophysiology was performed in brain slices containing substantia nigra and ventral tegmental area dopamine neurons to examine both pre- and postsynaptic changes. Interestingly, self-administration of methamphetamine produced an overall downward shift in the methamphetamine (100nM-3μM) concentration-response curve of D2-IPSCs compared to drug-naïve controls. In addition, self-administration of methamphetamine produced an increase in the paired-pulse ratio of D2-IPSCs that persists with subsequent stimulus events, indicating presynaptic effects on dopamine release. These results indicate an overall decrease in the strength of inhibitory synaptic transmission between midbrain dopamine neurons following methamphetamine self-administration. This would be expected to produce an increase in neuronal firing that could enhance the reinforcing properties of methamphetamine in experienced individuals.

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Sensitivity to reinforcement and punishment learning in active cocaine users

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Numerous studies have reported impaired decision-making in drug users. Deficits in decision-making may be linked to abnormal sensitivity to reinforcement and/or punishment-based contingencies, resulting in maladaptive choice. However, this research area is limited by methodological restrictions imposed by current behavioral measures of reinforcement and punishment sensitivity. Experimental tasks have generally been limited to those that have not been validated across multiple administrations or tasks that conflate reinforcement and punishment learning in a single outcome variable. The purpose of this study was to (1) measure sensitivity to reinforcement and punishment learning in individuals with cocaine use disorders using a behavioral task previously validated in non-drug using populations, and (2) to determine the moderating role of stimulus type (i.e., drug-associated versus neutral stimuli). Twenty active cocaine users (30% female) completed a probabilistic learning task, in which subjects were asked to classify images into categories (i.e., A versus B) with selections under probabilistic reinforcement or punishment contingencies. Stimuli were either neutral or cocaine-related images. Subjects completed the learning task during two sessions to determine the stability of performance over time. Subjects showed an overall enhanced sensitivity to punishment (65% optimal behavior) relative to reinforcement (52% optimal behavior) regardless of stimulus type. Performance was also stable over time from delays ranging 2 days to 2 weeks (i.e., no significant effects of session). This study extends the limited research on concurrently assessed reinforcement and punishment in cocaine using individuals by showing relative sensitivity to punishment over reinforcement learning. The development of a behavioral task that can measure reinforcement and punishment sensitivity across time will be useful for the longitudinal assessment of interventions targeting decision-making processes to reduce drug use behaviors.

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Adolescent drug pre-exposure fails to attenuate taste avoidance conditioning

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Briefly, past research completed in our laboratory has demonstrated that while a history of methylphenidate (MPH) in adulthood attenuates the ability of cocaine to induce taste avoidance (Wetzell et al., 2015), such a history in adolescence fails to impact the affective properties of cocaine or MPH in adulthood (Wetzell and Riley, 2012). To address whether the failure of adolescent history to impact adult taste avoidance learning was a function of the time intervening between pre-exposure and conditioning, we used a novel experimental design to investigate whether adolescents are capable of demonstrating a US pre-exposure effect when pre-exposed and conditioned in adolescence. In Experiment 1, non-pre-exposed adolescent rats conditioned with MPH displayed weak taste avoidance that was unaffected by drug pre-exposure, i.e., there was no evidence of a drug pre-exposure effect. To assess the generality of the findings, in Experiment 2 non-pre-exposed adolescents conditioned with the emetic LiCl displayed weak LiCl-induced taste avoidance that again was unaffected by drug history. Interestingly, adults displayed strong taste avoidance that was significantly attenuated by LiCl pre-exposure. The present work is consistent with past research which reports that adolescents are less sensitive to the aversive effects of drugs, resulting in relatively weak taste avoidance. The fact that they show no effects of drug history suggests that they do not attend to the drug's aversive effects, again indicating a relative insensitivity to these effects. We have argued that the aversive properties of drugs, indexed by CTA, limit drug use and abuse. That adolescents appear relatively insensitive to the aversive effects of drugs is consistent with past research and substantiates the claim that adolescence is a risk period for drug use and potential abuse.

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A novel neuropeptide regulator of cocaine-related behaviors

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Neuromedin U (NMU) is a neuropeptide enriched in the nucleus accumbens shell (NAcSh), a brain region associated with reward. 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). Here, we found that NMU Receptor 2 (NMUR2) is localized to presynaptic GABAergic neurons in the NAcSh originating from the dorsal raphe nucleus. Furthermore, NMU microinjection to the NAcSh decreased local GABA concentrations. Next, we evaluated the effects of NMU microinjection on cocaine-evoked behavior, namely behavioral sensitization to cocaine. When repeatedly administered throughout the sensitization regimen, NMU attenuated cocaine-evoked hyperactivity. Additionally, shRNA-mediated knockdown of presynaptic NMUR2 in the NAcSh using a retrograde viral vector potentiated cocaine sensitization. Treatment with NMU also decreased operant responding for cocaine self-administration as well. Together, these data reveal that NMUR2 modulates a novel GABAergic pathway from the dorsal raphe nucleus to the NAcSh to influence behavioral responses to cocaine.

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Effects of Nicotinic Antagonists and Partial Agonists on Nicotine's Behavioral effects in Squirrel Monkeys

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Nicotine addiction remains a major public health problem, with over 1.1 billion smokers worldwide and rapidly increasing use of electronic nicotine delivery systems. The behavioral effects of nicotine, as well as nicotinic partial agonists that are used to manage nicotine addiction (varenicline, cytisine), are thought to be primarily mediated by actions at the α4β2 nicotinic acetylcholine receptors (nAChR). In the present studies, this proposition was evaluated in squirrel monkeys by determining the effects of nicotinic-receptor agonists and antagonists alone and in combination on schedule-controlled performance maintained by food delivery. Results show that nicotine, varenicline and cytisine all produced dose-dependent decreases in food-maintained responding. In contrast, the non-competitive, non-selective antagonist mecamylamine (0.032-1.0 mg/kg) and the competitive α4β2 nicotinic receptor antagonist, DhβE (0.032-0.56 mg/kg) did not cause a decrease in food-maintained responding over the range of doses that could be safely tested. Pretreatment with mecamylamine (0.1-1.0 mg/kg) dose-dependently attenuated the rate decreasing effects of nicotine (10-fold rightward shift following 1.0 mg/kg) whereas DhβE (0.1-0.56 mg/kg) did not alter nicotine's rate decreasing effects. Interestingly, pretreatment with the nicotinic partial-agonists cytisine (0.032-0.1 mg/kg) produced a dose-dependent leftward shift in the dose-response curve for nicotine whereas varenicline (0.01- 0.032mg/kg) did not modify nicotine's effects on rates of responding. Preliminary data from studies of the modification of nicotine's discriminative-stimulus effects by nicotinic antagonists and partial-agonists in monkeys trained to discriminate (+)-epibatidine (an α4β2-selective nicotinic agonist) indicate a similar pattern of results. Collectively, these data strongly suggest that activation of the nicotinic acetylcholine receptors mediate nicotine's behavioral effects; however, they do not support a singular role for α4β2* nAChR mechanisms in mediating nicotine's behavioral effects.

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Is TAAR1 a potential therapeutic target for treating immune dysregulation in drug abuse?

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Understanding the biological mechanisms of drugs of abuse is essential to developing new medications to treat substance abuse. Discovered in 2001, Trace Amine Associated Receptor 1 (TAAR1) is a direct target of amphetamine, methamphetamine and MDMA. It is expressed in the brain reward circuity where it modulates dopamine transporter function and dopamine neuron firing rates. Newly-developed compounds that specifically target TAAR1 have recently been investigated in animal models as candidate therapeutics for methamphetamine, cocaine and alcohol abuse. These studies involving classic behavioral measures of drug response as well as drug self-administration strongly implicate TAAR1 as a potential therapeutic target for the treatment of addiction. In addition to its central actions, we demonstrated that TAAR1 is upregulated in peripheral blood mononuclear cells (PBMC) and B cells following immune activation, and that subsequent activation of TAAR1 by methamphetamine stimulates cAMP, similar to the function of adenosine A2 receptors which are also present in immune cells and play a critical role in the immune response. Here, we are investigating the relationship between TAAR1 and the adenosine A2 receptor at the level of cellular signaling and receptor dimerization. We hypothesize that both receptors synergistically elevate cAMP through their Gs coupling, and that specific TAAR1 drugs may have immunomodulatory effects through this shared signaling mechanism. This hypothesis is supported by the observation that methamphetamine is a potent TAAR1 agonist that has profound effects on immune system function. Accordingly, deciphering the role of TAAR1 in methamphetamine action and immune regulation may lead to the development of novel addiction therapeutics that combat both central addictive mechanisms as well as immunological aberrations that occur in drug abuse.

Poster Communications

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Effects of *d*-Amphetamine on a Delay Discounting Task: Individual Subject Differences.

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Impulsivity is associated with disorders such as substance abuse and attention deficit disorder. One form of impulsivity, the preference for smaller immediate rewards over larger delayed rewards, is modeled in the laboratory with delay discounting procedures. *d*-Amphetamine is both abused and prescribed to treat attention deficit disorder; however, its effects on discounting are not consistent across studies, which might result from differences among individuals in sensitivity to delay, *d*-amphetamine, or both. Those differences can be masked by analyzing group means. The present study aimed first to characterize individual differences in sensitivity to delay by using an adjusting delay task in which adult male rhesus monkeys (n = 3) chose between 2 pellets delivered immediately and 3 pellets delivered after a delay. The delay titrated within-session based on performance: two consecutive choices of the immediate or delayed reward decreased or increased, respectively, the delay by 25%. *d*-Amphetamine (0.1-1.0 mg/kg, *s.c.*) was assessed for its effects on adjusted delay. To determine the role of baseline delay in modulating drug effects, the size of the immediate reward was decreased from 2 pellets to 1 pellet (n = 2), which decreased the median adjusted delay from 50 and 57 s to 11 and 18 s, respectively. At the group level, no statistically significant effects of *d*-amphetamine were detected under either condition; however, for one subject *d*-amphetamine had robust and consistent effects under both conditions, dose-dependently decreasing discounting (i.e., increasing adjusted delay) and promoting exclusive choice for the delayed reward. Thus, discrepant effects of *d*-amphetamine in the literature might result, at least in part, from qualitatively different drug effects across individual subjects. The present data underscore the importance of individual subject analyses in detecting a reliable and qualitatively different effect that otherwise was masked by examination of group data; qualitative differences in drug effects among individuals could be related to vulnerability to abuse. Support: NIDA R01DA029254, K05DA017918, and T32DA031115.

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Interactions between cannabinoids and opioids: impact of constituent drugs and dose ratio on the antinociceptive effects of drug mixtures

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Pain continues to be a significant clinical problem, and mu opioid receptor agonists such as morphine and oxycodone are the most common treatment for many types of pain. Despite their widespread use, opioids produce numerous unwanted effects (e.g., constipation, abuse, dependence, and risk of overdose) and have a relatively narrow therapeutic window. The therapeutic window of opioids might be increased by combining them with another drug such that smaller doses of the opioid, in combination with another drug, produce the desired therapeutic effect in the absence of unwanted effects. Cannabinoid receptor agonists such as THC enhance the antinociceptive effects of opioids under many conditions, although factors impacting the interaction remain unclear. This study examined the antinociceptive effects of mixtures of morphine and either THC or the synthetic cannabinoid receptor agonist CP55940 in rats using a warm water tail withdrawal procedure. When administered alone, morphine (1.78-17.8 mg/kg), THC (3.2-32.0 mg/kg), and CP55940 (0.032-1.0 mg/kg) dose-dependently increased tail withdrawal latency from warm (50°C) water. In one group of rats (n=8), mixtures of morphine and THC increased tail withdrawal latency and the effects of all ratios of morphine to THC (3:1, 1:1, and 1:3) were additive. In another group of rats (n=8), mixtures of morphine and CP55940 also increased tail withdrawal latency; effects were greater than additive (synergistic) when the ratio of morphine to CP55940 was 3:1 or 1:1 and were additive when the ratio was 1:3. These results are consistent with studies showing that cannabinoid/opioid mixtures have antinociceptive effects and support the view that combining opioids with cannabinoids lowers the dose of the opioid required to produce antinociceptive effects. This study also shows that the interaction between cannabinoids and opioids depends, in part, on the constituent drugs as well as the ratio of doses in the mixture. Supported by USPHS grant K05DA017918.

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PPARγ Agonism to Treat White Matter Damage in Cocaine Use Disorder

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Cocaine use disorder is a chronic, relapsing condition characterized by compulsive drug seeking and taking even after prolonged abstinence. The disorder elicits behavioral, as well as structural, changes. Behaviorally, the disorder is characterized by increased impulsivity, impaired decision-making, and increased reactivity to cocaine-paired cues. At the structural level, it is characterized by damage to the white matter (WM) tracts that interconnect the grey matter (GM) structures which are thought to underlie drug-seeking behaviors. Rat models of the disorder display both phenotypes, showing an increased reactivity to cocaine-paired cues alongside WM and GM damage. Cocaine craving and relapse behaviors can be modeled in rodents following forced abstinence (FA) from chronic cocaine self-administration (SA). We discovered that the FDA-approved peroxisome proliferator-activated receptor γ (PPARγ) agonist pioglitazone (PIO, Actos™) attenuates cue reactivity to cocaine-paired cues in rats following FA from cocaine SA; *demonstrating the translational potential of PIO*. Importantly, this decreased cue reactivity is reversed by the PPARγ *antagonist* GW9662, showing that the reduced cue reactivity with PIO is mediated by PPARγ. Thus, ***we hypothesize*** that PPARγ agonism counteracts the cocaine-mediated damage to WM and GM underlying cue reactivity to cocaine-paired cues through the induction of markers for functional and structural integrity in WM. We are investigating expression of proteins related to WM integrity which are affected by chronic cocaine, and regulated by PPARγ and/or phosphorylated extracellular signal-regulated kinase, a protein which we have found to be in complex with PPARγ during memory consolidation and thus a potential co-regulator. Proteins of interest include myelin basic protein, aquaporin 4, myelin proteolipid protein, microtubule-associated protein 2, glial fibrillary acidic protein, neurofilament heavy chain, and brain-derived neurotrophic factor.

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Within animal comparison of neural activation patterns engaged by cocaine and non-drug reward

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Novelty seeking is a personality trait associated with an increased vulnerability for substance abuse. In rodents, elevated novelty seeking has been shown to be a predictor for elevated drug self-administration and compulsive use. While previous studies have shown that both novelty and drugs of abuse have actions within similar mesocorticolimbic regions, little is known as to whether the same neural ensembles are engaged by these two stimuli. In this project, we wanted to determine the activation patterns associated with novelty and cocaine. Using the TetTag mouse model (a dual transgenic reporter line that allows for long lasting temporally controlled tagging of active neurons), we compared neurons engaged by cocaine and novelty exposure. We investigated the infralimbic (IL) and prelimbic (PrL) prefrontal cortex (PFC), the nucleus accumbens (NAc) core and shell, the ventral hippocampus, and the basolateral amygdala for overlap between neurons associated with cocaine and novelty exposure, and found significant overlap in the NAc shell and IL PFC. To test the functional significance of overlap between neural encoding of non-drug reward and cocaine, we are using the TetDREADD mouse model; a variant of the TetTag mouse that yields activity-dependent expression of Gi/o coupled DREADD receptors (hM4Di) in a temporally controlled manner. TetDREADD mice were trained to self-administer cocaine and either novelty (operant sensation seeking: OSS) or food (10% sucrose) in different contexts to test the ability of silencing neurons engaged during one of these behaviors to affect expression of the other behavior. The data suggest that increasing Gi/o signaling in neurons engaged during cocaine self-administration can reduce OSS, but not food self-administration. Ongoing studies are further parsing the functional overlap of neurons involved in these behaviors.

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The Design and Testing of Long Acting Viral Mediated Anti-METH Immunotherapies

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Methamphetamine (METH) is among the most dangerous drugs of abuse currently in the United States and worldwide. There is currently no FDA approved pharmacological therapy available to treat METH abuse. Clinical trials are underway to test monoclonal antibodies (mAbs) that recognize, bind and neutralize METH as a pharmacokinetic antagonist and may provide protection for up to a month per dose. For this project, we used the variable heavy and light chain regions from a therapeutic anti-METH mAb joined by an amino acid linker and flanked by a FLAG epitope tag and a 6-histidine tail to form short chain variable fragments (scFvs). Using this truncated antibody fragment allowed us to create a novel gene therapy using adeno-associated viruses (AAV), which provides a 'constant infusion' of the scFv antibody fragments for a significantly longer duration of action. Initial studies with this AAV-scFv therapy have shown an expression of efficacious scFvs for greater than 7 months after a single $1x10^{12}$ vector copy dose in mice. Preliminary locomotor studies suggest that these anti-METH antibodies do indeed appear to alter locomotor activity at 0.3 mg/kg METH doses in mice, but unable to provide protection against METH at higher doses ($\geq$ 1.0 mg/kg). We believe this is a result of sub-optimal circulating serum concentrations of the scFvs. In an attempt to increase the circulating concentrations of the scFvs, we have inserted a 60 amino acid sequence that is capable of transiently binding to IgG antibodies and increasing the half-life of the circulating scFvs. This should result in greater serum concentrations, and thus increased protection against METH-induced physiological and behavioral effects, and initial data suggests that higher serum levels of anti-METH scFvs are achieved.

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Selective deletion of GIRK2 channels in dopamine neurons decreases cocaine sensitivity and increases cocaine self-administration in mice

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We investigated if the lack of G-protein-gated inwardly rectifying K+ subtype 2 (GIRK2) channels in dopamine neurons affect cocaine self-administration in mice. A *Girk2* conditional mouse line was generated and crossed with a line that expresses Cre recombinase under control of the dopamine transporter (DAT) promoter. This generated a conditional knockout mouse line where GIRK2 channels were selectively deleted in dopamine neurons expressing DAT ($GIRK2_{DA}KO$) (Kotecki et al., 2015). For our experiments, male $GIRK2_{DA}KO$ mice and their wildtype litter mates ($GIRK2_{DA}WT$) were implanted with indwelling catheters in the right jugular vein. A week after surgery, mice were trained to nose-poke for cocaine (0.5 mg/kg/inf) in daily 2 h sessions. Responses in the correct nose poke hole were rewarded on a fixed ratio 1 (FR1) for infusions 1 to 5, an FR2 for infusions 6 to 8, and an FR3 for the remainder of the daily session. No differences were found between the two genotypes in the average training sessions necessary to meet self-administration criteria ($GIRK2_{DA}WT$: 6.4 ± 0.7 days; $GIRK2_{DA}KO$: 7.0 ± 0.7 days). The mice were then advanced to seven days at an FR3 schedule, where mice from both genotypes reached a similar average rate of infusions ($GIRK2_{DA}WT$: 14.3 ± 1.2 inf; $GIRK2_{DA}KO$: 12.8 ± 0.8 inf). When the animals were exposed to increasing doses of cocaine (0.03, 0.1, 0.3, 1.0 and 3.0 mg/kg/inf), a significantly higher number of infusions were observed in $GIRK2_{DA}KO$ mice on days where a low dose of cocaine (0.03 - 0.3 mg/kg/inf) was available (Genotype x Dose: $p=0.026$). In a further analysis, we found that $GIRK2_{DA}KO$ have higher cocaine intake per session compared with their litter mates independently of the dose being tested (Genotype: $p = 0.024$; Genotype x Dose: $p = 0.079$). Together, these results indicated that deletion of Girk2 channels in dopamine neurons decrease sensitivity and increase cocaine intake without affecting cocaine self-administration acquisition.

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The neuroprotective agent, P7C3-A20, prevents paclitaxel-induced allodynia.

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Paclitaxel (PTX), a microtubule-targeting anticancer agent, produces a debilitating peripheral neuropathy that is accompanied by neuropathic pain. Currently, there are only marginally effective therapeutic interventions available, which forces patients to reduce or discontinue life-saving chemotherapy to cope with the pain. Recently, a newly identified agent, P7C3-A20, was found to be protective in several models of neurodegeneration, including Parkinson's disease and traumatic brain injury. Given that PTX triggers progressive degeneration of peripheral afferent neurons, this study was performed to evaluate the potential neuroprotective efficacy of P7C3-A20 in a rat model of PTX-induced peripheral neuropathy. We administered P7C3-A20 (10 mg/kg) or vehicle (Cremophor EL/DMSO/5% Dextrose; 1:1:3) intraperitoneally (i.p.) to Sprague-Dawley rats (250-300 g) everyday over a 28-day experimental paradigm. Following two days of treatment with P7C3-A20 or vehicle, rats also received 3 injections of PTX (11.7 mg/kg, i.p.) or vehicle (Cremophor EL/DMSO/5% Dextrose; i.p.) administered every other day. Treatment with P7C3-A20 did not alter body weights or leukocyte counts in control or PTX-treated rats. PTX treatment increased sensitivity to mechanical and cold, but decreased sensitivity to heat, stimulation of the hindpaw, evidence of peripheral neuropathy. Notably, rats that received P7C3-A20 treatment prevented the changes in nociceptive thresholds in response to PTX, suggesting that P7C3-A30 prevented the neurotoxic effects of PTX on peripheral sensory neurons. Taken together, this work suggests that P7C3-A20 is neuroprotective against PTX-induced peripheral neuropathy. P7C3-A20 may be an exciting new candidate to prevent peripheral neuropathy in patients undergoing cancer treatment with PTX.

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Heart rate and antinociceptive effects of morphine and Δ^9-tetrahydrocannabinol in rhesus monkeys

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Pain is a significant health problem that is often managed through the use of prescription opioids. However, opioids have a number of adverse effects that limit their use including constipation, abuse, overdose, and decreased cardiovascular function. One proposed solution to avoid these adverse effects is to use smaller doses of opioids in combination with drugs that produce antinociceptive effects through nonopioid mechanisms, such as cannabinoid receptor agonists. Opioid/cannabinoid combinations are very effective in preclinical models of pain; however, it is unclear whether doses of opioids and cannabinoids that have antinociceptive effects also have adverse effects. The mu opioid receptor agonist morphine and the cannabinoid receptor agonist Δ^9-tetrahydrocannabinol (THC) were examined in three rhesus monkeys for their antinociceptive effects using a warm water (50° C) tail withdrawal assay and for their effects on heart rate using radiotelemetry. Morphine and THC increased tail withdrawal latency in a dose- and time-related manner, with doses that were effective for antinociception also decreasing heart rate. For example, 1 mg/kg morphine and 1.78 mg/kg THC increased tail withdrawal latency from less than 4 sec (control) to an average of 10.2 and 12.4 sec, respectively; these same doses of morphine and THC decreased resting heart rate by as much as 23% and 30%, respectively. Thus, doses of an opioid or a cannabinoid that have moderate antinociceptive effects also decrease cardiovascular function. It remains to be determined whether smaller doses of opioids and cannabinoids that produce antinociceptive effects only when they are combined also impact cardiovascular function.

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Poster Communications

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Regulation of Astrocyte-Trace Amine Associated Receptor 1 Subcellular Distribution and Interacting Partners in the context of Methamphetamine and HIV-Associated Neurocognitive Disorders.

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As a psychostimulant, methamphetamine (METH) use leads to long-lasting, euphoric effects. Between 10- 15% of human immunodeficiency virus-1 (HIV-1) patients report METH abuse, which exacerbates HIV-1 infection, accelerating the onset of HIV-associated neurocognitive disorders (HAND) and immune dysfunction. Neuroinflammation, glial activation, oxidative stress and excitotoxicity contribute to METH and HIV neuropathogenesis. However, the mechanisms through which METH and HIV affect astrocyte function are unclear. Recently, we reported trace amine associated receptor 1 (TAAR1) as a novel astrocyte receptor for METH. Previous studies suggest TAAR1 activity may be regulated by G-protein promiscuity and desensitization by β-arrestin. We hypothesize that ***HIV-relevant stimuli upregulate astrocyte-TAAR1 expression and that METH exposure induces alterations in TAAR1 activation and intracellular localization, thus contributing to astrocyte dysfunction.*** To examine subcellular distribution TAAR1 expression was assessed by confocal microscopy in human astrocytes in the context of HIV and METH exposure. Changes in EAAT2, which could impair astrocyte ability to clear glutamate, were examined in parallel. To assess TAAR1 regulation by interacting partners, co-immunoprecipitation studies were performed, specifically to investigate β-arrestin activation and TAAR1-mediated calcium signaling *via* Gαq. These studies delineate how dysregulation of TAAR1 may contribute to astrocyte-mediated neurodegeneration during HAND and METH abuse, while also revealing a novel therapeutic target in astroglia.

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Brg1 in the Nucleus Accumbens regulates cocaine-seeking behavior

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Drug addiction is defined as a chronic, relapsing disease that is characterized by compulsive drug seeking and episodes of relapse despite prolonged periods of abstinence from the drug. Neurobiological adaptations, including transcriptional and epigenetic alterations, in key brain reward areas, such as the nucleus accumbens (NAc), are thought to contribute to this life-long disease state. The transcription factor SMAD3 is a key cellular component of the Activin-receptor signaling pathway, which we have previously demonstrated to be increased following long-term withdrawal from cocaine self-administration. SMAD3 acts as an essential transcriptional regulator of cocaine-induced gene expression through the interaction with chromatin remodelers, such as the ATPase Brg1, ultimately facilitating the ability of SMAD3 to bind to DNA promoters of target genes. However, the role of Brg1 in addictive-like behavior is still unclear. Here we describe the interaction of Brg1 and SMAD3 following abstinence from cocaine self-administration. We found that following seven days of withdrawal from cocaine self-administration, Brg1 and SMAD3 form a transcriptional complex, and that pharmacological inhibition of Brg1 attenuated cue-induced reinstatement behaviors while regulating genes associated with neuronal plasticity. Collectively, our data demonstrate that the SMAD3/Brg1 complex governs cellular and behavioral plasticity that mediate addictive-like behavior, and provides a potential therapeutic target for cocaine addiction treatment.

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Effects of Trace Amine-associated Receptor 1 Agonists on the Expression, Reconsolidation, and Extinction of Cocaine Reward Memory

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As a modulator of dopaminergic system, trace amine-associated receptor 1 (TAAR1) has been shown playing a critical role in regulating the rewarding properties of addicted drugs. It has been demonstrated that activation of TAAR1 decreased the abuse-related behaviors of cocaine in rats. However, the role of TAAR1 in specific stages of cocaine reward memory is still unclear. Here, using cocaine-induced conditioned place preference (CPP) model, we tested the effects of a selective TAAR1 agonist RO5166017 on the expression, reconsolidation, and extinction of cocaine reward memory. We found that RO5166017 inhibited the expression but not retention of cocaine-induced CPP. RO5166017 had no effect on the reconsolidation of cocaine reward memory. Pretreatment RO5166017 before extinction hindered the formation of extinction long-term memory. RO5166017 did not affect the movement during the CPP test, indicating the inhibitory effect of RO5166017 on the expression of cocaine-induced CPP was not caused by locomotion inhibition. Using cocaine intravenous self-administration model, we found that the combined TAAR1 partial agonist RO5263397 with extinction had no effect on the following cue- and drug-induced reinstatement of cocaine-seeking behavior. Repeated administration of the TAAR1 agonist during extinction showed a continually inhibitory effect on the expression of cocaine reward memory both in cocaine-induced CPP and cocaine self-administration models. Taken together, these results indicated that activation of TAAR1 specifically inhibited the expression of cocaine reward memory. The inhibitory effect of TAAR1 agonists on cocaine reward memory suggests that TAAR1 agonists could be a promising agent to prevent cocaine relapse.

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Motivation for, and intake of food are mediated by neuropeptide signaling in the PVN and DRN

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Motivation for high-fat food is thought to contribute to excess caloric 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 and body weight. NMUR2 also regulates feeding behaviors, including preference for high-fat foods and binge-type eating. Although these effects of NMUR2 have primarily been attributed to signaling in the paraventricular nucleus of the hypothalamus (PVN), a noted feeding center in the brain, notable levels of NMUR2 have been found in other brain regions involved in both feeding behavior and motivation, including the dorsal raphe nucleus (DRN). Here, we have employed a progressive ratio operant responding paradigm to explore the effects of NMUR2 signaling on motivation for food. We found that peripheral administration of the endogenous NMUR2 agonist, Neuromedin U (NMU), decreases operant responding for high-fat food in rats. Evaluation of cFos expression in response to peripheral NMU implicated the PVN and DRN as potential sites of action for NMU. Interstitial NMU infusion into either region mimics the effects of peripheral NMU on food intake and operant responding for food. These results identify the DRN as a novel site of action for NMU and demonstrate NMU-NMUR2 signaling as a novel regulator of motivation for highly reinforcing foods.

Poster Communications

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Increased side-chain length confers a greater dopaminergic phenotype and increased reinforcing efficacy to cathinone analogs of MDMA

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In recent years, synthetic cathinone compounds have been utilized in “Ecstasy” formulations in lieu of MDMA, some of which are congeners of MDMA. The current study aimed to assess structure-activity relations of the discriminative stimulus and reinforcing effects among three synthetic cathinone analogs of MDMA: methylone, butylone, and pentylone. Rats were trained to discriminate methamphetamine from vehicle. Dose-response studies were performed with each of the test compounds and the lowest substituting dose was then tested in the presence of a range of doses of the D1-selective antagonist SCH23390. A separate group of rats was trained to self-administer methamphetamine under a FR10 schedule of reinforcement. Rats then self-administered methamphetamine, MDMA, and the test compounds under a progressive ratio schedule of reinforcement. Each of the test compounds fully substituted for the discriminative stimulus effects of methamphetamine. SCH23390 fully and dose-dependently antagonized the methamphetamine-appropriate responding produced by these compounds with methylone being the most sensitive to the effects of SCH23390, followed by butylone, then pentylone. In the self-administration studies, breakpoints increased concurrently with side-chain length. Methylone’s breakpoint was higher than saline, but the same as MDMA. The breakpoints for butylone and pentylone were both greater than saline or MDMA, but only pentylone produced responding comparable to methamphetamine. These data indicate that as side-chain length increases, the sensitivity to SCH23390 decreases and self-administration increases, suggesting that side-chain length is positively associated with dopaminergic phenotype and reinforcing efficacy. Furthermore, these synthetic cathinones may drive compulsive use of “Ecstasy” given their presence in “Ecstasy” formulations and increased reinforcing efficacy relative to MDMA.

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A Systematic Review of Barriers and Facilitators to Implementing a Prescription Drug Monitoring Program

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Prescription drug monitoring programs are state-run systems used to mitigate misuse and diversion of scheduled medications, e.g., opioid analgesics. We conducted a systematic literature review to better understand the current state of 1. PDMP effectiveness and 2. factors influencing their utilization. The literature reveals mixed findings about the efficacy of PDMPs possibly due to variations in implementation approaches, inconsistent measures of effectiveness, and weak evidence limited by study design. Perceptions of effectiveness is a significant barrier to PDMP utilization.

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Context-dependent methamphetamine-induced locomotor sensitization in male and female adolescent rats after one pretreatment

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One-trial locomotor sensitization is the process by which a single exposure to a drug leads to a progressively higher locomotor behavioral response during a subsequent drug exposure. In adult rats, the context, or the environment where the initial drug administration took place, plays a key role in the development of this phenomenon. One-trial sensitization in young rats (postnatal days (PD) 21 or younger) is characteristically different. For instance, young rats typically demonstrate one-trial sensitization to cocaine and methamphetamine (METH), but the sensitization is context-independent (i.e., rats exhibit sensitization regardless of where the drug was given). Few studies have examined one-trial sensitization in adolescent rats. Thus the present study examined one-trial sensitization in adolescent rats to determine the ontogeny of context-dependent METH sensitization. Adolescent (PD 48) male and female rats were pretreated with saline or 3.0 mg/kg METH (IP) and immediately placed in a novel test chamber where locomotor activity was measured for 60 min. To assess for context-dependent sensitization, rats that were previously given saline in the novel chamber were injected with saline or 3.0 mg/kg METH (IP) in their home cage 45 min after being returned from the novel chamber. In contrast, rats given METH in the novel chamber were injected with saline in the home cage. The next day (i.e., PD 49), rats from each group were given a challenge injection of METH (0, 0.15, or 0.3 mg/kg, IP) in the novel test chamber and their locomotor activity was assessed for 90 min. Results show that female rats exhibited overall higher locomotor activity compared to male rats after administration of METH. However, both male and female rats exhibited one-trial sensitization that is context-dependent in a time-dependent manner (i.e., sensitization is evident during the first 30-60 min). These data indicate that one-trial sensitization in adolescent rats (PD 48) resembles of adult one-trial sensitization – in both cases it is context-dependent. To examine the ontogeny of this sensitized response, future studies examining earlier adolescent periods should be assessed.

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Previous Exposure to LSD Fails to Enhance the Psychomotor Stimulant Effects of d-Amphetamine in Male Sprague-Dawley Rats.

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The hallucinogenic effects of lysergic acid diethylamide (LSD) have been largely attributed to its high affinity for 5-HT_{2A} receptors. However, LSD also has a high affinity at several other monoamine receptors. The contribution of dopaminergic mechanisms to LSD’s behavioral effects is not well understood. Some authors have hypothesized that chronic treatment of rats with LSD may produce a persistent behavioral state characterized by sensitivity to dopamine agonists (Marona-Lewicka and Nichols, 2007). To address this hypothesis, the current investigation utilized a behavioral sensitization paradigm. Repeated exposure to psychostimulant drugs is known to produce progressive increases in locomotor activity and the expression of behavioral sensitization is correlated with changes in mesolimbic dopamine activity. To determine if repeated exposure to LSD alters dopaminergic activity, the present study investigated the locomotor stimulant effects of a low dose of d-amphetamine following a repeated dosing regimen with LSD. Forty male Sprague-Dawley rats were administered seven **intraperitoneal** injections of saline (n=16) or LSD (0.05, 0.1, 0.2 mg/kg; n=8 per dose) over a 7-day period with a 24-hr period between injections. Locomotor activity was assessed in test chambers for one hour before and one hour immediately after injections on days 1 and 7. On days 2-6, animals were injected and immediately placed back into home cages. After a 10-day drug washout period, 0.5 mg/kg d-amphetamine was administered I.P. to all LSD-treated animals and one group of saline-treated animals. The other group of saline-treated animals was administered saline. Activity was monitored in a similar manner to days 1 and 7. Results indicated a statistically significant increase in activity following repeated exposure to 0.05 mg/kg LSD. However, repeated LSD treatment did not produce behavioral sensitization to 0.5 mg/kg d-amphetamine. Additional experiments with a wider range of d-amphetamine doses and longer LSD treatment duration may be warranted to further evaluate the consequences of chronic LSD treatment on dopamine systems.

Poster Communications

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Adolescent voluntary ethanol drinking changes 50kHz ultrasonic vocalizations but not novelty and sensation seeking response.

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High novelty and sensation seeking (NSS) is positively correlated with earlier ethanol (ETOH) consumption, and sustained drinking into early adulthood. Our lab recently published NSS may change the affective response to amphetamine. Therefore, understanding the NSS response before and after voluntary ethanol consumption could elucidate important individual differences that promote sustained ETOH consumption. The present study aimed to understand NSS and affective response to rewarding stimulation—measured by ultrasonic vocalizations (USV)—before and after adolescent ETOH voluntary drinking. Thirty-eight male Long Evans rats were tested for their response to NSS using the inescapable novelty test. Then rats were tested for their affective response to play behavior (experimenter tickling) by measuring USV on the first exposure and fourth exposure to play behavior. USV were quantified as frequency modulated (FM), fixed frequency (FF), short, and trill calls. Rats were given access to 20% ETOH (w/v) for 8 weeks using the intermittent two bottle paradigm and 8 control rats only had water. After the 8 weeks of voluntary consumption rats were tested again for their response to NSS and for their response to rewarding stimulation. Results indicate that NSS response decreased after the ETOH voluntary consumption, but there was no difference between ETOH and control rats, indicating the decrease in NSS is likely due to age. Trill USV in response to a context associated with play behavior and in response to receipt of play behavior increased from the first to fourth exposure, indicating a conditioned association. After ETOH exposure, ETOH rats' trill USV increased in response to the play context but decreased in response to play behavior. This pattern was not observed in control rats. Our results indicate that novelty response is not directly changed by voluntary ETOH consumption. However, the affective response to contexts associated with reward and receipt of natural rewards change differently after ETOH exposure.

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In vivo effects of synthetic arylcyclohexylamine methoxetamine (MXE) in mice: thermoregulation, locomotor activity, and passive avoidance

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In recent years, synthetic analogues of well-characterized drugs of abuse have rapidly emerged, creating a massive 'grey market' of online designer drugs. One such drug is methoxetamine (MXE), an arylcyclohexylamine analogue of PCP and ketamine with purported dissociative effects similar to those substances. Despite reports of morbidity and mortality, and demonstration that MXE functions as a PCP-like non-competitive NMDA receptor antagonist in vitro, no in vivo studies with MXE have yet been published. In these studies, we sought to compare PCP and MXE in assays of thermoregulation, locomotor activity, and passive avoidance learning in order to discern relative potency and effectiveness across endpoints. For measurement of core temperature and motor activity, radiotelemetry probes were surgically implanted in mice, monitoring endpoints over a range of PCP and MXE doses. For measurement of acute amnestic effects, passive avoidance conditioning was conducted in drug-naïve mice which were then administered various doses of PCP or MXE immediately after exposure to the electrical stimulus. Retention trials were conducted to follow animals until step-through latency returned to baseline. PCP had biphasic effects on core temperature across the doses administered, eliciting transient increases in temperature at 30 mg/kg, and longer-lasting decreases in temperature at 100 mg/kg. In contrast, MXE only decreased core temperature at 30 mg/kg and 56 mg/kg, and the duration of these hypothermic effects was shorter than observed with PCP. Both PCP and MXE showed dose dependent stimulation of total activity measured over an 8 hour time course, although MXE was less effective than PCP. These data suggest that MXE has PCP-like effects in vivo, revealing a small part of the pharmacological profile of an emerging drug of abuse, that has remained unscheduled in the US. These studies are supported in part by the Systems Pharmacology and Toxicology Fellowship through the UAMS Translation Research Institute.

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Effects of "binge" administration of 3,4-methylenedioxypyrolvalerone (MDPV) or 3,4-methylenedioxymethamphetamine (MDMA) on place conditioning and passive avoidance learning in mice.

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3,4-Methylenedioxypyrolvalerone (MDPV) and 3,4-methylenedioxymethamphetamine (MDMA) are structurally-similar psychostimulants and constituents of commonly abused "bath salts" and "Molly," respectively. While both drugs induce psychostimulant effects by increasing the concentrations of synaptic monoamines within the central nervous system, their mechanisms of action and selectivity are distinct. MDPV functions as "cocaine-like" reuptake inhibitor, while MDMA functions as an "amphetamine-like" substrate/releaser. Users of MDPV and MDMA may re-administer the drug after the euphoric effect is lost, resulting in a "binge-like" pattern of use. To simulate this pattern of use, mice received four IP doses of 3 mg/kg MDPV, 3 mg/kg MDMA or saline, each injection separated by a 2-hr interval. Place-conditioning assays were preformed with three consecutive pairing days using 3 mg/kg MDMA or 0.3 mg/kg MDPV. Passive avoidance studies were conducted to assess the effects of the drug binges on motivational learning with the binge regimen separating the conditioning and post-conditioning latency test. These experiments show that binge administration of MDPV blocks place preference to MDPV and blunts place preference to MDMA without affecting passive avoidance learning. In contrast, binge administration of MDMA did not alter place preference to both MDMA and MDPV but did impair passive avoidance learning. These contrasting results suggest that binge MDPV and MDMA have distinct effects on motivational learning in mice, likely mediated *via* distinct persistent neurochemical effects.

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Reinforcing effects of the synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV) in rats.

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The abuse of designer stimulants (*bath salts*) has increased dramatically in recent years, with synthetic cathinones, such as 3,4-methylenedioxypyrovalerone (MDPV), accounting for ~25% of all new drugs of abuse. The current study used male Sprague Dawley rats (two groups of 16) to directly compare the reinforcing effects of MDPV to those of cocaine, a drug with a similar mechanism of action. Rats readily acquired self-administration when infusions of 0.032 mg/kg MDPV or 0.32 mg/kg cocaine were available under a fixed ratio (FR) 1 schedule of reinforcement. Although cocaine maintained stable patterns of responding under both FR1 and FR5 schedules, differential patterns of responding emerged when MDPV was made available under an FR5, with ~50% of rats exhibiting a ~3-fold increase in MDPV intake relative to their level of intake under FR1 conditions. Importantly, these differential levels of intake were also observed when MDPV (0.0032-0.1 mg/kg/inf) was evaluated under a multiple component schedule (25-min response period, 5-min blackout). In addition to making more responses during timeouts and blackouts, the high intake rats also responded at significantly more than the low intake rats when cocaine (0.032-1 mg/kg/inf) was substituted for MDPV. Cocaine-trained rats exhibited stable patterns of responding, and few responses during timeouts and blackouts, regardless of whether they were responding for cocaine or MDPV. In summary, these studies describe a behavioral phenotype characterized by high levels of MDPV intake, and high levels of responding during periods of signaled drug unavailability (i.e., timeouts and blackouts). Although this phenotype was not observed in any of the cocaine-trained rats, it appears to be transferable to other drugs once established. The degree to which these effects predict individual differences in the abuse-related effects of MDPV or *bath salt* preparations in humans is unclear.

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Metabolic fate of hallucinogenic NBOMes

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2,5-Dimethoxy-*N*-benzylphenethylamines (NBOMes) are very potent serotonin type 2A receptor (5-HT2AR) agonists and hallucinogenic in man. Illicit use of these psychedelic compounds has emerged in recent years, and several fatalities have been linked to their recreational use. In its [11C]-labeled form, one NBOMe (25B-NBOMe) was recently developed as a PET-ligand for clinical investigations of 5HT2AR ([11C]Cimbi-36). We have identified the phase I and phase II metabolites of 25B-NBOMe in pigs as well as in humans. We find that the primary route of metabolism is 5′-demethylation, followed by conjugation to glucuronic acid. Carbon-11 labeling of 25B-NBOMe in three different positions followed by in vivo evaluation in pigs and humans corroborated these findings.

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Identification of pre-motor cognitive impairments in Parkinsonian rats provide insight for possible early intervention

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Approximately 6.3 million people worldwide are currently diagnosed with Parkinson's disease (PD), with 60,000 new cases appearing every year in the United States. It is a brain disease that is characterized by irreversible damage and death to neurons that mediate behavior through the release of the neurotransmitter dopamine (DA). Eventually, the extreme loss of DA results in motor and cognitive impairments. Unfortunately, PD is currently not diagnosed until motor symptomology manifests, a state at which 80-95% DA is depleted in the brain. Unfortunately, there are no clinically relevant techniques that are available for earlier diagnosis. Our goal is to find subtle cognitive behavioral abnormalities that emerge at moderate DA depletions prior to motor difficulties. Specifically, we hypothesize that cognitive deficits will emerge during moderate DA loss before motor-impairments manifest. In current research, a model of PD is created in rats using bilateral infusions of 6-hydroxydopamine (6-OHDA) a neurotoxin to DA cells. To assess cognitive abilities in rats with variable DA depletions, animals are tested in an array of behavioral paradigms to evaluate associative learning, response learning, strategy shifting, and working memory motor. Subsequently, animal tissue samples are collected and DA concentrations analyzed with HPLC-ECD methodology. Preliminary data suggest that cognitive deficits may manifest before motor impairments are observed at more moderate levels of DA depletion. Data are currently being collected for working memory. These preliminary findings for early cognitive deficits may lead to earlier diagnosis and intervention of PD. The results of the present study will serve as a behavioral baseline for future studies to evaluate how neural changes due to stimulant drug exposure might be harnessed as a treatment.

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Evaluation of conditioning times in nicotine-induced condition place preference in female and male adolescent rats

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Research investigating the rewarding properties of nicotine, using the condition place preference (CPP) paradigm, has produced varying results with the degree to which place conditioning is observed. One factor that may mediate these differences is the duration of the conditioning session post nicotine exposure, as studies employ 10-30 min conditioning sessions. Thus, the present study sought to determine whether conditioning session length (15 vs. 30 min) results in varying expression of nicotine-induced CPP in female and male adolescent Sprague-Dawley rats. Specifically, rats were assessed for nicotine-induced CPP beginning on postnatal day (PD) 27 using an 11-day CPP procedure. On day 1 and 11, rats were tested for their preconditioning and postconditioning place preferences, respectively, during 15-min sessions. On days 3-10, rats were conditioned for 15- or 30- min per day with either nicotine (0, 0.022, 0.067, 0.2 or 0.6 mg/kg, subcutaneously) or saline on alternating days. Day 2 was a rest day. Results reveal sex differences in the rewarding effects of nicotine in rats that were conditioned for 15 or 30 min, as well as differences in the strength of CPP between the two conditioning durations. Specifically, both female and male rats found 0.067 rewarding when conditioned for 15 min in contrast to when they were conditioned for conditioned for 30 min. Overall, these results suggest that the length of the conditioning sessions may be important in interpreting the rewarding effects of nicotine.

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Differences in methamphetamine conditioned place preference between C57Bl/6 and 129/SvEv adolescent female mice.

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Men and women differ in their use and response to methamphetamine. Compared to men, women begin to use it at an earlier age, are more dependent on it and are more likely to initiate methamphetamine use to lose weight. While numerous studies have used rodent models for understanding the genetic and cellular basis of drug intake, the majority of these studies have been conducted in males. We have begun to study the neural basis of addiction in females by testing the rewarding effects of a low dose of methamphetamine (1 mg/kg) in a conditioned place preference paradigm in adolescent (postnatal day 41) female mice. We compared responses in two strains, C57Bl/6 and 129/SvEv, both of which are commonly used background strains of knockout mice. Mice were trained and tested during adolescence, because methamphetamine use is often initiated during adolescence and maturational changes during this stage of development have been suggested to affect drug response. Results show that adolescent female C57Bl/6 mice exhibit conditioned place preference for the compartment paired with methamphetamine, but adolescent female 129/SvEv mice fail to display this preference. The neural basis of this difference is being investigated by quantifying behaviorally-induced protein expression of the immediate early gene c-Fos in the nucleus accumbens, basolateral amygdala, and medial prefrontal cortex after CPP testing. Cell counts will be compared in methamphetamine-treated and saline-treated mice of each strain. Given that C57Bl/6 mice show higher novelty-seeking behavior than129/SvEv mice, our results are consistent with the association between high novelty seeking behavior and an increased risk for using drugs of abuse. *Supported by NIH grants G12MD007599, R25NS080686-06 and GM060665-16.*

Poster Communications

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Dietary supplementation with fish oil delays high fat chow-induced enhancement of sensitivity to the behavioral effects of dopamine D_2/D_3 receptor agonist quinpirole in adolescent male rats

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Eating a diet high in fat can lead to severe negative health consequences, including obesity and insulin resistance. Dietary supplements that are rich in omega-3 polyunsaturated fatty acids (e.g., fish oil) can reduce or prevent high fat diet-induced obesity and insulin resistance in rats. Eating a high fat diet also enhances sensitivity of rats to the behavioral effects of drugs acting on dopamine systems, including drugs that act indirectly (e.g., cocaine) and directly (e.g., quinpirole) on dopamine receptors. To test the hypothesis that dietary supplementation with fish oil prevents high fat diet-induced enhanced sensitivity to the behavioral effects of quinpirole (0.0032-0.32 mg/kg), a dopamine D_2/D_3 receptor agonist, adolescent male rats ate standard laboratory chow (17% kcal from fat), high fat chow (60% kcal from fat), or high fat chow supplemented with 20% fish oil (w/w; 68% kcal from fat). Similar to previous reports, the rats eating high fat chow without fish oil were more sensitive (e.g., leftward shift of the quinpirole dose-response curve) than rats eating standard chow to yawning induced by quinpirole. During the first weeks of testing, dietary supplementation with fish oil prevented this effect. That is, quinpirole dose-response curves were not different between rats eating high fat chow supplemented with fish oil and standard chow-fed controls. However, after 4 weeks of eating high fat chow with fish oil, sensitivity of rats in this group to the behavioral effects of quinpirole was also increased as compared to standard chow-fed controls. Quinpirole-induced hypothermia was unchanged by dietary condition. These results suggest that while diets high in fat increase sensitivity of individuals to drugs acting on dopamine systems in ways that might be relevant to drug abuse, dietary supplementation with fish oil can delay these effects, although the mechanism underlying this effect remains to be determined. These data add to a growing literature demonstrating the complex relationship between diet and drug abuse, and the health benefits of fish oil.

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The role of novelty response and adolescent ethanol exposure on oral ethanol self-administration in Long Evans rats.

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Alcoholism is a debilitating disease encompassed by both psychological and physical risk factors. Novelty and sensation seeking (NSS) is a risk factor for early ethanol experimentation and the development of alcohol dependence into adulthood. Similarly, higher rates of adolescent ethanol use are correlated with greater alcoholism later in life. However, knowing whether psychological or physical factors contribute to ethanol seeking in adulthood is not fully understood. In this study we tested whether psychological factors (NSS) or physical factors (adolescent ethanol vs no exposure) contributed to responding for oral ethanol self-administration on different schedules of reinforcement. Male Long-Evans rats were first tested for their response to novelty. Then 30 rats voluntarily consumed 20% ethanol for 8 weeks beginning around PND 50, and the remaining 8 rats only had water access during an intermittent two bottle choice paradigm. Then all animals were trained to lever press for ethanol using 5%, 10%, and 20% (w/v) using a schedule that incremented from FR-1 to FR-3 and then to FR-10. All test sessions were 30 minutes in length. Successful completion of the schedule resulted in illumination of the cue light above the lever and presentation of 0.1ml of 20% ethanol (w/v) for 5.9s. Repeated measures ANOVA analyses were conducted for each test phase. Results indicate that rats exposed to ethanol during adolescence responded more during the FR-1 testing. There was no effect of IEN but there was an effect of NPP, such that higher novelty preference resulted in greater ethanol responding. Analysis of the FR-3 results indicated adolescent ethanol exposure increased responding with no other significant effects. The results for FR-10 indicated that adolescent ethanol exposed rats responded more but this was marginally significant (p=.06), no other effects were observed. The results provide support that the choice to engage novelty is important for early self-administration, but alterations induced by ethanol exposure during adolescence are more important for ethanol seeking.

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Crabp2-and Fabp5-mediated retinoic acid signaling is a novel mechanism determining drug-taking behavior in rats

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Environmental enrichment produces protective depression and addiction phenotypes in rats. Rats reared in an enriched condition self-administer less cocaine and show antidepressant-like effects in the sucrose preference test. Our previous quantitative RNA sequencing study revealed that transcripts in the retinoic acid (RA) signaling pathway were significantly regulated by environmental enrichment and cocaine. In neurons, RA is involved in multiple intracellular signaling pathways by binding to different proteins, two of which are *Crabp2* and *Fabp5*. This study is to investigate the effects of *Crabp2* and *Fabp5* by knocking down expression of these two genes in rat nucleus accumbens to affect depression- and addiction-related behavior. In the results, knocking down *Crabp2*, but not *Fabp5*, decreased sucrose intake after 15min and 16hrs in the sucrose preference test indicating a depression-like effect. In sucrose operant responding, rats with *Crabp2* knockdown made fewer responses for sucrose pellets at 85% of free-feed body weight in FR1, FR2 and FR5. In cocaine self-administration, knocking down *Fabp5* significantly decreased acquisition of cocaine at 0.2 mg/kg/infusion. In maintenance responding, rats with *Fabp5* knockdown in NAc responded less for a low unit dose of cocaine. Ongoing experiments are testing drug induced reinstatement and cocaine self-administration under PR schedule. In conclusion, Decreased *Crabp2*-mediated RA signaling produces a decrease in motivation in operant responding. *Fabp5* knockdown produces a resistant addiction phenotype.

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Evaluation of the discriminable stimulus effects of 0.3 mg/kg 3,4-methylenedioxypyrovalerone (MDPV) and 1.0 mg/kg 4-methylmethcathinone (4-MMC) using a drug discrimination procedure in male Sprague-Dawley rats

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Previous reports using intravenous self-administration procedures in non-human experimental subjects have revealed that the synthetic cathinones, 3,4-methylenedioxypyrovalerone (MDPV) and 4-methylmethcathinone (4-MMC, mephedrone), can serve as relatively potent reinforcers with effects comparable to established drugs of abuse. These findings suggest these drugs possess high abuse potential and their consumption may develop into severe addiction among users. Relatively fewer studies have investigated the discriminable stimulus effects of synthetic cathinones using drug discrimination procedures. Moreover, the neurochemical mechanisms underlying the interoceptive stimulus effects of MDPV and 4-MMC are imperfectly understood. Further research using drug discrimination procedures will broaden understanding of the interoceptive effects produced by MDPV and 4-MMC. The present experiment investigated the discriminable stimulus effects of 0.3 mg/kg MDPV (n=8) or 1.0 mg/kg 4-MMC (n=8) using a two-lever drug discrimination procedure in male Sprague-Dawley rats. The MDPV- and 4-MMC-trained rats displayed no difference in the number of sessions required to reach the criterion for the acquisition of the discrimination. Stimulus generalization tests were conducted with the following compounds: MDPV (0.01-1.0 mg/kg), 4-MMC (0.01-3.0), *d*-amphetamine (0.03-1.0), methamphetamine (0.03-1.0), cocaine (0.1-10.0), 3,4-methylenedioxymethamphetamine (0.03-3.0), lysergic acid diethylamide (0.01-0.1), and fenfluramine (0.1-3.0). This study is currently in progress and full results will be forthcoming. Overall, it is generally expected that drugs producing serotonergic release will produce full-substitution in 4-MMC-trained rats, and those that increase dopamine efflux will produce full-substitution in MDPV-trained rats. This experiment will expand upon the current behavioral profile of MDPV and 4-MMC and may further assist in characterizing their subjective effects in habitual users.

Poster Communications

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Eating high fat chow enhances sensitivity of male, but not female, rats to the behavioral effects of dopamine D_2/D_3 receptor agonist quinpirole

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Eating high fat chow increases sensitivity of rats to drugs that act indirectly on dopamine receptors (e.g., cocaine). This effect is greatest in female adolescent rats. Eating high fat chow also enhances sensitivity of adult male rats to the behavioral effects of drugs that act directly on dopamine receptors (e.g., the dopamine D_2/D_3 receptor agonist quinpirole); however, it is not known if this effect is greater in adolescents. It is also not known if there are sex differences in this diet-induced enhancement that mirror those previously demonstrated with cocaine. To test the hypothesis that females are more sensitive than males to the diet-induced effects on quinpirole-induced yawning, male and female Sprague-Dawley rats (postnatal day 25) eating either standard laboratory chow (17% kcal from fat) or high fat chow (60% kcal from fat), were tested once per week with quinpirole (0.0032-0.32 mg/kg) for 8 weeks. Eating high fat chow increased sensitivity of male rats to the behavioral effects of quinpirole. Specifically, quinpirole induced more yawning in male rats eating high fat chow, (e.g., an increase in the maximal effect) as compared to standard chow fed controls. In comparison, adolescent female rats yawned significantly less than their male counterparts, and eating high fat chow did not increase the frequency of yawning. In contrast, hypothermia induced by quinpirole was unchanged by diet, and was comparable between sexes. These data suggest that alternative assays should be considered to measure sensitivity of female rats to the behavioral effects of dopamine receptor agonists. For example, other directly observable behaviors, such as locomotion or rearing, might provide a way to measure drug sensitivity in female rats. These results further demonstrate the importance of studying drug sensitivity in both male and female subjects.

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Sex differences in drug-induced plasticity following heroin self-administration

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Drug addiction is a chronic relapsing disease that persists long after the cessation of drug taking. Approximately 21.5 million Americans suffer from substance abuse disorders. 1.9 million of these cases involve opioid analgesics and 586,000 are heroin-related (SAMHSA, 2015). According to the CDC, the number of people reporting past-year heroin abuse has increased nearly 150% since 2007, and heroin-related overdose deaths increased 286% since 2002 (Jones, 2015). Plasticity in the central nervous system is thought to underlie substance abuse disorders. In both humans and rodents there are reports of sex differences in drug-taking behaviors. However, while many of these studies have focused on psychostimulants, very few have examined the role of sex differences in opiate addiction (Badiani et al., 2014; Carroll, 2002). In the present study we used a self-administration procedure with both male and female rats to examine the role of sex and hormones in the acquisition of heroin taking. Our results show that males and both intact and ovariectomized males respond similarly during heroin self-administration. Following self-administration, we examined morphological changes of medium spiny neurons of the nucleus accumbens, which is thought to be a measure of functional rewiring of the reward circuitry. In contrast to our behavioral findings, we found that while males showed a significant decrease in spine density as previously reported, heroin had no effect on structural plasticity in females. Our results demonstrate a divergence between behavioral and neurobiological outcomes following drugs of abuse. These findings reiterate the importance of investigating both behavior and neurobiology across sexes in an effort to identify potential targets for novel interventions to treat opioid addiction.

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IKK Isoform Expression in Brain Regions Associated with Alcohol Dependence

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Evidence has shown a connection between pro-inflammatory neuroimmune signaling and the development of alcohol abuse, particularly mediated the activation of nuclear factor kappa-B (NF-κB), which then transcribes numerous pro-inflammatory chemokines and cytokines. Important mediators of NF-κB are Inhibitory kappa-B kinases (IKKs) that exist in four isoforms: Alpha (α), Beta (β), Gamma (γ), and Epsilon (ε). IKKs regulate NF-κB by phosphorylating the inhibitor of NF-κB (IκB), thus targeting it for degradation in the proteasome. Our lab has shown that IKKβ knockdown in the nucleus accumbens (NAc) and amygdala (AMY) via lentiviral vector delivery, and treatment of animals with IKKβ antagonists, decreases voluntary ethanol drinking in mice. However, there is no complete expression profile of IKK isoforms in brain regions commonly associated with alcohol abuse such as the prefrontal cortex (PFC), NAc, AMY, and the ventral tegmental area (VTA), especially specific cell type profile in neurons, astrocytes, and microglia. We hypothesized IKKs are expressed throughout the brain, primarily in neurons based upon the findings described above. Adult male alcohol-naive C57BL/6J mice were perfused, brains were harvested, sectioned, and categorized by brain region. Sections were stained for IKKα, β, γ, or ε and with cell-specific markers using double-labeled immunohistochemistry. Composite cross-sectional images of each brain region were taken using fluorescent light microscopy and analyzed using ImageJ to determine the number of cells expressing each IKK isoform and the cell type colocalization. Subcellular localization of IKKs was confirmed with confocal microscopy. We found that all isoforms of IKK were highly expressed in the PFC, NAc, and AMY, but to a lesser degree in the VTA. Subsequently, every isoform was expressed in all three cell types, but was primarily neuronal. This expression profile of IKKs in C57BL/6J mice will aid in future research investigating the role of neuroimmune signaling within the context of alcohol abuse. Supported by NIH/NIAA (AA06399) and the INIA Consortium (AA013520).

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

				Score
Section	✓	**Criteria**	**Comments**	Score each section (1-weak to 5-strong) sum total score
Introduction		Clear objectives		
		Clear background		
		Appropriate Rationale		
Methods		Appropriate design		
		Appropriate detail		
		Clear explanation		
		Other		
Results		Clear description		
		Appropriate detail		
		Other		
Summary		Clear		
		Concise		
		Other		
Conclusions		Not a summary		
		Supported by data		
		Alternative conclusions considered		
		Other		
Style		Clear voice		
		Dynamic inflection		
		Eye contact		
		Appropriate pace		
		Enthusiasm		
		Other		
Organization		Logical flow		
		Adequate time for each section		
		Other		
Visuals		Visible		
		Clear		
		Other		
Overall				

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Notes

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***.


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