Behavior, Biology, and Chemistry: Translational Research in Addiction (BBC)

San Antonio, Texas
La Quinta Inn and Suites Medical Center
4-5 March 2017

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Addiction Research Treatment & Training Center of Excellence

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BBC Publications

BBC 2011

Stockton Jr SD and Devi LA (2012) **Functional relevance of μ–δ opioid receptor heteromerization: A Role in novel signaling and implications for the treatment of addiction disorders: From a symposium on new concepts in mu-opioid pharmacology.** Drug and Alcohol Dependence Mar 1;121(3):167-72. doi: 10.1016/j.drugalcdep.2011.10.025. Epub 2011 Nov 23

Traynor J (2012) **μ-Opioid receptors and regulators of G protein signaling (RGS) proteins: From a symposium on new concepts in mu-opioid pharmacology. Drug and Alcohol Dependence Mar 1;121(3):** 173-80. doi: 10.1016/j.drugalcdep.2011.10.027. Epub 2011 Nov 29

Lamb K, Tidgewell K, Simpson DS, Bohn LM and Prisinzano TE (2012) **Antinociceptive effects of herkinorin, a MOP receptor agonist derived from salvinorin A in the formalin test in rats: New concepts in mu opioid receptor pharmacology: From a symposium on new concepts in mu-opioid pharmacology.** Drug and Alcohol Dependence Mar 1;121(3):181-8. doi: 10.1016/j.drugalcdep.2011.10.026. Epub 2011 Nov 26

Whistler JL (2012) **Examining the role of mu opioid receptor endocytosis in the beneficial and side-effects of prolonged opioid use: From a symposium on new concepts in mu-opioid pharmacology.** Drug and Alcohol Dependence Mar 1;121(3):189-204. doi: 10.1016/j.drugalcdep.2011.10.031. Epub 2012 Jan 9

BBC 2012

Zorrilla EP, Heilig M, de Wit, H and Shaham Y (2013) **Behavioral, biological, and chemical perspectives on targeting CRF1 receptor antagonists to treat alcoholism.** Drug and Alcohol Dependence Mar 1;128(3):175-86. doi: 10.1016/j.drugalcdep.2012.12.017. Epub 2013 Jan 5

BBC 2013

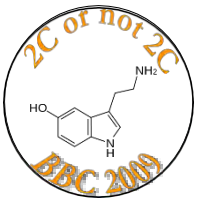
De Biasi M, McLaughlin I, Perez EE, Crooks PA, Dwoskin LP, Bardo MT, Pentel PR and Hatsukami D (2014) **Scientific overview: 2013 BBC plenary symposium on tobacco addiction.** Drug and Alcohol Depen- dence Aug 1;141:107-17. doi: 10.1016/j.drugalcdep.2014.05.013. Epub 2014 Jun 2. Erratum in: Drug Alcohol Depend. 2014 Nov 1;144:290

BBC 2014

Reith ME, Blough BE, Hong WC, Jones KT, Schmitt KC, Baumann MH, Partilla JS, Rothman RB and Katz JL (2015) **Behavioral, biological and chemical perspectives on atypical agents targeting the dopamine transporter. Drug and Alcohol Dependence Feb 1;147C:1-19. doi: 10.1016/j.drugalcdep.** 2014.12.005. Epub 2014 Dec 18

BBC 2015

Grandy, DK, Miller, GM and Li, JX (2016) **"TAARgeting addiction"– The Alamo bears witness to another revolution.** Drug and Alcohol Dependence Feb 1;159: 9-16. 10.1016/j.drugalcdep.2015.11.014. Epub 2015 Nov 22



Acknowledgements

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Program Overview

FRIDAY 3 MARCH 2017

3:00 PM – 5:00 PM	Pathways to Careers in Science Workshop
4:00 PM – 6:00 PM	Registration
5:15 PM	Bus departs from UT Health to La Quinta
6:00 PM	Buses depart from La Quinta to Opening Reception at La Vista Terrace
6:00 PM – 9:00 PM	**BBC Opening Reception, La Vista Terrace**

SATURDAY 4 MARCH 2017

7:00 AM – 5:00 PM	BBC Registration
8:00 AM – 8:05 AM	Welcome and Opening Remarks
8:05 AM – 10:25 AM	Plenary Symposium: *The opioid epidemic: history, formulations, regulations, and emergencies* (Chairs: Andrew Coop, and James H Woods) **Lewis S Nelson**; *From opiophobia to abuse deterrent formulations: the making of an opioid epidemic.* **Mansoor Khan**; *Abuse deterrent formulations: design strategies and evaluation* **Silvia N Calderon**; *Prescription opioids: abuse potential, scheduling and the current opioid epidemic* **Andrew Coop**; *Beyond formulations: solving the opioid epidemic with new chemical entities*
10:25 AM – 10:40 AM	Coffee Break
10:40 AM – 12:10 PM	Open Oral Communications 1 (Chair: Thomas M Keck)
12:10 PM - 1:25 PM	Lunch
12:30 PM – 1:15 PM	Tietronix Presentation and Discussion
1:25 PM – 2:55 PM	Open Oral Communications 2 (Chair: Amanda L Sharpe)
2:55 PM – 3:10 PM	Coffee Break and Poster Session I Set Up
3:10 PM – 4:25 PM	Poster Session I
4:25 PM – 5:25 PM	Special Lecture: **Sam Quinones**; *Dreamland: America's opiate-addiction epidemic and how we got where we are today* (Chair: Andrew Coop)
5:25 PM – 5:45 PM	Poster Break Down and Set Up
5:45 PM – 7:00 PM	Poster Session II and Book Signing
7:00 PM – 9:00 PM	Dinner After Dinner Speaker **Jack Bergman**; *Contextual factors in the reinforcing effects of drugs* (Chair: Ellen A Walker)
9:00 PM – 11:00 PM	Hospitality and Entertainment

SUNDAY 5 MARCH 2017

7:45 AM	Travel Awardee Group Photo
8:00 AM – 9:30 AM	Open Oral Communications 3 (Chair: Gail D Winger)
9:30 AM – 9:45 AM	Coffee Break
9:45 AM – 11:15 AM	Open Oral Communications 4 (Chair: David N Kearns)
11:15 AM – 11:30 AM	Coffee Break
11:30 AM – 12:30 PM	Special Lecture: **Christopher R McCurdy**; *Development and clinical translation of sigma receptor ligands as diagnostics and therapeutics for pain* (Chair: James M Cook)
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

Program Details

Friday 3 March 2017

Opening Reception

La Vista Terrace on the Riverwalk

6:00 PM	Buses depart from La Quinta
6:30 PM - 9:00 PM	Reception
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 La Vista Terrace 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 $50.00.

Saturday 4 March 2017

Welcome and Opening Remarks 8:00 AM - 8:05 AM

Plenary Symposium (Chairs: Andrew Coop and James H Woods)

The opioid epidemic: history, formulations, regulations, and emergencies

The abuse of prescription and illicit opioids is at epidemic proportions, resulting in a public health crisis. Tackling such a complex issue will require interdisciplinary approaches involving basic science, engineering science, epidemiology, regulatory guidance, and patient and healthcare worker education. The symposium will focus on four such interrelated areas, specifically the history of how the epidemic grew, approaches to reducing diversion using formulation, the science behind the development of federal regulations, and a discussion of the optimal pharmacological profile required for new opioids to prevent abuse. The goal is the education of all attendees in the numerous interconnected factors that require solving as society moves to eliminate the opioid abuse epidemic.

8:05 AM – 8:40 AM	**Lewis S Nelson** Rutgers University, New Jersey Medical School From opiophobia to abuse deterrent formulations: the making of an opioid epidemic.
8:40 AM – 9:15 AM	**Mansoor Khan** Texas A&M University Abuse deterrent formulations: design strategies and evaluation
9:15 AM – 9:50 AM	**Silvia N Calderon** US Food & Drug Administration Prescription opioids: abuse potential, scheduling and the current opioid epidemic
9:50 AM – 10:25 AM	**Andrew Coop** University of Maryland School of Pharmacy Beyond formulations: solving the opioid epidemic with new chemical entities

Coffee Break 10:25 AM – 10:40 AM

Oral Communications 1 (Chair: Thomas M Keck)

10:40 AM – 10:55 AM **Christina Cruz**, UT Health San Antonio
The impact of social support on physiological responses to stress in opioid-using pregnant women: a mixed methods study

10:55 AM – 11:10 AM **Eric A Wold**, University of Texas Medical Branch
Positive allosteric modulation of the serotonin 2C receptor as a novel neurotherapeutic strategy for cocaine addiction

11:10 AM – 11:25 AM **Matthew Clasen**, American University
Cocaine increases permeability of the blood-brain-barrier in the hippocampus: implications for drug use and abuse

11:25 AM – 11:40 AM **Kathleen Borgmann**, University of North Texas Health Science Center
TAARgeting astrocyte mitochondrial dysfunction during HIV-associated neuroinflammation and METH exposure.

11:40 AM – 11:55 AM **Justin Siemian**, University at Buffalo
Inhibition of Ca2+ signaling attenuates the antinociceptive but not discriminative stimulus effects of the imidazoline I2 receptor agonist 2-BFI in rats.

11:55 AM – 12:10 PM **Drew Townsend**, University of Mississippi Medical Center
Reinforcing and antinociceptive effects of nalfurafine and oxycodone mixtures in male rats.

Lunch 12:10 PM – 1:25 PM

Tietronix Presentation and Discussion 12:30 PM – 1:15 PM

Oral Communications 2 (Chair: Amanda L. Sharpe)

1:25 PM – 1:40 PM **Michelle Land**, University of Texas Medical Branch
The Serotonin 2C Receptor (5-HT2CR) Cys23Ser single nucleotide polymorphism associates with receptor function and localization in vitro

1:40 PM – 1:55 PM **Andrea Dimet**, University of Texas Medical Branch
Functional & structural effects of targeting PPARgamma in a cocaine use disorder model

1:55 PM – 2:10 PM **Anqi Walbaum**, University of Arkansas for Medical Sciences
Acute and Chronic treatment combined with safety evaluation of ZZ204G, a novel analgesic

2:10 PM – 2:25 PM **Rachel Altshuler**, University of Michigan
Investigating the effects of PKCβ inhibitors on amphetamine-mediated behaviors in rats

2:25 PM – 2:40 PM **Michael Leonard**, Tufts University
Binge-like cocaine self-administration is differentially augmented by intra-VTA CRF microinfusion or social defeat stress in rats

2:40 PM – 2:55 PM **Robert Fuchs**, Louisiana State University Health Sciences Center - New Orleans
Elevated brain-derived neurotrophic factor levels in the reward system of alcohol-dependent animals

Coffee Break and Poster Session I Set Up 2:55 PM – 3:10 PM

Maharaj Ticku Memorial Travel Fellowship for New Investigators

Travel Awardee

Poster Session 1 3:10 PM – 4:25 PM

Special Lecture: Sam Quinones 4:25 PM – 5:25 PM (Chair: Andrew Coop)
Dreamland: America's opiate-addiction epidemic and how we got where we are today

Poster Breakdown and Poster Session II Set-up 5:25 PM – 5:45 PM

Poster Session II and Book Signing 5:45 PM – 7:00 PM

Dinner 7:00 PM – 9:00 PM
Additional Tickets can be purchased in advance or at the registration desk for $70.00

After Dinner Speaker: Jack Bergman (Chair: Ellen A Walker)
Contextual factors in the reinforcing effects of drugs

Hospitality and Entertainment 9:00 PM – 11:00 PM
Come and enjoy the fun in the San Jose Room!

Sunday 5 March 2017

Travel Awardee Group Photo 7:45 AM

Oral Communications 3 (Chair: Gail D Winger)

8:00 AM – 8:15 AM	**Allison Doyle Brackley**, UT Health San Antonio FDA-approved drug paroxetine targets GRK2 to enhance peripheral delta opioid receptor-mediated analgesia
8:15 AM – 8:30 AM	**Samantha McClenahan**, University of Arkansas for Medical Sciences Cardiovascular (CV) and locomotor effects of 3, 4-methylenedioxypyrovalerone (MDPV) in male and female Sprague-Dawley (SD) rats
8:30 AM – 8:45 AM	**Alessandro Bonifazi**, National Institute on Drug Abuse Novel bivalent ligands based on the sumanirole pharmacophore reveal dopamine D2 receptor (D2R) biased agonism and potential allosteric modulation
8:45 AM – 9:00 AM	**Christopher Tschumi**, UT Health San Antonio Neurotensin-induced plasticity temporally modulates GABAergic input to midbrain dopamine neurons.
9:00 AM – 9:15 AM	**Suky Martinez**, Division of Substance Use Disorders, New York State Psychiatric Institute/ Columbia University Medical Center Effects of pioglitazone, a PPARγ agonist, on the subjective and reinforcing effects of tobacco cigarettes
9:15 AM – 9:30 AM	**Craig Werner**, University at Buffalo The role of hippocampal activin signaling in perpetuated cocaine craving

Coffee Break 9:30 AM – 9:45 AM

Oral Communications 4 (Chair: David N Kearns)

9:45 AM – 10:00 AM — **Rachel Slack**, National Institute on Drug Abuse
Design and synthesis of novel bromine-containing paroxetine derivatives toward structure-function analyses with the serotonin transporter.

10:00 AM – 10:15 AM — **Jessica Anand**, University of Michigan
Novel mu opioid receptor agonist/delta opioid receptor antagonist ligands with reduced development of adverse effects

10:15 AM – 10:30 AM — **Thomas Keck**, Rowan University
Functional and high-affinity binding of dopamine D4 receptor-selective partial agonists as pharmacological tools to study substance use disorders.

10:30 AM – 10:45 AM — **Sarah Withey**, McLean Hospital/Harvard Medical School
Concurrent evaluation of the antinociceptive and response disrupting effects of opioids

10:45 AM – 11:00 AM — **Audrey Hager**, UT Health San Antonio
Cocaine effects on dopamine neurons in mice are reduced by deletion of GIRK2 channels specifically in dopamine neurons and with cocaine self-administration experience.

11:00 AM – 11:15 AM — **Megan Moerke**, Virginia Commonwealth University
Role of mu opioid receptors in mediating the effects of amphetamine on cocaine-vs.-food choice in rhesus monkeys.

Coffee Break 11:15 AM – 11:30 AM

Special Lecture: Christopher McCurdy 11:30 AM – 12:30 PM (Chair: James M Cook)
Development and clinical translation of sigma receptor ligands as diagnostics and therapeutics for pain

Presentations of Awards for Travel, Oral and Poster Presentations 12:30 PM

Adjournment and Lunch 12:30 PM – 1:30 PM

See you at BBC 2018!

Oral Communications

The Impact of Social Support on Physiological Responses to Stress in Opioid-Using Pregnant Women: A Mixed Methods Study

Cruz, Cristina, Puga, Frank, and Cleveland, Lisa[1]

[1]School of Nursing, University of Texas Health San Antonio, San Antonio, TX USA.

Opioid use during pregnancy exposes both the mother and the child to potential long-term negative health outcomes. Children prenatally exposed to drugs are at risk for impaired emotional regulation and cognitive functioning, while substance using pregnant women are at risk for anxiety, depression and accidental overdose. The aims of this study were to investigate the relationship between the social environments, perceived stressors, stress reactivity, and birth outcomes for opioid using pregnant women Pregnant women with an opioid-use disorder participated in focus groups or semi-structured interviews to collect qualitative data regarding daily stressors. Quantitative data was collected by using the following instruments: 1) the 10-item Perceived Stress Scale to measure stress level, 2) the Patient Health Questionnaire-9 to measure depressive symptoms, and 3) the Medical Outcomes Study Social Support Survey to measure perceived social support. Finally, saliva samples were collected in order to measure resting cortisol levels, a biomarker of stress and hypothalamic-pituitary-adrenal axis (HPA axis) functioning. Data analysis is currently in progress. Preliminary results suggest that social support acts as a buffer to stress by decreasing the biological sensitivity of the body to psychological stress reactions, possibly due to positive effects to the HPA axis. Therefore, shielding the mother and baby from the deleterious effects of stress caused by the social environment of the mother. The results of this study will help inform interventions that improve social support and birth outcomes in mother and baby dyads affected by substance use.

Positive Allosteric Modulation of the Serotonin 2C Receptor as a Novel Neurotherapeutic Strategy for Cocaine Addiction

Wold, Eric A.[1,2], Wild, Christopher T.[1,2], McAllister, Carrie[2], Ding, Ye[1], Anastasio, Noelle C.[1,2], Fox, Robert G.[2], Stutz, Sonja[2], White, Mark A.[3], Chen, Haiying[1], Allen, John A.[1,2], Cunningham, Kathryn A.[1,2], Zhou, Jia[1,2].

[1]Pharmacology and Toxicology, [2]Center for Addiction Research, [3]Sealy Center for Structural Biology & Molecular Biophysics, The University of Texas Medical Branch, Galveston, TX

Evidence supports that the serotonin 2C (5-HT2C) receptor, a G protein-coupled receptor (GPCR), is dysregulated in several neurological maladies, including mood disorders and drug abuse. Our focus of study is cocaine use disorder, a devastating brain disorder characterized by multiple episodes of relapse following periods of abstinence and withdrawal. Interestingly, the 5-HT2C receptor is functionally relevant to behaviors that drive relapse vulnerability, such as impulsivity and cue reactivity. Previous studies in rodents have shown that 5-HT2C receptor reductions promote these relapse-associated behaviors and 5-HT2C receptor agonists can suppress them. Therefore, we hypothesize that rationally designed 5-HT2C receptor positive allosteric modulators (PAMs) will beneficially and safely enhance 5-HT2C receptor signaling and suppress relapse-associated behaviors. To this end, we have designed, synthesized and pharmacologically characterized a series of 5-HT2C receptor PAMs, *in vitro* and *in vivo*. Our efforts towards a novel neurotherapeutic have generated promising lead compounds, CYD-1-79 and CTW0415, which display selective enhancement of 5-HT signaling at the 5-HT2C receptor, as measured by intracellular calcium release, and good blood brain barrier penetrance in rat. Excitingly, preclinical behavioral studies in rats dosed with 1 mg/kg of 5-HT2C receptor PAM have demonstrated suppression of impulsivity and context-induced and cue-reinforced cocaine seeking. We believe that positive allosteric modulation of the 5-HT2C receptor is a promising neurotherapeutic strategy, and with further lead optimization and development will prolong abstinence from cocaine and provide an essential therapeutic tool for the fight against addiction.

Cocaine increases permeability of the blood-brain-barrier in the hippocampus: Implications for drug use and abuse

Clasen, Matthew[1]; Kearns, David[1]; Davidson, Terry[1]; Riley, Anthony[1]

[1]Center for Behavioral Neuroscience. American University, Washington, D.C. 20016

Davidson and his colleagues have recently demonstrated that diets high in saturated fats and sugar increase blood-brain-barrier (BBB) permeability that results in the infusion of cytokines and microglia that selectively damages the hippocampus (Davidson et al., 2012; Kanoski et al., 2010). Such damage has been shown to reduce hippocampal-dependent inhibitory control, as measured by the Pavlovian serial feature negative (SFn) task, further driving increased high fat diet intake spurring the vicious cycle of obesity (Davidson et al., 2014). This same rationale was used to study another excessive behavior, specifically, increased drug use and its consequent pathology addiction. Recently, we have found that rats exposed chronically (up to 20 days) to cocaine (18 mg/kg per day) display functionally identical changes in BBB permeability (Experiment 1) and loss of inhibitory control (Experiment 2) of responding in tasks thought to be mediated by the hippocampus. Like with obesity, we have argued that drug intake affects tight junctions in the BBB that increase its permeability to cytokines and glia that selectively damage the hippocampus. The resulting loss of inhibitory control from such damage allows the escalation of drug intake that causes more damage and consequently even greater drug use, i.e., a vicious cycle similar to that posed for excessive eating and the resulting obesity. Such a position does not argue that drug escalation and addiction are not mediated in other significant brain areas, e.g., mesolimbic system, medial prefrontal cortex, orbitofrontal cortex, but only that the BBB and the hippocampus may also play a role and should be investigated for their possible contributions to drug-taking behavior and addiction. Given the abovementioned parallels between obesity and addiction, it might be expected that a history with one would affect the likelihood of the other, i.e., animals that develop obesity with exposure to a high fat Western diet would show a more rapid or higher level of drug escalation when exposure to the diet is stopped and they are given free access to the drug. This hypothesis is currently being investigated.

TAARgeting Astrocyte Mitochondrial Dysfunction during HIV-associated neuroinflammation and METH Exposure.

Kathleen Borgmann[1] and Anuja Ghorpade[1,2]

[1]Institute for Molecular Medicine, University of North Texas Health Science Center, Fort Worth, TX, USA. [2]Research, University of North Texas Health Science Center, Fort Worth, TX, USA.

Methamphetamine (METH) use exacerbates HIV-1 infection, accelerating the severity and onset of HIV-associated neurocognitive disorders (HAND), along with immune dysfunction and resistance to antiretroviral therapy. Neurocognitive impairment is more prevalent in HIV+ METH users than either HIV+ or METH+ alone. A common neurotoxic mechanism during HIV CNS infection is mitochondrial impairment leading to oxidative stress. METH directly and indirectly contributes to mitochondrial impairment; however, the mechanisms regulating mitochondrial homeostasis and overall oxidative burden in astrocytes are not well understood in the context of HIV-associated neuroinflammation and METH abuse. We have reported that astrocyte-trace amine associated receptor 1 (TAAR1) is induced by HAND-relevant stimuli and binds METH, leading to cAMP/calcium signaling and impaired glutamate clearance during HIV. We hypothesize that *METH-abuse in HAND modulates astrocyte-TAAR1 levels and activity, regulating astrocyte-mediated neurotoxic outcomes, including mitochondrial damage and increased oxidative burden.* Here we report METH-mediated impairment of astrocyte mitochondrial recycling during prolonged exposure in the context of HIV, including enlarged mitochondrial size, mitofusin recruitment, increased oxygen consumption and resulting oxidative burden. Further, astrocyte TAAR1 appears to regulate mitochondrial recycling, indicating that it may be a valid therapeutic strategy to target astrocyte-mediated neurodegeneration in HAND and METH abuse.

Inhibition of Ca2+ signaling attenuates the antinociceptive but not discriminative stimulus effects of the imidazoline I2 receptor agonist 2-BFI in rats.

Justin Siemian[1], Yanan Zhang[2], 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.

Recent research has established the imidazoline I_2 receptor as a promising target for the development of novel analgesics. However, despite a strong understanding of imidazoline I_2 receptor-mediated behavioral effects, little is known about its post-receptor signaling mechanisms. This study examined the effects of several inhibitors of Ca^{2+} signaling mechanisms on two behavioral effects of the prototypical imidazoline I_2 ligand 2-BFI. The von Frey test was used to examine the antinociceptive effects of 2-BFI in complete Freund's adjuvant (CFA)-induced inflammatory pain in rats. A two-lever drug discrimination paradigm in which rats were trained to discriminate 5.6 mg/kg (i.p.) 2-BFI from saline was used to examine the discriminative stimulus effects of 2-BFI. The L-type Ca^{2+} channel blockers verapamil and nimodipine, the calmodulin antagonist W-7, and the internal Ca^{2+} release inhibitor ryanodine dose-dependently attenuated the antinociceptive effects of 2-BFI. Oxycodone-induced antinociception was unaffected by verapamil and nimodipine. In contrast, verapamil, nimodipine, and W-7 did not affect the discriminative stimulus effects of 2-BFI. These results suggest that the antinociceptive effects of 2-BFI involve intracellular Ca^{2+} elevation and/or downstream Ca^{2+}/calmodulin signaling, whereas the discriminative stimulus effect of 2-BFI is mediated by a distinct, independent mechanism.

Reinforcing and antinociceptive effects of nalfurafine and oxycodone mixtures in male rats.

Townsend, E Andrew[1]; Naylor, Jennifer E[2]; Negus, S Stevens[3]; Edwards, Shelley R[4]; Qureshi, Hina N[4]; McLendon, Hunter W[1]; McCurdy, Christopher R[5]; Sufka, Kenneth J[5] and Freeman, Kevin B[1]

[1]University of Mississippi Medical Center, Jackson, MS; [2]National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR; [3]Virginia Commonwealth University, Richmond, VA; [4]Millsaps College, Jackson, MS; [5] University of Mississippi, University, MS

Previous work has shown that kappa opioid receptor agonists can decrease the abuse-related effects of mu opioid receptor agonists and produce additive antinociception. However, the clinical utility of traditional kappa agonists is limited by their dysphoric and psychotomimetic side effects. A clinically-available atypical kappa opioid agonist (i.e., nalfurafine), which does not appear to have the same side effects as traditional kappa agonists, may be useful in the development of an abuse-deterrent opioid analgesic. The current study investigated whether nalfurafine could reduce the reinforcing effectiveness of a mu agonist (i.e., oxycodone) while producing additive thermal antinociception. In Experiment 1, a progressive-ratio (PR) self-administration procedure was used to compare the reinforcing effects of oxycodone (0.056 mg/kg/inj) available alone or as a mixture with co-administered nalfurafine (0.32, 1, 3.2 µg/kg/inj), which corresponded to oxycodone/nalfurafine ratios of 175:1, 56:1, and 18:1, respectively. In Experiment 2, full PR dose-effect functions were determined for oxycodone alone and for the oxycodone/nalfurafine mixtures (i.e., 175:1, 56:1 and 18:1). Experiment 3 compared thermal antinociception dose-effect curves produced in a hot-plate test by oxycodone, nalfurafine, and the three mixtures. Nalfurafine dose-dependently decreased the reinforcing effects of oxycodone in Experiment 1. In Experiment 2, the reinforcing effectiveness of oxycodone decreased as a function of nalfurafine in the mixture. Furthermore, the 18:1 mixture did not function as a reinforcer in Experiments 1 or 2. In Experiment 3, oxycodone and nalfurafine produced dose-dependent antinociception when administered alone, and all mixtures produced additive antinociception. These results suggest that the addition of nalfurafine could decrease the abuse liability while augmenting the analgesic effect of oxycodone.

The Serotonin 2C Receptor (5-HT_{2C}R) Cys23Ser Single Nucleotide Polymorphism Associates with Receptor Function and Localization *In Vitro*

Land, Michelle A[1,2], Gaziova, Ivana[3], Cunningham, Kathryn A[1,2] Moeller, Gerry F[1,4] Elferink, Lisa A[1,3] and Anastasio, Noelle C[1,2]

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The application of pharmacogenetics provides an opportunity to greatly improve treatment outcome by identifying potential biomarkers to facilitate the development of personalized pharmacotherapies for cocaine use disorder. A non-synonymous SNP of the human 5-HT_{2C}R gene that converts a cysteine (Cys) to a serine (Ser) at amino acid codon 23 (Cys23Ser) appears to impact 5-HT_{2C}R pharmacology at a cellular and systems level. Cys23Ser SNP has been linked to changes in efficacy of psychiatric therapeutics and clinically to several psychiatric disorders and related behaviors, including impulsivity and cocaine cue reactivity, and thus may serve as a biomarker for cocaine use disorder-related behaviors. While the functional impact of this SNP is not well understood, overall the Ser23 variant could impact behavioral and pharmacological responses, possibly due to reduced function. The ultimate level of 5-HT_{2C}R functionality is determined by a culmination of factors, such as effective coupling to/activation of intracellular signaling components and trafficking/endosomal recycling. We hypothesized that the Cys23Ser SNP alters 5-HT_{2C}R intracellular signaling via changes in receptor subcellular localization *in vitro*. We generated CHOp38 cell lines *stably* expressing the Cys23 or Ser23 variant. 5-HT evoked a concentration-related Ca_i^{2+} release in the Cys23 (EC_{50}~0.8 nM) and the Ser23 (EC_{50} ~4.1 nM) cell lines. The Ser23 variant demonstrated 44% lower maximum 5-HT-induced Ca_i^{2+} release vs the Cys23 variant ($p<0.05$). Western blot data indicate lower 5-HT_{2C}R plasma membrane expression, but not total homogenate, in the Ser23 vs the Cys23 cell lines ($p<0.05$). Thus, the Ser23 variant exhibits a distinct pharmacological and subcellular localization profile vs the Cys23 variant. Our novel cellular model system will be the first to systemically explore how the Cys23Ser SNP alters 5-HT_{2C}R functional capacity and sets the stage for future interrogation of the impact of the Cys23Ser SNP upon impulsivity and cocaine cue reactivity in animals.

Functional & Structural Effects of Targeting PPARgamma in a Cocaine Use Disorder Model

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Cocaine use disorder is associated with both structural and behavioral adaptations, which are recapitulated in rodent models. Structurally, the disorder has been characterized in human users by alterations in the white matter (WM) tracts and gray matter (GM) structures which underlie cocaine-seeking behaviors. Repeated exposure to cocaine is also associated with altered brain structure in rodents, and cocaine self-administration (SA) results in enduring behavioral modifications (e.g., cocaine-seeking) seen during forced abstinence (FA). We discovered that the FDA-approved peroxisome proliferator-activated receptor γ (PPARγ) agonist pioglitazone (PIO, Actos™) attenuates cocaine-seeking in rats when PIO is administered during FA from cocaine SA. Importantly, this effect of PIO is reversed by pretreatment with the PPARγ *antagonist* GW9662. Thus, ***we hypothesize*** that PPARγ agonism counteracts the cocaine-mediated alterations in WM and GM underlying persistent cocaine-seeking behavior through the induction of markers for functional and structural integrity. Using RNA-Seq and Ingenuity® Pathway Analysis, we identified interaction networks of genes regulated by PPARγ agonism in our rat model. Now, with Protein Simple Wes™ technology, we are investigating the expression of proteins important to WM and GM integrity, and also reported in other models as being modulated by cocaine exposure and regulated by PPARγ and/or phosphorylated extracellular signal-regulated kinase (phospho-ERK). Phospho-ERK is a protein which we have found to be in complex with PPARγ, and thus a potential co-regulator. Current results suggest that the expression of key proteins important to WM and GM integrity are modulated by PPARγ agonism (e.g., aquaporin 4) and/or by chronic cocaine exposure and abstinence (e.g., ERK2), with regional specificity in expression changes. Our work reveals novel regulation of select proteins that may drive PPARγ-mediated attenuation of cocaine-seeking behavior, providing new targets for normalization of cocaine-mediated brain deficits and behavior.

Acute and Chronic Treatment Combined with Safety Evaluation of ZZ204G, a Novel Analgesic

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Purpose: Painful diabetic neuropathy is a common complication of diabetes and is treatment resistant. Some α9α10 nicotinic acetylcholine receptor (nAChRs) antagonists have been reported to be analgesics for treatment of neuropathic pain. In this work, ZZ204G, a potent α9α10 nAChRs blocker is studied in a diabetic neuropathy model after acute and chronic treatment. Metabolic cage studies were incorporated to expand the safety profile. Methods: Male Sprague Dawley rats were used in this study. A single dose of streptozotocin (65 mg/kg) was injected i.p. to induce diabetes. The pinprick sensitivity threshold (PST), paw pressure withdrawal threshold (PPT), hot plate withdrawal threshold (HPT) and hot water tail-flick latency (TFL) were measured before and after drug administration (i.p.). For acute treatment, various doses of ZZ204G were tested; in chronic studies, 1.8 mg/kg ZZ204G or vehicle were administered daily for 9 days, with HPT and PST tests conducted on day 1, 3, 5 and 7. Metabolic cage experiments were conducted on the day 2, 4, 6 and 8, collecting water intake, food consumption, urination, and defecation measurements during 5 hours post drug injection. Results: In the acute study, ZZ204G showed long-lasting and dose-dependent antinociceptive effects in HPT, TFL and PST tests but only weak activity in the PPT test. ZZ204G exhibited higher potency in diabetic compared to normal rats. No hyperalgesia or tolerance to chronic drug treatment was developed in either normal or diabetic rats. ZZ204G produced strong diuretic effects in normal rats, but had very little effect on food consumption and defecation. Slower weight-gain was observed in ZZ204G-treated normal rats versus diabetic rats. Conclusion: ZZ204G administered acutely or chronically produced antinociceptive/analgesic actions in superficial pain assays in both normal and diabetic rats without producing tolerance or hypersensitivity. Thus, ZZ204G may be a promising agent for treatment of superficial mechanical and burning pain caused by diabetic neuropathy.

Investigating the effects of PKCβ inhibitors on amphetamine-mediated behaviors in rats

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Amphetamine (AMPH) are a class of stimulants abused worldwide. AMPHs cause an increase in extracellular dopamine (DA) levels through the reversal of function of the dopamine transporter, a process enhanced by protein kinase Cβ (PKCβ). PKCβ inhibitors block AMPH-stimulated DA release *in vitro* but their effects *in vivo* are not well understood. The goal of this study was to determine the effects of PKCβ inhibitors on AMPH-mediated behaviors. In all experiments, 10 pmol enzastaurin (ENZA), a PKCβ inhibitor, were administered into the lateral ventricles (*i.c.v.*) of male Sprague-Dawley rats 3 or 18 hours before evaluating AMPH-stimulated behaviors. Locomotor activity was measured following the administration of 0.32-3.2 mg/kg AMPH *s.c.* Additional rats were trained to self-administer AMPH (0.032mg/kg/inf) or sucrose pellets in daily sessions and to extinguish responding in the absence of the reinforcer. In striatal tissue of rats pretreated with ENZA, PKC activity was measured through immunodetection of a PKC substrate. An 18-h pretreatment, but not a 3-h pretreatment, of ENZA attenuated AMPH-stimulated locomotor activity, but this effect was surmounted by large AMPH doses. Consistent with locomotor experiments, only an 18-h pretreatment of ENZA reduced the number of AMPH infusions in a self-administration session by over 80%. ENZA did not alter the number of sucrose pellets earned in a session. An 18-h pretreatment, but not a 3-h pretreatment, of ENZA blocked AMPH-stimulated increases in PKC activity in the striatum, suggesting that ENZA takes time to effectively decrease PKC activity. Our results show that ENZA can block AMPH-stimulated behaviors, most likely in a surmountable manner but requires long pretreatment times to be effective. Furthermore, ENZA decreases AMPH reinforcement without altering responding for natural rewards, suggesting that the effects of ENZA may be specific to AMPH or drug reinforcement. These results suggest that PKCβ inhibitors could serve as a good therapeutic intervention for AMPH abuse. Future work will investigate the mechanisms by which PKCβ inhibition alters these behaviors. Funded by DA11697 and T32-GM007767

Binge-like Cocaine Self-Administration is Differentially Augmented by Intra-VTA CRF Microinfusion or Social Defeat Stress in Rats

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Exposure to intermittent social defeat stress elicits CRF release into the VTA, and induces long-term modulation of mesocorticolimbic dopamine activity in rats. These adaptations are associated with an intense cocaine-taking phenotype, which can be prevented by CRF receptor antagonists. The present studies examine the extent to which infusion of CRF into the VTA is sufficient to escalate cocaine-taking behavior, in the absence of stress experience. Additionally, we aimed to quantitatively characterize changes in cocaine valuation that may promote binge-like cocaine intake. Male Long-Evans rats were microinjected into the VTA with CRF (50 or 500 ng/side), vehicle (aCSF), or subjected to social defeat stress, intermittently over 10 days. Animals were then trained to self-administer IV cocaine according to a fixed-ratio (FR5) schedule of reinforcement. Performance was evaluated on a within-session behavioral economics threshold procedure to determine individual demand for cocaine, and rats were subsequently exposed to 24-hr extended-access "binge". Rats that experienced social defeat or received intra-VTA CRF microinfusions (50ng) both took significantly more cocaine than controls over the 24-hour "binge", but showed distinct patterns of intake. Behavioral economic analysis revealed that individual demand for cocaine strongly predicts binge-like consumption, and demand elasticity (α) is augmented by intra-VTA CRF, but not by social defeat. The observed effects of CRF on cocaine-taking were also prevented by intra-VTA pretreatment with CP376395, but not Astressin-2B. We demonstrate that repeated infusion of CRF into the VTA augments cocaine valuation, and intensifies binge-like drug intake in a CRF-R1-dependent manner. Conversely, the persistent pattern of cocaine bingeing induced by social defeat stress may suggest impaired inhibitory control, independent of reward valuation.

Elevated Brain-Derived Neurotrophic Factor Levels in the Reward System of Alcohol-Dependent Animals

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Alcoholism (or alcohol use disorder) affects approximately 7% of adults in the United States, and almost 25% of adults report binge drinking once per month or more frequently. A major challenge faced by alcoholics is relapse during withdrawal periods. Despite the striking prevalence of alcohol dependence, the molecular mechanisms through which neuroadaptations cause recurrent excessive drinking remain poorly understood. Clarification of this process would provide important information for the development of novel treatments to assist individuals in limiting their drinking.

One explanation for excessive alcohol use may pivot on the extracellular signal-related kinases (ERKs), which are downstream effectors of the brain-derived neurotrophic factor (BDNF) ligand and tropomyosin receptor kinase B (TrkB) receptor. It has been long known that ERK phosphorylation (pERK) is upregulated in numerous regions of the rat brain (e.g. amygdala, frontal cortex) during periods of alcohol withdrawal, making the BDNF-TrkB-ERK pathway a major subject of investigation in addiction and translational psychiatry.

A critical region of the brain involved with addiction is the ventral tegmental area (VTA), which exhibits higher ERK phosphorylation during cocaine and heroin dependence. We therefore hypothesized that BDNF-TrkB-pERK signaling in the VTA drives escalated drinking and alcohol-seeking behavior. To test this hypothesis, rats were made dependent via chronic intermittent ethanol vapor exposure and we assessed alcohol-drinking and alcohol-seeking behaviors using operant methods in dependent and non-dependent rats. We also used Western blotting to measure changes in BDNF and pERK levels in the VTA between these two groups. Our preliminary findings describe increased BDNF levels in dependent rats, providing an important insight into the molecular mechanisms underlying the transition to alcohol dependence.

FDA-approved drug paroxetine targets GRK2 to enhance peripheral delta opioid receptor-mediated analgesia

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Opioid analgesics remain the gold standard for the treatment of pain. Most FDA-approved opioids target the mu opioid receptor (MOR). However, adverse systemic side effects contraindicate long-term administration. Alternatively, activation of the delta opioid receptor (DOR) results in a reduced side effect profile in rodents and non-human primates. To further reduce systemic side effects and abuse potential, targeting peripheral opioid receptors is an attractive alternative to current therapies. Unfortunately, plasma membrane opioid receptors of the periphery do not readily respond to their agonists unless primed by inflammation. The phenomenon of peripheral DOR incompetence would be expected to limit the effectiveness of locally administered DOR agonists to patients with severe inflammatory pain. This may contribute to the absence of FDA-approved drugs that target peripheral DOR, despite the potential benefits.

We recently identified a novel, non-internalizing role for G protein-coupled receptor kinase 2 (GRK2) in maintaining peripheral DOR analgesic incompetence. GRK2 knockdown in primary sensory neurons significantly enhances peripheral DOR-mediated analgesia in vivo in non-inflamed tissue. Multiple groups have demonstrated that paroxetine, an SSRI approved by the FDA to treat multiple conditions, is a potent, selective GRK2 inhibitor. Here, we report that paroxetine dose-dependently reduces chronic GRK2 association with plasma membrane DOR in rat peripheral sensory neurons, thereby enhancing receptor activity. Paroxetine also enhances peripheral DOR-mediated analgesia without the requirement for inflammatory priming. Furthermore, paroxetine's effect on DOR activity was notably antagonized by GRK2 overexpression in sensory neurons. Together, these results suggest that the FDA-approved drug paroxetine targets GRK2 to enhance peripheral DOR competence in sensory neurons, improving analgesic efficacy in non-inflammatory pain conditions.

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Cardiovascular (CV) and locomotor effects of 3, 4-methylenedioxypyrovalerone (MDPV) in male and female Sprague-Dawley (SD) rats

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Racemic MDPV is a synthetic cathinone with a CNS mechanism of action similar to cocaine and reported CV toxicity in humans. Although some CV effects are reported in male rats, effects in females are not reported. For these studies, DSI radiotelemetry devices were implanted in adult male and female SD rats (n=7/group). After acclimation, the rats were administered IP saline, escalating doses of MDPV, and a "binge" regimen of four total injections at 2 h intervals. Heart rate (HR), blood pressure (BP), core temperature, and locomotor activity were recorded for 24 h after treatment. For comparison, a separate group of males (n=6) received a similar regimen of cocaine. Results showed handling and injection of saline or drug increased HR and BP above established baseline, and HR and BP took longer to recover dependent on MDPV dose. Compared to females, males showed a longer duration of increased HR with increasing MDPV dose. BP showed dose-dependent increases in male and females, with females showing greater increases than males. Males were more sensitive to locomotor effects of MDPV, exhibiting stereotypy at doses that were producing maximal stimulation for females. Cocaine did not produce greater HR, BP, or locomotor effects than MDPV despite being tested up to a 10-fold higher dose. MDPV did not significantly alter thermoregulation in males or females. Preliminary studies (n=2 rats/sex) show the effects of 5.6 mg/kg MDPV are superimposable with 2.8 mg/kg (*S*)-MDPV, suggesting that the (*S*)-enantiomer is solely responsible for effects of the racemate. In conclusion, significant sex-dependent differences were found in MDPV-induced locomotor activity, BP, and duration of increased HR. However, at these doses neither cocaine nor MDPV produced profound cardiovascular effects outside of a physiological range.

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Novel bivalent ligands based on the sumanirole pharmacophore reveal dopamine D_2 receptor (D_2R) biased agonism and potential allosteric modulation

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Several neuropsychiatric disorders have been associated with hypoactivation or hyperactivation of specific dopamine transmission pathways involving the D2R subtype. Sumanirole, originally developed for the treatment of Parkinson's disease and restless legs syndrome, is a full agonist showing moderately high D2R affinity (Ki = 46 nM) and modest D2R selectivity (D3R/D2R = 12). Despite failing in clinical trials, sumanirole has served as a valuable template for lead optimization and structure-activity relationship (SAR) studies. In this study, we applied a bivalent molecular approach to combine the primary pharmacophore of sumanirole with a large library of secondary pharmacophores with linkers of different length, rigidity and lipophilicity. We synthesized new classes of compounds allowing us to develop SAR to evaluate how their affinity and selectivity for the D2R subtype change when: i) linkers and secondary aromatic pharmacophores are substituted in positions N-1 and/or N-5 of the sumanirole primary scaffold; ii) different secondary pharmacophores, varying in their physiochemical properties and chirality are inserted with the aim to recognize a specific secondary binding site; iii) linkers connecting the two pharmacophores vary in length (ranging from 4 to 12 methylene units), rigidity and chirality (presence of a cyclopropyl moiety in the linker) or hydrophilicity (di-, tri- or tetraethylene glycol chains). All newly synthesized compounds were evaluated in radioligand competition binding assays as well as in 5 different functional BRET constructs: i) Gi protein engagement, ii) Gi protein activation, iii) Go protein activation, iv) adenylyl cyclase inhibition, and v) β-arrestin2 recruitment, allowing us to identify for the first time full agonists showing selective D2R G-protein bias profiles. Moreover, additional in vitro and in vivo studies are currently underway in an attempt to relate mechanism to behavior.

Neurotensin-induced plasticity temporally modulates GABAergic input to midbrain dopamine neurons.

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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 acutely modulates midbrain dopamine neuron excitability through multiple mechanisms, including a decrease of GABA mediated inhibition of dopamine neurons. However, it is the mechanism by which NT depresses GABA signaling is not known. Here we utilize whole cell patch-clamp electrophysiology of dopamine neurons in mouse brain slices to show that NT acts both presynaptically to increase $GABA_A$ and postsynaptically to decrease $GABA_B$ receptor-mediated currents in the substantia nigra in mice. Bath perfusion of NT produced a sustained potentiation of $GABA_A$ inhibitory postsynaptic currents (IPSCs) without affecting $GABA_A$ receptor-mediated currents elicited via iontophoresis of GABA. NT also produced an increase in the co-efficient of variation of $GABA_A$-IPSC amplitudes, again suggesting a presynaptic locus of potentiation. Conversely, NT caused depression of $GABA_B$-IPSCs as well as iontophoretically elicited $GABA_B$ receptor-mediated currents, and the similarity in magnitude of these two effects suggests a postsynaptic locus of depression. As the kinetics of $GABA_A$ signaling are significantly faster than those of $GABA_B$ signaling NT temporally modulates GABAergic signaling at midbrain dopamine neurons. 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 and related disorders.

Effects of pioglitazone, a PPARγ agonist, on the subjective and reinforcing effects of tobacco cigarettes

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Aims: In rodents, the peroxisome proliferator-activated receptor agonists, pioglitazone (PIO), reduces nicotine self-administration and reinstatement of drug seeking. Prior to the current study, the ability of PIO to alter the abuse potential of nicotine had not been assessed in controlled, clinical laboratory settings.

Methods: Smokers were randomized to either active (45 mg, n=14) or placebo (0 mg, n=13) PIO maintenance for a 3-week inpatient study. On the 1st-4th test days, participants could self-administer cigarettes using a verbal choice procedure. On the 5th&12th days, participants smoked 10 puffs of their usual brand of cigarettes and completed subjective effects questionnaires, later participants completed a progressive ratio self-administration task. The 8th-11th test days were identical to the 1st-4th with the exception that during one-week de-nicotinized cigarettes were available, and the other week nicotinized cigarettes were available.

Results: Craving for cigarettes was significantly lower in participants maintained on 45 mg of PIO compared to participants maintained on 0 mg PIO, but these effects were only observed when participants had been smoking nicotinized cigarettes during the previous week. PIO maintenance did not alter the reinforcing, positive, or negative subjective effects of nicotine.

Conclusion: The results suggest that PIO may be useful in decreasing craving for cigarettes. The current study did not replicate the robust preclinical findings. As the first clinical investigation for this indication, these data are encouraging and provide a direction for further inquiry.

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The role of hippocampal activin signaling in perpetuated cocaine craving

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Relapse susceptibility in cocaine addiction is often attributed to drug seeking that is provoked by exposure to drug-associated cues. Drug-dependent plasticity in the reward circuitry of the brain, including the nucleus accumbens (NAc) and hippocampus (HPC), underlies drug-seeking behavior. The transforming growth factor (TGF)-β superfamily is a family of multifunctional proteins that regulate a wide variety of cellular responses, including synaptic and epigenetic plasticity. Recent studies from our lab have shown that the TGF-β superfamily members, SMAD3 and activin A, regulate spine morphology and gene expression in the NAc to mediate relapse behaviors following cocaine exposure in animal models of addiction. Therefore, TGF-β signaling modulates cocaine-dependent plasticity through multiple signaling cascades. However, the role of hippocampal TGF-β signaling in relapse-like behaviors has yet to be examined. Here, we show that following extended-access cocaine self-administration, activin A is increased in the HPC after a cue-induced seeking test on withdrawal day (WD)30, when cocaine seeking is intensified, but *not* on WD1. We then examined the role of activin A signaling in cocaine-seeking behavior. Blockade of activin signaling via intra-dorsal (d)HPC microinjections of follistatin, an endogenous activin A antagonist, or an anti-activin A antibody attenuated cocaine seeking on WD30 but *not* on WD1, while viral-mediated overexpression of Activin 2a receptor (AcvR2a) increased cue-induced seeking on WD30. Together, these data demonstrate that activin A in the dHPC regulates expression of intensified cue-induced cocaine seeking behavior during prolonged withdrawal following extended-access self-administration.

Design and synthesis of novel bromine-containing paroxetine derivatives toward structure-function analyses with the serotonin transporter.

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The serotonin transporter (SERT) recycles extracellular serotonin (5-HT) into the presynaptic neuron, essential for healthy brain function. Disruption of this tightly regulated process leads to diseases, such as obsessive-compulsive disorder, autism, epilepsy and depression, making it a primary target for the treatment of these disorders; however, despite the SERT's success as a drug target, the relationship between the its structure on an atomic level and its function is still poorly understood.

Over 80% of the three-dimensional macromolecular structure data in the Protein Data Bank were obtained by X-ray crystallography. Regardless, membrane proteins like SERT are challenging crystallographic targets in part because they often form crystals that diffract to relatively low resolution (e.g., ~3.5-4 Å); therefore, it is difficult to accurately place the functional groups that are critical to determine protein-ligand interactions. This problem can be surmounted if the drug is modified so that one of its atoms is replaced with a chemically similar but more electron dense atom, as would occur with halide replacement (e.g., bromine for fluorine). Because the "heavier" bromine absorbs X-rays much more strongly than the "lighter" fluorine, the X-ray scattering yields an anomalous signal that can then be used as a "beacon" to accurately orient the molecule.

Paroxetine (Paxil®), a selective serotonin reuptake inhibitor, binds SERT with picomolar affinity. It was, therefore, chosen for chemical modification introducing the heavy atom, bromine by either 1) appending a bromophenyl via varying linker chains to the paroxetine piperidine nitrogen or 2) replacing the paroxetine fluorine with bromine via a multi-step, target-driven synthesis. These novel analogs were tested for their ability to inhibit 5-HT uptake at wild type human SERT. Further studies include analyzing the binding of these and additional paroxetine analogs at SERT mutants.

Novel Mu Opioid Receptor Agonist/Delta Opioid Receptor Antagonist Ligands with Reduced Development of Adverse Effects

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Mu-opioid receptor (MOR) agonists are widely used for pain management, but produce adverse effects, such as tolerance, dependence, and euphoria. Studies suggest that the co-administration of a MOR agonist with a delta opioid receptor (DOR) antagonist produces antinociception with reduced side effects; we developed a series of MOR agonist/DOR antagonist peptidomimetics that produces opioid-mediated antinociception in the warm water tail withdrawal (WWTW) assay in C57BL6/N mice after peripheral administration. Three of these peptidomimetics, **AAH8, AMB46,** and **AMB47,** and morphine were evaluated for the development of tolerance and dependence after five days of twice daily treatment with escalating doses of drug (10-50 mg/kg *ip*). Tolerance was measured by shifts in dose response curves in the WWTW before and after repeated drug treatment; physical dependence was evaluated by naltrexone-precipitated withdrawal jumping. The rewarding effects of morphine and **AAH8** were evaluated using a conditioned place preference (CPP) assay. For CPP studies, twice daily conditioning sessions with saline and drug (10 mg/kg *ip*) were performed for 5 days followed by a preference test on day 6. Repeated administration of morphine and **AMB46,** but not **AAH8** or **AMB47,** produced 3-5-fold rightward shifts in the dose response curves in the mouse WWTW. Injection of naltrexone precipitated fewer jumps in mice treated repeatedly with **AAH8** or **AMB47** as compared with morphine or **AMB46.** Conditioning with morphine, but not **AAH8**, produced significant CPP. Interestingly**,** reduced development of adverse effects appears to correlate with balanced affinity for MOR and DOR *in vitro*. Overall, the mixed efficacy opioid ligands may be better alternatives to traditional opioids for chronic pain management, producing antinociception without development of tolerance and dependence and potentially less abuse potential. Future studies will evaluate the mechanism by which these compounds act. This work was supported by NIDA Grant 5 T32 DA00726 and NIH Grant DA003910.

Functional and high-affinity binding of dopamine D4 receptor-selective partial agonists as pharmacological tools to study substance use disorders.

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The dopamine D4 receptor (D4R) is enriched in the prefrontal cortex where it is believed to modulate cognition, attention, and executive function. Previous studies, using D4R ligands of varying efficacy, determined that D4R agonism may improve cognition while D4R antagonism may reduce drug-taking behavior. Developing novel D4R-selective ligands will allow further exploration of the biological roles of D4R signaling and may lead to new pharmacotherapies for neuropsychiatric disorders.
Herein, we describe a rational drug design strategy leading to the design, synthesis, *in silico* and *in vitro* analyses of novel D4R partial agonists. A library of ligands structurally related to the prototypical D4R partial agonist A-412997 was synthesized and evaluated for binding affinity and *in vitro* efficacy in D4R-expressing HEK293 cells. The novel compounds were partial agonists or antagonists (as determined by cAMP and β-arrestin functional assays), and several featured improved D4R affinity and subtype selectivity over the parent compound. A D4R homology model was created using the high-resolution X-ray structure of D3R in complex with a ligand (3PBL). Using experimental affinity values, the best docking score function was selected and subsequently used to predict the binding affinities of the novel library. After model validation, an *in silico* screen was used to design a second generation library that is currently being evaluated.

Concurrent Evaluation of the Antinociceptive and Response Disrupting Effects of Opioids

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Opioids remain the most widely prescribed drug class in the treatment of moderate to severe pain, yet their clinical application is often hindered by their broad profile of undesirable effects. Numerous animal models of nociception have been developed to assay the effects of nociceptive stimuli on unconditioned behavioral reactions (Le Bars et al., 2001), but the response to thermal stimuli remains the most common method for assaying opioid antinociception across species. However, such assays typically do not provide information regarding behaviorally disruptive effects of opioids that may accompany antinociception. Based on treatment goals, the concurrent production of such side-effects and antinociception may be an important clinical consideration. To address this consideration, we modified the warm water tail withdrawal procedure, initially described by Dykstra and Woods (1986) to concurrently determine the effects of opioids on both tail withdrawal latency (antinociception) and food-maintained behavior (reinforcement density, response rate) in squirrel monkeys. Sessions were comprised of four 5-min response components, each preceded by a 10-min long timeout during which cumulative doses of drugs could be administered. During each component, the completion of a 10-response fixed-ratio in the presence of stimulus lights initiated food delivery and a 30-sec short timeout (STO) during which stimulus lights were off and tail withdrawal latency was measured. Data show that all six opioid agonists tested produced dose-dependent antinociceptive effects and, as expected, dose-dependent disruption of response rates. Preclinical therapeutic ratios (PTRs), i.e., the ratio of ED_{50} values for the two measures, show that nalbuphine demonstrated the highest PTR (5.17), reflecting significant antinociception with only minimal response rate disruption. Oxycodone, heroin, buprenorphine and methadone all produced similar PTRs (0.78-1.28), whereas butorphanol yielded a significantly lower PTR (0.29). These data show that the traditional tail withdrawal assay can be modified to provide a useful index of the behavioral selectivity of antinociceptive drugs.

Cocaine effects on dopamine neurons in mice are reduced by deletion of GIRK2 channels specifically in dopamine neurons and with cocaine self-administration experience.

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Dopaminergic neurons are key mediators of substance abuse and addiction-related behaviors. In the midbrain, somatodendritic dopamine (DA) release activates inhibitory postsynaptic currents through D2 autoreceptors to increase a G-protein gated inward rectifying potassium subtype 2 (GIRK2) conductance in DA neurons. Cocaine is a highly addictive stimulant that alters the mesolimbic DA pathway; however the role of the GIRK2 channel in DA neuron adaptations during cocaine abuse is unclear. These experiments used a knockout mouse line ($GIRK2_{DA}KO$) where GIRK2 channels were selectively deleted in neurons expressing the DA transporter. Male $GIRK2_{DA}KO$ mice and their wild-type littermates ($GIRK2_{DA}WT$) acquired cocaine self-administration during daily 2 h sessions to nose-poke for IV infusions of cocaine (0.5 mg/kg/infusion) on an FR 3 schedule until responding was stable. Electrophysiological recordings were taken from $GIRK2_{DA}KO$ and $GIRK2_{DA}WT$ mice under 3 different conditions: one day following cocaine self-administration, naïve-controls, and after extended abstinence from cocaine. In brain slices containing midbrain DA neurons, adaptations in DA neuron activity were measured in response to bath perfusion of cocaine. Results indicate no difference in DA neuron activity between naïve $GIRK2_{DA}KO$ and $GIRK2_{DA}WT$ mice and both acquired self-administration at a similar rate. Interestingly, immediately following cocaine-self administration, DA neurons of $GIRK2_{DA}KO$ mice displayed increased baseline excitability and decreased sensitivity to cocaine. This effect was transient, after a period of abstinence DA neurons returned to naïve-like levels of cocaine sensitivity and was mediated by D2 autoreceptors. These results indicate that GIRK2 channels in DA neurons could play an important role in cocaine-abuse related neuroadaptations.

Role of mu opioid receptors in mediating the effects of amphetamine on cocaine-vs.-food choice in rhesus monkeys.

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Amphetamine maintenance reduces cocaine use in both preclinical and clinical assays. Although the mechanism responsible is unknown, amphetamine promotes the release of endogenous opioids and opioid receptor activation contributes to some effects of amphetamine. The current study examined the contribution of mu opioid receptor activation in mediating effects of amphetamine in an assay of cocaine vs. food choice in rhesus monkeys. Adult male rhesus monkeys (n=5) with indwelling double-lumen catheters were trained to respond for concurrently available cocaine infusions (FR10) and food pellets (FR100) during daily sessions comprised of five cycles across which the unit cocaine dose increased by half-log increments (0, 0.0032-0.1 mg/kg/injection). Cocaine choice was evaluated during treatment with amphetamine, morphine (mu opioid receptor agonist), naltrexone (mu opioid receptor antagonist), and combinations of naltrexone with either morphine or amphetamine. Drug treatments were administered as hourly intravenous infusions over a 7-day period. Amphetamine ($F_{2,44}$=11.68, p<0.0001) and morphine ($F_{3,41.2}$=23.32, p<0.0001) both decreased rates of responding; however, unlike amphetamine, morphine increased cocaine choice ($F_{3,36}$=14.67, p<0.0001). Naltrexone antagonized the rate-decreasing effects of both morphine and amphetamine at naltrexone doses that had no effect on rate when administered alone. Additionally, the combination of amphetamine plus naltrexone increased the number of choices made for food ($F_{2,8}$=5.64, p=0.03) while simultaneously decreasing the number of choices made for cocaine ($F_{2,8}$=7.14, p=0.017). Collectively, these results suggest that mu opioid receptor activation contributes to rate-decreasing effects of amphetamine maintenance, but opposes amphetamine-induced decreases in cocaine choice. Thus, combination of amphetamine with naltrexone may be superior to amphetamine alone, increasing the reallocation of behavior from drug to non-drug alternatives with lower abuse liability. Supported by R01DA026946 and T32DA007027.

Poster Presentations

Poster 1-1

The Effects of Cannabidiol (CBD) on Δ 9 -Tetrahydrocannabinol (THC) Self-Administration in Male and Female Long-Evans Rats.

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Despite widespread marijuana use in humans, few rodent models exist demonstrating significant Δ 9 -tetrahydrocannabinol (THC) self-administration, possibly due to THC's concurrently occurring aversive effects which impact drug reward. Given that marijuana contains a number of phytocannabinoids in addition to THC, it's possible that one of these compounds could influence THC IVSA in rodents. Interestingly, one such phytocannabinoid, cannabidiol (CBD), has been reported to antagonize some of the aversive effects of THC. Accordingly, in the following experiment, male and female Long-Evans rats were trained to self-administer THC over a 3-week period and then were assessed for the effects of CBD on responding for THC or for the establishment of cocaine self-administration. Consistent with previous research, THC self-administration was modest and only evident in a subset of animals (and unaffected by sex). Cocaine self-administration was high and evident in the majority of animals tested, indicating that the design was sensitive to drug reward. Interestingly, there was no effect of CBD pre-treatment on THC IVSA at any CBD:THC dose ratio. Further work on animal models of THC self-administration and the factors that affect its display remains important to provide procedures to assess the basis for and treatment of marijuana use and abuse.

Poster 1-2

Ventilatory-depressant effects of opioids alone and in combination with cannabinoids in rhesus monkeys

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Pain is a serious health problem that is frequently treated with prescription opioids. However, the doses of prescription opioids needed to effectively treat pain are often similar to or the same as doses that decrease respiration, resulting in a narrow therapeutic window. By combining opioids with other drugs that act through non-opioid mechanisms, such as cannabinoid receptor agonists, it might be possible to increase the potency of opioids to produce antinociception without altering their potency to decrease respiration. When combined with the cannabinoid receptor agonist CP 55,940, smaller doses of the *mu* opioid receptor agonist fentanyl are needed to produce antinociception; the current study investigated whether CP 55,940 increases the potency of fentanyl to decrease respiration. Three rhesus monkeys breathing air received fentanyl alone or in combination with CP 55,940, and minute volume (V_E), tidal volume (V_T) and ventilatory frequency (f) were monitored with a head plethysmograph. When given alone, fentanyl (0.00032 – 0.1 mg/kg, s.c.) dose-dependently decreased V_E to an average of 68 ± 12% and V_T to 67 ± 10% of control, respectively, while f was not appreciably changed. An ineffective dose of CP 55,940 (0.01 mg/kg) decreased the slope of the fentanyl dose-response curve without altering the dose of fentanyl needed to decrease V_E to 70% of control. A larger dose of CP 55,940 (0.032 mg/kg) decreased V_E to 81 ± 4% and V_T to 81 ± 4% of control and shifted the fentanyl dose-response curve downward, such that a slightly smaller dose of fentanyl decreased V_E to 70%. Thus, pretreatment with a cannabinoid receptor agonist increases the potency of fentanyl to produce antinociception to a much greater extent than it increases the potency of fentanyl to alter ventilation. These findings support the hypothesis that the therapeutic window for opioids increases when they are coadministered with a cannabinoid receptor agonist; thus, opioid/cannabinoid combinations might be as effective but also safer than an opioid alone for treating pain. Supported by USPHS Grants R01DA05018, T32DA031115, and Welch Foundation Grant AQ-0039

Poster 1-3

A translational bioinformatics approach for AUD drug discovery.

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Using transcriptomics for drug discovery or repurposing is a promising approach for identifying successful pharmacotherapies. Computational approaches that integrate gene expression signatures of drugs and diseases have successfully identified drugs for several complex disorders, but these approaches have not yet been applied to psychiatric illnesses. We focus here on Alcohol Use Disorder (AUD), a complex psychiatric disorder with strong genetic, as well as environmental, risk factors. High Drinking In the Dark mice are a genetic model of AUD risk. They have been selectively bred (from the genetically diverse HS/Npt line) to achieve intoxicating blood alcohol levels after a short, binge-like drinking session. The genetic risk factors in HDID mice cause changes in brain gene expression that may underlie their deleterious alcohol drinking patterns. Thus, we focused on the transcriptome as a molecular signature to identify drugs that will "correct" the aberrant gene expression changes associated with excessive alcohol consumption. We used differences in brain gene expression between HDID and HS/Npt mice to query LINCS (Library of Integrated Cellular Signatures), a database populated with the gene expression signatures of thousands of compounds, and predict drugs that will decrease alcohol consumption. Our analysis identified terreic-acid and pergolide as novel compounds that drastically reduced alcohol intake and BALs in HDID mice. This provides the first evidence that brain gene expression data can be combined with evolving informatics tools, such as LINCS, to identify drugs that will decrease drinking in animal models of alcoholism. We propose that other novel compounds suggested by our investigation might have therapeutic potential for AUDs and that our approach could be adopted more broadly to identify or repurpose compounds for other complex diseases.

Poster 1-4

Effects of orally self-administered MDPV on locomotor activity and sensitivity to haloperidol in mice

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The active constituents of illicit "bath salts" function as psychostimulants similar to cocaine and amphetamine. 3,4-methylenedioxypyrovalerone (MDPV) is a commonly abused constituent of these products and has become a major concern. In these studies, mice were fluid restricted for 21 h, then presented with 3 h access to water or 0.3 mg/ml MDPV, a concentration previously shown to be preferred over quinine solutions, to induce locomotor stimulant effects, and to condition a place preference to an environment paired with its availability. To study chronic drug effects, mice were chronically presented with the opportunity to consume 0.3 mg/ml MDPV for a period of 10 days in order to assess escalation of intake, sensitization or tolerance to locomotor stimulant effects, and sensitivity to haloperidol-induced catalepsy. Similar volumes of fluid consumption were observed in mice chronically presented with water or MDPV over the 10 day access period, but MDPV intake escalated resulting in approximately twice as much MDPV consumed on the last three days as compared to day 1, and mean total drug intake over 300 mg/kg. Consumption of MDPV stimulated locomotor activity on each of the 10 access days, but although intake significantly increased across days, motor activity did not. Comparing locomotor stimulant effects on the first day (when intake was low) to the 10th day (when intake was high) indicated greater locomotor effects across all time points on day 1, perhaps suggesting tolerance to locomotor stimulant effects. No persistent effects on motor activity were observed during a 3 week MDPV washout period, but mice with a history of MDPV consumption were less sensitive to haloperidol-induced catalepsy 23 days after cessation of MDPV access than were control mice, perhaps suggesting a persistent opposing "pro-psychotic" effect elicited by chronic MDPV. Select brain regions from all animals were collected and will be assayed to determine region-specific alterations in markers of dopamine and glutamate. These studies supported by DA039195, DA022981 and the UAMS Center for Translational Neuroscience.

Poster 1-5

12- & 15-HETE block antinociceptive signaling of delta opioid (DOR) and kappa opioid (KOR) receptors, but not of DOR-KOR heteromers, in peripheral nociceptors

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Opioid receptor systems expressed by nociceptors are quiescent for antinociception under basal conditions, but become responsive following exposure to inflammatory mediators (e.g., carrageenan, bradykinin (BK) or AA) that produce COX-dependent AA metabolites. Following prolonged inflammation, opioid receptor systems again become non-responsive due to production of LOX-dependent AA metabolites, 12- and 15-HETE. Here we examined LOX-dependent regulation of DOR-KOR heteromer signaling and antinociception in primary cultures of adult rat peripheral sensory neurons (ex vivo) and in the carrageenan model of inflammation (in vivo). Ex vivo, we compared the effects of 12- and 15-HETE on inhibition of PGE2-stimulated cAMP accumulation by the DOR agonist, DPDPE, the KOR agonist, U50488 and the DOR-KOR heteromer agonist, 6'-GNTI. Addition of 12- and 15-HETE blocked DPDPE- and U50488-mediated inhibition of PGE2-stimulated cAMP accumulation. By contrast, 12- and 15-HETE had no effect on 6'-GNTI-mediated inhibition of PGE2-stimulated cAMP accumulation. In vivo, we compared the abilities of DPDPE, U50488 and 6'-GTNI to inhibit carrageenan induced thermal allodynia in the rat hind paw. All agonists completely reduced carrageenan-induced thermal allodynia 15 min after intraplantar (i.pl) injection of carrageenan (500 ug). 3h or 24h after carrageenan administration (i.pl), neither DPDPE nor U50488 produced antinociceptive responses. However, responsiveness was restored following i.pl. injection of the 12/15-LOX inhibitors. Interestingly, the heteromer agonist 6'-GNTI completely inhibited the nociceptive response when administered (i.pl.) 3h or 24h after carrageenan, and was not affected by LOX inhibitors. Thus, DOR-KOR heteromers, in contrast to DOR or KOR, appear to remain functionally competent for a prolonged period of time under inflammatory conditions, suggesting that they may be suitable targets for development of peripherally restricted pain medications. Supported by William and Ella Owens Medical Research Foundation, NIH/NIGMS R01 GM 106035 and NIH/NIDA R21 DA 038645.

Poster 1-6

Factors and Policies Affecting Opioid Prescribing Patterns in Active Duty Patients between 2006 and 2014

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Background: Between 2001 and 2009, opioid analgesic prescriptions in the Military Health System (MHS) quadrupled to 3.8 million. The sheer quantity of opioid analgesics available set the stage for issues related to misuse, abuse, and diversion. To address this issue, the DOD implemented at least 20 directives between 2006 and 2012 to improve opioid prescribing trends. To characterize opioid use in the active duty population during this period (2006-2014), we examined opioid prescribing trends for active duty service members (ADSM), compared the trends in the civilian population and explored the potential role of military-specific factors in changes in opioid use in the MHS. Methods: Annual prescription counts were compared for the general and active duty populations. Interrupted time series models were created to examine changes in the proportion of ADSM receiving an opioid prescription before and after December 2011. Additional models incorporated other military factors over the same period including returning OEF/OIF/OND troops, wounded in action, and auto regressive effects. Results: Between 2006 and 2014, 1,516,979 active duty personnel filled 7,119,945 opioid prescriptions. Although both military and civilian populations had fewer prescriptions after 2011, the military population a larger decrease of prescriptions dispensed each year than the civilian population. Models measuring changes after 2011 showed significant changes in the proportion of ADSM that received at least 1 prescription in a given month leading to a decrease of 1.77% of ADSM receiving an opioid prescription and significant increases of .0264% for every thousand wounded in action service members. Conclusions: Trends after 2011 were found to be significant even when included in models with other variables and appears to be a significant factor in decreasing the proportion of ADSM receiving an opioid prescription.

Poster 1-7

Relative reinforcing effects of the synthetic cathinone 3,4-methylenedioxy-N-methylcathinone (methylone) in rats

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The abuse of designer drugs, such as bath salts, is a serious global public health problem. Methylone (3,4-methylenedioxy-N-methylcathinone), is a synthetic derivative of cathinone and a common constituent of bath salts preparations. The current study used three groups of male Sprague Dawley rats (n=12 per group) to directly compare the reinforcing effects of methylone to those of another synthetic cathinone, MDPV (3,4-methylenedioxypyrovalerone), and cocaine. When available under a fixed ratio (FR) 1 schedule of reinforcement, all groups of rats readily acquired lever pressing for methylone (0.32 mg/kg/inf), MDPV (0.032 mg/kg/inf), or cocaine (0.32 mg/kg/inf). Methylone was able to maintain a stable pattern of responding under an FR5 schedule. Dose response curves generated under an FR5 schedule suggest that methylone maintains less responding and is less potent than MDPV (peaks of 60 inf at 0.1 mg/kg methylone and 250 inf at 0.0032 mg/kg MDPV, respectively). When compared under a progressive ratio schedule, methylone was the least potent and effective of the three drugs, maintaining a maximum of 16 infusions, compared to 27 infusions for MDPV and 23 infusions for cocaine. Together, these findings demonstrate that even though methylone functions as a reinforcer, it is less effective than other widely used cathinones such as MDPV, or cocaine. These differences suggest that methylone may have a lower potential for abuse than drugs such as MDPV and cocaine.

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Poster 1-8

Sex-specific efficacy of the synthetic cannabinoid CP 55,940 in a mouse model of chronic pain

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Treatment of chronic pain presents a challenge not sufficiently covered by current medications such as opioids. In animal models of chronic pain, treatment with synthetic cannabinoids, such as CP55,940, show promise. This study evaluates the efficacy of CP55,940 in a mouse model of chronic pain induced by weekly injections of the chemotherapeutic agent cisplatin. Additionally, the effects of co-administration of a JNK inhibitor, SP600125, alongside the CP55,940 were tested. JNK inhibitors have previously been demonstrated to slow the development of tolerance to the pain-relieving effects of both morphine and the phytocannabinoid, THC. The results of these experiments suggest a sex-dependent mechanism to both the anti-allodynic effects of SP600125 and CP55,940. The anti-allodynic effects of SP600125 were less pronounced and shorter acting in female mice versus males. Females treated with CP55,940 also displayed a dose dependent and shortened therapeutic window compared to males. Finally, SP600125 was ineffective at delaying the development of tolerance to the anti-allodynic effects of CP55,940 in either males or females. Our findings suggest that tolerance to CP55,940 is mediated through a pathway other than the classical JNK-GPCR mechanism seen with THC. Future studies should investigate both the sex differences in cannabinoid agonist efficacy and the role of JNK signaling pathway in pain, as well as investigation into a JNK-GPCR independent mechanism of cannabinoid receptor tolerance to synthetic agonists such as CP55,940.

Poster 1-9

Ethanol and sucrose demand and preference in rats

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The aims of the present study were threefold. The first aim was to apply Hursh & Silberberg's (2008) exponential demand model to ethanol (20% v/v) and sucrose in order to perform within-subjects comparisons of their essential values. The second aim was to assess the capacity of EV to predict reinforcer preference. The third objective was to determine whether a month of intermittent access to ethanol would alter the EV of either reinforcer or preference between them. Rats underwent demand-curve training wherein the FR requirement increased over 2-3 session increments in the following order: FR1, 2, 4, 8, 16, 32, 64. Subsequently rats' reinforcer preference was established using a discrete-trials choice procedure. Then, half of the rats received four weeks of intermittent access to ethanol in their home cage before re-determining their demand for ethanol and sucrose and their preference between them. The mean EV of ethanol was significantly lower than that of sucrose. When given a choice, the majority of rats preferred sucrose over ethanol. Individual differences in the degree of preference were predicted by individual differences in the relative valuations of the two reinforcers. Rats for which the EV of sucrose was relatively large compared to that of ethanol chose sucrose more frequently. Intermittent access to ethanol had no effect on demand for ethanol or sucrose and did not affect the choice between them. The results of the present study indicate that for rats, ethanol is a relatively weak reinforcer compared to sucrose. Results also suggest that preference between ethanol and a non-drug alternative is driven by the relative values of the two reinforcers available. Manipulating the values of ethanol or the non-drug alternatives might be expected to alter preference. Given that preference in this experiment was predicted by relative reinforcer valuation, this suggests that excessive ethanol intake may be reduced by decreasing the value of ethanol or by increasing the value of an alternative reinforcer.

Poster 1-10

Abuse-Related Effects of Mixtures of Cocaine and Caffeine under Self-Administration in Rats

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Cocaine is widely abused around the world, and its reinforcing effects are well described in the scientific literature. However, prior to sale cocaine is often mixed/adulterated with other drugs like caffeine. This study aims to determine if caffeine alters the abuse-related effects of cocaine by using dose-addition analyses to characterize the nature of the interactions between cocaine and caffeine in male Sprague-Dawley rats. Using a progressive ratio (PR) schedule of reinforcement, dose-response curves were established for cocaine (0.032-1.78 mg/kg/inf) and caffeine (0.1-1.78 mg/kg/inf) alone, prior to evaluating the reinforcing effects of mixtures of cocaine and caffeine. Because the nature of drug-drug interactions can vary depending upon the composition of the mixture, cocaine and caffeine were evaluated at three fixed ratios (3:1, 1:1, 1:3) of their ED50s to maintain responding under the PR schedule. Dose-addition analyses were used to calculate predicted additive dose-response curves, which were compared to those which were experimentally determined. In isolation, both drugs maintained dose-dependent responding with cocaine being a significantly more effective reinforcer than caffeine. When combined, the reinforcing effects of cocaine and caffeine were no different than predicted for an additive interaction, regardless of the ratio at which they were mixed. Together, these results suggest that the addition of caffeine does not enhance the abuse-related effects of cocaine; however, it is unclear whether similar interactions exist with regard to their toxic effects.

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Poster 1-11

Examining the capacity of nAChR antagonists to block the effects of nicotine in tolerant C57BL/6J mice

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The proposed mechanism of action of common smoking cessation aids relies on their ability to antagonize the effects of nicotine. However, it is unclear how repeated exposure to nicotine impacts the capacity of nicotine to be antagonized. Here, the rate-decreasing and hypothermic effects of nicotine, the nonselective nAChR antagonist mecamylamine, and the α4β2* nAChR antagonist dihydro-β-erythroidine (DHβE) were studied in male C57BL/6J mice before, during, and after discontinuation of a daily nicotine treatment that consisted of 1.78 mg/kg nicotine administered three times daily. Under all three conditions, nicotine decreased response-rate and rectal temperature with respective ED_{50} values of 0.44 and 0.82 mg/kg prior to nicotine treatment, 1.6 and 3.2 mg/kg during nicotine treatment, and 0.74 and 1.1 mg/kg after discontinuation of nicotine treatment. Chronic nicotine treatment did not significantly increase sensitivity to the rate-decreasing effects of mecamylamine and DHβE. Prior to, and after discontinuation of, nicotine treatment, mecamylamine and DHβE significantly antagonized the rate-decreasing and hypothermic effects of nicotine. During chronic nicotine treatment, mecamylamine and DHβE no longer antagonized the rate-decreasing effects of nicotine, but still antagonized the hypothermic effects of nicotine. These data suggest that the rate-decreasing and hypothermic effects of nicotine may have different mechanisms of action, and that during chronic nicotine treatment, some of its effects may be mediated by non-nAChRs.

Poster 1-12

Endogenous glutamate augmentation within infralimbic cortex attenuates the incubation of cocaine-craving in rats.

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Incubation of craving is paralleled with an incubation of extracellular glutamate (GLU_{EC}) within the ventromedial prefrontal cortex (vmPFC). Prior evidence posits an inhibitory role for the infralimbic cortex (IL) and a potentiating role for the prelimbic cortex (PL) subregions of the vmPFC during incubation. As no study has directly examined the role for vmPFC GLU_{EC} in the incubation of cocaine-seeking, the present study aimed to fill this gap. It is hypothesized that increasing GLU_{EC} in the IL using the excitatory amino acid transporter inhibitor threo-β-benzyloxyaspartate (TBOA) will attenuate incubated drug-seeking. Conversely, increasing GLU_{EC} in the PL should potentiate drug-seeking. Male Sprague-Dawley rats (n= 91) were trained for 10 days to lever-press for cocaine (0.25 mg/infusion; 6 h/day), the delivery of which was signaled by a 20 second tone-light cue. Rats were then divided into 3 or 30-day withdrawal (WD) groups at which point they were microinjected with vehicle or 300 µM TBOA (0.5µl/min/side) into either the IL or PL and given a 30-min extinction test during which responding resulted in presentation of the cues but no cocaine. The next day, rats were tested again to assay for any carry-over effects of TBOA. Increasing GLU_{EC} via TBOA infusion into the IL temporarily reduced incubated drug-seeking behavior at 30WD, but not at 3WD. On the other hand, TBOA into the PL did not influence drug-seeking. This observation was supported by a significant 3-way interaction between Treatment (VEH vs. TBOA) X Withdrawal (3 vs. 30 days) X Test (Cue test 1 and 2) interaction [$F(1,38)= 4.12$, $p< .05$]. The present findings are consistent with prior evidence that IL activity facilitates extinction of incubated drug-seeking. Such results argue that pharmacotherapeutic strategies aimed at increasing GLU_{EC} in the IL may have potential for reducing cue-elicited craving and behavioral reactivity in protracted withdrawal to facilitate addiction recovery.

Poster 1-13

Mobile Use Patterns among Low-Income Parents Enrolled in Outpatient Substance Abuse Treatment

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Evidence-based family treatments for adolescent substance use (SU) disorders are associated with significant decreases in SU and parenting improvements. Unfortunately, 60-70% of treatment-receiving adolescents relapse, with parallel patterns of decline also seen in post-treatment parenting. A potential way to boost treatment effects may be to increase the availability of post-treatment interventions via cost-effective technologies like mobile phones. Regrettably, few studies have explored mobile phone patterns of marginalized substance abusing populations. Thus, this study sought to determine the accessibility, utilization, and preference for mobile phone use among 103 (78.6% female; 75.7% Hispanic; M age = 42.6) parents of teens participating in outpatient substance abuse treatment. Survey collection among teens is ongoing and will be presented at the conference. Results indicated that the vast majority of parents used a cell phone as their primary phone (97.1%), with smart phones (83%), particularly Androids (68.7%), being the most popular. Parents were more likely to have pay-as-you-go (41.4%) contracts, and only 15% endorsed changing their phone number more than once in the past year. Report of accessibility matched the clinic's ability to reach parents. Moreover, 91% of parents reported they would be receptive to receiving text messages with parenting tips as aftercare support. Preferred content areas included: strategies for monitoring teen SU (56%), strategies for using consequences (62%), suggestions for encouraging positive activities (62%), and ways to improve parent-child communication (63%). This data will help researchers design mobile-based interventions both during and after treatment.

Poster 1-14

Effects of Exposure to a Cafeteria Diet in Adolescent and Adult Rats on Delay Discounting: Alterations on Dopaminergic Sensitivity

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Childhood obesity predicts obesity in adulthood. Correlational studies suggest that childhood obesity is related to consumption of foods that are high in fat and sugar. Experimental studies on diet-induced obesity (DIO) support these correlational studies and provide evidence for causation, however, it is unclear if there are critical periods during development in which the brain is more vulnerable to the reward-altering effects of high-fat/high-sugar diets. To assess the influence of developmental timing of dietary exposure on DIO, we exposed rats to a high-fat, high-sugar cafeteria-style diet for 8 weeks starting at postnatal day (PND) 21 or PND 73. Following the diet exposures, the rats were tested on a delay discounting task, in which preferences for smaller, immediate vs. larger, delayed food outcomes were assessed. Once behavior was stable, acute administrations of haloperidol (0.03 – 0.1 mg/kg) were administered to assess the extent to which diet-induced changes in dopamine D2 (which is a mechanism of food reward) influence impulsive food choice. Analyses revealed no diet- or age-related differences in baseline levels of delay discounting; however, rats fed a high-fat, high-sugar diet did show greater haloperidol-induced shifts in impulsive responding. These findings suggest haloperidol may unmask dietary, but not age-related, alterations in impulsive behavior. These findings also support a growing behavioral- and neuro-economic literature (i.e. Reinforcer Pathology Model) that extended exposure to a high-fat, high-sugar diet show similar behavioral and neural outcomes as chronic self-administration of psychoactive drugs of abuse.

Poster 1-15

Affective Properties of the Second Generation 'Bath Salt' α-pyrrolidinopentiophenone (α-PVP): An Assessment of Aversion and Reward.

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Background: α-pyrrolidinopentiophenone (α-PVP), a second generation "bath salt" that is similar to MDPV, has recently been reported to be rewarding in a variety of pre-clinical models. Given that a number of drugs of abuse have both rewarding and aversive effects, the balance of which is thought to influence abuse potential, the present study attempted to extend the analysis of the affective properties of α-PVP by assessing its ability to induce taste avoidance, an index of a drug's aversive effects. This assessment was made in a combined CTA/CPP design that allowed a concurrent evaluation of the relationship between α-PVP's aversive and rewarding effects. Body temperature was also examined. Methods: Male Sprague-Dawley rats were exposed to a novel saccharin solution, injected with 0, 0.3, 1 or 3 mg/kg α-PVP (IP) and placed on one side of a place conditioning apparatus. On the next day, they were injected with vehicle, given access to water and placed on the other side. This procedure was repeated for a total of four times after which saccharin avoidance and place preferences were assessed. Results: α-PVP induced dose-dependent taste avoidance as well as increases in time spent on the drug-paired side (although not dose dependent). α-PVP induced dose-dependent hyperthermia. Conclusions: α-PVP, like MDPV and other drugs of abuse, has both aversive and rewarding effects. It will be important to assess how various experiential and subject variables impact these effects and their balance to predict abuse liability.

Poster 1-16

Toll-like receptor 4 (TLR4) activation alters anxiety-like behavior in an animal model of post-traumatic stress disorder (PTSD).

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There is a growing body of evidence demonstrating the role of inflammation in stress-related disorders. Toll-like receptor 4 (TLR4) is one receptor type involved in innate immune responses to stress and may play a role in some aspects of these disorders. The goal of this study was to determine if TLR4 activation factored into behavioral changes seen in an animal model of post-traumatic stress disorder (PTSD). To test this idea, we examined male and female rats that were either TLR4 gene knockout (KO; n=18) or wild type (WT) controls (n=18). We obtained baseline behavioral measures on three assays of anxiety- and depressive-like behaviors: 1) elevated plus maze (EPM); 2) open field test (OFT); and 3) two-bottle choice sucrose preference test (SPT). We then subjected the rats to a stressor that induces a PTSD-like condition – exposure to predator odor. This exposure was conducted using a conditioned place aversion (CPA) protocol. Rats were confined to one side of a 2-compartment apparatus for 15-min during the morning. That evening, rats were confined to the other distinct compartment and exposed to predator odor (bobcat urine) for 15 minutes. We performed CPA testing 24 hours post-exposure and again at 10 days post-exposure. In these tests, rats had access to both compartments and time spent on the odor-paired side over the 15-min test was tabulated. Rats were re-tested on EPM, OFT, and SPT within 48 hours of predator odor exposure. We observed no group or sex differences in aversion behavior in the CPA tests. Male KOs exhibited heightened anxiety-like behaviors as measured by EPM and OFT compared to male WTs. Female KOs displayed increased anxiety-like behavior on OFT but not on EPM compared to female WTs. Males of both groups showed decreased sucrose preference post-exposure, with male KOs exhibiting increases in stress-induced polydipsia compared to WTs. No effects on sucrose preference were seen in females of either group. These data indicate that TLR4 activation may play a protective role in psychological functioning following exposure to a traumatic stressor.

Poster 1-17

Evaluation of dopamine and serotonin receptor antagonists on 3,4-methylenedioxypyrovalerone (MDPV) discrimination in male Sprague-Dawley rats.

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3,4-Methylenedioxypyrovalerone (MDPV) is a novel synthetic cathinone reported to have a high potential for abuse and to produce adverse medical consequences when used recreationally. Recent preclinical research indicates the psychopharmacology of MDPV is comparable to both cocaine and 3,4-methylenedioxymethamphetamine (MDMA). Despite the recent influx of research on the psychopharmacology of MDPV, few studies have employed drug discrimination methods to discern the neurochemical mechanisms involved in its interoceptive stimulus effects. The aim of the present study was to investigate the effects of dopamine (DA) and serotonin (5-HT) antagonists on the discriminative stimulus effects of MDPV. Seven adult male Sprague-Dawley rats were trained to discriminate 1.0 mg/kg MDPV from vehicle under an FR 20 schedule of food reinforcement. Once reliable stimulus control was established with MDPV, antagonism tests were conducted with the selective D1 receptor antagonist, Sch 23390 (0.01, 0.03, 0.1, 0.3 mg/kg), the D2 antagonist sulpiride (10, 20, 40 mg/kg), and the 5-HT2 antagonist pirenpirone (0.16, 0.32, 0.64, 1.28 mg/kg). Sch 23390 dose-dependently attenuated MDPV discrimination and completely blocked its effects at the highest dose tested, whereas sulpiride and pirenpirone failed to block MDPV discrimination. Additional antagonist tests are currently in progress with other selective 5-HT antagonists. These preliminary results indicate a predominant role for D1 DA receptors in mediating the interoceptive stimulus effects of MDPV.

Poster 1-18

The Microglial Transcriptome and Ethanol Consumption: Computational Drug Repurposing

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Emerging evidence suggests that chronic ethanol consumption perturbs neuroimmune pathways and can thereby regulate behavior and produce detrimental effects on the nervous system. Microglia, the immune cells of the brain, are recognized as having an important role in this response. However, it is unknown which microglial transcripts are mediating this response and whether these changes can be identified when looking at an ad-mixture of brain cell types. The purpose of this study is to identify the microglial gene expression changes in response to chronic ethanol consumption and to use this data to identify drugs that may normalize the neuroimmune response. We focused on the prefrontal cortex (PFC), a brain region that is highly involved in the neuroimmune response to ethanol. C57Bl/6J mice had access to both ethanol and water using and every other day 2-bottle choice paradigm or water only for 70 days (35 drinking days). We then prepared microglia from the PFC using magnetic beads and collected a total homogenate reference sample and isolated RNA from both. RNA was sequenced at a depth of 20 million reads using NextSeq500. DESeq was used to identify ethanol-responsive transcripts in both the total homogenate and microglia. Results reveal a unique set of transcripts that are differentially expressed in microglia but not in the total homogenate. Weighted gene co-expression network analysis (WGCNA) was used to identify clusters of alcohol responsive transcripts. As expected, many of the microglial changes are related to immune signaling. We compared the gene expression signature of chronic alcohol exposure in microglia with data from the Library of Integrated Cellular Signatures (LINCS), which contains gene expression response profiles to more than 19,000 compounds. We used this computational genomics approach to identify novel neuroimmune-related compounds that target dysregulated gene networks specifically in microglial cells.

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Poster 1-19

Interactions between reinforcement history and drug-primed reinstatement: Studies with MDPV and mixtures of MDPV and caffeine.

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"Bath salt" preparations often contain multiple compounds, with synthetic cathinones, such as MDPV (3,4-methylenedioxypyrovalerone), and caffeine being two of the most common constituents. Caffeine is frequently added as an inexpensive alternative that is thought to mimic and/or enhances some of the stimulant-like effects of MDPV. Since caffeine is a widely-used drug, and cathinone users report high amounts of drug cravings, this study aimed to evaluate whether the composition of the self-administered drug alters the response to drug-primed reinstatement. To explore this issue, Sprague Dawley rats were trained to self-administer MDPV (0.032 mg/kg/inf) or a mixture of MDPV + caffeine (0.0288 mg/kg/inf and 0.66 mg/kg/inf, respectively). Following stable responding, rats underwent extinction for a minimum of seven sessions and until responding occurred at levels less than 15% of when drug was available. Then, cue-induced and drug-primed reinstatement tests were performed to evaluate the effectiveness of MDPV (0.032-1.0 mg/kg) and caffeine (1.0-32 mg/kg) to reinstate responding for stimuli previously associated with either MDPV alone or MDPV + caffeine. In both groups, pretreatments of MDPV and caffeine dose-dependently increased responding on the previously reinforced lever. However, while MDPV and caffeine pretreatments were similarly effective in reinstating behavior in the MDPV + caffeine group, pretreatments of MDPV were more effective at reinstating responding than caffeine in the MDPV group. These findings not only suggest that caffeine is effective at reinstating responding previously reinforced by stimulant drugs, but also that the composition of the self-administered drug or drug mixture can impact the effectiveness of drug primes to reinstate responding. Future studies will investigate how interactions among bath salts constituents can influence their effectiveness at promoting relapse-related behaviors.

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Poster 1-20

Preweanling Methylphenidate Exposure Enhances Oxycodone Reward in Male and Female Late Adolescent Rats

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Methylphenidate (MPH) is commonly prescribed to treat the symptoms for ADHD in preschool-age children. However, its long-term effects on behavior remain unclear. While previous research has shown that MPH pre-exposure predicts an enhancement of morphine reward in adults, little research exists studying the effects of said exposure on the prescription opiate, Oxycodone (OXY) in late adolescents. Oxycodone abuse among adolescents has increased in recent years. Using the conditioned place preference (CPP) paradigm, we previously demonstrated a dose-dependent preference for oxycodone-related cues in this age group. Since MPH has been found to enhance drug reward, we examined the effects of MPH on adolescent rat OXY CPP, hypothesizing that MPH rats would show OXY CPP at doses insufficient for saline rats, suggesting higher sensitivity to OXY reward. Male and female rats were intraperitoneally injected with either 2 mg/kg MPH or saline, twice daily, from postnatal day (PD) 11-20. They were then assessed for OXY CPP using an 11-day procedure beginning on PD 40. During pre-conditioning and post-conditioning sessions, rats were tested for their baseline and final place preference in a two-compartment paradigm, in 15-min sessions. During conditioning (PD 42-47), rats underwent daily 30-min sessions, receiving alternating Oxycodone (0, .033, 0.1, 0.3 mg/kg) and saline injections in distinct compartments. Oxycodone was given in the non-preferred compartment and saline in the preferred, according to baseline data. As hypothesized, both male and female rats that underwent MPH pre-exposure showed OXY-induced CPP at doses that were insufficient for saline rats. MPH appears to enhance susceptibility for OXY reward, an important consideration for doctors prescribing either drug.

Poster 1-21

Interactions between Kappa and Mu Opioid Receptor Agonists: Effect of the Ratio of Drugs in the Mixture.

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Pain is the leading reason for seeking medical care. Moderate to severe pain is commonly treated with mu opioid receptor agonists, despite their well-documented adverse effects (e.g., constipation, abuse). Kappa opioid receptor agonists have antinociceptive effects but also adverse effects, including dysphoria and diuresis, that have precluded their use in the clinic. A kappa/mu opioid mixture might reduce the dose of each drug needed to produce therapeutic (antinociceptive) effects while avoiding or reducing the adverse effects that occur with larger doses of each drug alone. The current experiment compared antinociceptive and hypothermic effects of the kappa opioid receptor agonist spiradoline in combination with the mu opioid receptor agonists morphine and etorphine to test the hypothesis that a kappa/mu mixture selectively enhances antinociceptive effects. Dose-effect functions were determined in 7 male Sprague Dawley rats for spiradoline (5.6 – 56.0 mg/kg), morphine (3.2 – 32.0 mg/kg), and etorphine (0.001 – 0.1 mg/kg) for antinociception (latency to remove the tail from warm [40, 50, and 55oC] water) and for rectal body temperature. All drugs increased tail withdrawal latency in a dose-related manner. Spiradoline decreased body temperature by 3oC, whereas morphine, but not etorphine, increased body temperature. ED50 values were used to determine the doses for mixtures in ratios of 3:1, 1:1, and 1:3, 1:10. Spiradoline:morphine and spiradoline:etorphine in 3:1 and 1:1 ratios produced additive antinociceptive effects, and in 1:3 and 1:10 ratios produced supra-additive antinociceptive effects. Neither morphine nor etorphine altered the hypothermic effects of spiradoline. If kappa/mu mixtures do not enhance other adverse effects (e.g., constipation, dysphoria), then these mixtures might have greater therapeutic potential than mu opioids alone.

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Poster 1-22

Differences of wheel running locomotor activity in mice administered MDMA and MDPV at high and low ambient temperatures

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3,4-Methylenedioxymethamphetamine (MDMA) and 3,4-Methylenedioxypyrovalerone (MDPV) are two common psychoactive drugs of abuse that act on monoamine transporters. MDMA is non-selective across monoamines, and acts as both a passive reuptake inhibitor and as a substrate for release at serotonin, norepinephrine, and dopamine transporters. MDPV is a passive reuptake inhibitor specific for catecholamine reuptake transporters. Despite their differences in mechanism of action, MDMA and MDPV have similar discriminative stimulus effects, chemical structures, and function as locomotor stimulants. In this regard, previous reports have indicated that MDMA and MDPV administration differentially affect wheel running in rats. Further, our lab and others have shown that the stimulant effects of MDPV are potentiated at high ambient temperatures, while those of MDMA are not. In the present studies, we compared the effects of MDMA and MDPV on wheel running activity at a cool (20°C) and warm (28°C) ambient temperature in mice. Animals were first allowed unrestricted access to running wheels for 3 days, then injected with saline, or 1, 3 or 10 mg/kg MDMA or MDPV while wheel revolutions were monitored for 6 hours at both experimental ambient temperatures. Under saline control conditions, wheel running was variable across animals, but was generally stable for a given animal across days, and was not affected by ambient temperature. Administration of MDPV dose-dependently increased wheel running activity at both ambient temperatures, while MDMA dose-dependently suppressed wheel running behavior at both ambient temperatures. Because MDMA releases serotonin while MDPV does not, the role of serotonin in the effects of these drugs on wheel running was investigated using fenfluramine to add a serotonin release component to the effects of MDPV and using p-CPA to deplete serotonin prior to MDMA administration. Results of these mechanistic studies will be presented. These studies supported by DA039195 and the UAMS Center for Translational Neuroscience.

Poster 1-23

Evaluation of the functional selectivity profiles of U50,488 analogues at peripheral Kappa Opioid Receptors (KOR).

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Functional selectivity describes the ability of agonists to differentially regulate individual signaling pathways coupled to a given receptor. By fine-tuning the structure of a ligand, the activity of therapeutically efficacious signaling can be enhanced whereas signaling that leads to adverse effects can be minimized. Here, we evaluated the ability of SJ-1-147, SJ-1-163, and SJ-1-171, structural analogues of selective KOR-agonist U50,488, to differentially activate pathways known to regulate peripheral KOR-mediated antinociception. In both primary cultures of adult rat peripheral sensory neurons and in CHO cells transiently expressing rat KOR, all three analogues inhibited PGE2-mediated cAMP accumulation with similar potencies and efficacies to U50,488. However, unlike U50,488, all three analogues did not increase the activity of extracellular signal regulated kinase (ERK). In primary cultures of rat peripheral sensory neurons, U50,488 inhibited PGE2/Capsaicin-mediated CGRP release. However, the concentration response curve (CRC) was U-shaped, but rendered monotonic in the presence of the ERK inhibitor, U0126. By contrast, the CRCs for inhibition of CGRP release for all three test compounds were monotonic (not U-shaped), which is consistent with the loss of ERK signaling by the structural modifications. In a rodent model of thermal nociception, intraplantar (i.pl.) injection of peripherally-restricted doses of U50,488 produced antinociception with an inverted U-shaped dose response curve (DRC). By comparison, i.pl. injection of SJ-1-147 produced antinociception with a peak magnitude similar to U50,488, however, the DRC for 1-147 was monotonic. Overall, our data suggest that structural modifications of a KOR ligand can selectively alter its efficacy for individual signaling cascades, which may lead to improved therapeutic outcomes for peripherally-mediated analgesia. Supported by NIH/NIDA RO1 DA 038645.

Poster 1-24

Examining the involvement of the BMP pathway following cocaine self-administration in rats

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Drug addiction is a chronic brain disease, which is characterized by compulsive use of a drug despite negative consequences. Relapse occurs even after prolonged periods of abstinence from the drug due to drug-dependent plasticity that occurs in brain structures involved in reward and motivation, including the nucleus accumbens (NAc). The transforming growth factor (TGF)-β superfamily is a family of multifunctional proteins that regulate a wide variety of cellular responses, including spine plasticity and gene expression. Studies from our lab have shown that the TGF-β superfamily members, SMAD3 and Activin A, in the NAc are important for relapse-like behaviors following cocaine exposure in animal models of addiction. However, the role of the BMP pathway, which is a part of TGF-β signaling, has not yet been studied in addiction. Here we found that there is an increase in SMAD1 protein, a member of the BMP pathway, during a 7-day abstinence period following short access cocaine self-administration in rats. We also found a decrease in Smurf1 protein, an E3 ubiquitin-protein ligase which regulates the degradation of SMAD1. After a 30-day abstinence period following extended access cocaine self-administration, we again found a decrease in Smurf1. Together, these data suggest the BMP pathway may be involved in drug-dependent neuronal and behavior plasticity. Next, we will determine if there is a functional role for SMAD1 in relapse-like behaviors and also examine the expression of SMAD1 in the NAc at later abstinence periods following cocaine exposure in rats.

Poster 1-25

Pattern of drug dosing during conditioning affects the expression of alcohol-induced conditioned place preference in periadolescent male and female rats

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Alcohol is the most commonly abused recreational substance that is first consumed during adolescence. Preclinical research examining the rewarding effects of alcohol in adolescence, as assessed using the conditioned place preference (CPP) paradigm, have resulted in weak or inconsistent results. The present study examined whether ascending doses of alcohol during conditioning produce more robust alcohol-induced CPP compared to a fixed dosing regimen during conditioning. Support for this hypothesis is indicated by recent studies demonstrating more robust cocaine-induced CPP using ascending doses of cocaine during conditioning compared to fixed doses during conditioning. Beginning on postnatal day (PD) 23, male and female periadolescent rats underwent a 10-day alcohol CPP procedure. On days 1 and 10, rats were tested for their pre-conditioning and post-conditioning place preferences, respectively, during 15-min sessions. On days 2-9, rats were conditioned for 15-min with saline or ethanol on alternative days. During ethanol conditioning days, rats were randomly assigned to receive either ascending alcohol doses (0.0063-2.0 g/kg, intraperitoneally) or fixed alcohol doses (0.5, 1.0, or 2.0 g/kg, intraperitoneally). The results indicated that while both males and females established preference using fixed high doses (2.0 g/kg) of ethanol, only males established preference using ascending low doses (0.5 g/kg). Overall, these results suggest that the pattern of doses used during conditioning sessions may play an important role in elucidating the rewarding effects of alcohol.

Poster 1-26

Acute methylphenidate administration reduces attentional bias in cocaine users, but does not change behavioral inhibition.

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Incentive salience theories posit that drug cues elicit a conditioned motivational state for drug use, which may contribute to the difficulty in discontinuing use. Previous work has suggested that incentive salience of cocaine cues results in attentional bias and disrupts behavioral inhibition in cocaine users. Given that dopaminergic activity modulates motivational states, we hypothesized that acute stimulant administration would alter the magnitude of cocaine-cue attentional bias and cocaine-cue-induced disruptions in behavioral inhibition. This hypothesis was tested by administering 60 mg methylphenidate (MPH) and placebo orally to non-treatment-seeking cocaine users prior to completion of attentional bias and behavioral inhibition tasks. Participants completed a three-day, within-subjects study. Participants completed one practice session (non-dosing conditions) and two experimental sessions (placebo or MPH; counterbalanced order). Gaze time allocated to cocaine and neutral cues on the visual-probe task was the primary measure of attentional bias to cocaine cues. Inhibitory failures to "no-go targets" following cocaine cues or shapes (control cues) on the attentional bias-behavioral activation (ABBA) task and the traditional cued go/no-go task, respectively, were used to measure behavioral inhibition performance. Attentional bias to cocaine cues was present following placebo, but was not present following MPH administration. There was no change in behavioral inhibition on either the ABBA or cued go/no-go tasks, regardless of dose condition. Behavioral inhibition performance did not differ between the two tasks under both dose conditions. These results indicate that different psychopharmacological mechanisms modulate the salience of cocaine cues on attentional bias and behavioral inhibition, as increased dopaminergic activity reduced attentional bias, but did not alter behavioral inhibition.

Poster 1-27

Effects of 3,4-methylenedioxypyrovalerone (MDPV) Pre-exposure on the Aversive Effects of MDPV, Cocaine and Lithium Chloride: Implications for Abuse Vulnerability.

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Drug use is thought to be a balance of the drug's rewarding and aversive effects, and understanding how various factors impact these properties and their relative balance may provide insight into its abuse potential. In this context, the present study attempted to evaluate the effects of drug history on the aversive effects of 3,4-methylenedioxypyrovalerone (MDPV), one of a variety of synthetic cathinones (collectively known as "bath salts"). Different groups of male Sprague-Dawley rats were exposed to either vehicle or MDPV (1.8 mg/kg) once every fourth day for five total injections prior to taste avoidance conditioning in which a novel saccharin solution was repeatedly paired with either vehicle, MDPV (1.8 mg/kg), the related psychostimulant cocaine (18 mg/kg) or the emetic lithium chloride (LiCl) (13.65 mg/kg). In animals pre-exposed to vehicle, all three drugs induced significant and comparable taste avoidance relative to animals injected with vehicle during conditioning. MDPV pre-exposure attenuated the avoidance induced by both MDPV and cocaine (greater attenuation for MDPV than cocaine), but had no effect on that induced by LiCl. These findings suggest that a history of MDPV use may reduce or attenuate MDPV and cocaine's (but not LiCl's) aversive effects. These changes in MDPV's aversive effects may be important to its and cocaine's potential use and abuse given that the overall balance of reward and aversion may be shifted.

Poster 1-28

Addressing Structural Flexibility at the A-Ring on Salvinorin A: Discovery of a Potent Kappa Opioid Agonist with Enhanced Metabolic Stability.

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Previous structure-activity studies on the neoclerodane diterpene salvinorin A have demonstrated the importance of the acetoxy functionality on the A-ring in its activity as a kappa opioid receptor agonist. Few studies have focused on understanding the role of conformation in these interactions. Herein we describe the synthesis and evaluation of both flexible and conformationally restricted compounds derived from salvinorin A. One such compound with spirobutyrolactone functionality was synthesized in a single step from salvinorin B and has similar potency and selectivity to salvinorin A (EC_{50} = 0.6 ± 0.2 nM, μ-,δ- > 10,000 nM). Microsomal stability studies demonstrated that this rigid spirobutyrolactone was more resistant to metabolism than salvinorin A. Evaluation of analgesic and anti-inflammatory properties revealed similar *in vivo* effects for both the rigid derivative and salvinorin A. To our knowledge, this study represents the first example of bioisosteric replacement of an acetate group by a spirobutyrolactone to produce a metabolically resistant derivative compound.

Poster 1-29

Organic cation transporter 3 upregulation in serotonin transporter deficient mice potentiates ethanol-induced serotonin clearance impairments

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Genetic reductions in serotonin transporter (SERT) function, resulting in attenuated clearance of extracellular serotonin (5-HT), are associated with increased likelihood of alcohol use disorders. Indeed, genetic (SERT+/- or -/-) or pharmacologic reductions in SERT function exacerbate the 5-HT clearance impairment elicited by ethanol, suggesting ethanol is acting at a site other than SERT to impair 5-HT clearance. A putative compensatory 5-HT mechanism is the organic cation transporter 3 (OCT3), which is increased in SERT-deficient mice. The objective of the present study was to determine if ethanol is acting at OCT3 to inhibit 5-HT clearance in wildtype and SERT-deficient mice. We used high-speed chronoamperometry to detect 5-HT uptake in the hippocampus or striatum of wildtype and SERT-deficient mice. Ethanol was applied locally in conjunction with blockers of OCT3 (corticosterone), SERT (fluvoxamine), norepinephrine transporter (NET; reboxetine), or dopamine transporter (DAT; GBR 12909; striatum only). Application of the OCT3 blocker did not increase the impaired 5-HT uptake resulting from ethanol in hippocampus or striatum of any SERT genotype, indicating that ethanol does indeed act via OCT3 to impair 5-HT uptake. Presence of a SERT inhibitor in SERT wildtype and +/- mice potentiated ethanol impairments in hippocampal 5-HT uptake. Reduced hippocampal and striatal 5-HT uptake from ethanol was exacerbated in SERT-/- mice by NET and DAT blockers, respectively, indicative of their promiscuous (and compensatory) uptake of 5-HT. Thus, OCT3 is a target for ethanol. Further, its blockade of OCT3-mediated 5-HT uptake is pronounced when SERT function is genetically or pharmacologically reduced, and other compensatory transporters not targeted by ethanol (e.g., NET, DAT) are inactivated. The present data therefore highlight the importance of considering genetic SERT status and compensatory transporter function (i.e., OCT3, NET, and DAT) in individuals with alcohol use disorders, and when evaluating SSRI efficacy, adherence, and treatment outcomes.

Poster 1-30

The efficacy of lidocaine in disrupting cocaine cue-induced memory re-consolidation

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Cue-induced craving memories, linked to drug-seeking behaviors, require key molecular processes for memory reconsolidation. Lidocaine, a sodium channel blocker, inhibits NMDA receptor activation and suppresses nitric oxide and ERK production. These processes are required for memory re-consolidation; inhibiting them may reduce cue-related craving memories in cocaine dependent subjects. This study was designed to assess the efficacy of lidocaine in decreasing cue-induced cocaine craving and cocaine use. Treatment-seeking cocaine-using participants (n=33) were recruited for this study. Personalized craving and relaxation (devoid of any type of drug cues) scripts were developed. Participants were then randomly assigned in a double-blind design to either receive lidocaine and a cocaine craving script (lidocaine/cue), saline and a craving script (saline/cue), or lidocaine and a neutral script (lidocaine/neutral). Immediately following the personalized script, lidocaine or saline was administered. One week following the infusion, cue-induced craving was assessed in the same paradigm without an infusion. Cocaine use and craving were assessed for an additional 3 weeks. There was no significant effect of group on craving or cocaine use over the 4 week follow-up period. However, there was a significant increase in craving during the first week following infusion in the lidocaine/cue group relative to the other two groups. Elevation in heart rate following infusion was also associated with increased cocaine use and craving in participants who received a lidocaine infusion (lidocaine/cue and lidocaine/neutral). Our findings suggest that lidocaine did not decrease cue-induced craving or subsequent cocaine use. Lidocaine may have enhanced the craving response in the lidocaine/cocaine-cue group, resulting in increased cocaine use the week following administration. Funded by R21DA045936 and UL1TR000451.

Poster 1-31

Design and synthesis of novel ligands targeting opioid receptors

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Opioids, which have been used medicinally as well as recreationally for more than four thousand years, are the among the most potent, and effective group of drugs for the treatment of pain. However, the clinical use of these drugs produce unfortunate side effects, such as tolerance, addiction, respiratory depression, nausea, constipation, etc, which plague their use. Further, the abuse of prescription opioids has also emerged as a worldwide health and social burden. The ligand-receptor interactions between opioids and G-protein-coupled opioid receptors are extremely complex. The discovery of new ligands able to interact with opioid receptors by diverse mechanisms might be useful for the exploration of ligand-receptor interactions, as well as lead to new agents for the relief of pain and for the treatment of addiction. Finding a drug without some or all of the side-effects produced by opioids has been the object of the research of many researchers over the past hundred years. To date there are no potent analgesics available that are free from side-effects, although there are a few new structural types of compounds in the various phases of clinical trials that are said to have fewer of the more unfortunate side-effects of opioids. We are engaged in modifying structures known to interact with opioid receptors in order the study the effect of these modifications. Herein, we report on the design, synthesis and evaluation of novel selective hydromorphone analogs with diverse N-substituents that will hopefully target a combination of opioid receptors. Hydromorphone is a semi-synthetic opioid that has a key role in the area of chronic and acute pain relief as an alternative to morphine. Some of our compounds have been found to have sub-nanomolar affinity for mu receptors and a few also have high affinity for delta receptors. In agreement with the suggestion from our former quantum chemical study of a para-nitrophenethyl substituted opioid, our analogue had a mu Ki = 0.5 nM and delta Ki=6 nM. Other newly synthesized ligands had even higher affinity for both mu and delta receptors.

Poster 1-32

The effects of cannabidiol on Δ^9-tetrahydrocannabinol (THC) induced place aversions and taste avoidance in male and female rats.

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Background: Like other abused drugs, marijuana use and abuse are likely a function of the balance of its rewarding and aversive effects. One factor that may modulate this relationship is the varying phytocannabinoid compounds and ratios found within cannabis. Cannabidiol (CBD), is a phytocannabinoid of particular interest, given that it modulates a number of Δ^9-tetrahydrocannabinol's (THC) effects, including anxiogenesis. Accordingly, it is important to investigate if CBD is able to reduce the aversive effects of THC and potentially contribute to the abuse of marijuana. Methods: Male and female Wistar rats underwent a combined place and taste conditioning procedure in which they were given access to a novel saccharin solution, injected with either vehicle, CBD (0.075, 0.75 mg/kg), THC (0.75 mg/kg) or several combinations of CBD and THC (1:10 dose ratio 0.075 mg/kg CBD and 0.75 mg/kg THC, 1:1 dose ratio 0.75 mg/kg CBD and 0.75 mg/kg THC) and then placed in a distinct chamber of a place conditioning apparatus. Results: THC induced place aversions and taste avoidance. At the 1:1 dose ratio, CBD had a small (and inconsistent) attenuating effect on THC place aversions. At the lower CBD dose ratio (1:10), CBD failed to modulate THC-induced place aversions. CBD did not attenuate THC-induced taste avoidance. There was no effect of sex. Conclusions: CBD weakly and inconsistently attenuated THC's aversive effects. These results may reflect the specific CBD:THC dose ratios examined or the doses of CBD assessed. The current findings suggest that CBD content in cannabis likely has a minimal effect on vulnerability to marijuana use and abuse

Poster 1-33

Implication of Disrupted Serotonin:Glutamate Synergy Upon Impulsivity.

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High impulsivity, broadly defined as action without sufficient foresight, has been noted in cocaine-dependent human subjects, and contributes to relapse in cocaine use disorder. There is evidence that glutamate (Glu) and serotonin (5-HT) neurotransmission within the corticoaccumbens circuit are critical drivers of the cognitive and/or behavioral dimensions underlying impulse-control disorders. Vesicular glutamate transporters (VGLUTs) sequester cytosolic Glu into synaptic vesicles for release from the presynaptic terminal. VGLUT3 is localized on heterogeneous neurons that have been demonstrated to co-release Glu and 5-HT. Thus, VGLUT3 dysfunction may play a role in levels of 5-HT and Glu release, resulting in aberrant synaptic alterations underlying impulsivity. Of note, VGLUT3 has been causally linked to cocaine-mediated behaviors in part through strengthened postsynaptic receptor plasticity in rat models. We hypothesized that an imbalance in VGLUT3, Glu-receptive AMPAR and 5-HT-receptive 5-HT_{2C}R homeostasis in the nucleus accumbens (NAc) associates with individual differences in impulsivity. Outbred male Sprague Dawley rats were identified as high (HI) or low (LI) impulsive using the one-choice serial reaction time (1-CSRT) task. Following phenotypic identification, NAc synaptosomal protein was extracted and VGLUT3, AMPAR, and 5-HT_{2c}R protein levels determined via immunoblot. HI rats expressed higher NAc synaptosomal VGLUT3 ($p<0.05$), but lower GluA1 AMPAR ($p<0.05$) and 5-HT_{2C}R ($p<0.05$), vs LI rats. There was a positive correlation between NAc VGLUT3 expression ($r=0.643$, $p=0.02$) and impulsivity. These data putatively suggest that in HI rats, elevated VGLUT3 expression may augment Glu:5-HT tone resulting in a compensatory downregulation of NAc Glu and 5-HT-responsive receptors, as a component of homeostatic synaptic plasticity. Taken together, an imbalance in 5-HT- and Glu-mediated synergy in the NAc may represent a novel neurochemical substrate associated with differential levels of inherent impulsivity and that rebalancing these systems may ultimately support behavioral recovery in disorders marked by impulsivity.

Poster 1-34

Fluoxetine administration during adolescence reduces food intake via meal size but does not alter meal pattern parameters in later life

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We previously reported that exposure to fluoxetine (FLX) during adolescence results in altered sensitivity to mood-related stimuli in adulthood, as inferred by forced swim and social defeat paradigms. To further investigate how early FLX exposure influences feeding later in life, we measured chow intake and meal pattern parameters in male rats. Postnatal day (PD) 35 rats were injected with FLX (0 or 20 mg/kg) for 15 consecutive days (PD35-49). During adulthood, the animals were exposed to chronic variable stress (CVS) for 14 days (PD74-88). During drug treatment, FLX-exposed rats decreased intake by reducing meal size but displayed no significant changes in meal number. Consequently body weights were significantly lower than that of controls by PD40. No significant group differences in meal pattern parameters were observed after drug treatment completion (PD50), or in body weight by early adulthood (PD65). Furthermore, both groups responded similarly to a palatable diet (45% fat, 17% sucrose) presented during adulthood (PD74-88). Finally, no significant group differences in meal pattern parameters were observed following a CVS schedule. Whereas juvenile FLX administration results in enduring changes in mood-related measures, here, no long-term changes in ad libitum feeding behavior are observed. Support: NIH GM109811, NIH DK019302

Poster 1-35

Role of Medial Prefrontal Cortex NMDA Receptors in Inherent Impulsivity.

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Impulsivity is a complex, multifaceted trait that represents a significant component of cocaine use disorder and relapse vulnerability. Glutamate neurotransmission in the medial prefrontal cortex (mPFC), an important brain region in decision-making and goal-oriented behaviors, has implications in inherent impulsivity. The N-methyl-D-aspartate receptors (NMDARs) are glutamate receptors that are localized throughout the brain, including the mPFC. Functional receptors are heterotetramers composed of at least two NMDAR1 (GluN1) subunits and two NMDAR2 (GluN2A-D). Localization of these receptors within the synapse plays an important functional role within the mPFC. GluN2A-containing NMDAR are predominantly found in the synapse, while GluN2B-containing NMDAR are primarily localized extrasynaptically. Here, we tested the hypothesis that individual differences in impulsivity are driven by the composition of the NMDAR complex, specifically the expression and localization of the NMDAR subunits, within the mPFC. Outbred male Sprague Dawley rats were identified as high (HI) or low (LI) impulsive using the one-choice serial reaction time (1-CSRT) task; the upper and lower quartile of animals were identified as HI or LI rats, respectively. Following phenotypic identification, mPFC synaptosomal protein was extracted from HI and LI rats to assess the composition of the NMDAR complex via immunoblot and/or immunoprecipitation techniques. Synaptic localization was investigated by immunoprecipitation for GluN2A or GluN2B with subsequent western blotting for postsynaptic density 95 (PSD95). Performance on the 1-CSRT task was rapidly acquired and the HI/LI phenotype was stably expressed across training. HI rats had lower mPFC GluN1 and GluN2A, but higher GluN2B synaptosomal protein expression ($p<0.05$) vs LI rats. Interestingly, co-immunoprecipitation analyses indicate a higher GluN2A:PSD95 synaptosomal protein complex in HI vs LI rats ($p<0.05$). Thus, there is a possible transformation of the mPFC NMDAR complex composition and/or synaptic localization that may underlie high inherent motor impulsivity. Increased understanding of the complex regulation of NMDAR balance within the mPFC as it relates to individual differences in impulsivity may lead to a better understanding of risk factors and treatments for cocaine dependence and relapse.

Poster 1-36

Utilizing Providers' Feedback to Develop Opioid Risk Mitigation Tools for the Military Health System

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Background: Clinical Decision Support (CDS) tools provide healthcare providers with helpful knowledge and detailed information to enhance patient healthcare and decision-making in the clinical workflow. Successful implementation of opioid risk mitigation tools will likely benefit from the integration of provider feedback during development and implementation planning. Methods: We conducted 26 semi-structured telephone interviews with providers from a large military health facility to assess (a) knowledge, attitudes, and behaviors regarding opioid prescribing management and monitoring; and (b) barriers and facilitators to integration of opioid-related CDS in their environment. Interview schedules were developed to assess key domains of the Promoting Action Research in Health Services (PARIHS) framework; interviews were coded for PARIHS constructs as well as emergent themes in providers' responses. Findings: Twenty-six providers representing emergency medicine, pain medicine, behavioral health, pharmacy, and primary care participated. Providers noted a variety of factors (e.g. time and workload constraints and integration with electronic health records) likely to affect the design, utility and integration of these opioid risk mitigation tools in Military Health Facilities. Providers' recommendations including ensuring rapid access to patient-specific information such as a list of medications and quantity of dose. Providers also made recommendations regarding report content and presentation, e.g., noting the importance of real-time data and easy login access. Conclusion: Findings were used to develop opioid risk mitigation tools and plan for implementation and evaluation. As a result of this pre-implementation feasibility assessment, we modified our strategy to focus on opioid risk mitigation tools that support providers in recognizing patterns for patients' pain and opioid use over time, as well as linking them with key recommendations for safe opioid prescribing and follow-up care. In preparation for a pilot, next steps include a secondary expert review process.

Poster 1-37

Synthesis of N-Substituted 8-Hydroxyphenylmorphans: Potential Promiscuous Ligands for the Mu and Delta Opioid Receptors

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Over the past 15 years, there has been a steady increase in the number of deaths in the United States from opioid drug overdose. Specifically, the number of deaths attributed to heroin overdose has risen from 2,000 deaths in 2002 to nearly 13,000 deaths in 2015. A combination of the increased availability of prescription opioid painkillers, the increase in Mexican heroin production and the arrival of illicit fentanyl has led to a major public health crisis. Because opioid based analgesics still play an important role in the management of chronic or severe pain, the need to find a new the need to find a new analgesic with fewer negative side-effects and to find alternative treatment agents to ameliorate addictive diseases has become a critical goal. Previous work in our group has identified 9β-hydroxy-N-phenethyl-5-phenylmorphan as the compound with the highest affinity to date for the -opioid receptor (MOR) in the 5-phenylmorphan series. We believe that the 8-hydroxyphenylmorphan (PM) derivatives will show similar affinity for both the MOR and -opioid receptor (DOR). It is hoped, with some expectation of success from previous studies on a related substrate, that some of these new compounds will act as mu agonists and delta antagonists, the combination of interactions that has been said to produce analgesics with fewer side-effects, without tolerance and dependence, and perhaps a different type of treatment agent. The synthesis and chiral resolution of the PM derivatives is presented in the poster.

Poster 1-38

Oxycodone, hydrocodone, and morphine differentially affect gene expression.

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The chronic use of opioid medications is known to lead to complications such as the development of tolerance, hyperalgesia, allodynia, dependence, abuse, and addiction. Use has been shown to increase the risk of developing comorbid mental disorders such as anxiety, depression, and alcoholism. This implies a shared mechanism underlying these disorders, and indeed recent research has revealed that D2DRs play a role in all three. Recent research revealed that opioids disturb the signaling of the D2DRs, which may account for this association. We recently observed that various opioids differentially modulate the responses of the D2DRs and have differential effects on the activity of signaling molecules. Additionally, these drugs have been shown to differ in their efficacy in the treatment of burn pain and chronic pain. Thus, in the current study we examined the differential effects of oxycodone, hydrocodone, and morphine on striatal gene expression. Specifically, mice were administered with saline or the various opioids. Twenty four hours after the final injection, striatal tissue was dissected. Following this, RNA was extracted and high throughput next generation sequencing was used to examine the mouse genome. Subsequently, we used RT-PCR to confirm the results for selected candidate genes. In mice given morphine, 79 RNAs were dysregulated, 33 of which were unique to morphine, 15 of which were shared with oxycodone, 9 of which were shared with hydrocodone, and 22 of which were shared with both oxycodone and hydrocodone. In mice given hydrocodone, 71 RNAs were dysregulated, 27 of which were unique to hydrocodone, and 13 of which were shared with oxycodone. Most surprisingly, in mice given oxycodone, 179 RNAs were dysregulated, 158 of which were unique to oxycodone. This data suggests that opioids differentially affect the transcription of RNAs related to cell signaling molecules such as β-arrestin-2. These data provide strong evidence that there are differences between opioid drugs with regard to their effects on opioid receptors, D2DRs, intercellular signaling, and the dopamine reward system. This information should be considered by physicians when deciding which opioid medication is most efficacious in specific clinical scenarios, and least likely to have harmful effects.

Poster 1-39

Relative reinforcing effectiveness of second-generation synthetic cathinones

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Bath salts preparations contain synthetic cathinones which interact with monoamine transporters and function as either monoamine uptake inhibitors or releasers. Although widespread abuse has resulted in some of these cathinones being classified as Schedule I by the Drug Enforcement Administration, clandestine chemists skirt these laws by altering the chemical structures of first-generation cathinones (i.e., MDPV, methylone, and mephedrone). However, little is known about how these modifications impact the abuse-liability of second-generation cathinones (e.g., α-PVP, α-PPP, MDPPP, and MDPBP). Since greater selectivity for DAT over SERT has been suggested to be an important determinant of a drug's abuse liability, we aimed to test the hypothesis that drugs with structural modifications that produce selective dopamine uptake inhibition are the strongest reinforcers (α-PVP>MDPV>α-PPP>MDPPP≈MDPBP>cocaine). Thus, demand curves were obtained in male Sprague Dawley rats (n=11) trained to self-administer cathinones, by increasing the response requirement across sessions according to the following series: 3, 10, 18, 32, 56, 100, 178, etc. Behavioral economic analyses were used to determine the relative reinforcing effectiveness of the second-generation cathinones α-PVP, α-PPP, MDBPB, and MDPPP, to the first-generation cathinone MDPV, and cocaine. All drugs evaluated maintained high levels of responding; however, each of the cathinones maintained responding at larger fixed ratios than cocaine. Interestingly, demand for α-PVP, MDPV, MDPBP, and MDPPP was greatest (α=0.7x10-5), followed by α-PPP (α=1.8x10-5) and cocaine (α=3.0x10-5), which does not appear to support hypotheses regarding DAT selectivity and reinforcing effectiveness. These data suggest second-generation synthetic cathinones are highly effective reinforcers (~2-4x stronger than cocaine), but the mechanism that accounts for this remains unclear.

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Poster 1-40

Is phase amplitude coupling modulated by noradrenergic innervation in the olfactory bulb in the awake behaving mouse?

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The ability to learn and to form memories is crucial for everyday life. It is due to these abilities that our lives are enhanced and our personalities are shaped. Therefore, it is not surprising that often diseases that affect these abilities are devastating and individuals affected are often unable to care for themselves. Cognitive dysfunctions are a growing problem as the older population is substantially affected and as we know the aging population is increasing worldwide. Therefore, to be prepared to deal with this growing problem, it is crucial to understand what contributes to learning and memory and what factors contribute to its decline. Neuromodulators such as noradrenaline appear to play a crucial role in learning and memory. The goal of this project was to understand the role of noradrenaline in learning of olfactory discrimination in a go-no go task. To this end mice expressing halorhodopsin under the dopamine-beta-hydrolase (DBH) promoter were implanted with fiber optic light guides and tetrodes in the olfactory bulb. Preliminary results show substantial coupling of the gamma local field potential (LFP) within the phase of the theta LFP (phase amplitude coupling, PAC, Tort et al., J. Neurophys. 104, 1195, 2010). We are exploring whether as mice learn to discriminate between odors PAC is modified when we inhibit noradrenergic fibers by light activation of halorhodopsin in the olfactory bulb of the DBH-Cre mice.

Poster 1-41

A novel role for Sox10 in mediating cellular and behavioral responses to heroin

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Drug addiction is a chronic relapsing disease, which is characterized by episodes of compulsive drug seeking. Opiate addiction has dramatically increased, becoming a worldwide epidemic with great societal and financial burdens. While several studies have focused on drug-dependent changes in neurons, the role of glia in opiate addiction remains largely unstudied. RNA sequencing (RNA-seq) from the prefrontal cortex of male rats following heroin self-administration revealed a change in several genes associated with Oligodendrocyte differentiation and maturation. Oligodendrocytes function to provide support and insulation to axons via generation of a myelin sheath, and thus are critical for the maintenance of neuronal function. Specifically, we found an up-regulation of the non-neuronal transcription factor Sox10, which is critical for the differentiation of Oligodendrocyte precursor cells to mature, myelinating Oligodendrocytes. To examine the regulation of Sox10 following heroin self-administration, we used Chromatin Immunoprecipitation (ChIP), and found that heroin exposure results in an increase of Brg1 binding on the Sox10 promoter at Smad3 and AP-1 binding elements- two key regulators of drug induced gene expression. To directly test the functional role of Sox10 in mediating heroin-induced behavioral plasticity, we overexpressed Sox10 selectively in the PFC. Surprisingly; Sox10 overexpression decreased the motivation to obtain heroin infusions in a progressive ratio test, while not altering the acquisition or maintenance phases of heroin self-administration. Together, these data demonstrate a critical, and perhaps compensatory, role of Sox10 and Oligodendrocytes in regulating the motivation for heroin.

Poster 1-42

Medial frontal cortex glutathione levels and temperature are increased in GT-tg bigenic mice expressing HIV-Tat protein: A proton MRS study.

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While brain temperature is considered a stable homeostatic measure, its regulation is critical to maintain normal function. Many drugs of abuse induce inflammation, oxidative stress (OS) and robust metabolic activation, all of which can elevate brain temperature and damage neurons, especially when coupled with fever and/or HIV infection. We used proton magnetic resonance spectroscopy (MRS) of the medial frontal cortex (mFC), an area involved in cognitive control and adversely impacted by drugs of abuse and HIV-Transactivator of Transcription (Tat) protein expression, to assess effects of Tat protein on temperature and OS. Controlled Tat expression in GT-tg bigenic mice potentiates reward for alcohol, cocaine, and opiates. Adult male GT-tg bigenic mice (N=30) were treated with saline or doxycycline (100 mg/kg, IP) for 7 days to induce Tat expression. Mice underwent in vivo 9.4 Tesla proton MRS of the mFC one day later. MRS spectra were acquired using a STEAM sequence for the analysis of glutathione (GSH), which reflects OS, and temperature by comparing chemical shifts of the temperature-sensitive water resonance to the N-acetylaspartate resonance. Dox-treated mice expressing Tat exhibited higher temperature ($p<0.05$) and GSH levels ($p<0.01$) compared to controls. Pearson correlation analysis found a positive association between temperature and GSH levels ($r= 0.47$, $p=0.023$). As GSH is the principal endogenous antioxidant, this effect may reflect a compensatory response to Tat-induced OS. The correlation between GSH and temperature suggests that Tat-induced OS may be increasing mFC temperature. Many proteins are sensitive to OS and dysregulation of such proteins could lead to neuronal dysfunction, potentiation of drug reward, or brain injury.

Poster 1-43

Design and Synthesis of Hydrogen-Bonding Analogs of 3-Methylfentanyl and their Interaction with Opioid Receptors.

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Fentanyl-based opioids, the 4-anilidopiperidine class of analgesics, are a medically important class of compounds. Some of these compounds are quick-acting, others have a long duration of action, and many are exceedingly potent analgesics that are effective against severe and chronic pain. Concomitant with their useful attributes are the side-effects common to all opioid analgesics: respiratory depression, constipation, tolerance and physical dependence. To explore the functional selectivity of fentanyl analogs and possible ameliorate their abusability and adverse effects, we investigated the addition of a hydrogen-bonding group to one of the most potent analogs, 3-methylfentanyl, to strategically modify its binding with the □-opioid receptor. We report the design and synthesis of these compounds, and their respective activity at the □-opioid receptor.

Poster 1-44

Investigation of the reinforcing effects of delta-opioid receptor agonist, SNC80, in self-administration in rats.

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Delta opioid receptor (DOR) activation produces many stimulant-like properties, such as increased locomotor activity and conditioned place preference. However, DOR agonists are generally thought to lack reinforcing effects because SNC80 failed to maintain self-administration behavior in monkeys and did not enhance intracranial self-stimulation thresholds in rats. To further probe these potential differences, the current studies investigated the reinforcing effects of the DOR agonist, SNC80, in self-administration studies in male Sprague Dawley rats. Drug naïve male rats were given access to self-administer various doses of SNC80 (0.01, 0.032, 0.1, 0.32, or 0.56 mg/kg/injection) or 0.56 mg/kg/injection cocaine on a fixed ratio 1 (FR1) and a progressive ratio (PR) schedule of reinforcement. SNC80 was also substituted in rats trained to self-administer cocaine on a FR30 schedule of reinforcement. Responding for SNC80-paired cues only or for SNC80 infusions in the absence of cues was also evaluated. Responding for SNC80 infusions varied by more than 20% between consecutive days in some rats; however, SNC80 produced an inverted-U shaped dose response curve and maintained very similar levels of responding as cocaine. At least half of the rats self-administering 0.32 mg/kg/injection SNC80 convulsed within minutes of the first two infusions of SNC80, however, continued to self-administer throughout the session and consecutive sessions. SNC80 (0.32 mg/kg/injection) substituted for cocaine on a FR1, but not a FR30, schedule of reinforcement. Unlike cocaine, SNC80 maintained low breakpoints on a PR schedule of reinforcement. In the absence of SNC80, responding for SNC80-paired cues rapidly extinguished. In the absence of drug-paired cues, SNC80 failed to maintain responding unlike cocaine. Overall, these data suggest the DOR agonist SNC80 may have weak reinforcing effects in rats.

Poster 2-1

Designer Drug Efficacy: Application of fixed dose mu-opioid agonist and antagonist mixtures.

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Receptor theory predicts that fixed-proportion mixtures of a competitive, reversible agonist and antagonist at a common receptor will result in antagonist proportion-dependent downward shifts in mixture dose-effect curves. This prediction suggests the potential to manipulate apparent efficacy of an agonist+antagonist mixture by manipulating agonist/antagonist proportion. The aim of the present study was to test this hypothesis by evaluating effects of fixed-proportion mixtures of fentanyl+naltrexone in rhesus monkeys in two behavioral procedures: schedule-controlled operant responding and warm-water tail withdrawal. Experiments were conducted in a total of 8 adult male rhesus monkeys with 4 monkeys serving as subjects in each behavioral procedure. Fentanyl (0.001-0.056 mg/kg, IM) alone, naltrexone (0.032-1.0 mg/kg, IM) alone, and fixed-proportion mixtures of fentanyl+naltrexone (1:0.074, 1:0.22, and 1:0.74) were administered in a cumulative dosing procedure, in which drug or drug mixture doses were increased in either quarter-log or eighth-log increments in 15-min intervals. The proportions were based on relative Kd values of fentanyl and naltrexone at mu receptors in monkey brain (Emmerson et al, 1992). Fentanyl alone produced dose-dependent decreases in rates of schedule-controlled operant responding and dose-dependent antinociception at both 50° and 54°C in the assay of warm-water tail withdrawal. Up to the largest dose tested, naltrexone did not alter either response rates or nociception. Consistent with predictions of receptor theory, naltrexone produced a proportion-dependent decrease in the effectiveness of fentanyl to decrease rates of operant responding. Furthermore, pretreatment with a single dose of the 1:0.74 fentanyl+naltrexone mixture produced an approximate 10-fold rightward shift in the potency of fentanyl alone to decrease rates of operant responding. Warm water tail withdrawal experiments are ongoing. Fixed-proportion agonist+antagonist mixtures may be useful to manipulate apparent drug efficacy for basic research or therapeutic purposes.

Poster 2-2

In vitro and in vivo effects of abused synthetic cannabinoid 5F-AB-PINACA

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Synthetic cannabinoids (SCBs) are psychoactive drugs of abuse that bind to cannabinoid type-1 receptors (CB1R). SCBs exhibit high receptor affinity at CB1Rs, where they function as highly efficacious agonists. In rodents, these drugs decrease core temperature and suppress locomotor activity. In this study, the pharmacological profile of the novel abused SCB 5F-AB-PINACA was determined in vitro using competition binding (affinity) and GTP□S binding (efficacy) in CHO-hCB1-Rx membranes, and in parallel studies the effects of 5F-AB-PINACA on core temperature and locomotor activity were assessed using biotelemetry probes in mice. After surgical recovery, mice received a vehicle injection, and then increasing doses of 5F-AB-PINACA (0.3, 1.0, 3.0, and 10 mg/kg) every other day. In binding studies, 5F-AB-PINACA bound to CB1Rs with high affinity (Ki = 3.2 nM) and functioned as a full agonist. In mice, dose-dependent hypothermic and locomotor depressant effects were observed which resolved within 2 hr, suggesting a relatively short duration of action for this compound compared to other SCBs. Because tolerance to hypothermic effects of other cannabinoids is typically observed with chronic administration, a separate group of subjects received 10 mg/kg 5F-AB-PINACA each day for 5 consecutive days, then underwent a 14 day drug washout period, then received a final drug administration to assess persistence of tolerance. To determine whether the in vivo effects of 5F-AB-PINACA are mediated by CB1Rs, separate groups of mice received an injection of vehicle or 10 mg/kg of the CB1R antagonist rimonabant 60 min prior to an injection of 10 mg/kg 5F-AB-PINACA or vehicle. Because the telemetry studies indicated maximal hypothermic effects 45 min after drug administration, mice were tested in the cannabinoid tetrad battery 45 min after 5F-AB-PINACA or vehicle injection. Results from the tolerance and tetrad experiments will be presented and discussed. These studies supported by DA039143 and the UAMS

Poster 2-3

Modular Total Synthesis Approach Towards Salvinorin A Inspired Designer Opioids

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The natural product salvinorin A is the prototypical non-nitrogenous opioid receptor ligand and has atypical pharmacology compared to classical morphine-derived opioids. Drugs inspired by and built upon this natural product scaffold yield valuable probes for understanding opioids and are potentially capable of circumventing some of the known abuse liabilities associated classical alkaloid opioids. As such, an adaptable total synthesis approach of designer opioids based upon the salvinorin A scaffold is desirable and potentially valuable for the development of analgesics with reduced abuse liability and drug abuse pharmacotherapies. Our total synthesis approach permits functionality to be introduced deliberately within the molecules with the goal of systematically exploring their activity by in vitro studies at opioid receptors and ultimately in animal models of pain and addiction. We have designed molecules able overcome potential shortcomings in salvinorin A, such as rapid metabolism, so that they may be useful for clinical pharmacotherapies. The desired chemical scaffolds have been accessed by a straightforward approach to bisenone 14-membered macrolides that are capable of undergoing a transannular Michael reaction cascade to assemble the tricyclic neoclerodane core representative of salvinorin A. The compounds produced provided access to otherwise unattainable molecular features on salvinorin A by semisynthesis on plant-derived material. The tricyclic neoclerodane core has been synthesized with manipulations targeting key features that are required for activity and an array of salvinorin A inspired structures was accessed.

Poster 2-4

Assessment of the positive reinforcing effects of opioid/cannabinoid mixtures using a food/drug choice procedure

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Cannabinoids such as THC enhance some (e.g., antinociceptive) but not other effects of mu opioids such as morphine, indicating that opioid/cannabinoid mixtures might be a safe and effective treatment for pain. Cannabinoids fail to enhance and often decrease self-administration of heroin, suggesting that opioid/cannabinoid mixtures do not have greater abuse potential as compared to opioids alone. Previous studies used single-response procedures which do not easily differentiate changes in reinforcing effects from changes in other (e.g., generalized rate decreasing) effects, so the interaction between opioids and cannabinoids with regard to reinforcing effects remains unclear. This study used a choice procedure to examine the reinforcing effects of opioid/cannabinoid mixtures relative to a non-drug alternative. Rhesus monkeys responded under a concurrent schedule wherein responding on one lever delivered 3 sucrose pellets and responding on the other lever delivered i.v. infusions of the mu opioid remifentanil (0.032-1.0 µg/kg/infusion) alone or in combination with THC (32 or 100 µg/kg/infusion). Monkeys responded predominantly for food over saline and small unit does of remifentanil, and with larger doses of remifentanil responding for remifentanil increased while responding for food decreased. For two monkeys, the dose-effect curve for the remifentanil/THC mixtures did not differ from the curve for remifentanil alone, suggesting that THC did not alter the potency of remifentanil. However, for a third monkey, the dose-effect curve for the remifentanil/THC mixture was left of the curve for remifentanil alone, suggesting that THC modestly increased the potency of remifentanil. Overall, THC did not substantially impact the reinforcing effects of remifentanil; although for one monkey there was evidence of modest enhancement. These data both indicate that decreased heroin self-administration observed in earlier studies might have been due to non-specific rate-decreasing effects of the cannabinoids on operant behavior and demonstrate the utility of choice procedures for studying the reinforcing effects of drug mixtures relative to a non-drug reinforcer such as food. Supported by the NIH (R01DA005018) and the Welch Foundation (AQ-0039).

Poster 2-5

Gender Differences in Cocaine-Induced Ultrasonic Vocalizations Are Modulated by the Medial Preoptic Area

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Evidence indicates that the medial preoptic area (mPOA) in the hypothalamus plays a modulatory role in the regulation of cocaine response, both neural and behavioral activity, as evidenced by conditioned-place preference and microdialysis experiments. The mPOA is also a major regulator of gender-sensitive behavioral differences across various species and for a variety of behaviors. In rodents, a commonly employed approach for inferring affective states involves measuring their ultrasonic vocalizations (USV). In this set of experiments we tested whether the mPOA modulates cocaine-induced changes in USV and possible gender differences that may occur in response to drug administration. To this end, 60 Sprague-Dawley rats (males=31, females=29) received either a lesion or sham lesion of the mPOA. Baseline USV measures were obtained, over 3-days, followed by subsequent sessions of cocaine administration, and USV recordings. Results indicate that females displayed a greater number of vocalizations compared to males; however, this gender difference disappeared with lesions of the mPOA. Cocaine increased vocalizations in both males and females, compared to baseline. Like with baseline, this increase was greater in females than males, but also disappeared with lesions of the mPOA. These findings point to the mPOA as a modulator of affective response to cocaine and, moreover, a modulator of gender-differences that manifest after cocaine administration.

Poster 2-6

A-85380 and nicotine: Some stimulus-related effects of nicotinic-receptor-agonists in rats.

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A-85380 is a more selective α4β2-nicotinic-receptor agonist than nicotine in binding studies, and it is an excellent PET ligand widely utilized in humans (Reuter et al., 2006). Selectivity of binding and operant behavioral effects among agonists and antagonists have seldom been compared to discern similarity. Freitus, Carroll, and Negus (2016) showed that A-85380 increased the rate of brain self-stimulation, an effect that nicotine failed to produce. The A85380- and nicotine-related effects were antagonized by dihydrobetaerythroidine (DHbE). We have found A-85380 to be more potent than nicotine as a discriminative stimulus in the rat, and A-85380 was more efficacious and more potent than nicotine as an intravenous reinforcer and punisher in rats. All effects of A-85380 and nicotine that we have examined were antagonized by mecamylamine, but not all by DHbE. Behavioral comparisons among similar agonists and antagonists can lead to unexplained behavioral consequences, posing interesting issues for theory development. (Research supported by NIMH Grant 107499)

Poster 2-7

Effects of Trace Amine-associated Receptor 1 Agonists on Morphine-related behaviors

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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. Our recent unpublished date also showed that TAAR1 full agonist RO5166017 and partial agonist RO5263397 decreased nicotine-related behaviors, which suggests that TAAR1 may be a potential target for treatment of stimulants abuse. However, the role of TAAR1 in morphine-related behaviors is still unknown. Here, we tested the effects of TAAR1 agonists on several morphine-related behaviors. We found that TAAR1 agonist RO5263397 did not affect naltrexone-induced conditioned place aversion or naloxone-precipitated jumping behavior in morphine-dependent mice. Furthermore, RO5263397 had no effect on the analgesic effect of morphine. Taken together, these results indicated that activation of TAAR1 may have no effect on morphine-related behaviors.

Poster 2-8

The essential value of heroin, but not saccharin, predicts preference between these reinforcers in rats.

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Several recent studies have investigated choice between heroin and a non-drug alternative reinforcer in rats. A common finding in these studies is that there are large individual differences in preference, with some rats preferring heroin and some preferring the non-drug alternative. The primary goal of the present study was to determine whether individual differences in how heroin or saccharin is valued, based on demand analysis, predicts choice. Rats lever pressed for heroin infusions and saccharin reinforcers on fixed-ratio schedules. The essential value of each reinforcer was obtained from resulting demand curves. Rats were then trained on a mutually exclusive choice procedure where pressing one lever resulted in heroin and pressing another resulted in saccharin. After seven sessions of increased access to heroin or saccharin, rats were reexposed to the demand and choice procedures. Demand for heroin was more elastic than demand for saccharin (i.e., heroin had lower essential value than saccharin). When allowed to choose, most rats preferred saccharin. The essential value of heroin, but not saccharin, predicted preference. The essential value of heroin was higher in heroin-preferring rats than it was in saccharin-preferring rats, but these subgroups did not differ in how they valued saccharin. The essential value of both reinforcers increased following a week of increased access to heroin, but similar saccharin exposure had no effect on essential value. Preference was unchanged after increased access to either reinforcer. To the extent that choice models addiction-related behavior, these results suggest that overvaluation of opioids specifically, rather than undervaluation of non-drug alternatives, could identify susceptible individuals.

Poster 2-9

The neural correlates of methamphetamine-induced conditioned place preference in adolescent female mice of two strains.

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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. Despite this sex difference in drug taking behavior, research using rodent models generally focuses on the genetic and cellular basis of drug intake in male rodents. Our research examines the neural basis of addiction in female mice by testing the rewarding effects of methamphetamine (1 mg/kg) in a conditioned place preference paradigm in adolescent (postnatal day 41) female C57Bl/6 and 129/SvEv mice. The neural basis of this difference was investigated by quantifying behaviorally-induced protein expression of the immediate early gene c-Fos when animals were tested drug-free. We found that C57Bl/6 mice exhibit conditioned place preference for the compartment paired with methamphetamine, but 129/SvEv mice fail to display this preference when compared to saline-treated control mice of the same strain. Conditioned place preference in C57Bl/6 mice was associated with significantly more c-Fos positive cells in the shell of the nucleus accumbens, the basolateral amygdala, and the CA1 subregion of the hippocampus. Group differences were not found in the nucleus accumbens core, basomedial amygdala, central nucleus of the amygdala, or the dentate gyrus of the hippocampus. In contrast, drug- and saline-treated 129/SvEv mice did not demonstrate differences in c-Fos expression in any of the analyzed brain regions. Additional experiments are currently being conducted in adolescent male mice of the same two strains to investigate whether there is a sex difference in the rewarding effects of methamphetamine and activation of the brain regions associated with this effect. Supported by NIH grants G12MD007599, R25NS080686-06 and GM060665-16.

Poster 2-10

Effects of Δ9-THC on Memory in Ovariectomized and Intact Female Rats

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The cannabinoid receptor agonist, Δ9-tetrahydrocannabinol (Δ9-THC), is a psychoactive constituent of marijuana, a popular recreational drug, and has been shown to produce sex-specific changes in learning and memory. The purpose of this study was to uncover the effects of hormone status on memory, and how these effects alter the acute disruptive effects of Δ9-THC (0.32 -3.2 mg/kg) on memory in female rats. To do this, intact and ovariectomized (OVX) female rats were trained on a repeated acquisition and delayed-performance procedure. During the acquisition phase of this procedure, rats acquired a 4-response sequence (CRLC, LRCL, RLCR, etc) that changed daily. Sequence acquisition was followed by a delay phase (1 minute to 24 hours) and a delayed-performance phase in which rats were required to emit the previously acquired sequence. Responding was maintained under a second-order fixed-ratio 3 for food presentation. Δ9-THC or vehicle was administered 30 minutes prior to the delayed-performance phase in order to specifically target memory retention, which was assessed by percent savings. Response rate and the percentage of errors were also recorded. Under non-drug conditions, delay-dependent decreases in percent savings were observed in both groups. However, the effect on retention was greater in OVX than intact rats. Acute administration of Δ9-THC produced dose-dependent decreases in response rate and percent savings, and increases in percent errors in both intact and OVX rats after a 1-hour delay. At 0.56 mg/kg Δ9-THC, OVX rats showed greater sequence retention than intact rats. Increasing the delay from 1 to 3 hours produced a leftward shift in the percent-savings curve for both intact and OVX rats. These results suggest that hormone status directly impacts retention under an acquisition and delayed-performance procedure, and acute administration of Δ9-THC produces both delay-dependent and dose-dependent effects on memory in intact and OVX female rats

Poster 2-11

Decreased sensitivity to the rewarding properties of cocaine in adult female c57bl/6 mice exposed to fluoxetine during adolescence

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Accumulating preclinical evidence indicates that early-life exposure to psychotropic medications results in long-lasting altered behavioral responses to drugs of abuse – suggesting a risk of enhanced drug liability, later in life. However, to date, these preclinical experimental approaches have been conducted primarily using male subjects. This is surprising given that females, when compared to males, are more likely to be diagnosed with mood-related disorders, and thus, to be prescribed with psychotropic drugs, such as antidepressants. Therefore, to examine whether long-lasting alterations to the rewarding properties of drugs of abuse are exhibited as a result of juvenile antidepressant exposure, we exposed adolescent female mice to the selective serotonin reuptake inhibitor (SSRI) fluoxetine (FLX). We selected FLX given that it is the only SSRI approved by the US Food and Drug Administration for the treatment of pediatric depression. Specifically, female c57bl/6 mice were exposed to FLX in their drinking water (250 mg/L) during adolescence (postnatal days [PD] 35-49), and were later assessed in adulthood (PD 70+) on behavioral responsivity to cocaine (0, 2.5, 5, 7.5 mg/kg) place conditioning (CPP). Our results show that adult female mice pretreated with FLX during adolescence displayed a decreased preference for environments previously paired with cocaine, when compared to saline-pretreated controls. Collectively, our data suggest that adolescent exposure to the antidepressant FLX mediates behavioral adaptations that endure into adulthood, and that are indicative of a decreased sensitivity to the rewarding properties of cocaine in female mice.

Poster 2-12

Effects of Amphetamine Maintenance on Abuse-Related Behavioral Effects of MDPV in Rats.

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Maintenance on the dopamine transporter (DAT) substrate amphetamine decreases cocaine use clinically and blunts the abuse-related behavioral and neurochemical effects of cocaine in rats as measured by intracranial self-stimulation (ICSS) and in vivo microdialysis of nucleus accumbens (NAc) dopamine (DA) levels. The current study tested the effectiveness of 7-day amphetamine maintenance in rats to decrease abuse-related behavioral and neurochemical effects of another abused DAT ligand, the selective DAT uptake inhibitor methylenedioxypyrovalerone (MDPV). We hypothesized that MDPV would increase NAc DA concentrations and facilitate baseline ICSS and that amphetamine maintenance would blunt these effects. Male Sprague-Dawley rats were used for all studies. For ICSS, rats were implanted with electrodes targeting the medial forebrain bundle, and responding on a lever was reinforced by pulses of electrical brain stimulation in a frequency-rate ICSS procedure. Effects of MDPV (0.1-1.0 mg/kg) were determined before and after 7-day treatment with saline or 0.32 mg/kg/hr amphetamine (n = 6 each) delivered by a subcutaneously implanted minipump. Data were analyzed by two-way ANOVA followed by a Holm-Sidak post hoc test. For microdialysis, separate groups of rats were implanted with cannulae targeting the NAc, and dialysates were analyzed for concentrations of DA before and after administration of MDPV (0.1-1.0 mg/kg). MDPV dose-dependently facilitated ICSS and increased NAc DA levels. Amphetamine maintenance produced a submaximal facilitation of ICSS throughout treatment. However, in contrast to previous results with cocaine, MDPV retained efficacy to produce a further abuse-related facilitation of ICSS. Amphetamine maintenance produced an increase in baseline NAc DA levels and blunted the DA response to MDPV. These studies suggest that amphetamine maintenance has weaker efficacy to blunt abuse-related effects of MDPV than of cocaine.

Poster 2-13

Antagonism of neurotensin receptors in the ventral tegmental area decreases methamphetamine self-administration in mice

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Neurotensin is a peptide found in the brain and known to modulate dopamine neurotransmission and dopamine-related behaviors. Recently, we reported that neurotensin depresses inhibitory post-synaptic currents mediated by dopamine D2 autoreceptors in midbrain dopamine neurons, thus enhancing or potentiating dopamine neurotransmission. In line with this finding, the rewarding properties of neurotensin in the ventral tegmental area has been documented using electrical and optogenetic self-stimulation, showing that neurotensin is able to sustain operant behavior. Here we test the hypothesis that neurotensin input in the ventral tegmental area facilitates methamphetamine self-administration in mice. For this, male DBA/2J mice were implanted with an indwelling catheter in the right jugular vein and a bilateral cannula in the ventral tegmental area. A week after surgery, mice were trained to nose-poke for an intravenous infusion of methamphetamine (0.05 mg/kg/infusion) in daily operant sessions of 2 h. Animals receiving microinfusions of the neurotensin receptor antagonist SR142948A in the ventral tegmental area (10 ng/per side), during the first five days of methamphetamine exposure, required on average more days of training to acquire methamphetamine self-administration ($P=0.0075$ vs. Saline). The SR142948A group also showed a decreased number of infusions during acquisition and stabilization of methamphetamine self-administration ($P<0.001$ vs. Saline). The effect induced by SR142948A was not related to changes in basal locomotor activity or changes in methamphetamine induced-locomotion. Our results suggest that neurotensin receptor activation in the ventral tegmental area facilitate acquisition of methamphetamine self-administration

Poster 2-14

Methylone: "Ecstasy" by another name

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Following increased governmental intervention regarding the sale of novel psychoactive substances, the synthetic cathinone derivative methylone has been diverted from "bath salts" into "Ecstasy" formulations in lieu of MDMA; however, it is unknown what effects substitution with methylone may have on "Ecstasy" use. In the current study, we evaluated the pharmacology of methylone in parallel with MDMA using in vitro and in vivo techniques. We assessed the activity of methylone and MDMA at SERT using whole-cell patch clamp electrophysiology. We determined the dopaminergic and serotonergic contributions to the discriminative stimulus effects of both compounds in rats trained to discriminate methamphetamine, DOM, or MDMA from vehicle and utilized the D1-selective antagonist SCH23390 and the 5-HT2A/2C antagonist pirenperone to further probe mechanistic differences. Furthermore, we tested for substitution of methylone and MDMA in rats trained to self-administer methamphetamine under continuous and progressive ratio schedules of reinforcement. Methylone, like MDMA, produced an inward current at SERT, indicative of an amphetamine-like substrate mechanism. Both methylone and MDMA fully substituted for the discriminative stimulus effects of methamphetamine and MDMA, but only partially for DOM. In methamphetamine-trained rats, SCH2330 fully and dose-dependently attenuated methamphetamine-appropriate responding by methylone and MDMA with similar potencies. SCH23390 and pirenperone both partially attenuated MDMA-appropriate responding by methylone and MDMA, but both antagonists were less efficacious against methylone than MDMA. Methylone and MDMA were both readily self-administered, but there were no significant differences in reinforcing efficacy between the two drugs under either schedule of reinforcement. These data indicate that methylone possesses similar mechanistic and reinforcing effects as MDMA, and its inclusion in "Ecstasy" formulations is unlikely to produce different subjective effects or increased compulsive use.

Poster 2-15

Examination of the neurochemical mechanisms that modulate sex differences in nicotine withdrawal.

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Introduction: Women are more vulnerable to tobacco use than men and experience greater symptoms of withdrawal during abstinence from nicotine in tobacco products. However, the neurochemical mechanisms that mediate sex differences in nicotine withdrawal are not well understood. Current work in our laboratory is focused on understanding the underlying neural circuitry of withdrawal within the nucleus accumbens (NAcc), where dopamine levels are decreased during withdrawal from nicotine. Our mechanistic hypothesis is that females display larger decreases in dopamine levels in the NAcc that are modulated via a greater gamma-aminobutyric acid (GABA)-mediated inhibition of dopamine in this region. To address this hypothesis, we assessed NAcc levels of GABA during nicotine withdrawal in male and female rats. Rats also received yohimbine to compare sex differences in response to a pharmacological stressor. Methods: Rats were prepared with an osmotic pump containing a dose of nicotine (3.2 mg/kg; base) that produces equivalent nicotine levels in female and male rats. Fourteen days later, the rats were prepared with dialysis probes in the shell of the NAcc. The following day, samples were collected every 20 min for a 1-hour period following baseline and administration of the nicotine receptor antagonist mecamylamine (1.5 and 3.0 mg/kg, ip) to precipitate withdrawal. Results: During nicotine withdrawal, females displayed a significantly larger increase in GABA release than males. Similarly, females displayed a larger increase in GABA release in response to administration of the pharmacological stressor, yohimbine. Discussion: Our results suggest that females display larger withdrawal-related increases in GABA release than males. This provides evidence for a potential mechanism involving GABA mediated sex differences in nicotine withdrawal. In addition, we are employing mass spectrometry methods assess the relationship between GABA and other neurotransmitters that may mediate sex differences in nicotine withdrawal.

Poster 2-16

Naltrexone reduces appetitive and consummatory responses to alcohol in a sex-dependent manner in rats.

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A wealth of animal studies provide support for the use of the mu-opioid antagonist, naltrexone, for the treatment of alcohol use disorders (AUDs). Although clinical studies show efficacy of naltrexone for AUDs, the data on whether it is differentially effective in males and females is mixed. Moreover, there are sex and gender differences in mu-opioid system that suggest naltrexone may alter alcohol self-administration differentially by sex in animals. The present study tested whether sex differences exist in the ability of naltrexone to decrease consummatory (e.g., numbers of reinforcers delivered) and appetitive behaviors (e.g., head entries into the dipper area) in an operant alcohol self-administration paradigm. Separate groups of male and female Sprague-Dawley rats (n's=6-11) were trained to lever press for either alcohol (10%; EtOH) or sucrose (3%; SUC) in standard operant chambers under a fixed-ratio 2 schedule of reinforcement. The effects of a broad range of naltrexone doses (0, 0.1, 0.3, 1, 3, & 10 mg/kg) were assessed in tests conducted under a progressive ratio schedule of reinforcement. In males, naltrexone administration led to dose-related decreases in consummatory behaviors in the EtOH group, but no decreases in appetitive behaviors were observed. Naltrexone administration did not alter appetitive or consummatory behaviors in the SUC group. In females, naltrexone administration led to dose-related decreases in consummatory behaviors in the EtOH group, but only decreased appetitive behaviors at the 10 mg/kg dose. Interestingly, the 3 mg/kg dose of naltrexone increased appetitive and consummatory behaviors in the SUC group. Together, our findings suggest that naltrexone is more effective in reducing consummatory behaviors for alcohol in males and appetitive behaviors in females. These findings highlight the need for further investigations assessing the effectiveness of pharmacological treatments for alcohol use disorders in both genders.

Poster 2-17

Overexpression of a stress peptide in the nucleus accumbens increases nicotine self-administration in female rats in an and ovarian-hormone dependent manner

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Female rats display enhanced reinforcing effects of nicotine and heightened negative affective states produced by withdrawal as compared to males. Recent work has revealed that stress hormone systems within the local circuits of the nucleus accumbens (NAcc) modulate sex differences in the negative affective states produced by nicotine withdrawal. The present study expanded this work by examining the role of stress hormone systems in promoting the reinforcing effects of nicotine. This was achieved by comparing nicotine self-administration in female and male rats that received over-expression of the stress hormone, corticotrophin-releasing factor (CRF) in the NAcc. A group of ovariectomized (OVX) females were also included in order to examine whether our behavioral effects are ovarian-hormone mediated. Separate groups of rats received intra-NAcc infusions of the adeno-associated virus CRF (AAV-CRF) or a control vector (AAV-GFP). The animals were then prepared with a jugular catheter for extended access (23-hour) to self-administration of escalating doses of nicotine (0.015, 0.03, and 0.06 mg/kg/0.1 mL). Each dose was self-administered for 4 days with 3 intervening days of nicotine abstinence. The results revealed that over-expression of CRF in the NAcc produced an increase in nicotine self-administration in intact females as compared to males and OVX females. These findings suggest that stress systems in the NAcc play a key role in modulating sex differences in the reinforcing effects of nicotine. Also, the contribution of stress hormones to promoting the rewarding effects of nicotine is ovarian-hormone dependent.

Poster 2-18

Estradiol in the Preoptic Area Modulates Behavioral and Neural Response to Cocaine

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The complement of circulating sex steroids is correlated with differing drug responses and may be responsible for some of the sex differences seen in response to drugs such as cocaine. Since the distribution of estrogen receptors in the brain is heterogeneous, the sex differences in cocaine response driven by systemic estradiol (E2) are likely to reside in one of several receptor-dense brain nuclei, such as the medial preoptic area (mPOA). To assess the role of the mPOA in the hormonal response to cocaine, we microinjected E2 or artificial cerebrospinal fluid (aCSF) into the mPOA one day prior to the systemic injection of either saline or cocaine hydrochloride (10 mg/kg) in a conditioned place preference (CPP) paradigm. Animals were also tested for differences in psychomotor activation and c-Fos in the nucleus accumbens (NAc) in response to cocaine after mPOA E2 or aCSF. Animals receiving cocaine expressed a significant psychomotor response but did not differ between hormone groups. However, animals that received E2 to the mPOA expressed significantly more CPP in response to cocaine than animals receiving aCSF. Animals that received cocaine had significantly increased c-Fos expression in the NAc core and shell, and animals receiving mPOA E2 had significantly more c-Fos in the posterior shell than animals receiving aCSF. Together, our results suggest that the mPOA influences hedonic but not psychomotor aspects of the cocaine response via an E2-sensitive circuit. This system may also underlie the sex differences in cocaine response among humans.

Poster 2-19

Novel and highly selective dopamine D3 receptor antagonists and partial agonists as potential treatments for opioid use disorders

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It is well known that short and long term modifications to dopamine transmission are associated with abused drugs and can lead to addiction. For nearly two decades, the dopamine D3 receptor (D3R) has been an attractive target for therapeutic development to treat neuropsychiatric disorders including drug dependence. D3R-selective ligands with high affinity and selectivity have been discovered, affording critical tools for cell-based assays that have been translated to in vivo models of drug abuse. We have recently reported VK4-116 that demonstrated high D3R binding affinity (K_i=6 nM) and >1700 fold selectivity over D2 and D4 receptors. VK4-116 showed excellent metabolic stability in both rat and monkey liver microsomes and its in vivo efficacy for oxycodone-related behaviors in rats was very promising. A second lead molecule, VK4-40 is a highly selective D3R partial agonist and a scale-up synthesis of both these lead molecules was needed for extensive behavioral evaluation. Further, as both were racemic mixtures, the synthesis and evaluation of their respective enantiomers were required. Hence in the current study, we developed an improved synthesis of the racemates as well as the synthesis of (R)- and (S)-VK4-116 and VK4-40, using chiral resolution through enantiopure intermediates. The resolved compounds were characterized by chiral HPLC (>96 % ee.) Moreover, separation by chiral preparative HPLC yielded the pure enantiomers (>99% ee) from the racemates. We found that the (R)-VK-116 was the eutomer (D3R K_i=5.9 nM) as was (R)-VK4-40 (K_i=0.23 nM). The enantiomers showed outstanding metabolic stability in both rats and human liver microsomes. Evaluation of the enantiomeric pairs for efficacy at D3R is underway. These data will be used to choose a lead molecule for clinical development.

Poster 2-20

The influence of social housing conditions on morphine-induced gene expression.

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Drug abuse is strongly influenced by socio-environmental factors. Our previous studies demonstrated that social housing conditions alter the propensity to acquire morphine reward and dependence in adolescent mice. Morphine-treated animals that are housed only with other morphine-treated animals (referred to as 'morphine only' animals) acquire morphine CPP significantly faster than morphine-treated animals which are housed with drug-naïve mice (referred to as 'morphine cage-mates'). Similarly, morphine only animals extinguished their morphine place preference at a significantly and markedly slower rate than the morphine cage-mates. Despite this behavioral evidence, little is known about the potential mechanisms for the differential effects of social housing. In the current study, we examined the role of social environment on modulation of striatal gene expression. Specifically, adolescent mice housed in the various social housing conditions were injected with saline or morphine (20 mg/kg) for 14 days. Twenty-four hours after the final injection, striatal tissue was dissected. Following this, RNA was extracted and high throughput next generation sequencing was used to examine the mouse genome. Subsequently, we used RT-PCR to confirm the results for selected candidate genes. Interestingly, we found that multiple genes were differentially altered in morphine-treated animals housed in different social housing conditions. In morphine only animals, 248 genes were up-regulated, and 252 genes were down-regulated. Conversely, in morphine-cage mates, only 73 genes were up-regulated, while 46 genes were down-regulated. Only 61 genes were similarly altered between the two groups. Our findings suggest that social environment may influence alterations on the genetic level and provide further evidence for a role of social environment in morphine reward and dependence.

Poster 2-21

Using a Choice Procedure to Assess Aversive Effects of Drugs in Rats.

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Prescription opioids (mu opioid receptor agonists) are frequently used to treat moderate to severe pain; however, these drugs are widely abused. Kappa opioid receptor agonists are not likely to be abused because they are devoid of reinforcing effects, but their clinical use has been precluded by adverse effects such as dysphoria. Kappa opioids in drug mixtures might be useful for treating pain. If adverse effects can be avoided, then kappa/mu mixtures might have therapeutic potential for treating pain and would be preferred to mu opioids alone. The present study established a choice procedure in rats in order to assess aversive effects of drugs. Male Sprague Dawley rats (n=12) were studied under to two conditions in which they chose between food and food + an i.v. infusion. In one condition the amount of food was equal for both alternatives (1 pellet), and in the second condition the amount of food paired with the infusion was 2 pellets. When saline was paired with 1 pellet and the alternative also was 1 pellet, rats responded on both levers approximately equally. Histamine (positive control; 0.32 – 3.2 mg/kg/infusion) paired with 1 pellet decreased choice for 1 pellet + an infusion (< 20% choice) with a concomitant increase in choice for 1 pellet without an infusion (> 80% choice). Rats completed all 100 trials and preferred 2 pellets paired with saline (> 90% choice) over 1 pellet. When the kappa opioid receptor agonist spiradoline (0.00032 – 1 mg/kg/infusion) or histamine (0.1 – 3.2 mg/kg/infusion) was paired with 2 pellets, the number of trials completed decreased dose-dependently without systematically affecting choice. Histamine selectively punished responding only when the reinforcer amounts were equal; this procedure can be used to characterize the aversive effects of kappa opioids and whether those effects might be attenuated by kappa/mu mixtures.

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Poster 2-22

Hydrocodone is more effective than morphine or oxycodone in suppressing burn-induced hyperalgesia.

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Pain is the most frequent complaint of burn-injured patients. Opioids are commonly used in the course of treatment. Previous findings indicate that various opioids have differential effects despite being considered clinically comparable, and there is a lack of studies that examine these differential effects. Here, we examined the ability of morphine, oxycodone, and hydrocodone to reduce pain in mice with a burn injury, as well as their ability to suppress the development of burn-induced hyperalgesia in both the injured and non-injured foot. Mice were examined for their baseline pain sensitivity thresholds using the von Frey Filaments test. Then, they were subjected to burn or sham injury, and treated orally with morphine, oxycodone, hydrocodone (20 or 40 mg/kg), or saline twice daily for 28 days. Pain thresholds were re-tested on days 4, 7, 11, 14, 21, and 28 post-injury. Hyperalgesia was observed 4 days post-burn in the injured foot, and intensified with time. Hyperalgesia emerged in the non-injured foot starting at D21. In the injured foot, 20 mg/kg morphine or oxycodone had only minimal effects to reduce hyperalgesia, and 40 mg/kg did not significantly change pain sensitivity threshold. Both 20 and 40 mg/kg hydrocodone significantly decreased pain sensitivity in the injured foot starting at D11 and continuing through the end of the study. Surprisingly, none of the opioids, including hydrocodone, significantly reduced hyperalgesia development in the non-injured foot of injured animals. This study demonstrated that hydrocodone is effective in suppressing the development of burn-induced hyperalgesia at the injury site; but that none of the drugs showed efficacy blocking hyperalgesia on the contralateral side. These findings underscore the need for additional studies on the differences among various opioids using clinically relevant pain models.

Poster 2-23

Differential expression of CaM Kinase II in the rat medial prefrontal cortex is associated with ethanol withdrawal-induced cognitive inflexibility

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Repeated cycles of ethanol (EtOH) intoxication and withdrawal dysregulate brain amino acid signaling that result in synaptic adaptations in the medial prefrontal cortex (mPFC) and impairments in cognitive function during protracted withdrawal. Although conceptualized as a homogenous region, the mPFC is functionally distinct, with dorsal regions facilitating drug-cue associations, whereas ventral regions modulate new learning in the absence of cues. An evaluation of the factors promoting glutamatergic transmission in these regions may provide insight on the mechanisms of EtOH-induced cognitive dysfunction. Here, we explored the hypothesis that chronic intermittent ethanol (CIE) exposure and withdrawal enhances expression of calcium/calmodulin-dependent protein kinase II (CaMKII) known to facilitate glutamatergic receptor activity. We used a rat model of strategy set-shifting 10-14d following the termination of CIE vapor inhalation procedures (14h EtOH/10h air, 5d/week, 4-5 weeks). Briefly, male Long-Evans rats were trained to lever press for palatable food pellets in standard operant chambers. Following CIE exposure (BAL: 217±10 mg/dL; n=11), rats were presented with a visual cue task in which both levers were presented simultaneously, along with a single illuminated cue light indicating the active lever. The number of trials, errors, and omissions were recorded until an established criterion was met. Rats were then presented with a set-shifting protocol in which the cue lights operated randomly, but only one lever remaining active throughout the session. No differences emerged during the initial task; however, during the set shift, EtOH rats required more trials and committed more errors than naïve controls (n=10; $P<0.05$). EtOH rats also exhibited an upregulation of phosphorylated CaMKII levels (109%±5 of control) in the dorsal but not ventral mPFC ($P<0.05$). The data suggest that EtOH withdrawal-induced cognitive inflexibility may be influenced by enhanced glutamatergic transmission in the dorsal mPFC, modulated in part by increased CaMKII expression.

Poster 2-24

Pharmacokinetics of Phosphatidylethanol 16:0/18:1 and 16:0/18:2 in Human Blood After 0.4 and 0.8 g/kg of Alcohol in a Clinical Lab Study

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Background. The purpose was to characterize the pharmacokinetics of two homologues of phosphatidylethanol (PEth) in uncoagulated, whole blood samples taken from participants in a human clinical lab study after consumption of two doses of ethanol. Methods. Male and female participants received either 0.4 or 0.8 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. 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 0.4 and 0.8 g ethanol/kg produced proportional increases in BrAC and 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 PEth (calculated as the AUC of the increase above baseline for PEth); (3) the mean rate of formation of PEth 16:0/18:1 was lower than that of PEth 16:0/18:2 after administration of 0.4 g/kg, but not 0.8 g/kg of ethanol, (4) The rate of formation of PEth 16:0/18:1 was lower than that of PEth 16:0/18:2 within subject in 40 of 45 participants regardless of dose, (5) the mean half-life of PEth 16:0/18:1 was longer than that of PEth 16:0/18:2. Conclusions. The results of this study confirm that PEth is a sensitive biomarker for ethanol consumption. The measurement of two PEth homologs may provide additional information about the level and time frame of drinking. (NIAAA RO1 AA022361)

Poster 2-25

Both the rewarding effects of nicotine and withdrawal from this drug are enhanced in hypoinsulinemic rats

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Introduction: The present study examined whether hypoinsulinemic rats experience greater reinforcing effects of nicotine and/or stronger negative affective states produced by nicotine withdrawal. Methods: Separate groups of rats received systemic administration of either vehicle or streptozotocin (STZ; 45 mg/kg). STZ is a drug that destroys insulin-producing beta cells in the pancreas, and as a result, elevates plasma glucose levels (250-550 mg/dL). Two weeks after STZ administration, place-conditioning procedures were utilized to compare the rewarding effects of nicotine (conditioned place preference; CPP) and negative affective states produced by withdrawal from this drug (conditioned place aversion; CPA) in vehicle- and STZ-treated rats. CPA and physical signs of withdrawal were compared following administration of the nicotinic receptor antagonist mecamylamine to precipitate withdrawal in rats that received continuous exposure to nicotine (3.2 mg/kg) for 7 days prior to and during conditioning. A subsequent study compared anxiety-like behavior (elevated plus maze and light/dark transfer) produced by nicotine withdrawal in vehicle- and STZ-treated rats. Results: Our conditioning studies revealed that STZ-treated rats displayed a more robust CPP produced by nicotine and a larger magnitude of CPA and physical signs of withdrawal as compared to vehicle-treated controls. STZ-treated rats also displayed higher levels of anxiety-like behavior during nicotine withdrawal versus controls. Conclusion: Both nicotine reward and withdrawal are enhanced in hypoinsulinemic rats. Our findings imply that the strong behavioral effects of nicotine promote tobacco use in persons with metabolic disorders, such as diabetes.

Poster 2-26

Infant feeding decisions among mothers receiving medication assisted treatment for an opioid use disorder

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A growing number of women of childbearing age are affected by an opioid use disorder (OUD). National rates of opioid use during pregnancy increased nearly fivefold between the years 2000 and 2009 (Patrick et. al., 2012). The Academy of Breastfeeding Medicine (2015) and the Association of Women's Health, Obstetrics & Neonatal Nurses (2016) recommend breastfeeding for women enrolled in consistent, comprehensive medication assisted treatment (MAT) who have no other contraindications. Breastfeeding has substantial protective benefits for infants including a reduction in Sudden Infant Death Syndrome (SIDs) (Hauck, 2011). Despite the known benefits and recommendations for breastfeeding, women with OUDs have significantly lower breastfeeding rates than other U.S. women. The CDC (2012), reports initiation rates of only 24-46% in this population compared to 74% for the general population (Healthy People, 2013). As rates of OUDs among childbearing women continue to increase, it is important to understand the infant feeding decisions of these women. Therefore, the purpose of this study is to explore the infant feeding decisions made by women receiving MAT. This study is part of a larger study focused on the impact of kangaroo mother care (a method of skin-to-skin mother infant holding) on mother-infant dyads affected by opioid use. Institutional Review Board approval was obtained prior to the onset of any data collection. A qualitative, case-study design is being used. Data are being primarily collected through semi-structured, individual, audio taped interviews with mothers no more than twelve months post-delivery. All women are in a MAT program. Thus far, fifteen women have been interviewed. Continuous qualitative content analysis is currently taking place. To date, three common categories have emerged: 1) what I've heard about breastfeeding and MAT, 2) who/what influenced my infant feeding decision, and 3) how I made my decision. These research findings will provide a basis for the development of effective and sustainable interventions to improve breastfeeding rates among women receiving MAT for an OUD.

Poster 2-27

Cellular actions of the novel atypical dopamine transporter inhibitor, JJC8-088, on mouse midbrain dopamine neurons

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Psychostimulants, such as cocaine, increase attention and induce euphoria, are commonly abused, and can damage human health up to and including death. Currently, there are no FDA approved pharmacological treatments for cocaine abuse. Cocaine, the prototypical dopamine (DA) transporter (DAT) inhibitor, 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 reduce cocaine-induced hyperlocomotion and self-administration in rodents, which suggests potential therapeutic benefits for human cocaine users. However, the cellular actions of atypical compounds are unknown. Currently, we are investigating the effects of a novel atypical DAT inhibitor, JJC8-088, on midbrain DA neurotransmission and cell excitability. We have found that high concentrations of JJC8-088 reduce midbrain dopamine neuron firing. Additionally, we have discovered concentration dependent effects of JJC8-088 on DA neurotransmission. We have evidence that this compound can reduce the effect of cocaine on DA neuron cell excitability of cells from naïve mice. Work is underway to determine how well JJC8-088 blocks the cellular actions of cocaine on midbrain dopamine neurons from mice that have had long-term exposure to cocaine. Our study of the cellular actions of JJC8-088 will give us a better understanding of which cellular actions of a compound allow for it to be useful in reducing the cellular actions of cocaine on midbrain DA neurons.

Poster 2-28

Antinociceptive effects of the first α2/ α3-subtype selective GABAA receptor positive allosteric modulator

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Pain remains a challenging clinical condition and spinal GABAA receptors are crucial modulators of pain processing. α2/α3-subtype GABAA receptors mediate the analgesic actions of benzodiazepines. Positive allosteric modulators (PAMs) at α2/α3-subtype GABAA receptors may have analgesic potential. Here we report the first selective α2/α3-subtype GABAA receptor PAM in in vitro and in vivo pain assays. KRM-II-81 demonstrated similar efficacy at α1/ α2/ α3 GABAA receptors and negligible efficacy at α4/ α5/ α6 GABAA receptors, with α2 and α3-subtypes being 17- and 28-fold more potent that α1 subtypes in HEK-293T cells expressing GABAA receptors with different α subunits. In contrast, KRM-II-18B showed significant efficacy at α1/ α2/ α3/ α5 subtypes, with similar potency at α1/ α2/ α3 subtypes. Both PAMs and morphine dose-dependently decreased 0.6% acetic acid- and 0.32% lactic acid-induced writhing, which was reversed by the benzodiazepine receptor antagonist flumazenil, confirming their action at the benzodiazepine binding site of GABAA receptors. Both PAMs and morphine all dose-dependently reversed 0.32% lactic acid (but not 0.6% acetic acid)-induced suppression of nesting behavior. Acetaminophen, but neither PAM, reversed acid-depressed locomotor activity. Combined, these findings suggest that KRM-II-81 is a selective α2/α3 subtype GABAA PAM with significant antinociceptive efficacy in chemical stimulation-induced pain in mice.

Poster 2-29

Locomotor stimulant effects of MDMA and its putatively less toxic deuterated form in mice

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There is a renewed interest in the use of 3,4-methylenedioxymethamphetamine (MDMA) for the treatment of psychiatric problems, however, the association between MDMA and neurotoxicity (perhaps via generation of reactive adducts during drug metabolism) may limit clinical utility. As such, efforts devoted to modifying MDMA's chemical properties to reduce its toxicity, but retain its desirable pharmacological effects, are worthwhile. In the present study, the locomotor effects of deuterated-MDMA (D-MDMA) were compared to MDMA in mice. Mice were assigned to a D-MDMA (n = 6) or MDMA (n = 6) treatment group following surgical implantation (ip) of neodymium magnets to record ambulatory activity. Mice received once daily injections (ip) of their respective drugs every other day in an ascending sequence (0, 3, 10, 30 mg/kg) for seven consecutive days, and ambulatory activity was continuously measured. Following a drug-free break, mice received a challenge injection of 10 mg/kg of D-MDMA or MDMA to assess locomotor sensitization. Last, the mice received once daily injections of (S)-methamphetamine every other day in an ascending sequence (1, 3, 10 mg/kg) and ambulatory activity was measured. The results revealed that D-MDMA produced dose-dependent increases in ambulatory activity similar to MDMA. 30 mg/kg MDMA produced greater levels of ambulatory activity than D-MDMA at 1.5 hour post-injection and the drugs' locomotor-increasing effects returned to saline-injection levels approximately 3.5 hours post-injection. MDMA was also more potent than D-MDMA at producing stereotypy. Results of the methamphetamine injections will be presented. Overall, these findings indicate that D-MDMA and MDMA are equipotent at increasing ambulatory activity and D-MDMA may be less behaviorally toxic than MDMA as evidenced by less repetitive movements.

Poster 2-30

Revision about the feasibility of gabapentin for treating substance use disorders

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The present revision overviewed the suitability of using gabapentin for treating different substance use problems. It was based on a total of 84 biographical references. The substances included in this revision were: alcohol, cocaine, opioids, methamphetamine, cannabis and tobacco. As a reference, gabapentin has been used in clinical or research settings for conditions like substance use disorders, epilepsy. behavioural decontrol, psychiatric diseases, amyotrophic lateral sclerosis, nociception, anxiety, neuralgia, restless legs syndrome, and bipolar disorder among others. The main conclusions of the revision were: 1) Gabapentin has been successful for alleviating alcohol withdrawal symptoms (90% successful results in 11 clinical studies), alcohol dependence and craving (80% successful results in 5 clinical studies). 2) More research is necessary for exploring the suitability of gabapentin for reducing alcohol relapse (one study with successful results). 3) Gabapentin has not been successful for treating cocaine dependence problems (33% successful results in 6 clinical studies). 4) Gabapentin has not been successful for alleviating cocaine relapse (one clinical study without success, and 33% successful results in 3 rodent studies). 5) Gabapentin has been successful for treating opioid withdrawal symptoms (75% successful results in 4 clinical studies). 6) More investigations are necessary for exploring the effectiveness of gabapentin for treating methamphetamine dependence (50% successful results in 4 clinical studies). 7) More research is recommended for evaluating gabapentin´s effectiveness for treating cannabis related problems (one study with successful results), and 8) Gabapentin has not been successful for treating tobacco dependence problems (33% successful results in 3 clinical studies).

Poster 2-31

Reinforcing Properties of Meta-Nicotine

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Metanicotine is much less potent than nicotine; it nevertheless substitutes completely for its discriminative effect at both low (0.03 mg/kg) and high (1.8 mg/kg) nicotine doses. Metanicotine's discriminative and response rate suppressing effects are blocked by dihydrobetaerythroidine suggesting that these effects are a4b2-nicotinic receptor mediated in the rat. Unlike nicotine, metanicotine (0.1 -3.2 mg/kg, i.v.) does not reinforce self-injection responding in animals that self-inject nicotine. These same rats also self-inject bupropion at a series of comparable doses. At these doses, metanicotine punishes responding that delivers small pellets of sucrose. Very preliminary data suggest that the profile of activity described for metanicotine is similar to the very potent agonist, epibatidine.

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Poster 2-32

Effects of a stress hormone antagonist in reducing drug addiction behaviors

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Despite awareness of the destructive effects of drug abuse, addiction persists. One feature of addiction is the susceptibility of relapse after stretches of abstinence. A theory that may account for relapse suggests that cues (e.g., paraphernalia) associated with drug taking increase the stress hormone corticosterone (CORT), and this may prompt renewed drug seeking (i.e., relapse). Pavlovian conditioning is used to measure what subjects learn about a cue that is predictive of reward. Research has shown that animals that attend the cue more ('sign trackers') rather than to the reward are more vulnerable to certain aspects of drug addiction. In the current research, a cue was paired with reward to first identify sign trackers. Subsequently, a CORT receptor antagonist was used to block or attenuate sign tracking behavior. The working hypothesis of this research was that PT150 (a generous gift from Palisades Therapeutics, LLC for the CORT receptor antagonist) would reduce the expression of drug addiction behaviors through the reduction of CORT. In the current experiment, time spent at a CS that predicts reward (CS+) served as a measure of drug addiction behaviors (sign tracking), and PT150 (or placebo) was administered to block CORT receptors following acquisition of sign tracking. A decrease in sign tracking was measured as reduced time spent at the cue. A linear regression analysis showed that Treatment significantly predicted sign tracking and, accounted for 20% off the variation in sign tracking, $F(3, 1316) = 24.47$, $p < .001$. Specifically, there was large negative correlation between TX and sign tracking, where subjects that received PT150 had a decrease in sign tracking expression in relation to those that received placebo, $r = 0.060$, $p < 0.05$. The current findings suggest that drug addiction behaviors may be associated with the stress hormone CORT, and may potentially be decreased by reducing stress hormones. Given the devastating effects of drug addiction, identification of a potential pharmacological intervention in the reduction of relapse would be of great value. Therefore, future research is needed to validate the use of PT150 in reducing behaviors associated with drug addiction.

Poster 2-33

Ovarian hormonal status influences 5-HT1B receptor agonist effects on cocaine self-administration in rats.

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Despite the detrimental effects of cocaine dependence there are no effective pharmacological treatments for this disorder. We previously found pharmacological evidence that the selective serotonin1B receptor (5HT1BR) agonist, CP 94,253 (CP) facilitates cocaine intake when given prior to a daily self-administration session, while the same agonist inhibits cocaine intake and attenuates drug seeking behavior following 21 days of protracted abstinence. It has been suggested that women face unique challenges in being more susceptible to craving and relapse to drugs of abuse. In part this is due to biological and physiological sex differences between males and females. Specifically, in females, peak levels of endogenous estrogen hormones correspond to an increase in cocaine intake, and an enhanced vulnerability to relapse. In this study, we investigated the effects of CP94253, a selective 5HT1BR agonist, on cocaine intake during the estrus and diestrus phases of the estrous cycle on a fixed ratio (FR) schedule of reinforcement during self-administration. Female Sprague-Dawley rats (n=15) were trained to self-administer 0.75 mg/kg, IV cocaine. Rats underwent training on an FR5 schedule of cocaine reinforcement and daily vaginal smears were taken after each session to monitor the estrous cycle. Once reinforcement rates stabilized, rats underwent pretreatment with CP94253 or vehicle and were tested 15 min later on an FR5 schedule of 0.75 mg/kg, IV cocaine for one hour and then the dose of cocaine was reduced to 0.375 mg/kg for the second hour of testing. This test procedure was repeated during the diestrus and estrus phases. This study is ongoing and thus far, preliminary findings no significant differences in active lever response rates or cocaine reinforcement rates between the cycle phases. However, CP appears to facilitate an increase in active lever response rates during the diestrus phase compared to vehicle pretreatment. The findings suggest that CP94253 effects on cocaine intake may vary depending on cycle phase, a result that has important implications for developing treatments for cocaine dependence in women.

Poster 2-34

Contribution of gonadal hormones to sex differences in rodent discriminative sensitivity to THC.

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Though public perception of the risks associated with the medical and recreational use of cannabis has declined dramatically in recent years, much remains unknown about how sex differences impact the effects and abuse liability of cannabinoids like Δ9-tetrahydocannabinol (THC), the primary psychoactive constituent of cannabis. Human data suggest that women experience greater positive subjective effects of cannabis than men and are also more likely to experience withdrawal symptoms upon cessation of use. Additionally, preclinical data demonstrate that female rodents are more sensitive to the reinforcing and discriminative effects of cannabinoids than males and also exhibit greater tolerance to the antinociceptive effects of THC. In order to better understand the biological causes for these observed sex differences, we investigated the impact of gonadal hormones on discriminative sensitivity to THC. Adult male and female Sprague Dawley rats were trained to discriminate THC (3 mg/kg and 1 mg/kg, respectively) from vehicle. Following acquisition, discrete and cumulative THC dose responses (0.3, 1, 3, and 10 mg/kg for males; 0.1, 0.3, 1, and 3 mg/kg for females) were assessed, after which rats were sham-gonadectomized (sham-GDX) or gonadectomized (GDX). GDX females received no hormone replacement (GDX+0) or estradiol (GDX+E2) via subcutaneous (s.c.) capsule. GDX males received no hormone (GDX+0) or testosterone (GDX+T). After surgery, three cumulative dose-response tests were conducted: the first following 14 days of recovery, the second after 4.5 days of twice daily vehicle administration (s.c.), and the third after 4.5 days of twice daily THC administration (10 mg/kg, s.c.). Pre-gonadectomy, response rates at each THC dose remained consistent in males and females for both dosing regimens (discrete and cumulative). Gonad removal increased discriminative sensitivity to THC in both males and females, an increase that persisted following chronic THC administration. These findings suggest that gonadal hormones contribute to discriminative sensitivity to THC in both males and females, though the extent to which these hormones underlie sex differences in the effects of THC warrants

Poster 2-35

The neuroprotective agent, P7C3-A20, prevents paclitaxel-induced peripheral neuropathy.

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The microtubule-targeting anticancer drug, Paclitaxel (PTX), produces debilitating peripheral neuropathy that is accompanied by neuropathic pain. We have found that the aminopropyl carbazole, P7C3-A20, prevents the development of PTX-induced neuropathic pain in rats. To further characterize the neuroprotective efficacy of P7C3-A20, we performed a dose-response study using our rat behavioral model of PTX-induced peripheral neuropathy. P7C3-A20 (2.2, 6.6, or 20 mg/kg, i.p., q.d.) or vehicle was administered to male Sprague-Dawley rats over a 16-day period. After two days of treatment, PTX (11.7 mg/kg, i.p.) or vehicle was injected every other day for three days. Nociceptive thresholds to mechanical and cold stimuli were measured periodically throughout the experimental period. P7C3-A20 dose-dependently attenuated PTX-induced mechanical and cold allodynia. Measurement of intraepidermal nerve fiber (IENF) density in paw biopsies revealed that treatment with PTX dramatically reduced IENF density that was blocked by P7C3-A20 in a dose dependent manner. Further, results of statistical analysis indicated strong correlations between IENF density and nociceptive threshold to mechanical and cold stimuli. In vitro experiments have shown that P7C3-A20 stimulates NAMPT, a critical enzyme in the NAD salvage pathway. Thus, we next determined if the protective effects of P7C3-A20 could be antagonized in vivo by the selective NAMPT inhibitor, FK866. As before, P7C3-A20 prevented the development of mechanical allodynia compared to PTX controls. By contrast, rats co-injected with FK866 and P7C3-A20 displayed persistent mechanical allodynia, indicating that FK866 blocked the protective effects of P7C3-A20. Analysis of IENF densities revealed that FK866 also blocked preservation of nociceptive fibers by P7C3-A20. Collectively, these data suggest that the protective effects of P7C3-A20 require function of NAMPT. P7C3-A20 may be an exciting new candidate to prevent peripheral neuropathy in patients undergoing cancer treatment with PTX. Supported by NIH P30 CA054174 (CTRC at UTHSCSA), 8UL1TR000149, and Calico Life Sciences LLC

Poster 2-36

Lorcaserin does not impact high fat diet-induced enhanced sensitivity to the behavioral effects of dopamine D2/D3 receptor agonist quinpirole

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The FDA recently approved lorcaserin, a serotonin (5-HT)2C receptor agonist, for the treatment of obesity. Although lorcaserin decreases feeding in both humans and animals, it is not known if lorcaserin will also treat the other effects of eating a high fat diet, such as enhanced sensitivity to drugs that act on dopamine systems. To test the hypothesis that lorcaserin reverses the effects of eating a high fat diet, male Sprague-Dawely rats were fed either standard chow (18% kcal from fat) or high fat chow (60% kcal from fat). Body weight and food consumption were monitored daily, and quinpirole-induced yawning and penile erections (0.0032-0.32 mg/kg, i.p.) were assessed periodically throughout the experiment. After 10 weeks, rats were assigned to treatment groups (vehicle, 0.1, or 0.32 mg/kg lorcaserin; i.p.) and treatment injections occurred once daily, one hour prior to the dark cycle. Doses of lorcaserin were selected because they have been shown previously to produce behavior associated with selective action at 5-HT2C receptors. Rats eating high fat chow gained more weight than rats eating standard chow, and body weight for rats eating high fat or standard chow was decreased by 0.32 mg/kg lorcaserin treatment. Quinpirole induced more penile erections among rats eating high fat chow, than rats eating standard chow; however, daily injections of lorcaserin had no impact on this effect, at least in a small cohort of animals (n = 2/3 per group). Lorcaserin has affinity for sites other than 5-HT2C, and as such, larger doses of lorcaserin, that have been shown to produce behavior associated with actions at these other receptor subtypes, were not studied in the present experiment. However, it is possible that larger doses of lorcaserin might result in the attenuation of the high fat diet-induced enhanced sensitivity to quinpirole demonstrated in the present report. Future directions will include examining a wider range of doses of lorcaserin, as well as examining other unconditioned behaviors produced by drugs that act on dopamine systems.

Poster 2-37

Dietary supplementation with fish oil reverses high fat diet-induced enhanced sensitivity to quinpirole-induced penile erections

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Eating a high fat diet can lead to negative health consequences, including obesity, insulin resistance, and enhanced sensitivity to drugs acting on dopamine systems. Dietary supplements that are rich in omega-3 fatty acids, such as fish oil, prevent these negative health consequences from developing, but it is not known if they can also reverse these effects, once they have developed. In order to test the hypothesis that dietary supplementation with fish oil will reverse high fat diet-induced enhanced sensitivity to quinpirole, a dopamine D2/D3 receptor agonist), male Sprague Dawley rats were fed either standard chow (17% kcal from fat), high fat chow (60% kcal from fat), standard chow or high fat chow supplemented with 20% (w/w) fish oil (n = 4/group). Body weight, insulin sensitivity, and sensitivity to quinpirole (0.0032-0.32 mg/kg), as indexed by quinpirole-elicited yawning and penile erections, were examined throughout the course of the experiment. Eating high fat chow enhanced sensitivity of rats to quinpirole-induced penile erections. Further, dietary supplementation with fish oil reversed this effect. That is, quinpirole-induced penile erection dose-response curves were not different between rats eating standard chow and rats eating high fat chow supplemented with fish oil. 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 reverse 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.

Poster 2-38

Altered responses to peripheral kappa opioid receptor (KOR)-mediated antinociceptive signaling in aged rats

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Little is known regarding the effects of aging on nociceptor (pain-sensing neuron) responsiveness or the functionality of opioid receptors expressed on nociceptors. We determined the effects of the kappa opioid receptor (KOR) agonist, Salvinorin A (Sal A), on nociceptors in young (4-months-old) and aged (26-months-old) Fisher x Brown Norway rats. Behavioral responses to noxious heat were measured following intraplantar (i.pl.) injections of Sal A. Sal A produced significant antinociceptive responses in aged rats only. Similarly, KOR-mediated inhibition of adenylyl cyclase activity was greater in neurons derived from aged versus young rats. Interestingly ip.l injection of arachidonic acid prior to Sal A now results in a significant antinociceptive response in young rats; with no additive effect in aged rats. Therefore aging alters KOR sensitivity to agonists in non-inflamed tissue; thus peripherally-restricted kappa agonists may be a valuable analgesic strategy for treating pain in the elderly.
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Poster 2-39

Activin A is increased in the nucleus accumbens following a cocaine binge

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Drug addiction is a long-lasting disease characterized by compulsive drug intake and episodes of relapse after prolonged periods of drug withdrawal. Neuronal and biological adaptations in key brain areas, such as the nucleus accumbens (NAc), are thought to contribute to this life-long disease. We previously demonstrated involvement of the activin 2a receptor in cocaine seeking following drug re-exposure. However, the role of its ligand activin A in cocaine relapse is still unknown. Here we measured activin A levels and expression in neurons, astrocytes, and microglia in the NAc after cocaine re-exposure following withdrawal from self-administration. Rats underwent 10 days of extended-access cocaine or saline self-administration, followed by 14 days of withdrawal. Rats were then given a 12-hour binge test, and then sacrificed for determination of activin A levels in the NAc by ELISA, or immunohistochemical analysis of expression in neurons, astrocytes, and microglia. A cocaine binge significantly increased levels of activin A in the NAc of animals that had self-administered cocaine prior to the 14-day withdrawal compared to saline controls. This was accompanied by an increase in the proportion of IBA1+ microglia in the NAc that were immunopositive for activin A. In contrast, the proportions of NeuN+ neurons and GFAP+ astrocytes that were immunopositive for activin A remained unaltered. In conclusion, these data suggest that increased secretion of activin A, particularly from microglia, in the NAc represents a novel potential target for the treatment of cocaine relapse.

Poster 2-40

Morphine Dose Dependently Restores Wheel Running in Mice with Inflammatory Injury

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Pain remains a significant clinical problem that contributes to the decline in functional capacity and quality of life in patients. Many studies on pain use a decreased response to a noxious stimulus as a measure of antinociception; however, a decreased response might also indicate general behavioral suppression (i.e., false positive). Voluntary wheel running in rodents provides a quantitative measure of functional capacity in the context of pain and decreases the likelihood of false positives by using an increase in pain suppressed behavior to indicate antinociception. This pilot study examined the effects of morphine on inflammation-induced decreases in wheel running. To assess nociception, 6-9 week old C57BL/6J male mice had continuous access to a running wheel for 3 days before receiving a unilateral intraplantar injection of Complete Freund's Adjuvant (CFA) 8 hours before the dark cycle. Mechanical allodynia and hind paw edema were measured daily 6 hours before the dark cycle. A second group of mice had 18 days of continuous access to a running wheel before receiving a CFA injection 8 hours before the dark cycle and a subcutaneous injection of saline or morphine (0.032, 0.1, 0.32, or 1.0 mg/kg) 30 minutes before the dark cycle. Mechanical allodynia and hind paw edema were consistently elevated 24 hours after CFA injection and persisted for several days. In untreated mice, wheel running was abolished 8 hours after CFA injection. Morphine-treated mice showed a dose-dependent increase in wheel running (running 63% and 73% of pre-CFA levels after receiving 0.32 [n=3] or 1.0 [n=2] mg/kg, respectively) compared with saline-treated mice (n=3) that ran at 24% of pre-CFA levels. While these differences did not reach statistical significance, likely related to the small number of subjects in each group, there is a positive trend indicating antinociception at these doses. This study demonstrates a clear and robust nociceptive effect indicated by a decrease in wheel running that is dose dependently restored by morphine. Future work will investigate novel therapeutic strategies for treating pain including combined treatment with existing drugs.

This study was conducted with the support of the Welch Foundation Grant AQ-0039.

Poster 2-41

Administration of Zolmitriptan, a 5-HT1B receptor agonist, attenuates nicotine-induced conditioned place preference in female and male adolescent rats

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Activation of 5-HT1B receptors has been shown to modulate the rewarding effects of cocaine and alcohol. To date, the role of 5-HT1B receptors in the rewarding effects of nicotine has not been investigated. To identify if these receptors play a role in nicotine reward, the nonselective FDA approved 5-HT1B agonist, Zolmitriptan (0.0, 3.0, or 10 mg/kg, SC), was administered to adolescent rats prior to conditioning with nicotine (0.0, 0.022, 0.067, or 0.2 mg/kg, IP) in a biased conditioned place preference (CPP) design. Results indicate that activation of 5-HT1B receptors decreased the rewarding properties of nicotine in both female and male rats in a dose dependent manner. Specifically, as the dose of the agonist was increased, a decrease in nicotine-induced CPP was evident. Altogether these results indicate that 5-HT1B receptors play a critical role in the rewarding properties of nicotine and further suggest that 5-HT1B receptors may be a novel target for nicotine dependence.

Poster 2-42

In vivo characterization of novel mu opioid receptor agonist/delta opioid receptor antagonist ligands: differences in CNS penetration

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Mu-opioid receptor (MOR) agonists are widely used in the treatment of pain but produce many adverse effects such as tolerance, physical dependence, constipation, and euphoria. Studies have suggested that co-administration of a MOR agonist with a delta-opioid receptor (DOR) antagonist may relieve pain with reduced adverse effects. Therefore, the goal of this study was to evaluate the antinociceptive effects of a series of mixed-efficacy MOR agonist/DOR antagonist peptidomimetics developed in the Mosberg lab. The antinociceptive effects of these peptidomimetics (cumulative doses, 1-32 mg/kg, ip) were evaluated using the 50°C warm water tail withdrawal assay (WWTW) in male C57BL6/N mice. Two compounds, AAH8 and AMB47 produced dose-dependent antinociception and reached the maximum cutoff at 10 mg/kg. However, two structurally similar compounds AAH9 and AMB39, were ineffective. We hypothesized that this lack of efficacy was due to an inability to cross the blood brain barrier. To test this hypothesis, we examined these compounds in the WWTW assay after both iv and icv administration. AAH9 and AMB39 elicited antinociceptive properties following icv but not iv administration suggesting that they could have antinociceptive effects if they reached the brain. Therefore, we then tested the effects of AAH9 and AMB39 in combination with a P-glycoprotein (PGP) inhibitor, Elacridar, to evaluate whether AAH9 and AMB39 may be PGP substrates. We found that after pretreatment with Elacridar, peripheral administration of AAH9 and AMB39 (and loperamide as a positive control) produced antinociception in the mouse WWTW assay, suggesting that PGP may efflux these compounds from the brain. Taken together, these data suggest that even structurally similar peptidomimetics may have different pharmacokinetic properties that limit their antinociceptive effects. Also, if the compounds can enter the CNS, then in vitro efficacy determinations may adequately predict in vivo efficacy. Understanding these pharmacokinetic properties may aid in the rational design of mixed efficacy peptidomimetic opioid ligands for the treatment of pain. This work was supported by NIDA:Grant 5 T32 DA00726 and NIH Grant DA003910.

Poster 2-43

Modulation of morphine effects by chronic naltrexone and naltrexone withdrawal in an intracranial self-stimulation (ICSS) procedure in rats

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ICSS is an operant procedure in which the primary dependent measure is the rate of reinforcement maintained by electrical stimuli delivered to a brain reward area, usually in rats. Drug efficacy to increase (or "facilitate") ICSS correlates with measures of reinforcing efficacy in drug self-administration procedures and serves as a measure of abuse-relate drug effects. In opioid-naïve subjects, mu opioid receptor agonists like morphine produce weak ICSS facilitation at low doses and primarily depress ICSS rates at higher doses. Chronic opioid agonist treatment produces tolerance to rate-decreasing effects and enhanced expression of ICSS facilitation. These results suggest that repeated mu agonist treatment can increase mu agonist abuse potential. Mu antagonists such as naltrexone are administered chronically in some therapeutic contexts, and withdrawal from chronic naltrexone treatment can sensitize mu receptors and increase mu agonist potency/efficacy to produce some effects. Accordingly, the present study evaluated the degree to which exposure to and withdrawal from chronic treatment with the mu antagonist naltrexone might enhance abuse-related morphine effects in an ICSS procedure. Male Sprague-Dawley rats were trained to lever press for brain stimulation to the medial forebrain bundle and implanted with osmotic pumps delivering naltrexone (0.001-0.1mg/kg/h, SC) or saline for 14 days (N=6 per dose). Cumulative morphine dose-effect curves (1-10 mg/kg, SC) were determined during and 1 day after pump removal. During and after saline treatment, morphine produced primarily dose-dependent rate-decreasing effects. Naltrexone dose-dependently blocked morphine effects during naltrexone treatment. Naltrexone withdrawal increased potency of morphine to decrease ICSS, but morphine potency/efficacy to produce ICSS facilitation was not increased. These results suggest that withdrawal from mu-antagonist doses of chronic naltrexone does not increase sensitivity to abuse-related morphine effects.

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Maharaj ("Raj") Ticku, PhD

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

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

See you at BBC 2018!

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