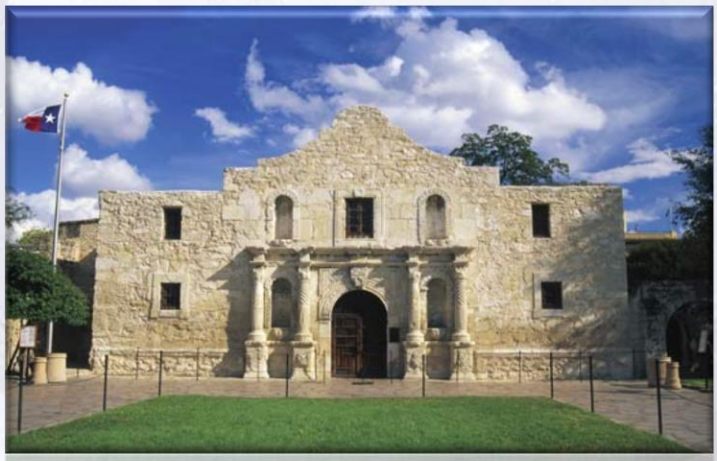
Behavior, Biology, and Chemistry: Translational Research in Addiction (BBC)

San Antonio, Texas
La Quinta Inn and Suites Medical Center
3-4 March 2018



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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* 121, 167-72. PMC3288266

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* 121, 173-80. PMC3288798

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* 121, 181-88. PMC3288203

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* 121, 189-204. PMC4224378

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* 128, 175-86. PMC3596012

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 Dependence* 141, 107-17. PMC4227301

BBC 2014

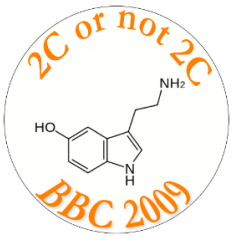
Reith ME, Blough BE, Hong WC, Jones KT, Schmitt KC, Baumann MH, Partilla JS, Rothman RB and Katz JL (2015) **Behavioral, biological and chemical perspectives on atypical agents targeting the dopamine transporter.** *Drug and Alcohol Dependence* 147, 1-19. PMC4297708

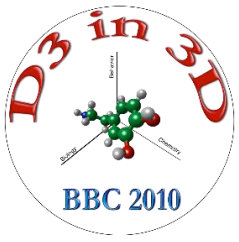
BBC 2015

Grandy DK, Miller GM and Li JX (2016) **"TAARgeting addiction"– The Alamo bears witness to another revolution.** *Drug and Alcohol Dependence*. 159, 9-16. PMC4724540

BBC 2016

Bachtell RK, Jones JD, Heinzerling KG, Beardsley PM, Comer SD (2017) **Glial and neuroinflammatory targets for treating substance use disorders.** *Drug and Alcohol Dependence* 180, 156-70. PMC5790191





Acknowledgements

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Drew Townsend

Christopher Tschumi

Kyle Urquhart

Alison Wakeford

Zijun Wang

Catheryn Wilson

Sarah Withey

Eric Wold

Jessica Wooden

Carlos Zamarripa

Xiao Zhang

Program Overview

FRIDAY 2 MARCH 2018

3:00 PM – 5:00 PM	**Pathways to Careers in Science Workshop** – UT Health Campus
2:00 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 on the Riverwalk
6:00 PM – 9:00 PM	**BBC Opening Reception, La Vista Terrace on the Riverwalk**

SATURDAY 3 MARCH 2018

7:00 AM – 5:00 PM	Registration
8:00 AM – 8:05 AM	Welcome and Opening Remarks
8:05 AM – 10:25 AM	Plenary Symposium: *The conundrum of cannabis and cannabinoids*
	Brian F Thomas; *Plants vs Zombies- The past, present, and future of cannabinoid chemistry*
	Jenny L Wiley; *Weed in the garden of science: pharmacology of THC and synthetic cannabinoids*
	Scott E Lukas; *Splendor in the grass: clinical and neurobiological effects of recreational and medical cannabis*
	Mark A R Kleiman; *How not to make a hash out of cannabis policy*
	(Chairs: Mark A R Kleiman, and Wouter Koek)
10:25 AM – 10:40 AM	Coffee Break
10:40 AM – 12:10 PM	Open Oral Communications 1 (Chair: Comfort A Boateng) 
12:10 PM - 1:40 PM	Lunch
12:25 PM – 1:25 PM	**Wondering about Women in Science**
1:40 PM – 3:10 PM	Open Oral Communications 2 (Chair: Galen R Wenger)
3:10 PM – 3:30 PM	Coffee Break and Poster Session I Set Up
3:30 PM – 4:30 PM	Special Lecture:
	James M Cook; *Design of benzodiazepine/GABA(A) ergic subtype selective ligands as potential nonsedating treatments for pain disorders, epilepsy and anxiety disorders with little or no tolerance*
	(Chair: Bruce E Blough)
4:30 PM – 5:45 PM	**Poster Session I**
5:45 PM – 5:55 PM	Poster Session I Take Down and Poster Session II Set Up
5:55 PM – 7:10 PM	**Poster Session II**
7:10 PM – 9:00 PM	Dinner
	After Dinner Speaker
	Michael J Kuhar; *The internet: we can teach you anywhere*
	(Chair: Brett C Ginsburg)
9:00 PM – 11:00 PM	Hospitality and Entertainment

SUNDAY 4 MARCH 2018

7:45 AM – 8:00 AM	Travel Awardee Group Photo
8:00 AM – 9:30 AM	Open Oral Communications 3 (Chair: Paul W Czoty)
9:30 AM – 9:45 AM	Coffee Break
9:45 AM – 11:15 AM	Open Oral Communications 4 (Chair: Katherine M Serafine)
11:15 AM – 11:30 AM	Coffee Break
11:30 AM – 12:30 PM	Special Lecture:
	Edward V Nunes; *Treatment of opioid use disorder: recent findings and next directions*
	(Chair: Jennifer S Potter)
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 2 March 2018

Opening Reception

La Vista Terrace on the Riverwalk

6:00 PM	Buses depart from La Quinta
6:30 PM - 9:00 PM	Welcome Reception – La Vista Terrace on the Riverwalk
8:30 PM – 9:00 PM	Buses depart for La Quinta

Enjoy the Alamo and 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 8:30 PM - 9:00 PM. A badge is required to board the bus and for dinner. Additional tickets can be purchased in advance or at the registration desk for $50.00.

Saturday 3 March 2018

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

Plenary Symposium — 8:05 AM – 10:25 AM

The conundrum of cannabis and cannabinoids (Chairs: Mark A R Kleiman, and Wouter Koek)

Many people are likely to associate cannabis or marijuana with illicit activities. However, there is evidence that cannabis can help in various medical conditions, and more and more US states are legalizing the use of "medical" and recreational marijuana. This symposium brings together leading experts who will share their insights into the chemical, pharmacological, clinical, and regulatory aspects of cannabis and cannabinoids.

8:05 AM – 8:40 AM **Brian F Thomas,** RTI International
Plants vs Zombies- The past, present, and future of cannabinoid chemistry

8:40 AM – 9:15 AM **Jenny L Wiley,** RTI International
Weed in the garden of science: pharmacology of THC and synthetic cannabinoids

9:15 AM – 9:50 AM **Scott E Lukas,** McLean Hospital, Harvard Medical School
Splendor in the grass: clinical and neurobiological effects of recreational and medical cannabis

9:50 AM – 10:25 AM **Mark A R Kleiman,** NYU – Marron Institute of Urban Management
How not to make a hash out of cannabis policy

Coffee Break — 10:25 AM – 10:40 AM

Oral Communications 1

10:40 AM – 12:10 PM (Chair: Comfort A Boateng)

10:40 AM – 10:55 AM **Lauren Campbell**, College of Charleston
Cortisol levels and situational use factors in cocaine-dependent women

10:55 AM – 11:10 AM **Shelley Edwards**, Milsaps College
Assessment of the kappa-opioid agonist, nalfurafine, on the reinforcing and antinociceptive effects of oxycodone in male and female rats

11:10 AM – 11:25 AM **JoLynn Giancola**, NIH – NIDA
Discovery of novel dopamine transporter inhibitors based on the modafinil scaffold for the treatment of psychostimulant abuse

11:25 AM – 11:40 AM **Aboagyewaah Oppong-Damoah**, Mercer University
Nanoparticle encapsulation of oxytocin increases its brain penetrance and duration of action in vivo

11:40 AM – 11:55 AM **Matthew Clasen**, American University
The effects of lifelong Western diet exposure on compulsive cocaine intravenous self-administration in male Sprague-Dawley rats

11:55 AM – 12:10 PM **Jeremy Cornelissen**, Virginia Commonwealth University
Role of mu-opioid receptor agonist efficacy on antinociceptive interactions between mu-opioid agonists and the nociceptin/orphanin FQ agonist Ro 64-6198 in rhesus monkeys

Lunch

12:10 PM – 1:40 PM

Wondering About Women in Science Lunch

12:25 PM – 1:25 PM

Issues related to Women in Science continue to be both topical and timely. During lunch, BBC attendees are invited for a frank and friendly moderated panel discussion on the challenges and opportunities women face moving forward in science. Significant time will be provided for audience questions and participation.

Oral Communications 2

1:40 PM – 3:10 PM (Chair: Galen R Wenger)

1:25 PM – 1:40 PM **Cassie Chandler**, University of Mississippi Medical Center
Regulation of relapse-like drinking and alcohol-seeking by ligands selective for GABAA receptors expressing the α5 subunit

1:40 PM – 1:55 PM **Justin Strickland**, University of Kentucky
Contribution of cocaine-related cues to concurrent monetary choice in humans

1:55 PM – 2:10 PM **I Daphne Calma**, Rush University
Cytochrome c translocation in methamphetamine-induced vulnerability for Parkinson's disease

2:10 PM – 2:25 PM **Mudassir Mumtaz**, New York State Psychiatric Institute
The effects of lorcaserin on the abuse potential of intranasal oxycodone

2:25 PM – 2:40 PM **Catheryn Wilson**, University of Arkansas for Medical Sciences
Convulsant and seizure-like effects of synthetic cannabinoids JWH-018 and 5F-AB-PINACA in mice: observational signs and in vivo electroencephalography

2:40 PM – 2:55 PM **Elisa Pabon**, University of Chicago
Field sobriety test for cannabis

Coffee Break and Poster Session I Set Up

3:10 PM – 3:30 PM

Maharaj Ticku Memorial Travel Fellowship for New Investigators

Travel Awardee

Special Lecture: James M Cook 3:30 PM – 4:30 PM (Chair: Bruce E Blough)

Design of benzodiazepine/GABA(A) ergic subtype selective ligands as potential nonsedating treatments for pain disorders, epilepsy and anxiety disorders with little or no tolerance

Poster Session I 4:30 PM – 5:45 PM

Poster Session I Take Down and Poster Session II Set Up 5:45 PM – 5:55 PM

Poster Session II 5:55 PM – 7:10 PM

Dinner 7:10 PM – 9:00 PM

Additional tickets can be purchased in advance or at the registration desk for $70.00

After Dinner Speaker: Michael J Kuhar (Chair: Brett C Ginsburg)

The internet: we can teach you anywhere

Hospitality and Entertainment 9:00 PM – 11:00 PM

Come and enjoy the fun in the San Jose Room!

Sunday 4 March 2018

Travel Awardee Group Photo 7:45 AM – 8:00 AM

Oral Communications 3 8:00 AM – 9:30 AM (Chair: Paul W Czoty)

8:00 AM – 8:15 AM **Christopher Tschumi**, Oklahoma Medical Research Foundation
Dopamine D2 autoreceptor signaling is depressed by neurotensin released from discrete inputs to midbrain dopamine neurons

8:15 AM – 8:30 AM **Marco Mottinelli**, University of Florida
NPFF receptors mediate opioid induced hyperalgesia and opioid tolerance. Preliminary data on new small molecule probes

8:30 AM – 8:45 AM **Rachel Altshuler,** University of Michigan
Protein kinase Cβ inhibition selectively decreases the reinforcing effects of amphetamine

8:45 AM – 9:00 AM **Brenda Gannon**, UT Health San Antonio
Individual differences in the self-administration of 3,4-methylenedioxypyrovalerone (MDPV) in rats: importance of behavioral flexibility

9:00 AM – 9:15 AM **Drew Townsend**, Virginia Commonwealth University
Development of an opioid vs. food choice procedure in rats: effects of reinforcer magnitude and extended opioid access

9:15 AM – 9:30 AM **Megan Moerke**, Virginia Commonwealth University
Effects of the α2/α3-subtype-selective GABAA receptor positive allosteric modulator KRM-II-81 on pain-depressed behavior in rats: comparison with ketorolac

Coffee Break 9:30 AM – 9:45 AM

Oral Communications 4 — 9:45 AM – 11:15 AM (Chair: Katherine M Serafine)

9:45 AM – 10:00 AM **Alison Wakeford**, Yerkes National Primate Research Center, Emory University
Examining the effects of a selective serotonin 2C (5HT2C) receptor agonist (WAY 163909) on cocaine self-administration in adolescent male and female rhesus macaques exposed to early life stress

10:00 AM – 10:15 AM **Brooke Schmeichel,** NIH – NIDA
Knockdown of hypocretin attenuates extended-access cocaine self-administration in rats

10:15 AM – 10:30 AM **Fernando de Moura**, McLean Hospital, Harvard Medical School
Nicotine as an adjuvant for μ-opioids: tail-withdrawal latency and disruptions in operant responding

10:30 AM – 10:45 AM **Alessandro Bonifazi**, NIH – NIDA
Novel tools to investigate the role of dopamine D2/D3 receptors in antipsychotic drug-induced metabolic disease

10:45 AM – 11:00 AM **Paul Czoty**, Wake Forest School of Medicine
Effects of the bifunctional mu opioid and nociceptin/orphanin FQ peptide (NOP) receptor agonists on ethanol drinking in rhesus monkeys

11:00 AM – 11:15 AM **Comfort Boateng**, High Point University
High-affinity and selective D_4R antagonist ligands as pharmacological tools to study substance use disorders

Coffee Break — 11:15 AM – 11:30 AM

Special Lecture: Edward V Nunes — 11:30 AM – 12:30 PM (Chair: Jennifer S Potter)

Treatment of opioid use disorder: recent findings and next directions

Presentations of Awards for — 12:30 PM

Travel, Oral and Poster Presentations

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

See you at BBC 2019!

Oral Communications

Oral Communication 1-1

Cortisol levels and situational use factors in cocaine-dependent women

Campbell, Lauren[1], Galuska, Chad[2], Sherman, Brian[3], and McRae-Clark, Aimee[4]

[1]Department of Psychology, College of Charleston, Charleston, SC USA; [2]Department of Psychology, College of Charleston, Charleston, SC USA; [3]Addiction Sciences Division, Medical University of South Carolina, Charleston, SC USA; [4] Addiction Sciences Division, Medical University of South Carolina, Charleston, SC USA.

Biological and situational stressors play important roles in cocaine relapse risk, yet there has been little investigation into their association. The current study extended previous research which found gender-specific susceptibility to cocaine craving and relapse under stressful conditions, by investigating the association between a measure of drug taking situations and cortisol levels in cocaine-dependent women during an in-vivo¬ cocaine-cue stress test preceded by a pharmacological stressor. In this double-blind, placebo controlled study, non-treatment seeking cocaine-dependent women (N=23) were administered yohimbine hydrochloride (21.6 mg) or placebo in a counterbalanced fashion prior to two cue reactivity stress procedures. The Inventory of Drug Taking Situations (IDTS), administered at baseline, is a 50-item self-report survey measuring antecedents to relapse. Cortisol levels were measured before and at the start of the cocaine cue stress test, and before and after yohimbine (or placebo) administration. We hypothesized that cocaine-dependent females with higher IDTS scores would have a greater cortisol response. Cortisol levels after yohimbine administration and before the cocaine-cue stress test were positively correlated with the negative ($p<.05$) and positive ($p<.01$) IDTS subscales. Cortisol levels during the cocaine-cue stress test were positively correlated with the negative ($p<.01$), positive ($p<.01$), and temptation ($p<.05$) subscales. These results may be useful in treatment settings where mindfulness about situational triggers can be used to identify physiological reactivity, patterns of use, and subsequent relapse. Future research might focus on other related physiological measures to see if they correlate similarly to IDTS scores in other populations.

Oral Communication 1-2

Assessment of the kappa-opioid agonist, nalfurafine, on the reinforcing and antinociceptive effects of oxycodone in male and female rats

Edwards, Shelley R[1]; Townsend, E Andrew[3]; Qureshi, Hina N[2]; Prisinzano, Thomas[4]; McCurdy, Christopher R[5]; and Freeman, Kevin B[2]
[1]Millsaps College, Jackson, MS; [2]University of Mississippi Medical Center, Jackson, MS; [3]Virginia Commonwealth University, Richmond, Virginia [4]University of Kansas, Lawrence, KS; [5]University of Florida, Gainesville, FL

Aims: We have previously reported in male rats that the atypical kappa-opioid agonist, nalfurafine, reduces self-administration of oxycodone in a dose-dependent manner and produces additive thermal antinociceptive effects when the two drugs are combined. However, this combination has yet to be tested in any endpoint in female subjects. The purpose of the current study was to determine if sex differences exist in nalfurafine's ability to modulate oxycodone's reinforcing and antinociceptive effects.
Method: Self-administration: Rats were trained to self-administer oxycodone (0.1 mg/kg; i.v.) on a progressive-ratio schedule of reinforcement and were subsequently tested with different doses of nalfurafine (0.32/1.0/3.2 ug/kg/inj) as a mixture with the training dose of oxycodone. Antinociception: Cumulative dose-effect functions were collected for oxycodone (0.32-5.6 mg/kg; s.c.) and nalfurafine (0.032-1mg/kg; s.c.), alone and as three mixture ratios (4:1, 11:1, 33:1; oxycodone:nalfurafine) using a hotplate test (52.5ºC). Drug interactions were assessed using dose-addition and isobolographic analyses.
Results: Preliminary data suggest that the potency of nalfurafine to decrease self-administration of oxycodone is greater in female than in male rats. The thermal antinociceptive potencies of oxycodone and nalfurafine were similar in males and females, yielding the same relative potency ratio of 11:1 oxycodone:nalfurafine. Furthermore, all three mixture ratios produced additive thermal antinociception in both sexes.

Conclusions: These results suggest that nalfurafine may be a more potent deterrent of abuse in females than males. However, the similarities in potency and additivity of the combination in thermal antinociception in male and female rats suggests that formulations made with these two drugs will have comparable therapeutic potency. CREDIT R01DA039167 to KBF FOR FUNDING

Oral Communication 1-3

Discovery of novel dopamine transporter inhibitors based on the modafinil scaffold for the treatment of psychostimulant abuse

Giancola, JoLynn B.[1]; Bonifazi, Alessandro[1]; Cao, Jianjing[1]; Slack, Rachel D.[1]; Gadiano, Alex[1,2]; Rais, Rana[2]; Slusher, Barbara S.[2] and Newman, Amy H.[1] *
[1]Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse, Intramural Research Program and [2]Johns Hopkins Drug Discovery, Baltimore, MD 21224, USA

Cocaine and methamphetamine are highly addictive psychostimulants, yet to date, no pharmacological treatment is available for these substance use disorders. Like cocaine and methamphetamine, the clinically available and wake-promoting drug modafinil binds to the dopamine transporter (DAT); however, unlike cocaine and methamphetamine, it has low abuse potential. We have recently developed several novel analogues, based on the modafinil scaffold (e.g. JJC8-016, JJC8-088, JJC8-089 and JJC8-091; Cao et al 2016, Zhang et al 2017) and tested them on intravenous methamphetamine self-administration in rats (Tunstall and Ho et al, 2017). Although several analogues were effective, the analogue with highest binding affinity (Ki = 2.6 nM) and selectivity for DAT (JJC 8-088) was least effective in these models of methamphetamine abuse, possibly due to its poor pharmacokinetics. Hence, we extended our structure-activity relationship study by chemically manipulating the oxidation state of the sulfoxide group and by replacing the metabolically susceptible piperazine ring of the JJC series with a variety of bioisosteres, including dimethylpiperazines and aminopiperidines, resulting in several novel lead molecules. Evaluation for binding affinities at DAT, SERT and sigma-1 receptors led to the selection of a subset of compounds that were evaluated for metabolic stability in liver microsomes. Within this subset, several compounds showed improved metabolic stability as compared to previous leads and have been selected for further pharmacokinetic and behavioral studies in rats. In total, these studies will serve to identify the next lead compound(s) for behavioral evaluation and development toward pharmacotherapeutic treatment of psychostimulant abuse.
(Supported by NIDA IRP)

Oral Communication 1-4

Nanoparticle encapsulation of oxytocin increases its brain penetrance and duration of action in vivo

Oppong-Damoah, Aboagyewaah[1], Zaman, Rokon U[1], D'Souza, Martin J[1], and Murnane, Kevin S[1]
[1] Department of Pharmaceutical Sciences, Mercer University College of Pharmacy, Mercer University Health Sciences Center, Atlanta, GA USA

The blood-brain barrier (BBB) serves as a major limitation to the delivery of therapeutics for central nervous system (CNS) disorders. Current methods to deliver large-molecule therapeutics to the CNS include intrathecal administration, direct surgical cannulation, and intranasal delivery. In this study, we utilized both in vitro and in vivo models to evaluate the brain uptake of oxytocin encapsulated nanoparticles (OT-NP) conjugated with two different brain targeting ligands. As OT is a highly prosocial molecule, and intranasal delivery of OT is being developed for Autism Spectrum Disorder and substance-use disorders, including alcoholism and cocaine-use disorder, intranasal administration was employed for in vivo bioimaging and efficacy evaluations. In vitro studies showed successful NP transport across a murine brain endothelial cell (Bend.3 cells) model of the BBB. Brain imaging studies with a LI-COR Odyssey bioimager showed significantly higher brain penetrance of indocyanine green (ICG) dye NP, with a peak intensity of brain ICG uptake at 2 hours. Dyadic social interaction experiments revealed significantly higher social interactions 2 hours after administration of both types of NPs, which was sustained for at least 3 days. Interestingly, the type of brain targeting ligand influenced the nature of the acute social interactions, suggesting differences in the kinetics of brain uptake or the organ selectivity for the brain. These multimodal data strongly support the use of our approach to developing a brain targeting and sustained-release formulation of oxytocin. This formulation can now be used to support intranasal delivery of oxytocin and potentially other neuropeptides.

Oral Communication 1-5

The effects of lifelong Western diet exposure on compulsive cocaine intravenous self-administration in male Sprague-Dawley rats

Clasen, Matthew[1]; Sanon, Thery[1]; Hempel, Briana[1]; Nelson, Katherine[1]; Kearns, David[1]; Davidson, Terry[1]; Riley, Anthony[1]
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Recent literature suggests that dysregulated food and drug intake may result from similar mechanisms that usurp the neural circuits mediating reward, motivation, learning and memory in the brain (Kenny, 2011a; Kenny, 2011b; Riley et al., 2016; Tomasi and Volkow, 2013; Tomasi et al., 2015). Given the physiological and behavioral parallels between dysregulated drug and food intake, it might be predicted that a history with one would affect the likelihood of the other, i.e., animals that display dysregulated consumption of a highly palatable diet would display potentiated levels of compulsive drug intake. Interestingly, the limited research on the topic has only investigated the effects of high fat diet (HFD) consumption on compulsive cocaine intravenous self-administration (IVSA) in adults (see Wellman et al., 2007; Puhl et al., 2011) rather than the potentially more clinically relevant levels of high saturated fats, carbohydrates and refined sugars which characterize the Western diet (WD) in adolescents. In an effort to build upon these preclinical models, the present experiment evaluated whether chronic exposure to a WD initiated and maintained throughout adolescence and adulthood influences compulsive cocaine IVSA in adults. Specifically, 60 male Sprague-Dawley rats were maintained on either a WD (n = 42) or chow diet (n = 18) beginning on postnatal day [PND] 21. After jugular catheter implantation (PND 70-71), all animals underwent cocaine IVSA (Fixed Ratio [FR] 1, FR5, FR10, FR20, Progressive Ratio [PR] and cue- and drug + cue-induced reinstatement) from PND 77-126. Animals maintained on the WD throughout adolescence and adulthood displayed higher rates of cocaine IVSA, greater reinstatement of drug-taking behaviors and less inhibitory control (characteristic of addiction-like behavior; Deroche-Gamonet et al., 2004), than animals maintained on the standard rodent chow diet. Although the mechanisms underlying these effects are unknown and require further research, these results suggest that a history of a WD impacts subsequent

Oral Communication 1-6

Role of mu-opioid receptor agonist efficacy on antinociceptive interactions between mu-opioid agonists and the nociceptin/orphanin FQ agonist Ro 64-6198 in rhesus monkeys

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Despite the clinical utility of mu-opioid receptor (MOR) agonists in the management of pain, use can also be limited by undesirable effects including sedation. One approach to enhance the therapeutic effects and minimize the undesirable effects of MOR agonists is to develop MOR agonist combinations with an adjunct that targets a different receptor system. The nociceptin/orphanin FQ (NOP) system has emerged as one possible target. However, the role of MOR agonist efficacy in MOR/NOP agonist interactions is unknown. 3 rhesus macaques (Maccaca mullata) were utilized in a warm water tail-withdrawal procedure and 3 macaques in an assay of schedule-controlled responding (SCR). Five MOR agonists (NAQ, buprenorphine, nalbuphine, oxycodone, and methadone) that varied in their efficacy to stimulate in vitro GTPgammaS activity were evaluated in each assay alone and following pretreatment the NOP agonist (0.1 mg/kg Ro 64-6198). Ro 64-6198 administered alone, up to 0.32 mg/kg, did not significantly alter tail withdrawal latencies. However, Ro 64-6198 alone produced dose- and time-dependent, and SB612111 (NOP antagonist) reversible decreases in rates of responding. NAQ was ineffective. Buprenorphine, nalbuphine, oxycodone, and methadone alone produced dose-dependent antinociception. Nalbuphine, oxycodone, and methadone produced dose-dependent decreases in rates of responding. NAQ and buprenorphine were ineffective. Ro 64-6198 pretreatment enhanced the antinociceptive of buprenorphine, nalbuphine, and methadone without enhancing the rate-decreasing effects of these MOR agonists. These results support the utility of NOP agonists as candidate adjuncts to MOR agonists.

Oral Communication 2-1

Regulation of relapse-like drinking and alcohol-seeking by ligands selective for GABAA receptors expressing the α5 subunit

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Existing treatments for relapse prevention are not uniformly effective, and identifying novel therapeutics may lead to improved outcomes for patients with alcohol use disorders (AUDs). α5GABAA receptors are implicated in the reinforcing and interoceptive effects of alcohol. However, the role of α5GABAA receptors in relapse to alcohol use is unknown. This study assessed the contribution of these receptors to relapse-like drinking using an alcohol deprivation effect (ADE) procedure and to cue-induced alcohol seeking using a reinstatement procedure in Sprague Dawley rats. In the ADE study, male rats had two months access to water and 5%, 10%, and 20% alcohol solutions on their home cage. Following this period, ¬¬the solutions were removed and water only was available. The ADE was measured upon re-exposure to alcohol solutions. Treatment with vehicle, the α5GABAA-selective inverse agonist L-655,708, or the α5GABAA-preferring agonist QH-ii-066 was initiated one day prior to alcohol re-exposure, and continued for four days. The results show a significant and dose-dependent reduction in the ADE by L-655,708; whereas QH-ii-066 exacerbated expression of the ADE. In the reinstatement study, male rats were trained to orally self-administer a 2% sucrose/10 or 15% alcohol solution, where every two lever presses (fixed-ratio 2) resulted in solution delivery and presentation of a cue light. Once responding was stable, self-administration was extinguished by omitting deliveries of alcohol and cues. Subsequently, the extent to which re-exposure to the cue, following pretreatment with vehicle, L-655,708 or QH-ii-066, reinstated alcohol-seeking behavior was determined. L-655,708 dose-dependently attenuated cue-induced reinstatement, while QH-ii-066 had no systematic effects. The results suggest a key role for α5GABAA receptors in alcohol relapse and point to inverse agonists at this subtype as potential pharmacotherapeutics.

Oral Communication 2-2

Contribution of cocaine-related cues to concurrent monetary choice in humans

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Theoretical accounts highlight the importance of drug-related cues for the development, maintenance, and persistence of drug-taking behavior. However, few human laboratory studies have evaluated the ability of drug-related cues to influence decisions between concurrently presented non-drug reinforcers. The overall purpose of this study was to evaluate the contribution of cocaine-related cues to concurrent monetary reinforcer choice in humans. In each of three experiments, participants with a cocaine use disorder completed a cued concurrent choice task. Choices for varying monetary values were evaluated in the presence of concurrent cocaine and neutral cues. Critical trials presented equal monetary values on the cocaine- and neutral-cued side (e.g., $0.05 on the cocaine side and $0.05 on the neutral side). These experiments tested the selectivity of cue-induced choice bias for cocaine-cued options to cocaine use history (Experiment 1), the specificity of this bias to cocaine-related cues (Experiment 2), and a potential attentional mechanism, as evaluated using eye-tracking technology (Experiment 3). A significant and robust bias for cocaine-cued monetary values was observed in all three experiments (mean percent choice = 65% to 77%). These experiments demonstrated that this choice bias was selective to individuals with a history of cocaine use (i.e., was not observed in controls) and was specific to cocaine-cued monetary values relative to categorized-neutral cues. Attentional and choice biases were not significantly related. This study provides evidence that drug-related cues impact behavior towards drug-related alternatives during decision-making events. Future research evaluating the prospective association of drug-cued choice with drug-taking behavior will help reveal the clinical relevance of these findings for substance use disorder.

Oral Communication 2-3

Cytochrome c translocation in methamphetamine-induced vulnerability for Parkinson's disease

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Methamphetamine (meth) abusers are at risk for developing Parkinson's disease (PD). We revealed that rats self-administering (SA) meth exhibit a forced abstinence (FA) time-dependent reduction in brain biomarkers for PD (Kousik et al. JPET 2014) indicating that meth initiates a pathological trajectory that may result in PD. Mitochondrial dysfunction underpins meth-mediated neuronal stress, and exposure to rotenone (a specific mitochondrial toxin) causes PD. Here we hypothesize that a meth-induced trajectory towards PD is associated with brain mitochondrial dysfunction. Male Sprague-Dawley rats self-administered meth (0.1mg/kg/0.1mL/infusion) daily for 2 weeks; controls were yoked to non-contingent (NC) infusions of saline or meth injections. To isolate the contribution of mitochondrial dysfunction in vivo, subclinical doses of rotenone were administered via subcutaneous osmotic minipumps during meth FA14-FA19. Assessments of mild PD-like motor deficits (forelimb bradykinesia) were performed weekly. Meth-SA rats exhibited progressive motor deficits on FA14 ($p<0.01$), while NC meth+rotenone rats exhibited deficits on FA21 ($p<0.01$). On FA56, meth+rotenone rats exhibited exacerbated deficits ($p<0.01$) compared to meth-SA+vehicle and NC meth+rotenone rats. This suggest that an interaction between meth and rotenone is present only with self-administered meth. Rats were sacrificed and PD-relevant brain regions were dissected out on FA62. Here, we report cytochrome c translocation, an early step in mitochondrial apoptosis, for the striatum. Meth-SA rats exhibited higher cytosolic levels ($p<0.01$) and lower mitochondrial levels ($p<0.01$) of cytochrome c compared to saline+vehicle and saline+rotenone, but no interaction between the two treatments was seen. Unexpectedly, mitochondrial cytochrome c was elevated in the NC meth+rotenone rats compared to all groups ($p<0.01$). These novel findings reveal that the mitochondrial toxin, rotenone exacerbates meth-induced PD-like motor deficits, but the behavioral effects are not associated with cytochrome c changes in the striatum. The findings also reveal dramatic differences in outcomes that depend on contingencies of meth administration.

Oral Communication 2-4

The effects of lorcaserin on the abuse potential of intranasal oxycodone

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Serotonin (5-hydroxytryptamine; 5HT) modulates a number of physiological functions including mood, appetite, and sleep. Growing evidence suggests that 5HT2c receptors are also involved in modulating impulsive behaviors and reactivity to drug-related cues. In preclinical studies, 5HT2c agonists inhibit morphine-induced dopamine release, and reduce cocaine, ethanol, and nicotine self-administration. Lorcaserin, is a selective, high-affinity agonist at the 5HT2c receptors subtype, recently FDA approved for treating obesity. The aim of this randomized, double-blind, inpatient study was to assess the ability of lorcaserin to alter the abuse potential of intranasal oxycodone in humans. Twelve opioid-dependent volunteers without chronic pain (11 male) were detoxified from opioids before being maintained on active lorcaserin (10 mg BID) or placebo. During the sample session participants received $10 and either intranasal oxycodone (10 mg) or placebo, and the subjective effects were assessed at various time points. For the next 4 days, following the sample session, participants had the choice to receive the same dose or money. These testing procedures were then repeated with the alternative maintenance medication (lorcaserin or placebo). Lorcaserin maintenance did not significantly alter oxycodone self-administration, or ratings of positive subjective effects (e.g. "I feel high," "I liked the dose," etc.). Meanwhile, craving for opioids was significantly higher ($p<0.001$) under active lorcaserin maintenance. This study was unable to replicate preclinical findings of the effects of 5HT2c agonists on the abuse potential of opioids. Although lorcaserin failed to show promising results regarding its interaction with oxycodone, clinical studies examining its effects on cocaine, alcohol, and tobacco may be warranted.

Oral Communication 2-5

Convulsant and seizure-like effects of synthetic cannabinoids JWH-018 and 5F-AB-PINACA in mice: observational signs and in vivo electroencephalography

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Synthetic cannabinoids (SCBs) are man-made chemicals that bind to cannabinoid type-1 (CB1) receptors, typically with higher affinity and efficacy than Δ9-THC, the main psychoactive constituent in cannabis. Abuse of SCBs is associated with more frequent and severe adverse events than use of marijuana, and convulsions and seizures are documented in the clinical literature following exposure to SCBs. Recently, SCBs have been demonstrated to induce convulsant activity in mice. In this study, we used an observational scoring procedure and in vivo electroencephalography (EEG) to assess the convulsant and seizure-like effects of SCBs from two different "generations" of abused substances representing distinct structural classes: JWH-018, a first-generation indolyl-based SCB, and 5F-AB-PINACA a third-generation indazole-based SCB. For observational studies, drugs were injected intraperitoneally (i.p.) into mice, which were immediately placed into 500 ml Pyrex beakers with mesh covering. Animals were observed continuously for convulsant effects, and scored in two separate 15-minute intervals. Both SCBs elicited convulsant effects which were blocked by prior treatment with the CB1 antagonist / inverse agonist rimonabant. In separate studies, mice received a headmount device and EEG recording leads implanted onto the skull. Mice were then placed into a round EEG recording cage, in which the headmount attached to a preamplifier and digitizer to record the EEG signals. The preamplifier and cable connecting to the digitizer were suspended from above on a swivel arm to allow the mice free movement. Results from EEG data show seizure-like activity following injection of 5F-AB-PINACA and JWH-018. Comparisons among drugs, doses, and observable signs versus EEG recordings will be presented. Supported by DA039143 and UAMS.

Oral Communication 2-6

Field sobriety test for cannabis

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Cannabis and its active ingredient delta-9-tetrahydrocannabinol (THC) have been shown to impair memory, reaction time and attention. However, it is difficult to assess these impairments in the nonlaboratory setting. We have developed a prototype for a phone application called Am I Stoned?. As a first step, we tested the app in a within-subjects double-blind placebo-controlled study with THC (0, 7.5, 15 mg). Participants completed both iPhone-based and standard computer tests of cognitive speed, reaction time, fine motor ability, and memory. As a secondary aim we also assessed participants' ability to estimate their performance impairment. Twenty-four healthy experienced non-daily cannabis users completed a laboratory study, which included three 4-hour experimental sessions in which participants consumed a capsule containing THC (7.5, 15 mg) or placebo. They completed all tasks at both two and three hours after taking the capsule. Performance was impaired by THC in three of the four computer tasks, but only one of the iPhone tasks. It is likely that the computer tasks were more sensitive to THC impairment than the app task because the computer tasks were longer (15-20 min compared to 5-7 min), providing more opportunity to detect a drug effect. With regard to self-assessments, subjects were in general accurate in their awareness of impairments on the tasks. In a follow-up study we will improve the tasks used in the phone application to increase their sensitivity to THC impairment. This research is likely to lead to sensitive field tests that will allow users to objectively evaluate their ability to perform psychomotor or cognitive tasks. The research will also identify conditions under which individuals are or are not aware of their impaired state.

Oral Communication 3-1

Dopamine D2 autoreceptor signaling is depressed by neurotensin released from discrete inputs to midbrain dopamine neurons

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Midbrain dopamine neurons play physiological roles in many processes including reward and motivated behavior. Neurotensin (NT) is a neuropeptide implicated in substance use disorders which modulates dopamine neuron excitability in part by decreasing dopamine D2 autoreceptor-mediated inhibition. However, the mechanisms involved in release and signaling of endogenous NT are poorly understood. Here we combined patch clamp electrophysiology of dopamine neurons in midbrain slices from transgenic mice with blue light stimulation to specifically activate either NT or dopamine neurons. We found that low frequency stimulation of dopamine neurons alone was sufficient to induce long-term depression (LTD) of dopamine D2 autoreceptor inhibitory postsynaptic currents (IPSCs) and that this LTD could be blocked by either chelation of calcium in the patched cell or by preincubating the slice with a non-selective NT type 1 and 2 receptor antagonist. Dopamine neurons do not synthesize NT, but rather take up NT via internalization of NT receptors. Consistent with this, in mice that expressed channelrhodopsin in NT neurons, blue light did not cause a channelrhodopsin-mediated excitation of dopamine neurons. However, low frequency stimulation of NT neurons did result in a depression of dopamine D2-IPSCs (though to a lesser extent than stimulation of dopamine neurons) and this depression was blocked by a non-selective NT type 1 and 2 receptor antagonist. Together, these results suggest that NT could be released either by dopamine neurons to act as a retrograde messenger or released by non-dopamine neurons to act as an anterograde messenger, and in both cases can cause LTD of dopamine D2 autoreceptor signaling. These findings improve our understanding of how NT functions physiologically and how NT-induced synaptic plasticity may contribute to substance use disorders.

Oral Communication 3-2

NPFF receptors mediated opioid induced hyperalgesia and opioid tolerance. Preliminary data on new small molecule probes

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Opioid misuse represents an increasing problem and in 2014, it was estimated to be affecting nearly 2.1 million people wtihin the United States and as much as 36 million people worldwide. In fact, opioids are still the most effective treatment for moderate to intense acute pain, even though the benefits associated to their use in chronic pain are still debated. Nevertheless, their use is hampered by a number of side effects, e.g. opioid induced hyperalgesia (OIH), tolerance and respiratory depression.

An anti-opioid system has been hypothesized as a homeostatic adaptation upon opioid system stimulation that lead to tolerance development. Neuropeptide FF system, which comprises two receptor subtypes (NPFF1 and NPFF2), has been characterized as an anti-opioid system and its activation produces OIH. RF9 (Simonin et al., 2006) and the more recent compound 46 (Journingan et al., 2014) proved capable to antagonize NPFF induced hyperalgesia in mouse models.

To better characterize the pharmacophoric requirements, we synthesized structurally simplified analogues of 46 and evaluated them for binding affinity at NPFF1-R and NPFF2-R. Structural modification of the substituent on the piperidine ring of our scaffold with different cycloalkanes and diversely substituted aromatic rings showed how in this region the NPFF2 receptor has stricter steric requirements compared to NPFF1 receptor. This could be exploited for future generation of more selective NPFF ligands. Similarly, the distance and angle of orientation of the guanidine group from the same piperidine core showed significant effects on selectivity between the two receptor subtypes.

In conclusion, the structural simplification of our compounds allowed for a better initial understanding of the different structural requirement between the two receptor subtypes, which can lead to future non-peptidic chemical probes with greater selectivity. Support by: DA034777 and P20GM104932

Oral Communication 3-3

Protein kinase Cβ inhibition selectively decreases the reinforcing effects of amphetamine

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Amphetamines (AMPH) are a class of stimulants that are highly misused worldwide. Despite the prevalence of AMPH misuse, there are no pharmacological therapeutic options for AMPH-use disorder. AMPH elicits its reinforcing effect through the dysregulation of extracellular dopamine levels in the nucleus accumbens. Protein kinase Cβ (PKCβ) is a signaling protein that is important for AMPH action in the nucleus accumbens; inhibition of PKCβ reduces AMPH-stimulated dopamine release. Rodents administered PKCβ inhibitors display decreased AMPH-stimulated locomotor activity as compared with control rats. The goal of this study is to determine if PKCβ inhibitors can also alter the reinforcing effects of AMPH in rats. To achieve this goal, male Sprague-Dawley rats were trained to self-administer 0.032 mg/kg/infusion AMPH or sucrose pellets. The first group of rats was trained to respond for AMPH or sucrose under a fixed-ratio 5 (FR5) schedule of reinforcement. The rats were administered 10 pmol enzastaurin, a PKCβ-selective inhibitor, or vehicle directly into the lateral ventricles (i.c.v.) 18 hr prior to a self-administration session. A second group of rats was trained to self-administer AMPH or sucrose pellets under a progressive ratio (PR) schedule of reinforcement and vehicle, 10, or 30 pmol enzastaurin were given i.c.v. 18 hr prior to a self-administration session. An 18-hr enzastaurin pretreatment in rats trained under an FR5 schedule significantly decreased the number of responses for AMPH by 80% as compared to vehicle. Enzastaurin also decreased AMPH-maintained responding on a PR schedule as compared with vehicle treatment, such that breakpoints decreased to levels observed in the absence of AMPH. There was no significant difference in responding for sucrose on PR or FR5 schedules of reinforcement following an enzastaurin pretreatment. All together, these results demonstrate that a PKCβ inhibitor, enzastaurin, can selectively decrease the reinforcing effects of AMPH. These findings support developing PKCβ inhibitors into potential therapeutics for AMPH-use disorder. Funding by: NIH grant R01 DA11697, T32-GM007767, Benedict and Diana Lucchesi Graduate Fellowship.

Oral Communication 3-4

Individual differences in the self-administration of 3,4-methylenedioxypyrovalerone (MDPV) in rats: importance of behavioral flexibility

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Recreational use of synthetic cathinones is associated with high rates of abuse, toxicity, and abnormal behaviors in humans, and we have shown that the DAT-selective synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV) can maintain abnormally high rates of self-administration in a subset of rats (i.e., high-responders). To further characterize the high-responder phenotype, 18 male Sprague-Dawley rats previously trained to self-administer 0.032 mg/kg/inf MDPV (n=6 high-responders, n=6 low-responders) or 0.32 mg/kg/inf cocaine (n=6) were allowed to self-administer MDPV under schedules of reinforcement designed to assess the ability of rats to adapt their behavior to meet new contingencies either within a response sequence (i.e., a chain schedule of reinforcement), or within a session (i.e., a multiple component schedule in which the active lever changed across the session). When the contingency changed within a response sequence, high-responders earned fewer infusions and made significantly more schedule-inappropriate responses than under baseline conditions. When the active lever changed across components, high-responders maintained high levels of drug intake but also made high levels of inappropriate responses (e.g., responding on the inactive lever or during timeouts and blackouts). In contrast, low-responders and cocaine-trained rats readily adapted their behavior to meet the new contingencies and made very few inappropriate responses under either schedule. The present data expand upon our work and indicate that MDPV can induce unusually high levels of habitual responses in a subset of rats. These findings are consistent with reported human drug-taking patterns and suggest high-responders may also have impairments in behavioral flexibility and/or executive function; however it remains unclear whether this relationship is causative or correlative. Supported by NIH grants R01DA039146 and T32DA031115 and the NIH IRPs of NIDA and NIAAA.

Oral Communication 3-5

Development of an opioid vs. food choice procedure in rats: effects of reinforcer magnitude and extended opioid access

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Aims: The aim of this work was to develop a drug self-administration procedure in rats that permitted within-session assessment of choice between a liquid food concentration and a range of fentanyl doses.

Methods: In Experiment 1, male (n=6) and female (n=6) rats were trained to respond under a concurrent FR5:FR5 schedule of fentanyl and liquid food reinforcement. The fentanyl dose was fixed (3.2 µg/kg/inj) and the liquid food concentration (0-100%) was manipulated across sessions. Experiment 2 determined within-session fentanyl vs. liquid food choice wherein increasing unit fentanyl doses (0-10 µg/kg/inj) were concurrently available with a fixed liquid food concentration (1.8-56%). Experiment 3 determined the effect of extended fentanyl access (FR5, 3.2 µg/kg/inj, 12h/d, 5d/week, 2 weeks) on within-session choice between fentanyl (0-10 µg/kg/inj) and liquid food (18%).

Results: In Experiment 1, increasing liquid food concentrations decreased fentanyl-maintained behavior, with 56% and 100% liquid food significantly decreasing fentanyl-maintained responding compared to water (0% liquid food). In Experiment 2, increasing the unit fentanyl dose resulted in a within-session, dose-dependent increase in fentanyl choice. Increasing the liquid food concentration decreased the relative reinforcing effectiveness of fentanyl (i.e., rightward shift of the choice dose-effect function). In Experiment 3, fentanyl intake increased across the 10-daily extended-access sessions. Although rates of responding were decreased for both reinforcers, the relative reinforcing effectiveness of fentanyl was significantly increased during the second week of extended access (i.e., leftward shift of the choice dose-effect function). No significant sex differences were detected.

Conclusions: These results demonstrate feasibility of training a within-session opioid vs. food choice procedure in rats. The sensitivity of opioid choice in rats to these environmental and pharmacological manipulations provides empirical support for the translational potential of this procedure to published drug vs. food choice procedures used in human and nonhuman primate studies.

Oral Communication 3-6

Effects of the α2/α3-subtype-selective GABAA receptor positive allosteric modulator KRM-II-81 on pain-depressed behavior in rats: Comparison with ketorolac

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Pain remains a clinical challenge, largely because existing analgesics have limited efficacy and produce side effects. Positive allosteric modulators (PAMs) at α2/α3-subtype GABAA receptors have emerged as a new class of candidate analgesics. This study examined effects of one such PAM, KRM-II-81, in an assay of pain-related behavioral depression in rats. Adult, male Sprague-Dawley rats (n=6-9 per group) were implanted with bipolar electrodes into the medial forebrain bundle and trained to respond for electrical brain stimulation in a frequency-rate assay of intracranial self-stimulation (ICSS). Injection of 1.8% lactic acid, i.p. served as an acute noxious stimulus to depress ICSS. Effects of KRM-II-81 (0.32-10 mg/kg, i.p.) and ketorolac (0.1-10 mg/kg, i.p.) were evaluated in the absence and presence of acid. Neither ketorolac nor KRM-II-81 alone altered ICSS. Ketorolac dose-dependently reversed acid-induced depression of ICSS, and effects of 1.0 mg/kg ketorolac lasted for at least 5 hours. KRM-II-81 (1.0 mg/kg) produced significant antinociception after 30 min that dissipated by 60 min. The benzodiazepine binding-site antagonist flumazenil (10 mg/kg, i.p.) had no effect alone or in combination with either ketorolac or KRM-II-81. The lack of ketorolac or KRM-II-81 effect on ICSS in the absence of acid suggests low abuse liability for both compounds. KRM-II-81 produced significant but less-reliable and shorter-acting antinociception than ketorolac, which blocked acid-induced ICSS depression, consistent with its clinical analgesic efficacy. The resistance of KRM-II-81 antinociception to flumazenil antagonism suggests either (a) relatively low affinity of flumazenil for the benzodiazepine binding site on α2/α3-subtype-selective GABAA receptors or (b) mediation of KRM-II-81 antinociception by some other mechanism of action. Despite these caveats, these results support further consideration of KRM-II-81 and related compounds as candidate non-opioid, non-NSAID analgesics with low abuse liability. Supported by R01NS070715, R01NS076517, MH096463 and T32DA007027.

Oral Communication 4-1

Examining the effects of a selective serotonin 2C (5HT2C) receptor agonist (WAY 163909) on cocaine self-administration in adolescent male and female rhesus macaques exposed to early life stress

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Early life stress (ELS) is a major predictor in the emergence of cocaine abuse later in life in humans, and rhesus macaques serve as ideal candidates to examine the relationship between ELS and cocaine use. Previous data also suggest serotonin 2C (5HT2C) agonists may be viable candidates in the treatment of ongoing cocaine use. Accordingly, the effectiveness of the 5HT2C agonist WAY 163909 (WAY) to decrease cocaine self-administration (COC SA) was examined in adolescent male and female rhesus macaques that experienced maltreatment (MALT) or competent maternal care (Control). During adolescence, animals were trained to respond under a fixed-ratio 20 response (FR 20) schedule of reinforcement to receive an infusion of cocaine (0.1 mg/kg/infusion). After meeting criteria for stable SA, animals progressed through a full dose-effect curve to establish the dose that engendered the highest response rate (EDMax), and were then examined under maintenance conditions. During each testing week, WAY pretreatments (3 consecutive daily treatments administered 45 min prior to sessions) were preceded by normal maintenance sessions without any pretreatments, which provided a baseline of responding. Each WAY dose (0.1-1 mg/kg IM) was tested weekly interspersed by weeks of vehicle treatment. WAY dose-dependently decreased COC SA with MALT animals demonstrating lower response rates in comparison to controls, and females demonstrating higher response rates in comparison to males. The addition of further animals will be critical in elucidating sex-specific responding, and clarifying the role of ELS in predicting potential vulnerability to cocaine use in adolescence.

Oral Communication 4-2

Knockdown of hypocretin attenuates extended-access cocaine self-administration in rats

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The hypocretin/orexin (HCRT) neuropeptide system regulates feeding, arousal state, stress responses, and reward, especially under conditions of enhanced motivational relevance. In particular, HCRT neurotransmission facilitates drug-seeking behavior in circumstances that demand increased effort and/or motivation to take the drug. The present study used a shRNA-encoding adeno-associated viral vector to knockdown Hcrt expression throughout the dorsal hypothalamus in adult rats and determine the role of HCRT in cocaine self-administration. Chronic Hcrt silencing did not impact cocaine self-administration under short-access conditions, but robustly attenuated cocaine intake during extended self-administration access, a model that mimics key features of compulsive cocaine-taking. In addition, Hcrt silencing decreased motivation for both cocaine and palatable food (i.e., sweetened condensed milk; SCM) under a progressive ratio schedule of reinforcement, but did not alter responding for SCM under a fixed ratio schedule. Importantly, Hcrt silencing did not affect food or water consumption, and had no consequence to general measures of arousal-dependent behaviors. At the molecular level, chronic Hcrt knockdown moderately reduced the downstream expression of dynorphin (DYN) and melanin-concentrating hormone (MCH) in the dorsal hypothalamus. These original findings support the hypothesis that HCRT neurotransmission promotes operant responding for both drug and non-drug rewards, preferentially under conditions requiring a high degree of motivation. Furthermore, the current study provides compelling evidence for the involvement of the HCRT system in cocaine self-administration also under low-effort conditions in rats allowed extended access, possibly via functional interactions with DYN and MCH signaling.

Oral Communication 4-3

Nicotine as an adjuvant for μ-opioids: tail-withdrawal latency and disruptions in operant responding

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Nicotine has been demonstrated to produce antinociception in preclinical models of pain, yet the extent to which nicotine also may enhance μ-opioid analgesia has not been established. Here, male squirrel monkeys (N=4) responded for 0.1 cc of 30% condensed milk (v/v in water) under a fixed ratio 10 schedule of reinforcement followed by a 30-s timeout, during which the distal portion of the subject's tail was immersed in either 35, 50, 52, or 55°C water and the latency to remove the tail was recorded (10 s maximum). Dose-response functions for tail-withdrawal latency and disruptions in operant responding were generated for four μ-opioid receptor agonists that varied in efficacy (fentanyl>oxycodone≥buprenorphine>nalbuphine) alone or in the presence of nicotine (0.1 mg/kg nicotine). Fentanyl, oxycodone, and buprenorphine dose-dependently decreased response rate. All drugs dose-dependently increased tail-withdrawal latencies at each water temperature. Nicotine (0.1 mg/kg) did not significantly alter the dose-related effects of any of the μ-opioids on operant behavior. Nicotine significantly increased the antinociceptive potency of oxycodone as evidenced by moderate (2-5 fold) leftward shifts in dose-response functions at all water temperatures, and the nicotinic antagonist mecamylamine (0.1 mg/kg) fully antagonized the nicotine-induced increases in the antinociceptive potency of oxycodone. Nicotine produced comparable (2-5 fold) increases in the antinociceptive potency of buprenorphine but did not significantly alter the effects of fentanyl. Nicotine increased the potency of nalbuphine to produce antinociception at 50ºC and 52ºC >50-fold and >30-fold, respectively, and at 55ºC, the tail-withdrawal latency of nalbuphine increased from 1 s to 5 s in the presence of nicotine. Inasmuch as disruptions of operant responding are an indicator of behavioral impairment produced by μ-opioid agonists, these results suggest that nicotine may increases the analgesic potency of μ-opioids without concomitantly increasing some of its deleterious side-effects.

Oral Communication 4-4

Novel tools to investigate the role of dopamine D2/D3 receptors in antipsychotic drug-induced metabolic disease

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Antipsychotic drugs (APDs) cause significant metabolic side effects and increase risk for type II diabetes (T2D) with consequent high rates of treatment discontinuation. The ubiquitous trait amongst all APDs is their antagonism at dopamine D2 (D2R) and D3 (D3R) receptors which may mediate APD-induced metabolic side effects. Dopamine (DA) signaling through D2R and D3R in the central nervous system (CNS) mediates appetite and feeding behaviors. Because both D2R and D3R are also expressed peripherally in insulin-secreting pancreatic beta cells, DA signaling outside the CNS may be involved in systemic metabolic regulation. Activation of these receptors in beta cells mediates an autocrine/paracrine negative feedback circuit where DA co-released with insulin inhibits further insulin secretion via D2R/D3R signaling. We hypothesized that agonism of peripheral D2R/D3R, may counter APD actions on beta cells and counter APD-induced metabolic disturbances. To avoid exacerbating psychosis by countering APD actions in the CNS, we have designed peripherally-limited D2R or D3R agonists via quaternization at the basic nitrogen. We examined these quaternary salts and their parent drugs in glucose-stimulated insulin secretion assays using a beta cell-derived cell line and in islets. Bromocriptine methiodide (BroMeI), the most promising quaternary analogue, was compared to its parent, bromocriptine, an FDA-approved drug used in T2D treatment, and evaluated for metabolic stability in mouse microsomes as well as for blood/brain plasma ratios. BroMeI is currently being evaluated in in vivo metabolic analyses in mice including indirect calorimetry, food intake and body weight in the presence or absence of APD treatment. In total, these studies will further illuminate mechanisms underlying APD-induced metabolic syndrome and may lead to improved APD design.

Oral Communication 4-5

Effects of the bifunctional mu opioid and nociceptin/orphanin FQ peptide (NOP) receptor agonists on ethanol drinking in rhesus monkeys

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Alcohol use disorder (AUD) persists as a devastating public health problem that lacks widely effective pharmacological interventions. Recent preclinical research has supported the therapeutic potential of targeting brain receptors for the neuropeptide nociceptin/orphanin FQ (NOP). Here we examined the effects of a novel orvinol analog BU08028 (Khroyan et al. 2011) in a monkey model of AUD. BU08028 has a similar pharmacological profile to the intermediate-efficacy mu opioid receptor agonist buprenorphine, but has higher affinity and efficacy at NOP receptors and lacks abuse potential (Ding H et al. 2016). Five adult female rhesus monkeys were provided free access to a 4% ethanol (EtOH) solution and water in daily 6-hr sessions. Monkeys also self-administered food pellets by pressing a lever under a fixed-ratio schedule. When daily EtOH intakes were stable (~3.0 g/kg), BU08028 (0.001-0.01 mg/kg), buprenorphine (0.01-0.056 mg/kg) or the mu receptor antagonist naltrexone (1.7-5.6 mg/kg, all drugs i.m.) were administered 60 min before the session. All drugs decreased EtOH intake in all monkeys, but naltrexone also significantly decreased food-maintained responding. BU08028 (0.01-0.017 mg/kg, s.i.d., i.m.), buprenorphine (0.003-0.56 mg/kg, s.i.d., i.m.) and naltrexone (1.0-3.0 mg/kg, s.i.d, p.o.) were also studied during chronic daily administration over several weeks. Each week, an assessment was made in each animal as to whether the drugs selectively decreased EtOH vs. food intake. If not, the dose was increased for the next week. If so, the same dose was given for two additional weeks. When administered chronically over several weeks, naltrexone did not selectively alter EtOH intake. In contrast, chronic BU08028 and buprenorphine decreased EtOH drinking without altering food-maintained responding. The data support further study of BU08028 and other bifunctional and NOP receptor agonists as potential pharmacotherapies for AUD.

Oral Communication 4-6

High-affinity and selective D4R antagonist ligands as pharmacological tools to study substance use disorders

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Dopamine D4 receptors (D4R) are G protein-coupled receptors predominantly expressed in the prefrontal cortex where they play an important role in cognition, attention, and decision making. Previous studies using D4R ligands of varying efficacies have determined that D4R signaling alters behavior in animal models of drug addiction and cognition. Developing novel D4R-selective ligands will allow more detailed investigations into the biological role of D4R signaling in the brain and assist in medication development for neuropsychiatric disorders, including Alzheimer's disease and substance use disorders (SUD). In order to develop new candidate medications for SUD, we have designed, synthesized, and pharmacologically evaluated novel D4R antagonist ligands. Starting with the D4R antagonist 2-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)propyl)benzo [d]thiazole as our parent compound, we optimized a next-generation compound library by using a computational modelling approach. We hypothesized that structural modifications of the parent compound template would produce novel ligands with high D4R binding affinity, receptor subtype selectivity, and efficacy. In this pursuit, we have produced a library of eighteen compounds with varied substitutions on the pyrimidinylpiperidinyl (PP) ring and/or the benzothiazole moieties. These novel ligands were synthesized and their in vitro binding affinities were determined using [3H]N-methylspiperone radioligand binding in HEK293 cells expressing dopamine D2-like receptors. By modifying the pyrimidinylpiperidinyl and benzothiazole moieties, we have identified several high-affinity compounds (Ki ≤ 4.85 nM) with >100-fold selectivity at the D4R versus D2 and D3 receptors. Based on binding profiles, a subset of analogues were evaluated in functional assays measuring β-arrestin recruitment and cAMP production. These new lead compounds will be further evaluated for effects in animal models of cognition and/or drug addiction.

Poster Presentations

Poster 1-1

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

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The dopamine D3 receptor (D3R) is an attractive target for development of medications to treat neuropsychiatric conditions including substance use disorders. D3R-selective ligands with high affinity have been discovered, affording critical tools for cell-based assays that have been translated to in vivo models of drug abuse. These ligands have been extensively investigated and have shown promising results in rodent models of self-administration and relapse-like behaviors. Nevertheless, to date, advancement to human studies has been limited. Recently, we reported VK4-116 and VK4-40 as high affinity and D3R selective lead molecules for the treatment of opioid use disorders (Kumar et al., 2016). Both compounds and their enantiomers showed excellent metabolic stability in rat liver microsomes and in vivo efficacy for oxycodone-related behaviors in rats. We previously reported that 3-F analogs of another lead molecule, (R)-PG648, resulted in promising pharmacological profiles (Kumar et al., 2014). Thus, we synthesized a series of novel analogs of the VK compounds by replacing the 3-OH with a F in the linker between the primary and secondary pharmacophores. Among these, ABS01-113, and ABS01-114 demonstrated high D3R binding affinity with Ki=0.48 nM and 2.09 nM, respectively. In addition, modification of the primary or secondary pharmacophores with a 3,4-(methylenedioxy)-phenyl group was also examined. Off target binding affinities, functional efficacies and metabolic profiles of these new lead compounds will be highlighted with the aim of identifying a lead molecule for clinical development.

Poster 1-2

Reinstatement of responding for MDPV and "bath salts" mixtures: influence of reinforcement history

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"Bath salts" preparations often contain multiple compounds, typically one or more synthetic cathinone (e.g., 3,4-methylenedioxypyrovalerone [MDPV]) and adulterants, such as caffeine. Though "bath salts" users report high amounts of drug craving, the degree to which this is impacted by a history of self-administering drug mixtures remains unclear. These studies aimed to evaluate the ability of MDPV, caffeine, and mixtures of MDPV+caffeine to reinstate responding as a function of the composition of the self-administered drug(s) (i.e. MDPV or MDPV+caffeine). Male Sprague Dawley rats self-administered either MDPV (0.032 mg/kg/inf; n=20) or MDPV+caffeine (0.0288 and 0.66 mg/kg/inf, respectively; n=20) before undergoing 7 days of extinction. Then, reinstatement tests were conducted to evaluate the effectiveness of saline (cues alone), MDPV (0.032-1.0 mg/kg), caffeine (1.0-32 mg/kg), and mixtures of MDPV+caffeine (in 3:1, 1:1, and 1:3 ratios) to reinstate responding on the previously reinforced lever. Pretreatments of MDPV and caffeine dose-dependently increased responding for stimuli previously paired with drug infusions and were equally effective, regardless of reinforcement history. Combinations of MDPV+caffeine had supra-additive interactions, reinstating responding to levels greater than was observed with either MDPV or caffeine alone, an effect that is consistent with previous findings of supra-additive interactions between the reinforcing and discriminative stimulus effects of MDPV and caffeine. Although these findings suggest that reinforcement history (MDPV or MDPV+caffeine) does not impact the effectiveness of MDPV or caffeine alone to reinstate responding, they also suggest that "bath salts" mixtures (MDPV+caffeine) may be more effective at promoting relapse-related behaviors than either drug alone.

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Poster 1-3

Design and synthesis of a novel hapten for use in heroin vaccines: testing the facial recognition hypothesis

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A novel heroin like hapten molecule with a linkage on the C14 position of the 4,5-epoxymorphinan backbone has been synthesized. A hapten-based vaccine against heroin must be able to induce specific antibodies that kinetically sequester heroin and its active metabolites before they are able to bind to the opioid receptors. Drugs of abuse such as heroin are too small to evoke an immune response; they must be conjugated to an immunogenic carrier protein such as tetanus toxoid. Attachment of the hapten to the carrier protein via covalent linker restricts the conformational freedom of the hapten and thereby bifurcates the hapten's structure into two immunologically defined faces. The attachment site is crucial for defining the cross-reactivity of hapten-induced antibodies. The cross-reactivity of the antibody, antibody titer, and antibody affinity influences the quality of immune response and consequently the biological efficacy of the heroin vaccine. Vaccines incorporating haptens linked at C3, C6, and N17 have been previously prepared. A heroin mimetic hapten with a 3-(tritylthio)propanamide linkage at the C14 position has been prepared in 6 steps from thebaine. The installation of the C-N bond at the C14 position of thebaine was achieved stereoselectively through a hetero Diels-Alder reaction utilizing acyl nitroso intermediates.

Poster 1-4

Adolescent traumatic brain injury alters the neurobiology of the reward pathway and increases cocaine drug seeking behavior

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Clinical studies identify traumatic brain injury (TBI) as a risk factor for the development of cocaine substance use disorder (SUD). Our previous pre-clinical studies in mice demonstrated moderate TBI during adolescence increased susceptibility to the rewarding effects of a subthreshold dose of cocaine during adulthood. Here we investigated how adolescent TBI affects rates of cocaine self-administration (SA) in rats. Further, TBI pathology reveals disrupted blood-brain barrier (BBB) status in the reward pathway. The implication of BBB changes post TBI, a hallmark of neuro-inflammation, may explain how the rewarding effects of cocaine shift as a consequence of TBI. A controlled cortical impactor induced moderate TBI in male adolescent (P42) Sprague Dawley rats. 2- weeks post injury, rats were trained to self-administer cocaine (0.1 or -0.5 mg/kg/inf) in daily 2-hr sessions under FR1 for 7 days. On day 8, rats were switched to a progressive ratio design in 4-hr sessions for another 7 days. Histology and gene expression assays were used for neuroinflammation and BBB integrity indices. At the high dose (0.5mg/kg/inf), adolescent TBI decreased cocaine SA and did not affect breakpoints. However, at the low dose (0.1mg/kg/inf), TBI increased cocaine SA. Additionally, we detected increased expression of immune response-associated genes and disrupted tight junction protein expression in microvessels isolated from the prefrontal cortex and nucleus accumbens of TBI rodents. Our studies suggest that TBI during adolescence may enhance the abuse liability of cocaine in adulthood and vulnerability to the rewarding effects of cocaine could be higher as a result of brain injury. Moreover, key pathological findings such as BBB changes in areas of the reward pathways support the notion that neuroinflammation may contribute to how rewarding effects of cocaine post-TBI are affected. 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

Pharmacogenetics study in Mu-opioid receptors: the key for developing individualized therapeutics

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The mu-opioid receptor (OPRM1), a G protein-coupled receptor (GPCR), has been shown to be associated with alcohol, opioid and other substance abuse disorders. Specific genetic mutations in OPRM1 have been shown in human and primates, from our studies and those of others, to affect behavioral and pharmaceutical response; however, the mechanisms responsible remain largely unknown. Studies of OPRM1 pharmacogenetics at cellular and molecular levels could further our understanding of the behaviors and to assist the development of personalized therapeutic OPRM1 ligands for patients and better understand the mechanisms through which OPRM1 exerts its effects on addictive behaviors. In this study, we explore whether ligand-induced GPCR downstream signaling pathways are biased across OPRM1 polymorphisms. Two single nucleotide polymorphisms (SNPs) that change protein sequence, C17T and A118G, exist on the N-terminal domain of the OPRM1 and are common in human populations. Additionally, we are testing a rhesus macaque SNP, C77G, which appears to be functionally and behaviorally parallel. We first transduce transcriptional response element inducible luciferase reporters from four pathways (NFkB, cAMP, MAPK/ERK, and MAPK/JNK) into multiple cell lines (SK-N-MC, CHO and HEK 293). We then transfect in a plasmid containing the specific variation of the OPRM1 and generate a concentration response curve with DAMGO, beta-endorphin, morphine or other mu-opioid agonists. Preliminary data finds that the potency of different ligands on downstream signaling pathways vary and are affected by genetic polymorphisms. These findings are similar in rhesus macaques and humans. This has implications not only for understanding the means by which the mu opioid receptor affects behaviors, but also for how genetic differences are likely to affect novel biased ligands.

Poster 1-6

Stereoselective effects of the second generation 'Bath Salt' a-pyrrolidinopentiophenone (α-PVP): Assessments of taste avoidance, thermoregulation, motor activity and stereotypies

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Work on α-pyrrolidinopentiophenone (α-PVP), a second generation "bath salt" that is similar to MDPV and cocaine, has been generally limited to the racemate, and with other synthetic cathinones there are differences between their enantiomers, e.g., differences in potency, general activity and mechanism of action. To address if the aversive effects of the enantiomers of α-PVP differ, the present studies examined the ability of 3.0 mg/kg racemic α-PVP and its S(-) and R(+) enantiomers to induce conditioned taste avoidance, thermoregulatory changes, motor activity and stereotypies (see Nelson et al., 2017) in adult male Sprague-Dawley rats (n = 32). In the taste avoidance assessment, subjects injected with racemic and S(-)α-PVP significantly decreased saccharin consumption from their own baselines and drank significantly less saccharin than those injected with vehicle and R(+). Groups Racemic and S(-) displayed significant increases in temperature following α-PVP and also displayed significant increases in motor activity following α-PVP (and elevated stereotypies) compared to Groups Vehicle and R(+). Under no conditions did Group R(+) differ from controls. In conclusion, the effects of α-PVP were stereospecific and functionally identical across a variety of measures of the aversive effects of the drug, e.g., taste avoidance, temperature, motor activity and stereotypies, for which the S(-) enantiomer was indistinguishable from the racemic mixture. R(+) was behaviorally inactive at the single dose assessed. These data suggest that for these behavioral and physiological endpoints, the S(-) enantiomer mediates the aversive effects of α-PVP (similar to that seen with MDPV). The present work may be important to understanding the use and abuse of α-PVP and related compounds as stereoselectivity be yet another factor to consider when evaluating abuse risk and treatment.

Poster 1-7

The biased mu-opioid agonist, TRV130, produces reinforcing and antinociceptive effects that are comparable to oxycodone in rats

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RATIONALE: Mu-opioid agonists (e.g., oxycodone) are highly effective at treating pain. However, they also produce reinforcing effects that increase their likelihood of abuse. Recent strategies in drug development have focused on opioids with biased receptor signaling profiles that favor activation of specific intracellular pathways over others with the aim of increasing therapeutic selectivity. TRV130, a biased mu agonist, produces antinociceptive effects comparable to the mu-agonist, morphine, with reduced side effects. However, no published self-administration data exist assessing TRV130's abuse potential. METHOD: In the present study, we assessed the relative reinforcing effects of TRV130 and oxycodone, a commonly-prescribed mu agonist, in self-administration under a progressive-ratio (PR) schedule of reinforcement. In addition, we assessed the relative potency and efficacy of TRV130 and oxycodone in a test of thermal antinociception (Hot Plate). For self-administration, male Sprague-Dawley rats (n=6) received intravenous TRV130 or oxycodone (0.01-0.32 mg/kg/inf) under a progressive-ratio (PR) schedule of reinforcement. For the Hot-Plate Test, male rats (n=6) received subcutaneous injections of TRV130 (0.1-3.2 mg/kg/inj) or oxycodone (0.1-5.6 mg/kg/inj) and response latencies were measured. For the PR test, maximum injections were analyzed with a repeated-measure ANOVA, and means across subjects were compared using Bonferroni Tests. For the Hot-Plate Test, relative potencies were determined with linear regression, and ED50 values were averaged and compared with a paired t-test. RESULTS: TRV130 and oxycodone were equi-effective as reinforcers, and TRV130 was slightly more potent in thermal antinociception than oxycodone. This study demonstrates that TRV130 produces similar reinforcing and antinociceptive effects to a commonly-prescribed opioid, and that a biased-signaling profile does not necessarily reduce abuse potential.

Poster 1-8

Sex differences in GABAergic transmission in the nucleus accumbens and interpeduncular nucleus during nicotine withdrawal

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Of all the alcohol consumed by U.S. adults, 75% is in the form of binge drinking, binge drinkers also have an increased risk for developing alcohol dependence (compared with non-binge drinkers). Additionally, mounting evidence substantiates a positive association between physical activity and alcohol consumption. To assess the interactive effects of binge alcohol and exercise on the brain, female adult Long-Evans rats (n=45) were randomly assigned to either control or alcohol groups and given a once-weekly alcohol (5 g/kg) or iso-caloric control dose via intragastric gavage for 11 weeks. After each alcohol dose, rats either remained sedentary or were given access to exercise wheels (2 hours/day for 3 days). Blood ethanol concentration (average 159.8 mg/dl) and behavioral intoxication were measured weekly and did not differ between binged groups. Brain tissue was collected 4 days following the final alcohol dose, and was stained using immunohistochemistry and target cells were then counted using stereology. Sedentary rats had a 19% reduction in remaining granule cells (NeuN) in the dentate gyrus of the hippocampus compared with sedentary controls, and exercise was found to fully reverse this effect. In comparison to sedentary controls, binge sedentary rats and all exercised rats showed increased hippocampal neurogenesis, indicated by DCX staining. There were no differences between groups in the number or nuclear volume of mPFC neurons (NeuN) or in neuronal activation in the mPFC or DG in response to water maze testing (c-Fos). Analyses of microglia in the hippocampus (IBA1) showed that exercise decreased the total number of microglia, and although binge sedentary animals had an increase in the number of activated microglia in the hippocampus when compared to sedentary controls, exercise was found to reduce the overall number of activated microglia. Together, these results show that weekly binge alcohol in female rats causes detectable neuronal damage and changes in microglial morphology in the hippocampus of adult female rats and that exercise may counteract these damaging effects.

Poster 1-9

Abuse liability and anti-addiction potential of the atypical Mu opioid receptor agonist IBNtxA

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OBJECTIVE: IBNtxA (3-iodobenzoyl naltrexamine) is a novel μ opioid receptor (MOR) agonist, a naloxone derivative, structurally related to the classical MOR antagonist naltrexone. Recent studies suggest IBNtxA preferentially signals through truncated MOR splice variants, producing a unique pharmacological profile resulting in potent analgesia with reduced side effects, including no conditioned place preference (CPP) when tested at a single dose. The purpose of this study is to 1) evaluate a range of IBNtxA doses to more fully assess its abuse liability and 2) determine the effects of IBNtxA on morphine CPP expression and reinstatement of morphine CPP.

METHODS: IBNtxA was synthesized and compared to morphine in standard analgesia and CPP expression assays. Following morphine CPP training, IBNtxA was tested for its effects in inducing CPP reinstatement on its own or attenuating morphine-primed reinstatement. Drug discrimination studies are underway.

RESULTS and CONCLUSIONS: IBNtxA represents an intriguing lead compound for preclinical drug development specifically targeting MOR splice variants, potentially creating effective analgesics with reduced side effects. Furthermore, IBNtxA could have use as an adjunct therapy in agonist replacement strategies (e.g., methadone). Current collaborative efforts are aimed at developing novel analogues of IBNtxA for further analysis and understanding ligand-receptor interactions across MOR splice variants using molecular modeling.

Poster 1-10

Effects of the single prolonged stress model of PTSD on opioid self-administration

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Of all the alcohol consumed by U.S. adults, 75% is in the form of binge drinking, binge drinkers also have an increased risk for developing alcohol dependence (compared with non-binge drinkers). Additionally, mounting evidence substantiates a positive association between physical activity and alcohol consumption. To assess the interactive effects of binge alcohol and exercise on the brain, female adult Long-Evans rats (n=45) were randomly assigned to either control or alcohol groups and given a once-weekly alcohol (5 g/kg) or iso-caloric control dose via intragastric gavage for 11 weeks. After each alcohol dose, rats either remained sedentary or were given access to exercise wheels (2 hours/day for 3 days). Blood ethanol concentration (average 159.8 mg/dl) and behavioral intoxication were measured weekly and did not differ between binged groups. Brain tissue was collected 4 days following the final alcohol dose, and was stained using immunohistochemistry and target cells were then counted using stereology. Sedentary rats had a 19% reduction in remaining granule cells (NeuN) in the dentate gyrus of the hippocampus compared with sedentary controls, and exercise was found to fully reverse this effect. In comparison to sedentary controls, binge sedentary rats and all exercised rats showed increased hippocampal neurogenesis, indicated by DCX staining. There were no differences between groups in the number or nuclear volume of mPFC neurons (NeuN) or in neuronal activation in the mPFC or DG in response to water maze testing (c-Fos). Analyses of microglia in the hippocampus (IBA1) showed that exercise decreased the total number of microglia, and although binge sedentary animals had an increase in the number of activated microglia in the hippocampus when compared to sedentary controls, exercise was found to reduce the overall number of activated microglia. Together, these results show that weekly binge alcohol in female rats causes detectable neuronal damage and changes in microglial morphology in the hippocampus of adult female rats and that exercise may counteract these damaging effects.

Poster 1-11

Sex differences in a novel triple knock-in mouse model of Alzheimer's Disease

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Alzheimer's disease (AD) affects millions and costs hundreds of billions yearly. Key AD symptoms include cognitive impairment and mood disorders. Women are disproportionally affected by the disease and comprise about two-thirds of the world's AD population. Despite this, major research efforts have thus far not resulted in a single effective therapeutic for AD. To address this challenge, we evaluated sex differences in brain pathology and behavior in a novel triple knock-in (KI) mouse model of AD. We employed histochemical staining techniques (hematoxylin and eosin and Congo red) to detect neutrophil infiltration and plaque deposition in the mouse brain. We also utilized both cognitive (Y maze) and affective (marble burying) behavioral tests in male and female mice. We used high pressure liquid chromatography coupled to electrochemical detection to relate changes in behavior to changes in monoamine neurochemistry. We used the head-twitch response (HTR) induced by 2,5-dimethoxy-4-iodoamphetamine (DOI) to compare sex differences in serotonin 2A receptor function. Our results indicate significant behavior deficits between sexes and genotypes. We have also detected and quantified amyloid plaques, neutrophil infiltration, and monoamine neurochemistry in both the cortex and the hippocampus of KI mice. Male wild-type mice exhibited the fewest number of head twitches at the peak of the dose-effect curve. We have successfully validated the novel mouse model using behavioral paradigms and Identified AD related brain pathology. Our data suggest that 5-HT2A receptors may be an important component of female vulnerability to AD.

Poster 1-12

Small-molecule Neuromedin U Receptor 2 agonists suppress food intake and decrease visceral fat in animal models

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Obesity is a continuing and substantial health problem in need of more effective medications. An innovative target pathway in this regard is neuromedin U, a neuropeptide shown to suppress food intake and attenuate weight gain in animal models. These effects of neuromedin U are thought to be related to agonism of the neuromedin U receptor 2 (NmUR2). Although neuromedin U itself reduces food intake in rats, small-molecule NmUR2 agonists have not been evaluated in any animal model of disease. We therefore evaluated two small-molecule NMUR2 agonists for their in vitro signaling and their in vivo efficacy. The NmUR2 agonists NY0116 and NY0128 were synthesized and both agonists induced calcium signaling in cultured cells. When tested in vivo, acute administration of rats with either compound significantly decreased high-fat diet consumption after 24 hours of feeding. Repeated administration of the compounds in mice decreased body weight and specifically decreased the percentage of visceral adipose tissue in obese mice. These results have confirmed two small-molecule NMUR2 agonists are efficacious in animal models to decrease fat content and body weight, suggesting NMUR2 is a potentially promising therapeutic target for metabolic disorders.

Poster 1-13

Effects of opioid mixtures on gastrointestinal motility in rats

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Prescription opioids (mu receptor agonists) are commonly used to treat moderate to severe pain despite well-documented adverse effects (e.g., constipation, abuse). Kappa opioid receptor agonists also have antinociceptive effects and might be useful for treating pain in drug mixtures. The kappa opioid receptor agonist spiradoline in mixtures with the mu opioid receptor agonist morphine has additive or supra-additive antinociceptive effects in rats, such that smaller doses of each drug are needed to achieve antinociceptive effects compared with either drug alone. The use of smaller doses in mixtures might reduce or avoid adverse effects that occur with larger doses. The current experiment determined the effects of morphine alone and spiradoline:morphine mixtures (in 3:1, 1:1, and 1:10 ratios based on antinociception experiments) on gastrointestinal (GI) motility, as measured by fecal output, in Sprague Dawley rats. Rats had 2 hours of access to wet chow before receiving an i.p. injection; fecal output then was counted and weighed hourly for the next 6 hours. All tests were separated by at least 5 days. Morphine (1-10 mg/kg) dose-dependently decreased fecal count and weight compared with saline. Increasing the dose of morphine in the spiradoline:morphine mixtures decreased fecal output and weight. When the dose of morphine in the mixtures was held constant and the dose of spiradoline was increased (e.g., the 1:1 mixture compared with the 3:1 mixture), fecal output and weight were reduced compared with saline. Only the dose of morphine in the mixture determined the effects on GI motility. Overall, spiradoline:morphine mixtures selectively reduce the dose of morphine needed to produce antinociceptive (therapeutic) effects. The potency of morphine alone to inhibit GI motility was 3-fold greater than the potency to produce antinociception, but in mixtures with spiradoline the relative potency of morphine across assays was similar. It remains unknown whether spiradoline:morphine mixtures have other adverse effects (abuse, respiratory depression, dysphoria) and whether interactions between spiradoline and morphine on these outcomes might be related to the ratio of each drug in mixtures.

Poster 1-14

Effects of the single prolonged stress model of PTSD on opioid self-administration

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Post-Traumatic Stress Disorder (PTSD) is a mental health disorder that affects six million veterans per year. PTSD is a debilitating disorder characterized by symptoms such as re-experiencing the traumatic memories; avoiding thoughts, people, and objects relating to the event; negative changes in mood; and the inability to focus. Roughly 20% of veterans with PTSD were also diagnosed with chronic pain. Veterans with PTSD/chronic pain are typically treated with benzodiazepines for anxiety, and opioids for pain. When these two drugs are used together, individuals are three to four times more likely to have a drug abuse disorder. This dramatically increases the odds of drug overdose or suicide attempts. The single prolonged stress model (SPS) of PTSD consists of physical restraint followed by a group swim, a brief isoflurane-induced anesthesia, and a seven-day recovery period where rats remained in their home cage undisturbed. Rats (5 SPS-treated, and 6 non-SPS controls) were initially trained to self-administer remifentanil (0.0032 mg/kg/inf.) under a fixed ratio (FR)1 schedule of reinforcement to assess differences in the acquisition of opioid self-administration. Rats were then moved to a FR3 schedule of reinforcement and dose-response curves were established to determine if stress impacted sensitivity to the reinforcing effects of remifentanil. Although SPS-treated and control rats acquired remifentanil self-administration at comparable rates, SPS-treated rats were earning slightly fewer infusions of remifentanil as compared to the non-SPS rats by the end of the 14-day period. The remifentanil dose-response curve for SPS-treated rats also appeared to be shifted to the left relative to the control dose-response curve, suggesting that SPS treatment increased the potency of remifentanil to function as a reinforcer. Differences in sensitivity to opioids following traumatic life events could account for the high rate of opioid abuse within the veteran population. Future studies will continue to explore the impact of stress and stress-associated stimuli on opioid self-administration.

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Poster 1-15

Fluoxetine induces long-lasting changes in sensitivity to the rewarding properties of cocaine in female C57BL/6 mice

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Preclinical literature indicates that exposure to psychotropic medications, during early development, results in long-term altered behavioral responses to drugs of abuse. However, to date, these studies have been conducted in male subjects only. This is surprising, given that females, when compared to males, are more likely to be diagnosed with mood-related disorders, and thus, be prescribed with psychotropic medications such as antidepressants. Therefore, the objective of this study is to assess whether exposure to the selective serotonin reuptake inhibitor fluoxetine (FLX) results in long-lasting alterations in sensitivity to the rewarding properties of cocaine, using female mice as a model system. Specifically, adult female C57BL/6 mice were exposed to FLX (in their drinking water, 250 mg/l) from postnatal days (PD) 70-84, a time frame that corresponds to early adulthood. Twenty-one days later (PD 105+), mice were assessed on behavioral responsivity to cocaine (0, 2.5, 5, 7.5 mg/kg) using the conditioned place preference paradigm. Our data demonstrate that female mice, previously exposed to FLX, display decreases in the total time spent in the drug-paired side-compartment, when compared to saline-treated controls. Collectively, this suggests that exposure to FLX leads to enduring decreases in sensitivity to the rewarding properties of cocaine.

Poster 1-16

Effects of plant-based cannabinoids on schedule-controlled behavior and memory in rats

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The purpose of this study was to examine 3 major cannabinoid constituents of the marijuana plant. These compounds included the major psychoactive compound, Δ^9-tetrahydrocannabinol (Δ^9-THC), the major non-psychoactive compound, cannabidiol (CBD), and the less studied compound, cannabinol (CBN). To examine the effects of these 3 compounds on schedule-controlled behavior, male rats were trained to respond under a multiple timeout (TO), fixed-ratio (FR) 20 schedule of food presentation in which cumulative doses could be given at the beginning of each 20-min timeout as a pretreatment. In addition, the effects of Δ^9-THC and CBD were assessed, alone and in combination, in female rats trained on a repeated acquisition and delayed-performance procedure. Under this procedure, rats learned a different 4-response sequence daily and sequence retention (memory) was tested following a 60-minute delay. Responding was maintained under a second-order fixed-ratio 3 schedule of food presentation. Drugs were administered 30 minutes prior to the end of the delay, and a percent savings measure was used to assess retention. Δ^9-THC and CBN, but not CBD, dose-dependently decreased response rates, without markedly increasing pre-ratio pauses under the multiple TO-FR schedule. Δ^9-THC also dose-dependently decreased percent savings and response rate, and increased percent errors on the repeated acquisition and delayed-performance procedure. Pretreatment with the cannabinoid type-1 receptor (CB1) antagonist, rimonabant, produced a rightward shift of the dose-effect curves for Δ^9-THC, suggesting that the disruptive effects of Δ^9-THC on both schedule-controlled behavior and memory were mediated by CB1 receptors. Interestingly, CBD had little to no effect on memory when administered alone, but pretreatment with CBD antagonized the disruptive effects of Δ^9-THC on memory. In summary, Δ^9-THC and CBN produced similar disruptions to schedule-controlled behavior in male rats, and Δ^9-THC and CBD produced contrasting effects on memory in female rats. Therefore, whole plant effects of marijuana may be difficult to predict, as they may vary based on cannabinoid composition.

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Poster 1-17

Estrogenic modulation of cocaine response in the medial preoptic area is dependent on biological sex

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Behavioral response to cocaine is sex dependent. Which neuroendocrine factors regulate these differences is still unclear. Evidence indicates that the medial preoptic area (mPOA) in the hypothalamus regulates cocaine response, both neural and behavioral activity, as evidenced by conditioned-place preference (CPP) and microdialysis experiments. The hormone estrogen, in particular, acts in the mPOA to modulate response to cocaine. Because the mPOA is a major regulator of sex-specific behavioral differences across various species and for a variety of behaviors, here we investigated whether modulation of cocaine by estrogen in the mPOA is dependent on sex. To this end, male and female rats were divided into groups receiving systemic cocaine or vehicle injections. These were then further subdivided into those receiving estradiol or vehicle microinjections directly into their mPOA, for a total of 8 groups. After receiving cocaine, animals were given a CPP and locomotor test to measure their behavioral responses to the drug. Results indicate an important role for estrogen in the mPOA modulating sex differences in the animal's response to the drug. Namely, estradiol microinjections enhanced cocaine-induced CPP in females but not in males. This confirms that cocaine response is sensitive to estrogenic signaling in the mPOA, as previously shown, and moreover, that this influence is dependent on biological sex.

Poster 1-18

The effects of intermittent dietary supplementation with fish oil on high fat diet-induced enhanced sensitivity to the behavioral effects of dopaminergic drugs

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Eating a high fat diet can lead to obesity, type 2 diabetes, and dopamine system dysfunction. For example, rats eating high fat laboratory chow are more sensitive than rats eating standard chow to the behavioral effects of dopaminergic drugs (e.g., cocaine and quinpirole). Specifically, drugs that act on dopamine systems produce unconditioned behavioral effects in rats, and these behavioral effects (quinpirole-induced yawning and cocaine-induced locomotion) are enhanced in rats eating high fat chow. Daily dietary supplementation with 20% (w/w) fish oil prevents this effect in rats; however, for beneficial effects of fish oil in humans, doctors recommend that patients take fish oil only 2-3 times a week. To test the hypothesis that intermittent (e.g., 2/7 days per week) dietary supplementation with fish oil prevents high fat diet-induced effects (e.g., weight gain and enhanced sensitivity to the behavioral effects of dopaminergic drugs) rats eating standard chow (17% kcal from fat), high fat chow (60% kcal from fat), and rats eating standard or high fat chow with 20% (w/w) intermittent (e.g., 2/7 days per week) fish oil supplementation were tested once weekly with cocaine (1-17.8 mg/kg, i.p.) or quinpirole (0.0032-0.32 mg/kg, i.p.) using a cumulative dosing procedure. Consistent with previous reports, eating high fat chow enhanced sensitivity of rats to dopaminergic drugs. That is, the quinpirole-induced yawning dose-response curve was shifted significantly to the left for rats eating high fat chow as compared to rats eating standard chow. Intermittent access to fish oil prevented this effect, since quinpirole-induced yawning was not different among rats eating standard chow and rats eating high fat chow supplemented with fish oil. However, dose-response curves for rats eating high fat chow and rats eating high fat chow with fish oil were not different, indicating that intermittent fish oil did not completely prevent high fat chow-induced enhanced sensitivity to quinpirole. Future experiments will focus on understanding the mechanism by which fish oil produces these beneficial effects.

Poster 1-19

Corticotropin releasing factor promotes appetitive 'cocaine-seeking' behavior and augments accumbens dopamine in rats

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Adverse life events often precipitate the initiation of –or relapse to- cocaine use in drug-dependent individuals. For example, acute stressors can potently exacerbate the extent to which drug-related stimuli elicit craving to seek and procure drug, perhaps via peptidergic modulation of mesolimbic dopamine circuitry. Indeed, dopaminergic signaling within nucleus accumbens core (NAcc) has been implicated in the attribution of motivational value to reward-associated cues. Therefore, the present studies were designed to examine the extent to which pharmacological manipulation of the stress peptide corticotropin releasing factor (CRF) within the NAcc alters responding for cocaine in the presence of conditioned stimuli. Additionally, we aimed to characterize parameters under which CRF recruits DA transmission within the NAcc. To that end, male Long-Evans rats were trained to self-administer cocaine intravenously under a chained schedule of reinforcement (FI-FR) in order to dissociate appetitive ('drug-seeking') from consummatory ('drug-taking') behavior. Completion of a fixed interval (5min.) was followed by 10 min of continuous reinforcement (0.4mg/kg cocaine; FR1) on another lever. Once stable responding was achieved, rats were microinjected with CRF (50 or 500ng) into the NAcc prior to self-administration sessions. Microinfusion of CRF dose-dependently increased responding during the fixed-interval link of the chained schedule, but did not affect subsequent cocaine intake. In parallel microdialysis experiments, CRF infusion into the NAcc elicited a modest increase in extracellular DA in drug-naïve rats. Ongoing studies will examine the effects of selective antagonists (CP376395 or Astressin-2B), in order to determine the relative contributions of CRF-R1 and CRF-R2 to CRF-potentiated responding. We also aim to extend neurochemical analyses to cocaine-experienced rats in the presence or absence of drug-associated stimuli. Taken together these preliminary data suggest a role for CRF in modulating appetitive drug seeking via interactions with NAcc DA, which may provide insight into mechanisms of stress-evoked drug seeking.

Poster 1-20

Muscarinic antagonists and anti-depressant-like effects in rodents: Some chemical forays toward new compounds

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Scopolamine, a non-selective muscarinic antagonist, is an effective antidepressant compound in humans. In rat models, it is clear that scopolamine's antidepressant-like effects may be mediated through an antimuscarinic effect. Unfortunately, scopolamine can produce cognitive impairment including memory disturbances in humans. These effects (antidepressant-like and cognitive impairment) are separable in principle. It is important to identify a muscarinic antagonist that may be able to relieve depression without disrupting cognitive effects. The 3-exo-1-azabicyclo[2.2.1]heptane, (3R)-1-bicyclo[2.2.2]octane, and N-methyltetrahydropyidine 1,2,4-oxadiazoles appear to be excellent chemical scaffolds for the generation of potent muscarinic agonists. Interestingly, addition of a methyl group to the 3-position of the 1,2,4-oxadiazole yields some of the most potent muscarinic agonists currently known. Yet, addition of a cyclopropyl group (3-position) to the 1,2,4-oxadiazole moiety appears to reduce efficacy and confer antagonist action at muscarinic sites. We are evaluating cyclopropyl analogs as antagonists of the muscarinic agonist, arecoline, in behavioral assays in anticipation of separating antidepressant-like activity from cognitive impairment. (Supported by NIMH Grant 107499).

Poster 1-21

A glucocorticoid receptor antagonist reduces sign-tracking behavior in male Japanese quail

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Addiction is characterized as a chronic debilitating disease because individuals with drug dependence disorders are highly susceptible of relapse (40-60%). One theory that may account for relapse suggests that drug cues (e.g., paraphernalia) may increase stress hormones, and this may prompt relapse. Repeatedly pairing a neutral cue with a reward is commonly utilized to measure what subjects learn about a cue that is predictive of reward. Research has shown that animals that attend to a cue more than to the reward (sign trackers) may be more vulnerable to drug addiction. Additionally, research has shown that sign tracking is associated with an increase in corticosterone (CORT), a primary stress hormone. The working hypothesis of this research was that PT150 (a generous gift from Palisades Therapeutics, LLC for the GR receptor antagonist) would reduce the expression of sign tracking through its downstream effects of reduced CORT. In the current experiment, time spent at a CS that predicts reward (CS+) served as a measure of sign tracking and PT150 (or placebo) was administered following acquisition of sign tracking. The main finding is that PT 150 reduced sign tracking. Furthermore, the effects of PT150 on sign tracking appear to be behaviorally specific in that there were no changes in time spent near the hopper during the CS+ (goal tracking). This is the first research, to date, to explore the effect of pharmacologically manipulating stress hormones on sign tracking, an addiction-like behavior. These results may be important because novel pharmaceutical interventions, such as PT 150, may stop or reduce the cascade of corticosterone in the presence of addiction-relevant stimuli that may instigate relapse.

Poster 1-22

Pharmacokinetics of phosphatidylethanol 16:0/20:4 Homolog in human blood after consumption of 0.4 and 0.8 g/kg alcohol in a laboratory clinical study

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Purpose. The purpose of this study was to characterize the pharmacokinetics of phosphatidylethanol (PEth) 16:0/20:4 homolog in uncoagulated, human blood samples taken from 18 participants in a clinical laboratory setting 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-minute period. Blood samples were collected before and throughout 6 hours immediately after alcohol administration, then after 2, 4, 7, 11 and 14 days of administration day. PEth 16:0/20:4 levels were quantified by liquid mass spectrometry. Breath ethanol concentrations were measure concurrently with each blood collection during the administration day, as well as transdermal ethanol concentrations (TAC) monitored constantly before, during and after ethanol administration day. Results. (1) Single doses of 0.4 and 0.8 g ethanol/kg produced proportional increases in BrAC and PEth 16:0/20:4 levels ; (2) the increase of PEth 16:0/20:4 from base line to Cmax was less than either PEth 16:0/18:1 or PEth 16:0/18:2 during the 6-hour period after ethanol administration; 3) the mean rate of formation of PEth 16:0/20:4 was lower than those of the other two homologs; 4) the mean half-life of PEth 16:0/20:4 was 2.18 days, which was shorter than that of either PEth 16:0/18:1 and PEth 16:0/18:2, which were 6.80 and 6.62 respectively. Conclusions. The results of this study further confirm that PEth homologs are a sensitive biomarker for ethanol consumption. The measurement of three PEth homologs appears to provide additional information about the level and time frame of drinking. (NCATS UL1TR001120-S1 and NIAAA R01AA022361)

Poster 1-23

Role of CYP26B1 knockdown in the Basal Lateral Amygdala in chronic pain induced anxiety and stress behavior

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There are several contributing factors that lead to drug addiction. One such factor is chronic neuropathic pain that leads to stress and potentially stress induced relapse of drug seeking. These behaviors are in large part activated by the Basal Lateral Amygdala (BLA) and the CYP26B1 enzyme. The CYP26B1 enzyme is endogenously responsible for metabolizing retinoic acid (RA). In an earlier study looking at CYP26B1 knockdown in the Nucleus Accumbens, we observed an increase in self-administration in the CYP26B1 knockdown in male Sprague Dawley rats. in rats or mice???. Based on transcriptomic data from our lab, we found that CYP26B1 was highly expressed in the neuropathic pain model within the BLA, more so than in the Nucleus Accumbens. Very little is known on the actual role RA and CYP26B1 play in the BLA with respect to stress induced by neuropathic pain. In order to test our hypothesis, we utilized an AAV short hairpin RNA knockdown and injected it bilaterally into the BLA of male Sprague-Dawley rats (n=10 per group) waited 2 weeks for local viral infection. Afterwards, we conducted a series of behavioral experiments such as social grooming, elevated plus maze, spontaneous locomotor activity, and sucrose preference. The purpose of this study is to further understand the role of stress associated with relapse behaviors.

Poster 1-24

Toll-like receptor 4 (Tlr4) heterozygous rats exhibit a low anxiety-like phenotype and are resistant to predator odor-exposure-induced behavioral changes

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While Toll-like receptor 4 (Tlr4) activity has been increasingly linked to anxiety, depression, and substance use disorders (SUDs), there is a considerable dearth of research examining this receptor's role in post-traumatic stress disorder (PTSD). With high rates of comorbidity between PTSD and SUDs, it is important to begin to consider this relationship. With this goal in mind, we exposed Tlr4 gene knockout (KO, n=22), heterozygous (HET, n=19), and wild type (WT, n=23) rats to predator odor and measured anxiety- and depressive-like behaviors over 48 hours post-exposure. We compared the behaviors of these animals to non-exposed controls (KO, n=26; HET, n=21; WT, n=36). Implementing this exposure in a conditioned place aversion (CPA) protocol, we first introduced each animal into an apparatus with free access to two contextually (tactile and visual) distinct chambers for 15 minutes in the morning and recorded baseline times spent in each chamber. The following morning, we confined animals to one distinct chamber for 15 minutes and exposed them to saline odor. That evening, we confined animals to the opposite distinct chamber for 15 minutes and exposed them to either bobcat urine odor (exposed group) or saline odor (non-exposed group). The following evening, we allowed animals free access to both chambers of the apparatus for 15 minutes and recorded times spent in each chamber. Immediately following exposure, we tested animals for sucrose preference (SPT) over a period of 24 hours. At 48 hours post-exposure, we measured anxiety-like and locomotor behaviors of all animals in both the open field test (OFT) and elevated plus maze (EPM). Regardless of odor-exposure, KOs demonstrated anxiety-like behavior in EPM testing as measured by reduced open arm and increased closed arm times. Genotype main effects were also seen in OFT, with KOs exhibiting reduced locomotion and HETs demonstrating less anxiety-like behavior than KOs or WTs. Odor-exposed KOs and WTs showed increased anxiety-like behavior in the OFT, with HETs demonstrating significant resistance to this effect.

Poster 1-25

Glutamate receptor homeostasis was altered in the prefrontal cortex after heroin self-administration

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Drug addiction is defined as a chronic, relapsing disease that is characterized by compulsive drug seeking and episodes of relapse despite prolonged periods of abstinence from the drug. Addiction is associated with neuroplasticity in the corticostriatal brain circuitry. The malfunction of glutamatergic projecting neurons from prefrontal cortex (PFC) to nucleus accumbens and ventral tegmental areas could constitute the pathological impairments in the ability to control drug-seeking behavior. However, the molecular mechanisms for the long-term heroin use induced neurobiological adaptations in PFC are still unclear. Evidences have shown that activation of glutamatergic system attenuates the heroin-seeking behavior. In order to understand the glutamatergic receptor involved mechanisms for heroin addiction, we measured the genes expression of glutamate receptor subunits NR1, NR2A, NR2B, GluR1 and GluR2, as well as regulators that are involved in the regulation of glutamatergic receptor homeostasis, such as Shank3 and activity-regulated cytoskeleton-associated protein (Arc) in the PFC after heroin self-administration. Mice underwent 14 days of saline or heroin self-administration (50ug/kg/infusion, 2h/session). One day after the last self-administration session, animals were sacrificed for the determination of gene expression by real-time PCR. Heroin self-administration significantly increased Shank3 mRNA level in the PFC of animals that had self-administered heroin compared to saline controls. There is also a slight increase of Arc mRNA in heroin group. There is no significant change for glutamate receptor subunits. In conclusion, these data suggest that increased Shank3 and Arc in PFC after repeated heroin exposure may contribute to the molecular mechanisms of imbalanced glutamate homeostasis, which results in the vulnerability for later on heroin relapse.

Poster 1-26

Differential discriminative stimulus effects of mephedrone and 3,4-methylenedioxypyrovalerone (MDPV) using a three lever discrimination design

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Abstract: Drug discrimination has unsurpassed utility in determining the mechanism of action of CNS active substances. Although typically employed using a simple drug/not drug discrimination (DN), variations exist in which a discrimination must be made between two different drugs (DD) or between two different drugs and a not drug stimulus (DDN). Some research suggests that the DDN procedure may be conceptualized as a combination of two separate DN procedures and findings from work with LSD and lisuride support that DDN procedures may be more sensitive to pharmacologically similar drugs than separate DN procedures. In previous research with synthetic cathinones, two popular and pharmacologically similar constituents, MDPV and 4-MMC, have exhibited an asymmetrical substitution pattern with a variety of training drugs. Therefore, six Sprague-Dawley rats were trained to discriminate between MDPV, 4-MMC, and saline vehicle in a three lever model of drug discrimination during the present experiment. Although insufficient data had been collected at the time of this abstract to make conclusions, it was hypothesized that animals would readily learn to discriminate 4-MMC, MDPV and saline vehicle mediated cues due to the more serotonergic effects of 4-MMC and more dopaminergic actions of MDPV. Moreover, it was hypothesized that more dopaminergic substances such as cocaine, amphetamine, and methamphetamine would fully substitute for an MDPV mediated cue, and mixed serotonergic/dopaminergic substances, such as MDMA would substitute for a 4-MMC mediated cue. Should these hypotheses be confirmed, the data would elucidate the neurochemical actions of both 4-MMC and MDPV, potentially leading to treatments for addiction to these substances.

Poster 1-27

Long-term inhibition of μ opioid receptor function

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According to the Centers for Disease Control, the rate of opioid-related overdose deaths in the US rose from 2.1 per 100,000 persons in 1999 to 8.8 per 100,000 in 2014. In 2016, more than 42,000 people have died due to overdose of opioids, including prescription drugs and heroin. The opioid receptor antagonist, naloxone (Narcan®, Evzio®) provides invaluable life-saving treatment for overdose victims. However, the half-life of naloxone (≈60 min) is shorter than many abused opioids and after initial recovery there is still risk of overdose death due to re-narcotization. In fact, packages of Narcan® and Evzio® contain two doses to allow for repeat dosing if necessary before emergency care arrives and patients receive naloxone by continuous intravenous drip. Consequently, there is an urgent need for a longer-acting opioid receptor antagonist that would prevent re-narcotization and thereby save lives. We have tested the effects of a new opioid receptor antagonist, codenamed SH-1, on human mu opioid receptors expressed in HEK cells. Using a bioluminescence, real-time assay to measure intracellular cAMP, we have found that SH-1 antagonizes the inhibition of forskolin-stimulated cAMP by the mu receptor agonist, DAMGO. At a concentration of 10 nM, pretreatment (15 min) of mu opioid receptor-expressing cells with SH-1 produced a rightward shift in the DAMGO concentration-response curve by ~20-fold (7 nM to 120 nM) and depressed the maximal DAMGO response by ≈35%. When cells were pretreated with SH-1 (10 nM) for 2 hrs, the DAMGO curve was shifted further to the right (≈70-fold) and the maximal response was further reduced by ≈70%. Furthermore, following 2 hrs of pretreatment followed by rigorous washing of the cells, naloxone-mediated antagonism of the DAMGO response was reversed, but not that of SH-1. The depression of the maximal DAMGO response, the time-dependent nature of the antagonism, and the lack of wash-out, suggest that SH-1is a pseudo-irreversible mu opioid receptor antagonist. Such a drug may be useful for the treatment of opioid overdose as the long-term antagonism of mu opioid receptors would prevent re-narcotization. This work was supported by a pilot grant to JHW and KAB from the Addiction Research, Treatment & Training Center of Excellence at UT Health San Antonio.

Poster 1-28

Pregnenolone inhibition and the affective properties of Δ^9-Tetrahydrocannabinol

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Background Pregnenolone is a neurosteroid precursor recently shown to function as a negative allosteric modulator at the CB_1 receptor. Injections of Δ^9-tetrahydrocannabinol induce a surge of endogenous pregnenolone in reward-related brain areas and mice trained to self-administer WIN 55,212-2 decrease responding after a pregnenolone injection. Taken together, these findings suggest that pregnenolone may part be part of a negative feed back system that responds to perturbations of the CB_1 receptor. These findings are particularly noteworthy in light of the weak evidence of THC's rewarding properties in pre-clinical rodent models. As such, blocking the surge of pregnenolone following cannabinoid administration could enable a display of THC-induced reward.
Methods Male Long-Evans rats underwent a baseline assessment of side preference in the CPP apparatus (Pre-test) prior to receiving 4 pairings of THC with one chamber and 4 pairings of vehicle with the opposite chamber (counterbalanced across 8 days). During conditioning, they received aminoglutethimide (AMG; 0 or 50 mg/kg; SC), an inhibitor of pregnenolone synthesis, prior to THC (0, 0.15, 1.5 or 15 mg/kg; IP). Following the abovementioned procedure, subjects were given a Post-test assessment of chamber preference.
Results THC induced significant place aversions at 1.5 and 15 mg/kg, collapsed across pre-exposure group (AMG or vehicle). Student t-tests at each pre-exposure and THC dose group revealed significant place aversions only in the AMG pre-exposed subjects at the two highest THC doses.
Discussion AMG potentiated the aversive properties of THC at an intermediate and high dose. These results suggest that inhibiting the surge of pregnenolone following THC administration enhances THC's subjective effects potentially by prolonging drug action.

Poster 1-29

Optimization of serotonin (5-HT) 5-HT2C receptor positive allosteric modulators as potential neurotherapeutics for cocaine use disorder

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Evidence supports that targeting the serotonin (5-HT) 5-HT_{2C} receptor (5-HT_{2C}R), a G protein-coupled receptor (GPCR), may provide therapeutic benefit for multiple disorders, including obesity, mood disorders and addiction. Our multidisciplinary effort is focused on developing small molecule therapeutics for cocaine use disorder, an acquired brain disorder characterized by multiple episodes of relapse following periods of abstinence and withdrawal. Interestingly, the 5-HT_{2C}R is functionally coupled to behaviors that drive relapse vulnerability, such as impulsivity and cue reactivity. Proof-of-concept studies in rodents have shown that 5-HT_{2C}R hypofunction promotes, and selective 5-HT_{2C}R agonists suppress, these relapse-associated behaviors. In contrast to traditional orthosteric agonists, positive allosteric modulators (PAMs) of the 5-HT_{2C}R are an attractive therapeutic mechanism, due to the possibility for greater selectivity and decreased receptor desensitization. Therefore, we hypothesize that rationally designed 5-HT_{2C}R PAMs will effectively and safely enhance 5-HT_{2C}R signaling and suppress relapse-associated behaviors. Thus far, our efforts have focused on two exciting and divergent molecular scaffolds: 1) Analogs of CYD-1-79, a lead 5-HT_{2C}R PAM discovered by our team, and 2) analogs of the endogenous signaling ligand oleamide. Our work towards a novel neurotherapeutic has generated promising lead compounds in both series, which display selective enhancement of 5-HT signaling at the 5-HT_{2C}R, as measured by intracellular calcium release, and measurable blood-brain barrier penetrance in the rat. Subsequent lead optimization has generated promising second generation compounds, and preclinical studies in rats have demonstrated efficacy in suppressing motor impulsivity and cue reactivity assessed as lever presses for cocaine-associated cues. We conclude that these novel 5-HT_{2C}R PAMs hold potential as a first-in-class neurotherapeutic for cocaine use disorder.

Poster 1-30

Order of fixed-ratio presentation does not impact demand for the opioid remifentanil

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Principles of behavioral economics have been used extensively to understand factors that control drug-maintained behavior (i.e., self-administration). One particularly useful tool is the demand analysis, which relates consumption of a commodity to its price. Consumption decreases with increasing price, and the rate at which consumption decreases reflects elasticity of demand. For drugs of abuse, elasticity is thought to be inversely related to abuse potential: drugs with relatively low elasticity have greater abuse potential than those with higher elasticity. In many preclinical studies, price is manipulated by varying the number of responses required to earn an infusion (i.e., fixed ratio [FR] schedule); however, in a preponderance of studies, the FR is presented in an ascending order, which could introduce sequence effects that influence estimates of demand. Surprisingly, almost no published studies have directly compared demand estimates from the commonly used procedure (ascending order) with a variant that might eliminate such potential confounding variable(s). This study examined the impact of the order of FR presentation by comparing demand for drug using ascending and mixed orders. Seven male Sprague-Dawley rats served as subjects. Lever presses delivered iv infusions of the mu opioid receptor agonist remifentanil (0.0032 mg/kg/infusion) according to an FR schedule, with a 5-second timeout following each infusion. The ratio varied across 3-session blocks, yielding a demand curve: consumption (infusions obtained) plotted as a function of price (FR). First, the FR was increased in quarter-log unit steps from 1 to 56. Then, the same ratio values were presented in a mixed order that varied across subjects. Under baseline conditions (FR1), rats took on average 66.5 (ascending order) and 69.7 (mixed order) infusions per session. Under both orders, the number of infusions obtained decreased as the ratio increased. Estimates of elasticity under the two conditions were not statistically different, indicating that the order of ratio presentation did not markedly impact estimates of demand and demonstrating the robustness of price as a source of control over operant behavior, including behavior maintained by drug reinforcers. Supported by the Welch Foundation (AQ-0039).

Poster 1-31

Effects of fluoxetine exposure during adolescence on adult learning in a rat model

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The effects of Fluoxetine (FLX) exposure during adolescence on later life are poorly understood. Adolescence marks a vital period when brain regions are undergoing critical developments that will have a lasting impact on how an individual learns and may be affected by chronic pharmacotherapy. Conditioned taste aversion (CTA), a learning paradigm, was used to assess the effect of adolescent FLX exposure on the acquisition and extinction of avoidance learning in adulthood. Male and female rats were randomly assigned to receive FLX (n = 7) or saline (n = 8). The experimental rats received FLX (20 mg/kg i.p) once daily for 15 consecutive days from postnatal days (PND) 35-49. FLX-injected rats gained body weight more slowly than vehicle-injected controls, and this effect was more pronounced in male than female rats. The CTA acquisition phase began when the rats reached adulthood (from PND 66) and consisted of saccharin and Lithium Chloride (LiCl) pairings across four days. All rats were presented 0.15 M saccharin followed by an i.p injection of LiCl (1.33 ml/100 g) to induce visceral malaise. There is some evidence to suggest adolescent FLX exposure changed the rate of CTA acquisition in males, but not females. In the CTA extinction phase, saccharin was presented without aversive consequences across 18 consecutive days. It does not appear that adolescent FLX treatment influenced the rate of CTA extinction but regardless of early treatment, females extinguished to the saccharin CTA faster than their male counterparts. The current findings provide evidence that FLX exposure during adolescence slows the rate of learning in male rats suggesting they may be more sensitive to alterations in the serotonin balance during adolescence. The steady growth in adolescent antidepressant use combined with our findings highlight the need for additional research in order to gain a better understanding of how alterations induced by pharmacotherapy interact with the developing brain to result potential in long-term consequences in adulthood.

Poster 1-32

Recruiting underrepresented populations for research: Building trust and rapport with research participants

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Vulnerable populations continue to be underrepresented in the research literature. This is particularly true for underserved and minority women. While efforts are being made to include disparate populations in research, little is known about effective strategies to promote engagement in research. Thus, the purpose of this project is to learn effective methods of rapport building while recruiting pregnant women participating in a methadone maintenance treatment program. Women with opioid use disorders were recruited to participate in a study that explores the impact of kangaroo mother care (a method of skin-to-skin mother infant holding) on mother-infant stress reactivity and attachment. Participants were recruited from a community-based, non-residential treatment facility for women that is operated by our local mental health authority. Key strategies implemented during the study recruitment process included: 1) establishing a relationship with women who receive services at the community treatment facility, and 2) incorporating suggestions from the women and treatment facility staff as we designed our study and research protocol. The impact of these strategies were assessed through review of consent logs, study regulatory documents, and follow-up interviews with participants. Data analysis is currently in progress. Preliminary data indicates that 61 pregnant and postpartum women have enrolled. Establishment of rapport and a trusting relationship between researchers and underserved and minority women has resulted in positive recruitment experiences. We have been able to foster these relationships through the weekly presence of research team staff members at parenting classes and integration of team members into the environment of the women's treatment facility. These strategies and our lessons learned may help guide future researchers who hope to conduct research with underserved and minority women and other vulnerable populations.

Poster 1-33

Predicting alcohol involvement: A novel statistical application of the AlcP300 event-related potential

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The ability to predict risk for binge drinking may help prevent negative health consequences linked to heavy drinking. An endophenotype linked to heavy drinking is the alcohol P300 (AlcP300): An EEG-derived event-related potential (ERP) expressed as a positive deflection in voltage. The amplitude of the AlcP3 is elicited by alcohol-related cues and is indicative of an implicit attention bias for alcohol; the AlcP3 amplitude is thus positively associated with heavy drinking. However, the AlcP3's role in multivariate predictive analyses has yet to be explored. This study aimed to predict binge drinking into non-bingers, infrequent, and frequent bingers using the AlcP3 electrophysiological measure along with age and survey-based variables like alcohol sensitivity, subjective perception of alcohol, positive urgency, and hangover intensity. Participants (N=98) were exposed to olfactory alcohol beverage cues while ERPs were recorded; participants then provided information about their alcohol use patterns. The six predictor variables were used in linear discriminant analysis (LDA) to classify participants into non-bingers, infrequent bingers, and frequent bingers. LDA maximizes inter-individual differences in the data to optimize classification of an outcome variable into groups. This group classification is an estimation probability as a function of the predictor variables. Inclusion of the AlcP3 in clustering algorithms such as LDA may have an important role in statistical diagnostics within alcohol research. To our knowledge, this is a novel statistical application of the AlcP3 in alcohol research.

Poster 1-34

Oxycodone-induced conditioned place preference in early adolescent male and female rats

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Opioid abuse has increased significantly in past years and has been perpetuated by pharmaceutical opioid prescriptions such as Oxycodone. Preclinical research has shown that adolescents have a heightened sensitivity to the rewarding effects of drugs like nicotine and cocaine. Surprisingly, little preclinical research has been done to establish the effects of Oxycodone in this period of development. We examined the rewarding effects of oxycodone in male and female adolescent rats using the conditioned place preference (CPP) paradigm, an established animal model of drug reward. Male and female rats were assessed for oxycodone-induced CPP using a 10-day CPP procedure beginning on postnatal day (PD) 27. During pre-conditioning and post-conditioning sessions, rats were tested for their baseline and final place preference, respectively, in 15-min sessions. During conditioning (PD 28-35), rats underwent 30-min sessions, during which they received alternating oxycodone (0, .01, .033, 0.1, 0.3, 1, 3, or 9 mg/kg) or saline injections in distinct compartments on alternating days in a counterbalanced order. Results indicated that male rats showed a significant shift towards the oxycodone-paired compartment at 0.1, 0.3, 1, 3 and 9 mg/kg of Oxycodone. In contrast, female rats showed a significant shift towards the oxycodone-paired compartment at 1, 3 and 9 mg/kg. The significance of male and female conditioned place preference for oxycodone in this study indicates that there is a need to further explore the neurobiology of opioid abuse in adolescence.

Poster 1-35

Characterization of the discriminative stimulus effects of MDPV, and structurally related synthetic cathinones in rats

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Bath salt preparations often contain multiple synthetic cathinones in addition to other stimulants such as caffeine. Although some common bath salts constituents (e.g., 3,4-methylenedioxypyrovalerone [MDPV], and α-pyrrolidinovalerophenone [α-PVP]) have been placed under Schedule I regulations, many of the structurally related synthetic cathinones that are also found in bath salts are not currently regulated, and are therefore legal. This study aims to characterize the discriminative stimulus effects of MDPV, and determine the whether these effects are shared by structurally related synthetic cathinones. Male Sprague-Dawley rats (n=8) were trained to discriminate 1.0 mg/kg MDPV from saline under a fixed ratio 10 schedule of lever responding for the delivery of a sucrose pellet. A dose-response curve and time course of the discriminative effects of MDPV were established. Five structurally related cathinones, including α-PVP, α-pyrrolidinopropiophenone [α-PPP], 3,4-methylenedioxy-α-pyrrolidinobutiophenone [MDPBP], and 3,4-methylenedioxy-α-pyrrolidinopropiophenone [MDPPP], and methylone, as well as the non-cathinone stimulants caffeine, cocaine were evaluated, in random order, for their capacity to increase MDPV-appropriate responding; the mu-opioid receptor agonist fentanyl was also evaluated. With the exception of fentanyl, each of these compounds produced dose-dependent increases in MDPV-appropriate responding. The substitution profiles of the synthetic cathinones is consistent with their rank order potency to maintain self-administration, and suggest that their discriminative stimulus effects are related to their potency to inhibit uptake at the dopamine transporter. Future studies will establish time courses for the discriminative stimulus effects of these compounds.

Poster 1-36

Juvenile Ketamine administration increases sensitivity to cocaine in adulthood

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Pediatric depression was not well recognized until relatively recent. Today, however, major depressive disorder (MDD) is commonly diagnosed in children and adolescents, and when left untreated, may result in negative consequences that extend into adulthood. It is estimated that children and adolescents who suffer from MDD are likely to develop conduct and anxiety disorders, and that up to 25% eventually develop substance abuse disorder. Consequently, this has resulted in a disproportionate increase in the prevalence of antidepressants prescribed to populations below 20 years of age. Recently, the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, has been shown to alleviate symptoms of MDD in individuals that suffer from treatment-resistant depression. However, little is known about the potential long-term consequences of exposure to ketamine during early development. This is particularly important to examine, given ketamine's abuse potential. To address this issue at the preclinical level, we examined whether ketamine exposure during adolescence results in long-lasting changes in sensitivity to the rewarding effects of sucrose (i.e., natural reward), as well as cocaine (i.e., drug reward). Specifically, male C57BL/6 mice were exposed to ketamine (0 or 20 mg/kg) during adolescence (postnatal days [PD] 35-49) and were later assessed in adulthood (PD 70+) on behavioral responsivity to a sucrose solution (1%), or cocaine (0, 5, 10, or 20 mg/kg) place conditioning (CPP). Our results demonstrate that adult mice pre-treated with ketamine during adolescence displayed enhanced preference for a sucrose solution, as well as environments previously paired with cocaine, when compared to saline pre-treated controls. Together, our findings suggest that exposure to ketamine during adolescence increases sensitivity to both natural and drug-rewards, later in life.

Poster 1-37

Assessing the motor and non-motor symptoms of Parkinson's disease in rats using the 6-Hydroxydopamine lesion model

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Parkinson's Disease (PD) is the second most common neurodegenerative disease throughout the United States. The symptoms of PD include impairments in motor functions, such as rigidity, tremor and postural instability and non-motor functions like mood and cognitive deficits. The motor symptoms arise due to selective destruction of nigrostriatal dopamine (DA) synthesis in nerve terminals of the striatum, including within the caudate putamen. Dopamine Replacement Therapy (DRT) is the standard treatment for motor symptoms of PD. DRT involves administration of the dopamine precursor levodopa or dopamine agonists to compensate for the dopamine depletion that occurs. DRT in PD has been associated with dopamine addiction and behavioral addictions. Thus, there is growing interest in studying newer therapeutic compounds for PD. Polyunsaturated omega-3 fatty acids have been associated with stimulation of neurotransmitter synthesis and anti-inflammatory and neuroprotective roles towards limiting neuronal destruction in cell culture and animal models, including in PD. Likewise, compounds that target cannabinoid and serotonin systems have demonstrated similar effects. Such compounds have also been shown to have beneficial effects on mood and cognition. Thus, there is growing interest in examining the role of polyunsaturated omega-3 fatty acids in the motor and non-motor symptoms of PD. To address this, we have generated and validated a 6-OH-DA lesion model of PD. We have validated that model using conventional neurochemical and behavioral assays for PD in rats, including rotational behavior and electrochemical determination of tissue levels of dopamine. In a separate series of studies, we developed a testing paradigm for use in Parkinsonian rats that allows for assessments of motor and non-motor function within the same subject. We will now use our validated procedures to assess the beneficial effects of polyunsaturated omega-3 fatty acids, cannabinoids, and serotonergics on the motor and non-motor symptoms of PD.

Poster 1-38

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

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Alcohol is the most commonly abused recreational drug in the United States. In 2015, approximately 6% of the adult population was diagnosed with an alcohol use disorder. Given that alcohol use typically begins in adolescence, it is imperative to evaluate the different factors influencing the rewarding properties of alcohol. Preclinical research using the conditioned place preference (CPP) paradigm, a validated animal model of drug reward, has demonstrated that the pattern of drug dosing plays a significant role in the rewarding effects of drugs of abuse. For example, administration of ascending doses of cocaine, as opposed to fixed doses, produces more robust cocaine induced CPP in rats. The present study examined whether the pattern of drug dosing during conditioning (ascending vs fixed) also influences the development of alcohol-induced CPP in adolescent rats. In experiment 1, 23-day-old male and female rats underwent a 10-day alcohol CPP procedure. Specifically, on days 1 and 10, rats were tested for their preconditioning and postconditioning place preferences, respectively, during 15-min sessions. On days 2-9, rats were conditioned for 15-min with saline or ethanol on alternating 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). In experiment 2, 31-day-old male and female rats went the exact same procedures. In experiment 1, male rats only exhibited alcohol-induced CPP using a fixed high dose (2.0 g/kg) of ethanol. In contrast, females demonstrated alcohol-induced CPP using fixed doses of (1.0, 2.0 g/kg) and an ascending dose (1.0 g/kg) of ethanol. In experiment 2, males exhibited alcohol-induced CPP using a fixed dose (0.5 g/kg) and ascending doses (0.5, 1.0, 2.0 g/kg) of ethanol. In contrast, females only demonstrated alcohol-induced CPP using a fixed high dose (2.0 g/kg) of ethanol. Overall, these results suggest that the pattern of doses during conditioning sessions, age, and sex may play an important role in elucidating the rewarding effects of alcohol in preclinical research.

Poster 1-39

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 opioid use disorders (OUD). Currently, medication assisted treatment (MAT), with methadone, is the standard of care for pregnant women with OUDs. Several national organizations recommend breastfeeding for women receiving MAT who have no other contraindications to breastfeeding. Further, breastfeeding offers multiple benefits for opioid-exposed infants including a reduction in NAS symptom severity and length of hospital stay. Despite the known benefits and recommendations for breastfeeding, little is known about infant feeding from the perspective of mothers receiving MAT for an OUD. Therefore, the purpose of this qualitative study is to explore the infant feeding experiences of mothers receiving MAT for an OUD. A multiple case study approach was used to explore the phenomenon of infant feeding experiences among mothers receiving MAT for an OUD from multiple perspectives including the mother, family members, health care providers, and social service providers (N=29). The study was grounded in an intersectional feminist perspective using the Socio-Ecological model as a sensitizing framework. The data was analyzed using qualitative content analysis. Three major themes emerged from the data analysis: *It's all for the baby*, *so that's why I did it*, and *between a rock and a hard place*. Findings from each theme describe the experiences of managing infant feeding from the perspective of the mother's family member, healthcare providers, and social service providers. The findings from the current study contribute to the body of knowledge surrounding infant feeding experiences in mothers receiving MAT for an OUD and highlight the major tenets of intersectionality. This knowledge provides a basis for creating and testing sustainable interventions as well as developing effective health policies to improve infant feeding outcomes in this population of mothers and infants.

Poster 1-40

Methamphetamine exposure and withdrawal impact gut microbiota in rats

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Methamphetamine (MA) is one of the most frequently used amphetamine-type stimulants in the United States. Individuals who repeatedly abuse MA can develop MA use disorder (MuD) —chronic, relapsing condition often triggered by withdrawal symptoms that develop following cessation of use. Given the lack of effective treatments for those with MuD, novel therapeutic targets must be considered. One potential target is the gut microbiome, which has an important influence on brain, behavior, and health as a part of the gut-brain axis. In this study, we evaluated the effects of MA administration (2 mg/kg, s.c.) on withdrawal- induced behaviors and gut bacteria in female Sprague Dawley rats (n=8). Saline (s.c.) was administered twice daily for 14 days, during which baseline behaviors (elevated plus maze (EPM) for anxiety-like behavior; forced swim test (FST) for depressive-like behavior) were assessed. Next, rats were given twice daily injections of MA for 14 days, followed by 4 days of withdrawal, during which performance on the EPM and FST were assessed. Fecal collections for microbiome analyses occurred at baseline (before saline administration), on day 5 of saline administration, day 14 of MA administration, and day 4 of withdrawal. Results indicated that MA withdrawal increased depressive-like behavior, with an increase in immobility time in the FST ($p<0.05$). Anxiolytic-like behavior was increased during withdrawal, indicated by a decrease in time spent in the closed arms of the EPM ($p<0.05$). Fecal microbiome analyses revealed MA administration and withdrawal significantly changed the relative abundances of several bacterial phyla including an increase in Firmicutes ($p<0.05$, vs. saline) and Actinobacteria ($p<0.05$, vs. saline) and a decrease in Cyanobacteria ($p<0.05$, vs. saline). No significant changes in Shannon diversity were observed. Taken together, our observations indicate MA exposure and withdrawal produce specific and lasting changes in gut bacteria. Such information will guide the choice of target therapeutics for MuD to test in future studies.

Poster 1-41

The effects of lifelong Western diet exposure on the affective properties of cocaine in male Sprague-Dawley rats

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Recent work from our laboratory has demonstrated that a lifelong history of a western diet (WD) increases compulsive cocaine intravenous self-administration (IVSA) in adult male Sprague-Dawley rats. One possible interpretation of these findings is that this dietary history influences the affective properties of drugs, i.e., their rewarding and aversive effects, resulting in more cocaine use. Work from our laboratory and others suggests that the overall affective response to a drug and its potential for use and abuse reflects the balance between its rewarding and aversive effects, i.e., the rewarding effects of a drug maintain it use and its aversive effects limit it. In this context, lifelong exposure to a WD may increase the rewarding properties of cocaine and/or decrease its aversive effects.

A common way to assess the aversive and rewarding effects of a drug concurrently is via the combined conditioned taste aversion (CTA) and conditioned place preference (CPP) design in which animals are given a novel taste, injected with a drug and then placed on one side of a place preference chamber. Under these conditions, one can assess both affective properties of the drug that contribute to its use.

To investigate whether lifelong WD exposure influences the rewarding and/or aversive effects of cocaine, 64 male Sprague-Dawley rats will be given ad-lib access to either a WD or chow beginning on Post-Natal Day 29 (PND 29) and for the duration of the experiment. On PND 79, these animals will undergo the abovementioned combined CTA/CPP procedure in which cocaine (or vehicle) is paired with a novel saccharin solution and environment. Changes in consumption and place preferences will be assessed.

Poster 1-42

Behavioral toxicity and locomotor effects of substituted amphetamines in mice

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Substituted amphetamines represent one of the largest and most pharmacologically-diverse classes of abused drugs. Amphetamine (AMPH) analogues with substitutions along the carbon chain typically retain psychostimulant effects, with those containing a ketone group at the beta carbon representing the cathinones, which are found in abused “bath salts” products. At the other end of the molecule, ring substitutions can dramatically alter pharmacological activity, and the addition of chlorine at the 4 position produces para-chloroamphetamine (PCA), the prototypical serotonin neurotoxin. An emerging abused cathinone analogue, 4-chloro-N-ethylcathinone (4-CEC), contains a chlorine at the 4 position (like PCA), and a ketone at the beta carbon (like all cathinones), but the in vivo effects of this drug are unknown. In order to begin to establish a structure-activity relationship for 4-CEC and related drugs, locomotor effects of a range of Cl-substituted and unsubstituted AMPHs and cathinones were determined in mice using an open-field photobeam system. In separate mice, a classical “binge” regimen consisting of one IP injection every 2 hours for 4 total injections was administered for each drug, and rectal temperatures and weight loss were tracked during the “binge.” Ten days after the final injection, mice were sacrificed and brain regions were collected for analysis of monoamine content. Like AMPH and methamphetamine, 4-CEC induced psychomotor-stimulant effects, but unlike the AMPHS, 4-CEC elicited lethal effects at a dose only slightly greater than that first producing motor stereotypy. Results of “binge” administration will be discussed, and structure-activity relationships will be highlighted. These studies supported in part by DEA/NCTR (224-16-0505R), VA (D-15-OD-002), NIDA (DA022981) and the University of Arkansas for Medical Sciences.

Poster 1-43

Mycobacterium vaccae immunization for cocaine addiction and relapse

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Cocaine addiction and relapse are major public health concerns, but lack current FDA-approved pharmacological treatments. Thus, there is a pressing need to develop new therapies to treat cocaine addiction. We sought to evaluate the translational potential of a novel immunotherapy—immunization with a heat-killed preparation of M. vaccae, a nonpathogenic environmental bacterium—for effects on the rewarding properties of cocaine and its potential to reduce relapse-like behavior. Supporting studies demonstrate that immunization with heat-killed M. vaccae has profound immunoregulatory effects that can prevent stress-induced exaggeration of neuroinflammation in the brain, prevent stress-induced sensitization of hippocampal microglia, alter serotonin signaling in the dorsal raphe nucleus, and attenuate stress- and anxiety-like behavioral responses in animal models of posttraumatic stress disorder and other anxiety disorders. Since chronic cocaine exposure induces neuroinflammation that may contribute to the development of addiction, and stress and anxiety are major triggers for relapse, we hypothesized that M. vaccae immunization may be a useful anti-addiction treatment that could alter the rewarding properties of cocaine and reduce relapse-like behavior. To test this hypothesis, we studied the effects of M. vaccae immunization on behavioral responses in tests of cocaine conditioned place preference (CPP) and stress-induced reinstatement of cocaine CPP. We found that M. vaccae immunization did not alter acquisition of CPP to 30 mg/kg cocaine but abolished stress-induced reinstatement of cocaine CPP. These data provide the first assessment of the translational potential of M. vaccae immunotherapy to treat substance use disorders; future experiments will evaluate the effects of M. vaccae immunization in self-administration and reinstatement models to further evaluate the translational anti-addiction potential of this treatment. Given the excellent safety record of M. vaccae immunotherapy in clinical trials, successfully demonstrating an anti-relapse effect in preclinical models would justify relatively rapid clinical evaluation of treatment efficacy.

Poster 1-44

Effects of neonatal caffeine exposure on locomotor activity in adolescent rats: Role of methylphenidate pretreatment

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Chronic neonatal caffeine exposure, depending on the age of initial treatment, increases locomotor activity later in life. This caffeine-induced hyperactivity has only been demonstrated in rats that are pretreated during postnatal days (PDs) 7-11, affecting adolescent (PD 25) and adult (PD 60) rats. The effect of administering methylphenidate to rats exposed to caffeine during the neonatal period has not been examined. The present experiment studied whether neonatal caffeine exposure produces hyperactivity in adolescent rats and if methylphenidate can alter this effect. Rats were pretreated with either saline or caffeine (20 mg/kg) on PD 7 for seven consecutive days (i.e., PD 7-13) and horizontal locomotor activity was assessed from PD 25-27. For five consecutive days thereafter, rats were pretreated with saline or methylphenidate (2.5 or 5 mg/kg). Results show that unlike previous research, neonatal caffeine exposure did not produce hyperactivity in adolescent rats. However, methylphenidate pretreatment resulted in an increase in the locomotor activity of rats and repeated treatment produced a sensitized locomotor response. Moreover, there was a modest effect of neonatal caffeine pretreatment on the development of methylphenidate-induced sensitization. These findings suggest that neonatal caffeine exposure during PD 7-13 may produce long-lasting changes in the reactivity to dopaminergic drugs later in development.

Poster 1-45

Colon barrier dysfunction in meth self-administering HIV-1 Tg rats; involvement of matrix metalloproteinase-9

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Gut barrier (GB) pathology is common in HIV-infected individuals and methamphetamine (meth) use is prevalent in the HIV-infected population. However, HIV-induced GB pathology in the context of meth use is unknown. We revealed that HIV-1 transgenic (Tg) rats that self-administer meth have reduced expression of GB junction proteins, zonula occludens-1 and claudin-1, and increased colon leakiness (Persons et al, 2018). Mechanisms underlying this GB dysregulation are unclear. Matrix metalloproteinases (MMP) are critical mediators of barrier integrity and function. In the brain, the MMP-9 subtype degrades tight junction proteins and promotes blood brain barrier breakdown. MMP-9 is transcriptionally regulated by the mitogen-activated protein kinase (MAPK) signaling pathways. In the brain, both HIV-1 proteins and meth engage MMP-9 and MAPK signaling cascades. To indicate whether MMP-9 is involved in GB pathology induced by HIV-1 proteins and/or meth, we examined colon samples taken from meth self-administering (SA) HIV-1 Tg and non-Tg rats (0.02-0.04mg/kg/0.05ml iv infusion) 2h/day for 21 days; cumulative meth intake was 4.5 ±0.3mg/kg and 5.2±0.5mg/kg, respectively. Controls were saline-yoked. One day following the last operant session, colon samples were harvested. Levels of MMP-9 and a component of the MAPK cascade, extracellular-regulated kinase (ERK), were evaluated by immunoblotting. A two-way ANOVA revealed a genotype effect for MMP-9 and the ratio of phosphorylated (activated) ERK to total ERK (pERK/ERK), but no meth effect. Post hoc analysis of relevant planned contrasts revealed differences between saline Tg and saline non-Tg rats. However, there was a consistent non-significant trend for MMP-9 and pERK/ERK to be increased by meth in Tg rats. These findings suggests a role for ERK and MMP-9 in GB pathology induced by HIV-1 proteins. We predict that with greater meth exposure, effects of the stimulant would also become apparent.

Poster 1-46

Lobelane and GZ-11608 differentially regulate function, but not expression, of the vesicular monoamine transporter-2 in a methamphetamine-dependent manner

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Vesicular monoamine transporter-2 (VMAT2) inhibitors, including lobelane and GZ-11608, represent potential therapeutics for methamphetamine (METH) use disorder. Behavioral tolerance develops to the reduction in METH self-administration following repeated lobelane, but not GZ-11608. To determine whether changes in VMAT2 function or expression underlie this difference, VMAT2 kinetic analysis and protein expression were evaluated following repeated lobelane and GZ-11608 treatment. Adult male Sprague-Dawley rats were treated (sc) for 17 days with saline (0.9% 1 ml/kg; 'saline-repeated') or METH (1.0 mg/kg; 'METH-repeated') or daily for 10 days with METH followed by 7 days of saline ('METH-withdrawal'). During the last 7 days of treatment, rats were pretreated (sc) daily with lobelane (5.6 mg/kg), GZ-11608 (17 mg/kg), or vehicle (15% kolliphor in saline, 2 ml/kg) 20 min prior to METH or saline. Locomotor activity was assessed on days 1, 11, and 17. VMAT2 function (maximal [3H]dopamine uptake, Vmax) and expression were determined using kinetic analysis and western blotting 24 h after the final treatment. Lobelane and GZ-11608 acutely decreased ($p<0.05$) METH-induced behavioral sensitization. Tolerance did not develop to the behavioral effect of either VMAT2 inhibitor, in contrast to previously observed tolerance to lobelane in the METH self-administration assay. Both VMAT2 inhibitors had no effect on locomotor activity in the METH-withdrawal group. While repeated METH had no effect on Vmax, METH withdrawal decreased (59%) Vmax, consistent with previous work. Both VMAT2 inhibitors increased Vmax, but only lobelane reached significance. Neither VMAT2 inhibitor had an effect in the repeated METH group. However, in the METH-withdrawal group, both inhibitors normalized the reduction in Vmax produced by METH-withdrawal. Further, there were no group differences in VMAT2 protein expression. Thus, these VMAT2 inhibitors altered METH's behavioral and neurochemical effects depending on the maintenance of METH administration.
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Poster 1-47

Negative incentive shifts in food reward engender oral ethanol self-administration in rats

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Signaled transitions between favorable and unfavorable situations, termed negative incentive shifts, engender behavioral disruption in the form of extended pausing on fixed-ratio (FR) schedules. We investigated if negative incentive shifts also produce ethanol self-administration. Ten male food-restricted Long-Evans rats lever pressed on a multiple FR FR schedule with signaled components producing either a large (4 pellet) or small (1 pellet) reinforcer. Thus, four transitions between reinforcers were arranged: from a just-received small reinforcer to a signaled upcoming-small reinforcer (small-small), small-large, large-large, and large-small (the negative incentive shift). After establishing a baseline of lever pressing during these transitions, rats were provided with concurrent access to a 10% sucrose solution (w/v) and licks were recorded as a function of transition type. Then, a mixture of 10% sucrose plus 10% ethanol (w/v) was investigated. The sucrose was then faded out resulting in rats self-administering a 10% ethanol solution (v/v). Water was available ad-libitum in home cages throughout all conditions. The negative incentive shift produced the longest pre-ratio pauses and produced the most ethanol consumption. Rats tended to drink during the onset of the session and during the negative incentive shift but drank less during the other transitions. A subsequent dose manipulation revealed that 5% and 10% ethanol solutions maintain a higher number of within session licks relative to 0% and 20% ethanol solutions. Negative incentive shifts in food reward initiate and maintain oral ethanol self-administration with the greatest number of licks occurring at 5% and 10% ethanol solutions.

Poster 1-48

The impacts of social support on motivation to change alcohol consumption among DWI offenders: Examination of three models of social support

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This study investigates the role of social support in motivating people with DWI arrests to change their drinking behaviors. Especially, this study examined three theoretical models of social support: the Main -effect model, the Buffering model, and the Optimal matching model. The Main effect model predicts that the association between social support and attitudinal change is mainly attributable to the beneficial effect of social support itself. The Buffering model claims that the role of social support is to provide individuals with a buffer from stressful events, suggesting a moderating effect of level of stress. Lastly, the Optimal matching model posits that social support can be beneficial when it matches to the needs of patients. A total of 119 DWI offenders were recruited either from correctional treatment facility (n=59) or community (n=60) and finished clinical interviews to assess demographic, physical/psychiatric conditions, and other psycho-social factors. The results showed that social support has an overall positive impact on increasing motivation to change among DWI offenders (i.e., main effect) and that social support can be beneficial for DWI offenders particularly when it matches to their specific needs (i.e. optimal matching). However, there were no significant interaction effects between social support and the degree of alcohol-related problems predicting motivation to change, rejecting the Buffering models.

Poster 2-1

Discriminative stimulus effects of benzylideneoxymorphone in rats

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Opioids remain the drugs of choice for treating moderate to severe pain, although adverse effects, such as the development of tolerance, are associated with their clinical use. Considerable evidence indicates that drugs acting concomitantly as agonists at μ opioid receptors and antagonists at δ opioid receptors produce antinociceptive effects that do not diminish with repeated administration (i.e. tolerance does not develop). One such drug, benzylideneoxymorphone, has been shown to produce antinociception, although it appears to have less efficacy than morphine at μ opioid receptors. The current study compared the discriminative stimulus effects of benzylideneoxymorphone to those of morphine to determine whether differences in the pharmacological profiles of benzylideneoxymorphone and morphine might impact acute effects other than antinociception. Eight rats discriminated 3.2 mg/kg morphine while responding under a fixed ratio 10 schedule of food presentation. Morphine dose dependently increased responding on the morphine lever, with a dose of 3.2 mg/kg producing ≥ 90% morphine-lever responding. A slightly larger dose of benzylideneoxymorphone (5.6 mg/kg) was needed to produce ≥ 90% morphine-lever responding and these effects were attenuated by naltrexone. Thus the discriminative stimulus effects of benzylideneoxymorphone are similar to those of morphine in terms of both potency and effectiveness. Although some effects (e.g. antinociception) of benzylideneoxymorphone differ from those of morphine, the discriminative stimulus effects are similar for the two drugs, suggesting that the unique pharmacological profile of benzylideneoxymorphone has little impact on effects that are highly selective for μ opioid receptors. Supported by Welch Foundation Grant AQ-0039 and the CUW School of Pharmacy.

Poster 2-2

Nicotine-induced upregulation of α4 nAchR subunits in midbrain dopamine neurons

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Tobacco use increases risk of health problems, including heart and lung disease and cancer. Nicotine is a component of tobacco that is reinforcing. Nicotine reinforcement and withdrawal symptoms make quitting smoking extremely difficult for many people. Drugs of abuse, including nicotine, increase dopamine levels in the striatum which is a brain area important for addiction. Nicotine binds to nicotinic acetylcholine receptors (nAChRs) on dopamine neurons, which increases dopamine neuron signaling. This mechanism is important for addiction to nicotine. Many types of protein subunits and combinations of subunits constitute nAChRs. We have investigated if α4 subunits of nAChRs expressed on midbrain dopamine neurons, are upregulated by mouse exposure to nicotine. Subjects of these experiments are adult mice with GFP tagged α6 nAChR subunits and mCherry tagged α4 nAChR subunits expressed in dopamine neurons. Imaging of the midbrain areas (ventral tegmental area, substantia nigra pars compacta, and substantia nigra reticulata) was performed using a confocal microscope. Fluorescence resonance energy transfer (FRET) analysis of fluorescent images was done using the Image J pixFRET software plugin.

Poster 2-3

Investigating the role of serotonin transporter, organic cation transporter 3, and plasma membrane monoamine transporter in the antidepressant-like effects of ketamine

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Twenty percent of adults are diagnosed with major depressive disorder, which is typically treated with selective serotonin reuptake inhibitors. However, this type of medication takes approximately six weeks to produce therapeutic effects. Recently, low doses of ketamine have been shown to produce rapid and long-lasting antidepressant effects. Studies that have begun to examine the mechanisms underlying these effects have focused on intracellular changes mediated by NMDA and/or AMPA receptors with limited studies focusing on serotonin. One study found an increase in extracellular serotonin while another found an inhibition of serotonin uptake following ketamine treatment. Together, these studies suggest a role for serotonin in the antidepressant-like effects of ketamine, and putatively one involving uptake-1 and uptake-2 transporters for serotonin. A few studies have examined whether ketamine has affinity for the serotonin transporter (SERT; uptake-1) or organic cation transporter 3 (OCT3, uptake-2). In order to investigate this in vivo, we performed in vivo chronoamperometry. Our results showed a decrease in clearance rate of serotonin after application of ketamine as well as an increase in signal amplitude. Next, we examined antidepressant-like effects of ketamine in SERT, OCT3, and plasma membrane monoamine transporter (PMAT, uptake-2) knockout mice bred on a C57BL/6J background. Ketamine did not produce antidepressant-like effects in the SERT, PMAT, or OCT3 knockout mice indicating that blockade of SERT, PMAT, and OCT3 may be necessary for the antidepressant-like effects of ketamine.

Poster 2-4

Effects of mutant cocaine esterase (ET CocE) on cocaine self-administration in rats

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Cocaine is one of the most used stimulants in the world, and despite high rates of overdose there are no effective treatments to reverse the toxic effects of cocaine. Previous studies of the effects of a mutant bacterial cocaine esterase (RQ CocE) suggest that increasing the rate of cocaine metabolism is able to reduce the reinforcing, discriminative stimulus, cardiovascular, and lethal effects of cocaine in rats. In an effort to increase the catalytic efficiency of CocE, the current studies evaluated a novel mutant CocE (A51E & S288T; ET CocE) which incorporates mutations to both the cocaine binding and catalytic sites of CocE. In order to determine if this increased efficiency translates to an increased potency to reduce cocaine effects in vivo, 12 adult male Sprague-Dawley rats were trained to self-administer cocaine, 6 that responded for cocaine (0.1 and 1.0 mg/kg/inf) or MDPV (0.01 and 0.1 mg/kg/inf), and 6 that responded for cocaine (0.032-1 mg/kg/inf) under a multiple-component FR5 schedule of reinforcement. Pretreatment with ET CocE (0.1-3.2 mg/kg; IV) and RQ CocE (3.2 mg/kg; IV) occurred immediately before sessions. A 3.2 mg/kg dose of RQ CocE produced a ~3 fold rightward shift whereas a 3.2 mg/kg dose of ET CocE produced ~10 fold rightward shift in the cocaine dose-response curve; low levels of responding were observed when saline was available. When administered prior to sessions in which rats could respond for either cocaine or MDPV, ET CocE affected responding for cocaine, but not MDPV. Together, these results show that ET CocE selectively reduces the reinforcing effects of cocaine with the novel mutations resulting in ET CocE being 3 fold more potent than RQ CocE. Although promising, additional studies are needed to further develop this enzyme for therapeutic use to counter cocaine toxicity and abuse.

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Poster 2-5

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

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Introduction: Previous research has demonstrated that hypoinsulinemic rats display greater rewarding effects of nicotine as compared to controls. The present study examined whether the latter effect is mediated via insulin systems in the nucleus accumbens (NAc), a terminal region of the mesolimbic pathway. Specifically, we examined whether insulin supplementation would: 1) normalize the strong rewarding effects of nicotine and/or 2) reverse changes in insulin-signaling proteins observed in the NAc of hypoinsulinemic rats. Methods: Rats first received vehicle or streptozotocin (STZ; 45 mg/kg), a drug that is toxic to insulin-producing cells and produces hypoinsulinemia. A subset of STZ-treated rats were implanted with an insulin pellet and controls received sham surgery. The rats were then given 23-hour access to saline or nicotine self-administration using an escalating dose regimen (0.03, 0.06 and 0.09 mg/kg/0.1 ml infusion). Changes in operant responding for food and water, plasma glucose levels, and changes in body weight were assessed each day of self-administration. In a follow up study, western blot analyses were employed to examine changes in insulin biomarkers (IRS-2 and IGF-1Rβ) in the NAc of vehicle-, STZ-treated, and STZ-treated rats that received insulin supplementation. Insulin biomarkers were examined 2 weeks after STZ administration, in order to assess protein changes at a corresponding time point to the behavior study. Results: STZ produced an increase in nicotine intake and glucose levels that were normalized to control levels following insulin supplementation. A similar pattern was observed with food and water intake. STZ also produced an decrease in IRS-2 and IGF-1Rβ levels that were normalized to control levels following insulin treatment. Conclusion: These data suggest that insulin systems in the NAc play an important role in modulating the strong rewarding effects of nicotine observed in hypoinsulinemic rats.

Poster 2-6

A novel 5-HT7 receptor antagonist, MC-RG19, decreases cue-induced reinstatement of cocaine seeking behavior

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The serotonin 7 receptor (5-HT7R) has been implicated in preclinical models of psychiatric conditions, including depression, anxiety, and psychosis. Moreover, 5-HT7Rs have also been shown to regulate amphetamine-induced dopamine release in the ventral tegmental area. Although it has been suggested that the receptor may be involved in addiction processes, no studies to our knowledge have investigated its role in psychostimulant-related behaviors. In this series of experiments, we tested a novel, highly selective 5-HT7R antagonist, MC-RG19, for effects on spontaneous locomotor activity and several cocaine-induced and cocaine-conditioned behaviors. We found that MC-RG19 (3, 5.6, and 10 mg/kg, i.p.) decreased spontaneous locomotion only at the 10 mg/kg dose and produced a trend toward a decrease in cocaine-induced (10 and 15 mg/kg, i.p.) locomotion at this dose as well. Reinstatement effects were demonstrated in rats that were trained to self-administer cocaine (0.75 mg/kg, i.v.), which was paired with light and tone cues, and subsequently underwent extinction sessions until cocaine-seeking behavior was extinguished. Rats pretreated with MC-RG19 (5.6 and 10 mg/kg) prior to reinstatement tests showed robust reductions in cue-induced reinstatement of cocaine-seeking behavior, whereas only the high dose of MC-RG19 (10 mg/kg) produced a trend toward a decrease in cocaine-primed (15 mg/kg, i.p.) reinstatement. Collectively, these findings suggest a role for the 5-HT7R in cocaine-related behaviors, and introduce a novel target for future medication development for cocaine dependence. In the future, our laboratory will be exploring how 5-HT7R's may be involved in opioid self-administration and seeking behavior with this novel 5-HT7R antagonist.

Poster 2-7

Preclinical assessment of dependence liability of furanyl fentanyl in mice

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The emergence of novel fentanyl analogues as drugs of abuse raises questions regarding their dependence liability. A recent concern is furanyl fentanyl, which exhibits high affinity (Ki=0.0279 nM) for □-opioid receptors, but only partial agonist efficacy (Emax=55.5%). In animal models, opioid withdrawal is typically precipitated by administration of an antagonist after exposure to an agonist, and manifests as quantifiable, somatic signs, with the frequency of vertical jumping typically considered a sensitive indication of withdrawal intensity. In these studies, antinociceptive effects of fentanyl and furanyl fentanyl were first determined using a warm-water tail withdrawal procedure. Then, to study withdrawal, mice were pretreated with either fentanyl (0.3, 1.0, 3.0 mg/kg) or furanyl fentanyl (1.0, 3.0, 10, 30 mg/kg) then administered half log increments of naloxone (3, 10, 30 mg/kg) to generate dose-effect curves for vertical jumping. Both opioids elicited dose-dependent antinociceptive effects, with furanyl fentanyl being 3-fold less potent than fentanyl (ED50 values = 0.132 and 0.385 mg/kg, respectively.) In withdrawal studies, a similar 3-fold potency difference was observed, with naloxone dose-dependently eliciting vertical jumping in mice treated with either opioid. However, 10 and 30 mg/kg naloxone elicited significant jumping in mice treated with 3.0 mg/kg fentanyl, but failed to elicit jumping in mice treated with 10 mg/kg furanyl fentanyl. These studies suggest that furanyl fentanyl elicits a similar dependence state to fentanyl in the mouse, although with lower potency. It may be the case that the high affinity of furanyl fentanyl for the □-opioid receptor would necessitate a higher than anticipated dose of naloxone in an emergency overdose situation. These studies supported in part by DEA/NCTR (224-16-0505R), VA (D-15-OD-002) and the University of Arkansas for Medical Sciences.

Poster 2-8

Administration of KRM-II-81, an A-1 SPARing GABA receptor ligand, exhibits decreased respiratory depressing effects compared to alprazolam

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Classic benzodiazepines act on receptors for the neurotransmitter, GABA, to facilitate GABA-induced dampening of neuronal activity. Previous studies have demonstrated that activation of certain GABA receptors lead to a decrease in oxygen consumption. Due to the variety of α-subunits that make up GABA receptors, the exact mechanism behind this respiratory depression is still unknown. Several studies suggest that respiration is mediated by GABAA receptors preferentially expressing α-1 protein subunits. In the present study, we compared in rats (n=8) the respiratory effects of a classic benzodiazepine, alprazolam, to a novel, α-1 sparing benzodiazepine, KRM-II-81. Respiration rate and the maximum and minimum pressure in a whole-body plethysmography chamber were recorded for each drug, in each animal. Calculations of respiratory frequency, tidal volume, and minute volume were compared by a one-way ANOVA. Results demonstrate that neither KRM-II-81 nor alprazolam produce a decrease in overall oxygen consumption. However, at anxiolytic doses, alprazolam, but not KRM-II-81, produced a decrease in respiration rate with no change in tidal volume. Thus, α-1 sparing compounds may be a safer option for the treatment of anxiety, particularly in patients who co-use other drugs with respiratory-depressant effects (e.g., ethanol, opioids).

Poster 2-9

Cocaine enhances the discriminative stimulus effects of Mephedrone

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Mephedrone (4-methylmethcathinone) is one of the major constituents of "bath salts." It is a drug with discriminative effects similar to CNS stimulants and it can produce auditory and visual hallucinations, as well as problematic cardiovascular effects. This study compared the discriminative stimulus effects of mephedrone (0.32-10 mg/kg) with other prototypical drugs with CNS effects, such as ketamine (1.8-18 mg/kg), bupropion (5.6-56 mg/kg), and 3,4-methylenedioxyamphetamine (MDA) (0.32-5.6 mg/kg). In addition, mephedrone was administered in combination with cocaine (5.6-32 mg/kg), which inhibits the reuptake of catecholamines and serotonin. Rats (n=6) were trained to discriminate an intraperitoneal injection of 3.2 mg/kg mephedrone from saline under a fixed-ratio 20 schedule. Following training, increasing cumulative doses of mephedrone produced dose-dependent increases in mephedrone-lever responding, with full substitution considered to be greater than 80% responding and partial substitution to be greater than 50% responding. During substitution tests, ketamine never produced more than 17% drug-lever responding. In addition, bupropion and MDA produced 36% and 77% drug-lever responding, respectively, without significantly decreasing response rate. When 3.2 mg/kg of cocaine was administered prior to increasing doses of mephedrone, there was no substitution for cocaine alone; however, this dose produced a rightward shift in the dose-effect curve for mephedrone-lever responding. However, when the dose of cocaine was increased to 10 mg/kg, there was 58% mephedrone substitution, and this dose substantially increased the mephedrone-lever responding of the low doses of mephedrone. These data suggest that mephedrone may be similar to cocaine in having a higher affinity for the serotonin transporter (SERT) than the dopamine transporter (DAT), but more efficacy at DAT than SERT. In addition, the capacity of cocaine to potentiate and attenuate mephedrone suggests the discriminative stimulus effects of the training dose of mephedrone are mediated predominately by dopamine rather than serotonin.

Poster 2-10

Dopamine transporter allosteric modulator SRI-32743 alters the effects of cocaine on dopamine neurotransmission in adult mice

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Background: Cocaine is a highly abused psychostimulant that inhibits dopamine (DA) uptake by blockade of the dopamine transporter (DAT). Despite knowledge and understanding of cocaine's main mechanism of action, there are no FDA-approved pharmacotherapies for treatment of cocaine-use disorder. Recently novel allosteric modulators of DAT have been identified that have nanomolar potency to partially inhibit DAT uptake, which may be useful as probes of biogenic amine transporter function and may have therapeutic potential.

Methods: Here we used both patch clamp electrophysiology in male and female mouse brain slices and high speed chronoamperometry in anesthetized mice to examine the effects of two novel ligands (SRI-32743 and SRI-35282) on dopamine neurotransmission and their ability to alter the effects of cocaine.

Results: Pretreatment with SRI-32743 blunted the cellular effects of cocaine by altering DAT function in a concentration-dependent manner. In addition, SRI-32743 decreased D2 receptor-mediated currents of midbrain DA neurons. In contrast, the ligand SRI-35282 demonstrated less ability to reduce the effects of cocaine.

Conclusion: These preliminary results are promising and further exploration of the effects of these allosteric DAT modulators on behavior will be important for determining their potential as pharmacotherapies for the treatment of cocaine-use disorder.

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Poster 2-11

Role of the plasma membrane monoamine transporter in ketamine's antidepressant-like effects

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Depression is a serious mood disorder, commonly treated with selective serotonin reuptake inhibitors (SSRIs), which inhibit the high-affinity low-capacity serotonin transporter (SERT). Unfortunately, SSRIs can take weeks to be of therapeutic benefit, and many patients also exhibit "resistance" or non-responsiveness to SSRI treatment. Clinical trials have shown that intravenous infusions of ketamine, an NMDA receptor antagonist, is an effective treatment for patients that are resistant to SSRIs, alleviating depressive symptoms within hours of administration. However, the mechanism(s) through which ketamine produces its antidepressant effect remains elusive. Other NMDA receptor antagonists do not have antidepressant effects, suggesting that ketamine must have actions at additional sites. Determining the nature of these sites could yield insights into developing novel therapeutic drugs for the treatment of depression, which lack ketamine's abuse potential. Ketamine's actions are known to be dependent on serotonin (5-HT), and ketamine is known to increase extracellular 5-HT, raising the possibility that ketamine inhibits 5-HT clearance. Consistent with this idea, we found that ketamine's antidepressant-like effects were lost in SERT knockout (KO) mice, suggesting that ketamine inhibits SERT mediated 5-HT clearance. We have previously shown that the antidepressant-like effects of SSRIs can be enhanced by co-administration of a blocker of "uptake 2", i.e. low-affinity high-capacity transporters, which includes the plasma membrane monoamine transporter (PMAT). Here we test the hypothesis that ketamine inhibition of PMAT-mediated 5-HT reuptake contributes to its antidepressant-like effects. To examine a possible role for PMAT in ketamine's antidepressant-like action, we assessed the effects of ketamine on the behavior of male adult wildtype and PMAT KO mice in the forced swim test, an assay used to determine the antidepressant-like activity of drugs. Ketamine's affinity for PMAT in vitro was determined by measuring its ability to inhibit uptake of the radiolabeled substrate [3H] MPP+ into human embryonic kidney (HEK) cells expressing human PMAT (hPMAT). Though ketamine was not a potent inhibitor of hPMAT-mediated [3H]-MPP+ uptake, ketamine failed to produce an antidepressant-like effect in PMAT knockout mice in the forced swim test, possibly indicating that PMAT expression is necessary for ketamine's antidepressant-like effect on mouse behavior, and may be another mechanism through which ketamine increases extracellular 5-HT.

Poster 2-12

Ketamine effects on temporal discrimination in reserpine induced depression in female rats

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Depression and subjective slowing of temporal perception has been linked by many studies since the 1960s (Thones and Oberfeld, 2015). Depressed patients will often report, "every hour seems like a year to me" or that "things seem to take forever". While the debate continues as to whether individuals who suffer from depression perceive time objectively different, trends in recent studies indicate a distinct over-production of "short" and an under-production of "long" time production tasks by depressive patients. Ketamine has been found to produce a rapid and robust antidepressant effects in treatment-resistant patients. It has also has been known to affect time perception when used recreationally. Clinical studies have shown that a sub-anesthetic dose of ketamine can have effects within an hour, which can last up to a week without a subsequent dose (Aan het Rot, Zarate, Charney, & Mathew, 2012; Ibrahim et al., 2012). In the current experiment, we studied if sub-anesthetic ketamine (5.0mg/kg i.p.) had any effects on time perception in depressed rodents. Specifically, female rats were trained on a fixed interval procedure (MacInnis and Guilhardi, 2006). Following the temporal training, we induced depression by a daily injection reserpine (0.2mg/kg i.p.) for two weeks. Depressed state was confirmed by a forced swim test 24 hour after the last reserpine injection. Subsequently, to establish ketamine's antidepressant effects, rodents were injected with ketamine and retested in the fixed interval and forced swim procedure. This study confirmed that both drugs exerted its prescribed effects in rodents. Notably, reserpine induces depression and the single injection of ketamine significantly reduced depressive symptoms as shown by an increased escaping behavior in the forced swim test. Interestingly, although reserpine induced depression in forced swim test it did not cause distortion in time perception.

Poster 2-13

Modular total synthesis of Salvinorin A inspired 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.

Our total synthesis approach allows for deliberate functionality introduction at various stages with the goal of systematically exploring their activity using in vitro studies at opioid receptors and ultimately in animal models of pain and addiction. We have designed molecules able to overcome potential shortcomings in the drug-like properties of 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 the key 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 modular synthetic protocol developed to access structural motifs inaccessible by semi-synthesis has successfully produced an array of compounds with a deliberately modified tricyclic core as well as the exploration of several different manipulations in order to help determine the key features of the molecule for its high potency and activity. Some of the more efficacious compounds in vivo are now moving into animal models with the goal of developing clinically relevant analgesics with reduced abuse liability and drug abuse pharmacotherapies.

Poster 2-14

Assessment of the priming strength of opioids before and during chronic naltrexone

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Opioid addiction is characterized as a chronic relapsing disorder in which renewed drug-seeking behavior during abstinence can be provoked by exposure to an opioid or opioid-associated cue. In laboratory subjects, drug-seeking behavior similarly can be reinstated by priming with the drug or drug-related stimuli. Naltrexone, a μ-opioid receptor antagonist, is used in the treatment of opioid addiction, however its ability to reduce reinstatement behavior in laboratory subjects is not well understood. Here we investigate changes in priming strength of opioid agonists during naltrexone (0.2mg/kg/day) treatment. Squirrel monkeys (n=4) were trained to self-administer i.v oxycodone. Full dose effect (D-E) functions for the priming strength of different opioids (i.e. number of injections self-administered when only vehicle is available) were determined before (baseline) and during chronic naltrexone treatment. At baseline, a pre-session priming injection of either full opioid agonists (oxycodone, heroin and methadone) or partial agonists (buprenorphine, butorphanol and nalbuphine) reinstated drug-seeking behavior in a dose-dependent manner. iPrecio™ mini-pumps delivered naltrexone (0.2mg/kg/day) through a sub-cutaneous catheter and the priming strength of each opioid agonist was reassessed. Naltrexone produced a ten-fold rightward shift in the D-E function for oxycodone self-administration (peak number of injections self-administered at 0.01mg/kg/inj pre-chronic vs 0.1mg/kg/inj during chronic treatment). Preliminary data (n=2) suggests naltrexone produces rightward shifts in the D-E functions for reinstatement of drug seeking behavior following a priming injection with the full opioid agonists, oxycodone and heroin, and rightward and downward shifts in the D-E functions for partial opioid agonists, buprenorphine, nalbuphine and butorphanol. Methadone-induced reinstatement was variable between the subjects but preliminary data suggests a rightward shift in the D-E function. Reduction in the priming strength of opioid drugs would represent a reduction in the ability of these drugs to provoke relapse in naltrexone-maintained individuals.

Poster 2-15

Electronic Nicotine Delivery system (ENDs) users report high levels of nicotine cravings during smoking and withdrawal periods, but low nicotine dependence and withdrawal rates

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Electronic nicotine delivery systems (ENDS) and electronic cigarettes (E-cigs) are marketed as a safer alternative to cigarettes; however, the research community is still investigating the short- and long-term effects of ENDS. Minimal research has evaluated the biological and psychological effects of ENDS on first time daily ENDS users (previously nicotine native). The present sought to evaluate several psychological (e.g. cravings, withdrawal, and dependence) and biological (heartrate, blood pressure, carbon monoxide concentration) measures under normal and withdrawal conditions. The study was composed of two experimental sessions with participants smoking their ENDS ad lib for the first session (baseline session) and abstaining from nicotine for 12 hours in the second session (withdrawal session). ENDs users has significantly higher craving scores on all measures of the tobacco cravings questionnaire short form during baseline and withdrawal session as compared to nonsmokers. During baseline and withdrawal sessions, ENDS users had a mean score of 7.32 (emotionality), 15.26 (expectancy), 5.49 (compulsivity), and 9.86 (purposefulness) - (nonsmokers had a score of 3.5 on all scales). ENDS were classified with low to moderate dependence based on the Fagerstrom Dependence Scale with a mean score of 2.67 and 3 on baseline and withdrawal sessions, respectively. There was a trend on the Minnesota Nicotine Withdrawal Scale as nonsmokers had a mean score of 7 and ENDS users had a score of 14. The mean CO reading was not significantly different between nonsmokers and ENDs users, which suggests that ENDS are safer in terms of combustible activity. Interestingly, this study found that ENDS users have significant craving score even when they are able to smoke, which may suggest that they are not receiving adequate nicotine with this time of delivery system.

Poster 2-16

Optimization of serotonin (5-HT) 5-HT2C receptor positive allosteric modulators as potential neurotherapeutics for cocaine use disorder

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Evidence supports that targeting the serotonin (5-HT) 5-HT2C receptor (5-HT2CR), a G protein-coupled receptor (GPCR), may provide therapeutic benefit for multiple disorders, including obesity, mood disorders and addiction. Our multidisciplinary effort is focused on developing small molecule therapeutics for cocaine use disorder, an acquired brain disorder characterized by multiple episodes of relapse following periods of abstinence and withdrawal. Interestingly, the 5-HT2CR is functionally coupled to behaviors that drive relapse vulnerability, such as impulsivity and cue reactivity. Proof-of-concept studies in rodents have shown that 5-HT2CR hypofunction promotes, and selective 5-HT2CR agonists suppress, these relapse-associated behaviors. In contrast to traditional orthosteric agonists, positive allosteric modulators (PAMs) of the 5-HT2CR are an attractive therapeutic mechanism, due to the possibility for greater selectivity and decreased receptor desensitization. Therefore, we hypothesize that rationally designed 5-HT2CR PAMs will effectively and safely enhance 5-HT2CR signaling and suppress relapse-associated behaviors. Thus far, our efforts have focused on two exciting and divergent molecular scaffolds: 1) Analogs of CYD-1-79, a lead 5-HT2CR PAM discovered by our team, and 2) analogs of the endogenous signaling ligand oleamide. Our work towards a novel neurotherapeutic has generated promising lead compounds in both series, which display selective enhancement of 5-HT signaling at the 5-HT2CR, as measured by intracellular calcium release, and measurable blood-brain barrier penetrance in the rat. Subsequent lead optimization has generated promising second generation compounds, and preclinical studies in rats have demonstrated efficacy in suppressing motor impulsivity and cue reactivity assessed as lever presses for cocaine-associated cues. We conclude that these novel 5-HT2CR PAMs hold potential as a first-in-class neurotherapeutic for cocaine use disorder.

Poster 2-17

Thermoregulatory and discriminative stimulus effects of MDMA and its putatively less toxic deuterated form in rodents

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There is a renewed interest in the use of 3,4-methylenedioxymethamphetamine (MDMA) to supplement the treatment of psychiatric problems. MDMA is known to produce neurotoxicity at sufficiently high doses possibly through the formation of reactive adducts during metabolism. Previous research indicates that deuterating compounds can improve their metabolic fates and substantially alter their therapeutic profiles. As such, deuterated MDMA (D-MDMA) may serve as a safer form of MDMA used in clinical settings. In the present study, the thermoregulatory effects of D-MDMA were compared to MDMA in mice. Mice were assigned to a D-MDMA or MDMA treatment group following surgical implantation (ip) of biotelemetry probes that simultaneously record horizontal counts and core temperature. Mice received once daily injections (ip) of their respective drugs every three days in an ascending sequence (10, 32, 56 mg/kg) and core temperature and horizontal movements were continuously monitored for 24 hours. In separate groups of mice, the selective serotonin 2A/2C antagonist ketanserin (1 mg/kg; ip) was injected 15 min before MDMA or D-MDMA (10, 32, 56, 100 mg/kg; injections separated by three days). The results revealed that MDMA and D-MDMA produced dose-dependent hyperthermic and locomotor stimulant effects, but MDMA more potently produced greater maximal effects in these measures. Moreover, pretreatment with ketanserin revealed that the hyperthermic effects of MDMA and D-MDMA are mediated by the 2A and 2C receptors, indicating similar pharmacodynamics. In a separate experiment, rats were trained to discriminate 1.5 mg/kg MDMA from saline and substitution tests were performed with MDMA and D-MDMA. Preliminary results revealed that MDMA and D-MDMA produce similar interoceptive effects. Together, these findings indicate that D-MDMA may produce therapeutic effects that are similar to MDMA, but with less risk of physiological toxicity.

Poster 2-18

Dopaminergic perturbations from food restriction and exercise are sex-dependently amplified during adolescence

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Eating disorders afflict at least 3 percent of teenagers and entail severe health consequences in addition to their psychological toll, but no effective treatments exist. The dopaminergic system, which regulates both eating behaviors and physical activity, undergoes a sensitive maturation period during adolescence. However, studies into the role of the dopaminergic system in ontogeny of eating disorders, and into dopaminergic system maturation in adolescents, are lacking. Here we measured function of the dopamine transporter (DAT), a critical regulator of dopaminergic signaling, using both in vivo high-speed chronoamperometry and locomotor assays of acute cocaine response. Employing an activity-based anorexia paradigm for 4-5 days, we investigated how food restriction, free exercise on a running wheel, or the combination thereof impacted DAT function in adult (postnatal day 90) and adolescent (postnatal day 30) Sprague-Dawley rats of both sexes. Food restriction alone or with exercise in adolescent rats of both sexes produced leftward shifts in the dose-response to the locomotor-promoting effects of cocaine. These same groups similarly exhibited significantly attenuated dopamine clearance, suggesting reduced DAT activity. Effects in adults were largely subdued, if present at all. Together, these findings suggest that adolescent plasticity of the dopaminergic system confers vulnerability to eating disorders and persistence of associated unhealthy behaviors (e.g., compulsive exercise). Therefore, drugs that enhance dopamine uptake or otherwise reduce dopamine signaling duration may prove efficacious in the treatment of emerging adolescent eating disorders. Ongoing experiments are evaluating striatal DAT expression in these animals, and future experiments will optimize longer term food restriction and exercise conditions in adolescents for investigation of pharmacologic interventions.

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Poster 2-19

Chemogenetic activation of ventral tegmental area GABA neurons, but not mesoaccumbal GABA terminals, disrupts responding to reward-predictive cues

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Cues predicting rewards can initiate reward-seeking behaviors and may be involved in relapse behavior in human addicts. Dopamine projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) are critical in regulating cue-motivated operant responding. However, even though approximately one third of mesoaccumbal projecting neurons are GABAergic, it is unclear how mesoaccumbal GABA neurons influence motivational processes and cue processing. Here we used a combinatorial viral vector approach to restrict activating designer receptors (DREADDs) to GABA neurons in the VTA of wild-type rats trained to respond during a distinct audiovisual cue for sucrose. In this cue-dependent instrumental task, we measured different aspects of motivation for the cue and primary reinforcer, while chemogenetically activating either the VTA-GABA neurons or their terminals in the NAc. Activation of VTA-GABA neurons decreased cue-induced responding and accuracy, while increasing latencies to respond to the cue and obtain the reward, yet the rats persisted in entering the reward cup. However, activation of the VTA GABA terminals in the accumbens had no effect on any of these behaviors. Together, we demonstrate that VTA-GABA neuron activity preferentially attenuates the ability of cues to trigger reward-seeking, while some aspects of the motivation for the reward itself are preserved. Additionally, the dense VTA-GABA projections to the NAc do not influence the motivational salience of the cue. Recently we have also determined that blocking CB1 receptors with rimonabant produces similar effects as VTA-GABA activation on incentive cue-induced behaviors. We are now exploring endocannabinoid regulation of VTA-GABA neurons in these behaviors, and whether GABA and endocannabinoid interactions in the VTA may serve as a novel target for future pharmacotherapies to treat substance use disorders.

Poster 2-20

Behavioral and subjective effects of 11-OH-THC

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Background: The metabolic pathway of Δ9-tetrahydrocanabinol (Δ9-THC), the major psychoactive component of cannabis, includes its CYP-mediated biotransformation into 11-hydroxy-Δ9-THC (11-OH-THC), a pharmacologically active metabolite. 11-OH-THC readily crosses the blood-brain barrier and produces behavioral and subjective effects similar to those of Δ9-THC. The effects of 11-OH-THC have not been broadly characterized and understanding of its potency relative to Δ9-THC remains inconclusive. We characterized the in vivo effects of 11-OH-THC in the rodent tetrad and drug discrimination assays and assessed in vitro cannabinoid-stimulated [35S]GTPγS binding.

Tetrad: Adult male and female mice were administered vehicle, Δ9-THC, or 11-OH-THC and subsequently tested in the tetrad for typical cannabimimetic effects (hypothermia, catalepsy, analgesia and locomotor effects). 11-OH-THC dose-dependently decreased body temperature and motor activity and increased catalepsy and analgesia at lower doses than Δ9-THC in both males and females.

Drug discrimination: Adult male and female mice trained to discriminate Δ9-THC from vehicle completed dose-response curves for Δ9-THC and 11-OH-THC. SR141716 (rimonabant) and SR144528, receptor antagonists for CB1 and CB2, respectively, were coadministered in order to assess receptor mediation. 11-OH-THC produced dose-dependent substitution for Δ9-THC at lower doses than Δ9-THC in both males and females, with substitution fully blocked by SR141716. SR144528 had no effect.

[35S]GTPγS binding: Cannabinoid-stimulated [35S]GTPγS binding was performed in adult male and female mouse cerebellum with Δ9-THC or 11-OH-THC. No significant differences were observed.

Summary and next steps: 11-OH-THC was more potent than Δ9-THC in measures of behavioral and subjective effects, despite no significant differences in binding. Future research should fully characterize the pharmacokinetic profile of Δ9-THC across routes of administration to elucidate the impact of active metabolites like 11-OH-THC, including possible contributions to sex differences in Δ9-THC effects.

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Poster 2-21

The impact of history on the aversive (punishing) effects of drugs in rats

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Initiation and maintenance of drug use as well as relapse have been hypothesized to be impacted by sensitivity to aversive effects of drugs. This study compared sensitivity to the kappa opioid receptor agonist spiradoline in rats with and without prior exposure to histamine to test the hypothesis that a history with one aversive drug might impair or facilitate the aversive effects of a second drug. Male Sprague-Dawley rats chose (100 trials/session) between a pellet alone and a pellet + an intravenous (i.v.) infusion. All rats were tested first with saline. Thereafter, half of the rats (8) were tested with histamine (0.32 – 1 mg/kg/infusion) followed by spiradoline (0.0056 – 0.056 mg/kg/infusion) while the other half (8) were tested with spiradoline followed by histamine. When choosing between a pellet and a pellet + saline, rats responded on both levers (indifference) and completed all trials. The rats that were tested first with histamine avoided a pellet + histamine, predominantly choosing a pellet alone (>80%). Rats that received histamine first also avoided a pellet + spiradoline, instead choosing a pellet alone (>70%). The rats that were tested first with spiradoline responded approximately equally on each lever, despite receiving spiradoline in doses that significantly decreased the number of trials completed; however, rats that were tested first with spiradoline avoided a pellet + histamine, choosing a pellet alone (>75%). This study shows that spiradoline is not aversive (punishing) in drug-naïve rats but is aversive after rats have a history of avoiding histamine. That histamine is a more effective aversive stimulus in naïve rats might be due to its very rapid onset and offset of action compared with spiradoline. This study suggests that avoidance of drug effects can be a learned behavior that generalizes to different drug classes when the aversive consequences are discrete. Experience with aversive effects might also impact reinforcing effects of drugs, with diminished sensitivity to aversive effects potentially predicting vulnerability to drug abuse. Support: USPHS Grants R25NS080684, F32DA043348, and T32DA031115, and the Welch Foundation [AQ-0039].

Poster 2-22

Effects of "bath salts" constituent α-pyrrolidinopentiophenone (α-PVP) and its enantiomers on locomotor activity and core temperature in mice

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α-Pyrrolidinopentiophenone (α-PVP), a psychostimulant in the cathinone class, is a commonly abused designer drugs known to users as "flakka" or "gravel." α-PVP is a catecholamine reuptake inhibitor, similar to the structurally-related cathinone MDPV. In addition to increasing locomotor activity, many psychostimulants also alter thermoregulation, and these effects may be impacted by ambient temperature. Biotelemetry probes simultaneously monitoring core temperature and motor activity were used to assess the effects of α-PVP at both warm and cool environmental temperatures in 6 groups of 6 adult male NIH Swiss mice. After recovery, all animals received intraperitoneal injections of saline, *S*-α-PVP, *R*-α-PVP, or the racemic *S,R*-α-PVP at either warm (28˚C) or cool (20˚C) environmental temperature. Escalating doses of α-PVP were administered every other day within each group, and core temperature and locomotor activity were recorded within the home cage for 24 hrs after drug administration. At 20˚C, racemic α-PVP and both enantiomers elicited dose-dependent locomotor stimulant effects. There was no observed potency difference between the racemate and the *S*-isomer, but the *R*-isomer was approximately 10-fold less potent than either the *S*-isomer or the racemic mixture. Maximum core temperature was dose-dependently increased following injection of either the racemate or *S*-isomer, but the *R*-isomer did not alter core temperature at any dose tested. Studies at 28˚C are ongoing and will be presented. These experiments suggest that, similar to traditional psychostimulants, α-PVP and its *S*-enantiomer elicit increased locomotor activity and core temperature in mice, while the *R*-enantiomer is at least 10-fold less potent. Environmental factors such as ambient temperature may modulate the effects of α-PVP. These studies supported by DA039195, GM110702 and DA022981.

Poster 2-23

Locomotor sensitization following cumulative dose 3,4-methylenedioxypyrovalerone (MDPV) in high- and low-impulsivity mice

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Behavioral phenotypes are known to be predictive of drug abuse liability. One of the common phenotypes studied is reactivity to a novel, inescapable environment, which is believed to be one measure of inherent impulsivity. This relationship has been extensively studied with traditional psychostimulants like cocaine and amphetamine, but whether it extends to novel psychoactive substances like the cathinone analogues found in abused "bath salts" products is unknown. In this study, 40 CD-1 mice were classified as high-, mid-, and low-responders (HR, MR, and LR, respectively) based on locomotor activity following a saline injection during exposure to a novel environment. This characterization of impulsivity can predict the effectiveness or potency of locomotor stimulant properties of a psychostimulant. Mice were tested in a single day using automated locomotor activity chambers. A baseline level of novelty-stimulated activity was recorded for 60 minutes, followed by additional 60 minute recordings of locomotor activity immediately after IP administration of saline, then of 1, 3, and 10 mg/kg cumulative 3,4-methylenedioxypyrovalerone (MDPV). No differences in novelty-elicited locomotor activity were observed during baseline testing, but mice displayed dramatic differences in locomotor activity following saline administration, allowing separation into HR, MR and LR groups. All animals showed dose-dependent locomotor increases following MDPV administration, with HR animals exhibiting the highest locomotor effects at each dose, followed by the MR animals, and finally the LR animals showing the least locomotor stimulation in response to MDPV. Following these initial studies, we tested the capacity of MDPV to induce locomotor sensitization in 16 experimentally-naïve subjects characterized as HR, MR or LR based on locomotor response to saline as described above. After the initial characterization and cumulative dosing procedure with MDPV, animals received daily injections of 3 mg/kg MDPV in the home cage for 5 days. Following 1 day with no injection, locomotor activity was reassessed using the cumulative dosing procedure. Finally, 6 days with no injection occurred prior to one last locomotor activity assessment with the cumulative dosing. Results of the sensitization studies will be discussed. These studies replicate previous findings with traditional psychostimulants like cocaine and amphetamine, and extend the predictive relationship between locomotor reactivity and stimulant effects to the common "bath salts" constituent MDPV. This information may be useful in identifying clinical populations vulnerable to MDPV abuse, and may inform treatment strategies for these populations. These studies supported by DA039195 and GM110702.

Poster 2-24

Effects of the second generation "bath salt" cathinone alpha-Pyrrolidinopropiophenone (α-PPP) on behavior and neurochemistry in mice

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Previous studies have shown that amphetamine derivatives deplete brain levels of monoamine neurotransmitters and affect learning and memory. Cathinones ("balt salts") are an emerging class of abused amphetamine derivatives and few studies have examined the persistent effects of exposure to cathinones on neurotransmitter levels and learning and memory. In the current study, we investigated the effects of the synthetic cathinone α-pyrrolidinopropiophenone (α-PPP) on anxiety, learning and memory, and brain monoamine neurochemistry. All studies were conducted in Swiss-Webster mice using a dosing regimen of α-PPP (80mg/kg) that has been used extensively to study the neurotoxicity of amphetamine derivatives (QID, q2h). Anxiety was studied using the elevated plus maze test. Working and recognition memory were assessed using the Y-maze and novel object recognition test (NORT), respectively. Regional levels regional levels of dopamine, serotonin, norepinephrine, and the metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) were determined in the pre-frontal cortex, striatum and hippocampus using high-pressure liquid chromatography. Behavior was assessed 4 days after the dosing regimen and neurochemistry was assessed the following day. α-PPP had no significant effect on anxiety in mice, yet it induced significant impairments in both working memory and recognition memory. There were few apparent changes in tissue monoamine levels, suggesting that these learning and memory deficits are related to changes in other neurotransmitter systems. Brain cholinergic systems are a likely candidate system as both Y-maze and NORT performance has been associated with this system. The current study establishes that exposure to α-PPP impairs learning and memory and suggests that it may have an influence on brain cholinergic systems. This research highlights the dangers of α-PPP and related cathinone derivatives and suggests a target system that should be explored in the development of compounds to treat their deleterious effects.

Poster 2-25

The Effects of the combined use of ibuprofen and ethanol on cell death of serotonergic neuronal SH-SY5Y cells

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Background: Ibuprofen, a non-selective nonsteroidal anti-inflammatory drug (NSAID), is a common over-the-counter (OTC) analgesic consumed for the treatment of acute and chronic pain (headaches, tenderness, and swelling). The abuse and adverse effects of OTC NSAIDS on the liver and kidney are well established, especially when taken with ethanol (E), and remain a cause of great concern. We hypothesized that chronic NSAID use also causes oxidative stress and cell death in sensitive brain regions. Thus, this study was designed to determine the effect of Ibuprofen, when combined to physiologically relevant doses of E on human SH-SY5Y neuronal cells (which mimic serotonergic neurons of the hippocampus, a brain region responsible for long term memory and emotions).

Methods: In vitro cultured human SH-SY5Y neuronal cells were exposed to varying doses of Ibuprofen (20-500µM), in the absence and presence of low (10mM) and high (88mM) concentrations of E for 24 hrs. Cell viability was measured using MTT assays. Cellular oxidative stress levels were determined by fluorometry using a free radical marker, DCFDA. Cell death was analyzed by poly-(ADP-ribose) polymerase (PARP), caspase-3 cleavage, cytochrome c release, using Western blotting.

Results: Cells treated either with low or high doses of E only exhibited no significant change in viability relative to untreated controls. Moreover, lower concentrations of Ibuprofen alone had no effect on cell survival in culture. However, there was a significant dose-dependent loss in cell viability, with 100µM Ibuprofen causing death of 40% of the cells. The combined use of ethanol and Ibuprofen increased oxidative stress, and a dramatic increase in PARP cleavage and cytochrome c release was observed.

Conclusion: Our results indicate that 100µM or higher Ibuprofen alone causes neuronal cell death. However, a combined exposure of ethanol with high concentrations of Ibuprofen significantly augments neuronal dysfunction and cell death. Together, these results suggest that the chronic and combined exposure to Ibuprofen and ethanol may lead to loss of serotonergic neurons.

Poster 2-26

The impact of social support, stress, and depressive symptoms in opioid-using women

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Perinatal opioid exposure negatively affects both the mother and the child leaving them at risk for 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. A relationship between prenatal stress and maternal states has been reported in the literature; however, little is known about the underlying social, physiological, and behavioral mechanisms mediating this relationship. The aims of this study are to investigate the relationship between the social environment, perceived stressors, stress reactivity, and mental health outcomes for opioid-using pregnant women. Data was collected by using the following instruments: 1) the 10-item Perceived Stress Scale and Daily Stress Inventory to measure perceived stress levels and stressful events, 2) MOS Social Support Survey to assess several aspects of social support, 3) PHQ-9 to determine if symptoms of depression were present, and 4) LEC, to explore trauma exposure. Finally, saliva samples were collected in to measure diurnal cortisol patterns and physiological response to stress.

Linear regression was used to examine social support as a predictor of perceived stress, depressive symptoms, and HPA-axis functioning. Data analysis is still in progress but preliminary findings suggest social support as a mediator for stress. The findings from this study will help inform interventions to improve social support resources for the in substance using women population, thus, potentially improving mental health outcomes.

Poster 2-27

Discriminative stimulus effects of α2/α3 subtype-selective GABAA receptor positive allosteric modulators in rats

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Nonselective GABAA receptor positive allosteric modulators (PAMs) are not suitable for clinical pain control due to various adverse effects unrelated to analgesia. Preliminary research in our lab suggests that α2/ α3 –subtype selective GABAA PAMs KRM-II-81 and NS16085 are effective against chronic pain in both neuropathic and inflammatory pain models. However, little is known about their discriminative stimulus effects. This study sought to examine the discriminative stimulus effects of KRM-II-81 and NS16085. Rats were trained to discriminate 3.2 mg/kg midazolam from its vehicle under a two-lever food-reinforced drug discrimination paradigm. A separate group of rats were trained to discriminate 3.2 mg/kg KRM-II-81 from its vehicle, but reliable discrimination was not acquired after 115 training sessions and this study was terminated. In rats discriminating 3.2 mg/kg midazolam, midazolam dose-dependently increased midazolam-associated lever responding and flunitrazepam completely substituted for this stimulus, while KRM-II-81 and NS16085, only partially substituted, and the doses were significantly larger than the doses that produced significant antinociception. In contrast, methamphetamine and morphine failed to increase midazolam-associated lever responding (< 20%). Rats were re-trained to a lower dose of 0.56 mg/kg midazolam and re-tested. The results were overall similar except that the midazolam and flunitrazepam dose-effect curves were shifted leftward as compared to the dose-effect curves tested under 3.2 mg/kg midazolam. Taken together, since the discriminative stimulus effects of midazolam is primarily mediated via α1-subtype GABAA receptors, the partial substitution of KRM-II-81 and NS16085 for midazolam discrimination suggests that these compounds have little in vivo pharmacological activity at α1-subtype GABAA receptors. These results support the notion that it is possible to separate the antinociceptive actions of selective α2/ α3 GABAA PAMs from their other behavioral effects such as discriminative stimulus effects.

Poster 2-28

Application of receptor theory to the design and use of fixed-proportion mu-opioid agonist and antagonist mixtures: Effects in an assay of drug discrimination in male and female rats

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Receptor theory predicts that fixed-proportion mixtures of a competitive, reversible agonist (e.g. fentanyl) and antagonist (e.g. naltrexone) at a common receptor will result in antagonist proportion-dependent decreases in apparent efficacy of the agonist/antagonist mixtures and downward shifts in the mixture dose-effect function. The present study tested this hypothesis in an assay of drug discrimination. Male (n=6-7) and female (n=7) rats were trained to discriminate fentanyl (0.04 mg/kg sc) from saline in a two-lever liquid food-reinforced discrimination procedure. Fentanyl alone (0.0032-0.056 m/kg, sc), naltrexone alone (0.032-0.32, sc), and fixed-proportion mixtures of fentanyl/naltrexone (1:0.054, 1:0.18, 1:0.30, 1:0.54) were administered in an acute-dosing procedure, and the proportions were based on published fentanyl and naltrexone K_d values at mu receptors in rat brain. Fentanyl produced dose-dependent discriminative stimulus effects up to doses that decreased rates of responding. Up to the largest dose tested, naltrexone failed to produce >10% fentanyl-appropriate responding. Consistent with receptor theory predictions, increasing naltrexone proportions decreased the effectiveness of fentanyl to produce discriminative stimulus effects. Maximum effects of fentanyl, naltrexone, and each mixture were used to generate an efficacy-effect scale. This scale was used to quantify (a) the efficacy requirement for fentanyl discrimination between male and female rats and (b) the efficacy of five opioids (methadone, morphine, buprenorphine, NAQ, and nalbuphine) that vary in their in vitro efficacies to produce agonist-stimulated GTPγS binding. Overall, these results suggest that a fixed-proportion agonist/antagonist mixtures may be useful to manipulate apparent drug efficacy for basic research purposes.

Poster 2-29

Glutathione levels cause changes in NF-kB signaling following ethanol exposure in microglia

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Microglia, the predominant immune cells of the CNS have dual function and control brain damage by either eliciting a classical neurotoxic inflammatory (M1 phenotype), or a neuroprotective (M2 phenotype) response. Accumulating evidence suggests that chronic exposure to low doses of ethanol sensitizes the immune system however, the underlying mechanism remains unclear. The purpose of the present study was to determine the effect of glutathione dysregulation and ethanol exposure on microglial dynamics and function. EOC13.31 microglia cells were divided into six groups: control, N-acetyl cysteine (NAC), Butathione Sulfoxamine (BSO), ethanol, ethanol + NAC, and ethanol + BSO. Cells were treated with 500uM (NAC) and 200 uM BSO for 18hrs, prior to 22mM Ethanol exposure for 24hrs. Microscopy-scratch wound assays, Western blotting were performed to determine microglia migration and the underlying signaling mechanism observed over the next 24 - 48hrs (ethanol withdrawal period). Increased processing of NF-kB p105 into p50 subunit, in the presence of ethanol exposure was observed. Under control and NAC treatment, microglia grew as a mixed population, consisting of predominantly rod-like structures in addition to a small percentage of rounded cells. Ethanol alone, BSO or BSO + Ethanol treatment resulted in > 50 % of microglia to adopt a round shape, even after 24 hrs-48 hrs of ethanol withdrawal. Pretreatment with NAC showed migration and presence of both rounded and elongated cells in the wound area after 48hrs, however, mitigated NF-kB subunit processing. Together, our results indicate that ethanol-induced oxidative stress diminishes microglia migration even after 48 hrs of exposure. Also, maintaining redox (GSH) levels promotes microglial migration up to 24-48hrs after ethanol withdrawal, and most importantly antioxidants homeostasis enhances signaling towards M2 morphological changes that are neuroprotective.

Poster 2-30

Characterization of a novel glutamatergic pathway linking feeding and reward centers of the brain

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Obesity is a growing health problem that currently affects 37.5 percent of the adult population in the United States. Pharmacotherapies for obesity have limited efficacy, often resulting in 5% weight loss or less. Obesity is caused, in part, by chronic overconsumption of high-fat food. High-fat food is extremely motivating, and overconsumption of high-fat food resembles addiction-like behavior, a phenomenon described as the addictive dimensionality of obesity. To date, neurobiological aspects of motivation for high-fat food remain underexplored, and represent an opportunity to investigate potential mediators. One such mediator is the paraventricular nucleus of the hypothalamus (PVN), a brain region that regulates food intake and energy balance. The PVN has been shown to project to the nucleus accumbens (NAc), a forebrain region that regulates motivation and reward. While PVN-> NAc has been described in the context of social reward, its role in motivation for high-fat food is not known. The goal of these studies was to determine the structural, functional and behavioral significance of PVN-> NAc on motivation for high-fat food. We used immunohistochemistry with anterograde (AAV2) and retrograde (AAV6) viruses to demonstrate that PVN-> NAc neurons co-localize with VGLUT, suggesting glutamtergic signaling. To characterize PVN-> NAc neurotransmission, we used an excitatory Designer Receptor Exclusively Activated by Designer Drugs (DREADD). Neurotransmitter release was quantified by microdialysis with on-line capillary electrophoresis and laser-induced fluorescence. Activation of PVN-> NAc induced glutamate release. We also used DREADD technology to investigate behavioral implications of PVN-> NAc activation on motivation for high-fat food. DREADD-mediated activation of PVN-> NAc decreased lever pressing on a progressive ratio schedule of reinforcement for high-fat food reinforcers compared to control, which is consistent with increased glutamate release.

Poster 2-31

The role of innate immune response in chronic alcohol abuse and other psychiatric disorders

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Immune response dysregulation has been related to a variety of psychiatric and neurological disorders such as chronic alcohol abuse, Alzheimer's and depression. However, we do not understand how immune response dysregulation compares across different psychiatric disorders. Clusters of co-expressed genes enriched in specific immune response and inflammatory genes had already been identified using a large-scale RNA-Seq dataset from 60 post mortem brain samples. To understand how immune response pathways in other brain disorders compare with alcoholism, we conducted a meta-analysis using two other publically available RNA-Seq datasets. The first dataset contained 29 control subjects, 21 subjects with major depressive disorder that committed suicide, and 9 subjects with major depressive disorder that did not commit suicide. The second dataset contained 24 control subjects, 24 subjects with schizophrenia, 24 subjects with bipolar disorder, and 24 subjects with major depressive disorder. Visualization of the data indicated that because of large batch differences, the gene expression data could not be combined directly across datasets.

Because combining datasets at gene expression level was not possible, we chose to use a systems-approach. We used Weighted Gene Co-expression Network Analysis to identify clusters of co-expression for each dataset. Hypergeometric testing was then used to find significant overlap with the immune-related clusters found in the alcoholism dataset. The gene clusters that overlapped greatly with the selected clusters in alcoholism were identified and EnrichR was used to assign GO terms and pathway names to these clusters.

In both datasets, we looked at, we clearly found an innate immune response signature and an overlap with results found in the alcoholism dataset. Pathways such as IL-6 signaling, NF-kB signaling and dysfunction of Toll-Like receptors were enriched. Common among all three datasets were gene clusters related Cd40 complex and type-1 and type -5 interferon complex. These results help us present a model of innate immune response and how it is affected in different psychiatric disorders. We also provide a method that can be used by others to combine multiple datasets at a system or a gene cluster level rather than at the raw gene expression level.

Poster 2-32

Discovery of novel cannabinoid receptor 1 negative allosteric modulators

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The endocannabinoid signaling system (ECSS) regulates stress and anxiety and contributes to the rewarding effects of drugs of abuse. There are therapeutic indications for inhibition of cannabinoid receptor 1 (CB1R) signaling; but CB1R antagonists (e.g., rimonabant) produce an unacceptable adverse effect profile in humans. An alternative approach to orthosteric antagonism is development of negative allosteric modulators (NAMs). CB1R-NAMs are a potentially safer alternative to inhibition of CB1R signaling; however, the presently available agents, Org 27965 and PSNCBAM-1, have lipophilicity (LogP > 5.0) and aqueous solubility (< 1 mg/mL) profiles suggestive of poor central bioavailability. Indeed, preliminary results from behavioral tests using Org 27965 have been mixed. Here, we describe efforts toward the discovery of CB1R-NAMs with improved physicochemical and “drug-like” properties. We synthesized a series of 13 amides and ureas predicted to have structural similarity to known CB1R-NAMs. In vitro evaluation (PathHunter, DiscoveRx) showed that halogenation (Br > Cl > F) improved potency in the urea series, and ring-constrained naphthyl groups were most potent in the amide series. The most active lead (CWC-1-002) showed CB1R-NAM activity against two synthetic CB1R agonists (CP-55,940 and WIN-55-212-2, pKb = 6.09 and 6.71, respectively) and the endocannabinoid, 2-AG (pKb = 6.49). CWC-1-002 showed similar potency against 2-AG compared to Org 27965 (pKb = 6.43). Physicochemical property analysis demonstrates that CWC-1-002 has lower LogP and topologic polar surface area (TPSA) compared to commercially-available CB1R-NAMs, suggestive of improved central bioavailability. A preliminary screen (NIMH Psychoactive Drug Screening Program) suggests CWC-1-002 has modest affinity for 5-HT, dopamine, and sigma receptors. These results indicate CWC-1-002 may be a useful lead compound to study the role of CB1R signaling in substance abuse and dependence disorders.

Poster 2-33

A novel neuropeptide regulator of cocaine self-administration

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Neuromedin U (NMU) is a neuropeptide expressed in the mesolimbic pathway. NMU receptor 2 (NMUR2) is a GPCR and found in addiction associated areas of the brain including the nucleus accumbens shell (NAcSh). NMU signaling regulates responses to drugs of abuse, and we recently demonstrated that NMU decreases cocaine sensitization through actions at NAcSh presynaptic NMUR2. Therefore, we evaluated the effects of NMU on cocaine self-administration. NMU's effect on taking of cocaine, motivation for cocaine, and responding for cocaine related cues were assessed by self-administration chamber responding after peripheral injection of NMU. The role of presynaptic NMUR2 in the NAcSh was evaluated using retrograde knockdown of NMUR2 followed by cocaine self-administration. NMU did not alter cocaine taking or latency at any dose. NMU, however, does attenuate responding on a progressive ratio in a dose dependent manor. Cue responding decreased at 0.3 mg/kg NMU but not at any other dose. Knockdown of presynaptic NMUR2 in the NAcSh has the opposite effect; no change in cocaine taking but potentiates progressive ratio and cue responding. NMU decreases aspects of motivation and relapse to cocaine in a rat model. The likely site of action for this behavioral effect is presynaptically expressed NMUR2 in the NAcSh. This work suggests NMUergic circuitry in the NAcSh is a key regulator of complex behaviors associated with cocaine use disorder.

Poster 2-34

Exploring the role of the endocannabinoid system in spatial memory consolidation using in vivo calcium imaging of acetylcholine input in mice with hippocampal CB1 deletion

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The hippocampus is well-known as the limbic center for memory consolidation and spatial navigation, as it receives input from a wide array of neuronal circuits. Acetylcholine input to the hippocampus is critical during memory formation, with abnormal cholinergic activity exhibiting major implications in memory-related disorders, such as Alzheimer's disease. The endocannabinoid (eCB) system, known for its modulation of marijuana's psychoactive and reinforcing aspects in the brain, is a wide neurochemical network that also plays a major role in memory consolidation. Specifically, we have recently found dense expression of the cannabinoid type 1 (CB1) receptor on cholinergic neurons that innervate the hippocampus, suggesting an important role in memory formation. To assess how eCB signaling regulates memory development, we generated a transgenic mouse line bearing a selective deletion of CB1 receptors on cholinergic neurons and monitored short-term spatial memory consolidation in a novel object recognition task. This particular test allows for habituation to the environment and familiarization to a set of objects before the introduction of a novel object. Spatial memory capacity was quantified by measuring the rodents' innate tendency to recognize novel objects familiar objects within an open field. Previous studies in the Cheer Lab have tested spatial memory in transgenic mice lacking the CB1 receptor, showing an increase in short-term memory function. To further understand cholinergic signaling in the hippocampus, we will employ in vivo calcium imaging through miniature endoscopes to visualize genetically-defined neuronal populations with single cell resolution in freely behaving mice. The light-weight nature of these novel miniature microscopes allows focused light in and out of deep brain structures, showing live neuronal activity during ethological tasks, such as the novel object recognition task. Results will elucidate the extent to which the eCB system regulates memory function within the hippocampus and offer insight into abnormal cholinergic activity that leads to memory-related symptoms during cannabis use, as well as in memory-related disorders.

Poster 2-35

The effects of eating a high fat diet on sensitivity of female rats to the reinforcing effects of methamphetamine

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Eating a diet that is high in fat contributes to increased risk of chronic diseases and mortality, even in the absence of obesity. Eating a high fat diet can also impact the same brain reward pathways that are targeted by drugs of abuse. Preclinical studies have demonstrated rats eating high fat chow are more sensitive to the unconditioned behavioral effects of drugs that act on dopamine systems (e.g., cocaine). However, the majority of evidence demonstrating that diet can impact drug sensitivity has investigated only male subjects, despite potential sex differences. To test the hypothesis that eating high fat chow increases sensitivity of female rats to the positive reinforcing effects of methamphetamine (0.01-1.78 mg/kg/infusion), female Sprague-Dawley rats (n = 30) were fed either standard chow (17% kcal from fat), high fat chow (60% kcal from fat), or given restricted access to high fat chow (such that their body weight was maintained, without the development of obesity) for 8 weeks. Following i.v. catheter implantation, rats were trained to respond for 0.1 mg/kg/infusion methamphetamine on a Fixed Ratio 1 schedule. Although there were no differences in acquisition (n = 4-6/group), future work will examine the relative reinforcing effectiveness of methamphetamine in rats eating different diets using a progressive ratio schedule of reinforcement. These data expand previous research, which has predominately focused on unconditioned behavior in male rats, and add to the growing literature on the effects of diet on drug sensitivity.

Poster 2-36

Monoamine re-uptake inhibitors potentiate the discriminative stimulus effects of 3,4-methylenedioxypyrovalerone (MDPV) 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 cocaine, but considerably more potent. Despite a recent influx of research on the psychopharmacology of MDPV, few studies have employed preclinical drug discrimination methods to discern the neurochemical mechanisms involved in its interoceptive stimulus effects. The present study trained six adult male Sprague-Dawley rats to discriminate 0.5 mg/kg MDPV from vehicle under an FR 20 schedule of food reinforcement. Once reliable stimulus control was established, MDPV (0.05, 0.1, 0.5 mg/kg), cocaine (2.5, 5, 10, 20 mg/kg), GBR 12909 (5, 10, 20, 40 mg/kg), and desipramine (3.2, 5.6, 10 mg/kg) were assessed for substitution. GBR 12909 (40 mg/kg) and desipramine (3.2 mg/kg) were subsequently assessed in combination with a range of MDPV doses to assess potentiation. Although cocaine fully substituted for MDPV, no dose of GBR 12909 or desipramine substituted for MDPV. However, the MDPV dose response curve was shifted to the left by pretreatment with either GBR 12909 or desipramine. Specifically, GBR 12909 enhanced the discriminative stimulus effects of 0.5 and 0.1 mg/kg MDPV and desipramine potentiated the effects of 0.1 mg/kg MDPV. These findings indicate that although MDPV's interoceptive cues appear to be most similar to those of cocaine, pretreatment with other monoamine reuptake blockers may enhance MDPV's interoceptive stimulus effects and potentially enhance its risk for abuse. Further research with additional selective monoaminergic agents is warranted to fully characterize the contribution of monoamines to the discriminative stimulus effects of MDPV.

Poster 2-37

The effects of daily docosahexaenoic acid administration on high fat chow-induced enhanced sensitivity to dopaminergic drugs

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Eating a high fat diet can cause negative health consequences, such as obesity, type 2 diabetes and enhanced sensitivity to drugs acting on the dopamine system. For example, rats eating high fat laboratory chow are more sensitive to the behavioral effects of direct- (i.e., quinpirole) and indirect-acting (i.e, cocaine) dopamine receptor agonists. Dietary supplementation with fish oil, which is rich in omega-3 fatty acids, can successfully prevent and treat this high fat chow-induced enhanced sensitivity to dopaminergic drugs. Fish oil contains two primary omega-3 fatty acids; eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), therefore the relative contribution of each fatty acid to the beneficial effects of fish oil are not known. To test the hypothesis that daily injections of DHA prevent high fat diet-induced enhanced sensitivity to the behavioral effects of cocaine (1.0-17.8 mg/kg; i.p.) or quinpirole (0.0032-0.32 mg/kg; i.p.), male and female rats ate standard laboratory chow (17% kcal from fat), or high fat chow (60% kcal from fat) and received daily injections of DHA or vehicle. Female rats eating high fat chow tended to be more sensitive to the locomotor-stimulating effects of cocaine than rats eating standard chow alone (n = 4/group). Daily injections of DHA did not prevent this effect. Although these results might suggest that EPA, and not DHA, is the likely omega-3 fatty acid driving the preventative effects of fish oil, only one dose of DHA has been examined thus far, in a subset of rats. Future experiments are focused on examining different doses of DHA alone and in combination with various doses of EPA to determine the relative contribution of each omega-3 fatty acid in mediating the beneficial effects of fish oil.

Poster 2-38

2-AG signaling through CB1 receptors regulates operant responding to predictive incentive cues for a sucrose reward

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The endocannabinoid system has been implicated in reward-seeking behavior, for example, inhibiting CB1 receptors disrupts operant responding for food and drug reinforcers as well as cue-induced reinstatement. Conversely, upregulation of 2-arachidonyl glycerol (2-AG) signaling via inhibition of its degradative enzyme, monoacyl glycerol lipase (MAGL), increases operant reward seeking. However, it is difficult to separate the effects of these drugs on motivation for the primary reinforcer or the incentive motivational properties of the reward-related cues. The goal of this study was to characterize endocannabinoid modulation of responding in an operant model dependent upon incentive cues (ICs). In this task, rats nosepoke during a distinct 8-second audiovisual cue to obtain 60 □l of a 10% sucrose solution. Rimonabant dose-dependently (1, 3, and 6 mg/kg, i.p.) decreased the response ratio (number of reinforced IC/total IC presented) while increasing the latency to nosepoke. However, the latency to enter the reward cup to obtain the reinforcer was only slightly increased at the highest dose, indicating a greater disruption in the motivational properties of the IC than consummatory behaviors. To test the contribution of 2-AG, we pretreated rats with the MAGL inhibitor MJN110 (1, 5, 10 mg/kg, i.p.) in a modified version of the IC task, in which the volume of sucrose delivered decreased incrementally across the 1-hr session, producing an overall lower baseline of responding. Under these conditions, MJN110 increased the response ratio, had no overall effect on the latency to nosepoke in response to the IC, but decreased the latency to enter the reward cup at the highest dose. Furthermore, pretreatment with rimonabant blocked MJN110's effects. Together these data support that CB1 receptor blockade preferentially decreases motivation for ICs, while enhancing 2-AG signaling increases motivation for the primary reinforcer.

Poster 2-39

Sex differences in high fat diet-induced enhanced sensitivity to the locomotor stimulating effects of methamphetamine and SKF 82958

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Eating a high fat diet impacts dopamine systems; the same brain reward pathways targeted by drugs of abuse. Preclinical studies have demonstrated that rats eating high fat laboratory chow are more sensitive to the behavioral effects of direct- and indirect-acting dopamine receptor agonists. While previous reports have examined diet-induced effects on behaviors produced by dopamine D2 and D3 receptor agonists, it is not known if eating high fat chow also enhances sensitivity of rats to the behavioral effects of dopamine D1 receptor agonists. While indirect-acting agonists like methamphetamine have been investigated in male rats, it is also not known if eating high fat chow impacts sensitivity of females to methamphetamine. To test the hypothesis that eating high fat chow enhances sensitivity of male and female rats to methamphetamine and the dopamine D1 receptor agonist SKF 82958, male and female Sprague-Dawley rats eating standard laboratory chow (17% kcal from fat) or high fat chow (60% kcal from fat) were tested once per week for 5 total weeks with SKF 82958 (0.01-3.2 mg/kg, i.p.) or methamphetamine (0.1-3.2 mg/kg, i.p.) using a cumulative dosing procedure. In an initial cohort of animals (n=3/group), eating high fat chow tended to increase sensitivity of female rats to SKF 82958 and methamphetamine, a trend that was less evident among male rats. That is, both drugs tended to induce more locomotor activity in females eating high fat chow than in rats in all other groups. Consistent with previous reports, females tended to be more sensitive compared to males to the locomotor-stimulating effects of both drugs, regardless of diet. These results highlight sex differences regarding the behavioral effects of dopaminergic drugs, and future investigation of both sexes will be necessary to fully understand the impact of diet on drug sensitivity.

Poster 2-40

A meta-analytic review of sex differences in nicotine intravenous self-administration

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Objective: This project reflects a meta-analysis that systematically reviewed the literature on intravenous self-administration (IVSA) of nicotine in female and male rats. The goal was to determine if sex differences in nicotine IVSA exist, estimate the magnitude of the effect, and identify potential moderators of the relationship between sex differences and nicotine consumption. Methods: Extensive search procedures identified 20 studies that met the inclusion criteria of employing both female and male rats in nicotine IVSA procedures. The meta-analysis was conducted on effect size values that were calculated from mean total intake or nicotine deliveries using the Hedges' unbiased gu statistic. Results: A random effects analysis revealed that overall females self-administered more nicotine than males (weighted gu=0.17, 95% CI [0.003, 0.34]). Subsequent moderator variable analyses revealed that certain procedural conditions influenced the magnitude of sex differences in nicotine IVSA. Specifically, higher reinforcement requirements (>FR1) and extended-access sessions (23 hours) were associated with greater nicotine IVSA in females versus males. Females also displayed higher nicotine intake than males when the experiment included a light cue that signaled nicotine delivery. Sex differences were not influenced by the diurnal phase of testing, dose of nicotine, or prior operant training. Conclusion: Overall, the results revealed that female rats display higher levels of nicotine IVSA than males, suggesting that the strong reinforcing effects of nicotine promote tobacco use in women. Ongoing empirical studies are examining the degree to which each of these moderator variables influences sex differences in nicotine IVSA

Poster 2-41

5-HT1B receptor agonist in the ventral tegmental area modulates cocaine self-administration

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Several experiments have demonstrated that systemic administration of serotonin 1B receptor (5-HT1BR) agonists and viral-mediated overexpression of 5-HT1BRs in the nucleus accumbens potentiates cocaine self-administration (SA). However, little is known about the neural pathways that underlie these 5-HT1BR agonist effects. In this study we investigated if intracranial administration of the selective 5-HT1BR agonist, CP 94,253, in the ventral tegmental area (VTA) modulated cocaine SA similar to the systemic effects previously observed. Male rats (n = 12) underwent jugular vein surgeries for implanting an indwelling catheter and bilateral guide cannula targeting the VTA. Rats were trained to lever press for cocaine (0.75 mg/kg, intravenous infusion) on a fixed ratio 5 schedule of reinforcement. Rats then underwent two separate tests for cocaine SA receiving bilateral infusion with CP 94,253 (1 µg/0.3 µL) prior to one test and vehicle (0.3 µL) prior to the other test, with order of these pretreatments counterbalanced across rats. We found that intracranial CP 94,253 administration in the VTA increased cocaine intake and lever responding similar to the effects of systemic CP 94,253 administration. Vehicle had no effect on cocaine intake or lever response rates. These results suggest that the VTA plays a role in mediating the effects of 5-HT1BR agonists on cocaine SA. Future directions include using DREADDs to assess if 5-HT neuronal silencing from the dorsal raphe nucleus to VTA produce similar effects.

Poster 2-42

Maternal opioid morbidity study

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Overdose by "ingestion of drugs" is the second leading cause of maternal mortality in the state of Texas; second only to maternal deaths caused by a cardiac event.1 While these statistics are concerning, little is known about the context of maternal overdose death. Therefore, using a qualitative exploratory design, this study aims to provide insight into the contextual factors surrounding maternal opioid relapse and overdose. The purposive sample for this study consists of women who have experienced an opioid use disorder relapse and/or overdose during pregnancy or within 365 days of the end of a pregnancy. Participants were recruited from community-based clinics for pregnant women receiving treatment for substance use disorders. In addition, family members, friends and the significant others of women who died of a maternal opioid overdose, were recruited to participate in the study. Semi-structured audio-taped individual interviews and focus groups were used to collect qualitative data and thematic analysis was used to analyze data. Findings from this study emphasize the importance of keeping the mother and infant together. Mothers separated from their infant due to the involvement of child welfare services should be followed closely and provided supportive, patient-centered services. A full spectrum of trauma-informed, harm reduction services provided within integrated community-based settings, are needed to address the multiple needs of these women

1. Texas Maternal Morbidity and Mortality Task Force and the Department of State Health Services (2016). Joint biennial report. Retrieved November 6, 2016 from: https://dshs.texas.gov/.../legislative/2016Reports/M3TFBiennialReport2016-7-15

Poster 2-43

Determination of opioid receptor preference and agonist versus antagonist activity: A tail wags dog experiment

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Previous work has shown that modifying the N-substituent of an opioid ligand to N-phenethyl can induce a change from a MOR agonist to an antagonist. Unfortunately, this behavior is not predictable nor is it consistent. The N-methyl and N-phenethyl derivatives of normorphine, noroxymorphone, norhydromorphone, and 6,7-benzomorphan have been found to be potent agonists, as well as N-methyl-5-phenylmorphan, but N-phenethyl-5-phenylmorphan acts as an opioid antagonist. We chose N-phenethylnorhydromorphone (HM) as our template and tried to modulate the functional behavior by changing the substituents on the phenyl ring. We hypothesized that we were unlikely to induce the change with such small modifications but we were also interested in the ligands' interactions with the DOR and MOR, namely because a dual MOR agonist and DOR antagonist has been suggested as a possible analgesic with fewer negative side-effects. We discovered that we could induce the change from agonist to antagonist with certain substitution patterns and one derivative did interact with both the MOR and DOR but was an agonist for both. The synthesis of HM derivatives and in vitro and in vivo data is presented in the poster.

Poster 2-44

Multiple discriminative stimulus effects of the α4β2*-selective agonists, ispronicline and metanicotine

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Ispronicline and metanicotine are selective ligands at central nicotinic acetylcholine α4β2* receptors (Gao et al. Pain 2010: 149, 33; Grady et al. Neuropharmacol 2010: 58, 1054). In our study, a group of rats was trained to discriminate the stimulus properties of the nicotinic AChR receptor agonist nicotine, and a separate group of rats was trained to discriminate the stimulus properties of the muscarinic AChR agonist arecoline. Ispronicline and metanicotine produced dose-related selection of the drug-appropriate response option in both the nicotine-trained and the arecoline-trained rats. The nicotine antagonist mecamylamine blocked the discriminative stimulus effects of ispronicline and metanicotine in both groups of rats, as did the α4β2*-selective antagonist, dihydro-beta-erythroidine. Neither antagonist blocked the discriminative stimulus effects of arecoline in these experiments. These data raise the possibility that ispronicline, metanicotine and similar drugs may have novel effects and require a more extensive characterization of receptor activities, through both agonists and antagonists (Research supported by NIMH Grant 107499)

Poster 2-45

Suspected adulteration of commercial kratom products with 7-Hydroxymitragynine

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Kratom (Mitragyna speciosa) is widely used for its physiological and behavioral effects, especially to treat pain and opioid addiction. Mitragynine, an active alkaloid from Kratom, is primarily responsible for Kratom's biologic and psychoactive effects. A minor alkaloid constituent of Kratom, 7-hydroxymitragynine, is 40-fold more potent than that of mitragynine. It causes tolerance, cross-tolerance to morphine, and physical dependence, and is thought to be responsible for Kratom abuse. In order to understand the possible adulteration of commercial Kratom products with potent 7-hydroxymitragynine, an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method was developed for simultaneous quantification of mitragynine and 7-hydroxymitragynine. Ten commercially available Kratom products were purchased and analyzed for mitragynine and 7-hydroxymitragynine levels. The analysis results showed evidence that some commercial Kratom products have substantially higher concentrations of 7-hydroxymitragynine than is found in raw Mitragyna speciosa leaves. These artificially elevated levels of 7-hydroxymitragynine in commercial Kratom products indicate that some commercially available Kratom products may be adulterated.

Poster 2-46

Munc 13-1 in learning and voluntary ethanol consumption in mice

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The role of the *munc 13-1* protein in alcohol-related behaviors has been little-studied, but holds promise for researchers modeling alcohol addiction. *Munc 13-1* is a pre-synaptic protein that is vital for the release of glutamate at the synapse. Mice heterozygous for this gene show a drastic decrease in glutamate transmission. When ethanol binds *munc 13-1*, it further decreases neuronal signal and antagonizes glutamatergic targets. In a previous study that partially knocked out the fly homolog *dunc 13-1*, changes to ethanol-related behaviors were observed. Compared to wildtype, flies that lacked *dunc 13-1* were more attracted to and consumed more ethanol. However, introduction of the rat *munc 13-1* gene *in vivo* decreased consumption of alcohol, suggesting that *munc 13-1* acts as a powerful mediator of ethanol consumption behavior. In the current study, we used a dual-solution Morris Water Maze paradigm to identify a possible phenotype in *munc 13-1* deficient mice. Adult C57BL/6J mice ($N = 64$) could choose to navigate the maze using distal cues to orient themselves, or they could simply go to where a cue was hanging, and the platform would predictably be beneath it. During 6 days of acquisition, heterozygous mice were slower to reach the platform when compared to their wildtype partners. To examine the role of *munc 13-1* in voluntary alcohol consumption behavior, we used both high-drinking (C57BL/6J) and low-drinking (129S1/SvlmJ) wildtypes and heterozygotes. Mice were exposed to 20% ethanol using the 4-day Drinking in the Dark paradigm for 6 consecutive weeks. For both strains of mouse, the interaction of time, genotype, and sex on alcohol consumption was not significant; nor was there a significant effect of genotype alone at each of the time points. However, there was a significant effect of sex at each week, with females drinking more than males. This study extends previous *Drosophila melanogaster* findings to a mammalian model, as well as insight into the neural changes that may occur as a result of decreased glutamate transmission.

Poster 2-47

ADHD-inattentive symptoms are related to decreased intrafamilial relationship quality after controlling for family history of substance use disorder

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Of the attention-deficit/hyperactivity disorder (ADHD) subtypes, inattentive-type – as opposed to hyperactive/impulsive type - is suggested to be most related to child-parent stress. Over the course of adolescence, the presence of ADHD-symptoms and child-parent stress may increase risk for the initiation and use of alcohol and drugs. However, no study to date has examined how inattentive vs. hyperactive symptoms relate to relationship quality in the context of general family functioning, or if ADHD subtypes and intrafamilial discord predict substance use initiation above and beyond a family history of substance use, a common risk factor. We hypothesized that the presence of inattentive symptoms – as opposed to hyperactive symptoms – would be a unique predictor of intrafamilial dysfunction and substance use initiation, even after accounting for family history of substance use. The current study examined a cohort of children between the ages of 10-12 who either had (n = 306) or did not have (n = 81) a family history of substance use disorder. ADHD symptoms of predominantly inattentive-type and predominantly hyperactive-type, as well as intrafamilial dysfunction and substance use initiation were assessed. Results found that family history of substance use was related to intrafamilial dysfunction. After controlling for family history, inattentive symptoms were significantly predictive of intrafamilial dysfunction, while hyperactive symptoms were not. However, only family history predicted substance use initiation, while hyperactive symptoms, inattentive symptoms, and intrafamilial dysfunction did not. To conclude, family history of substance use disorder confers stress and impacts intrafamilial functioning; this may be exacerbated for children with ADHD- inattentive subtype. However, only family history of substance use appears to be predictive of later substance use initiation.

Poster 2-48

Activation of TLR3 enhances reactive astrocytes and activated microglia: relationship to alcohol consumption

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Overactivation of neuroimmune signaling (e.g. toll-like receptors (TLRs)) has been linked to excessive alcohol consumption. TLRs initiate anti- and pro-inflammatory responses via two intracellular signal transduction cascades: (1) MyD88-dependent pathway; (2) TRIF-dependent pathway. All TLRs signal through MyD88, except for TLR3. Recently, we determined that activation of TLR3 regulates voluntary ethanol consumption in a sex-dependent manner. Additionally, little is known about which cell-types mediate TRIF-dependent increases in alcohol consumption. Therefore, we injected alcohol naive C57BL6/J male and female mice with TLR3 agonist polyinosinic:polycytidylic acid (poly I:C) and measured cell-type expression using both qRT-PCR and double label immunofluorescence. We investigated cell type markers for neurons (NeuN), reactive astrocytes (GFAP), unreactive astrocytes (ALDH1L1), and microglia (CD11b, IBA1). Activation of TLR3 by poly I:C increased reactive astrocyte expression in males. In females, poly I:C increased reactive astrocyte and microglia expression. This suggested that glial activation is a key component of how the TRIF-dependent pathway regulates alcohol intake. Therefore, to determine which cell-types may be critical to TRIF-dependent changes in alcohol intake we next examined cell-type specific expression in male and female mice exposed to both chronic alcohol exposure and poly I:C. Reactive astrocyte expression was significantly increased in both males and females exposed to chronic alcohol and poly I:C. However, microglia expression was decreased in females, providing a potential mechanism for why TLR3 activation in females decreases alcohol intake. This work provides the first analysis of cell-type specific effects of TLR3 activation in both sexes and indicates a potential novel role for astrocytic regulation of drinking behavior, which will be explored in future studies. Research supported by grants: U01 AA020926, P01 AA020683, AA013520, AA006399, F31 AA025499-02.

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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 2019!

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