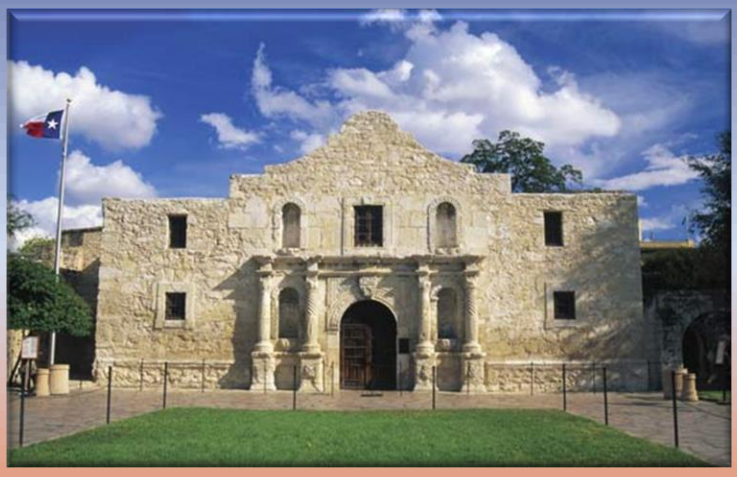
15TH ANNUAL BEHAVIOR, BIOLOGY, and CHEMISTRY:

Translational Research in Substance Use Disorders

San Antonio, Texas | Embassy Landmark | 25-26 March 2023



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NIH National Institute on Drug Abuse

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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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2012 – Jun-Xu Li
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2020 – T Lee Gilman
2022 – Corinde E Weirs
2023 – Justin C Strickland

Abby Loudermilk Travel Award

Abby Adair Loudermilk (1979-2018), lawyer, writer, and community volunteer, obtained her law degree at St. Mary's University and had her own private practice. She was known for her sharp wit, boisterous laugh, and her kind, compassionate spirit. Had her life not been cut short by addiction, Abby would still be supporting people today in ways big and small. The Abby Loudermilk Travel Award, established by her lifelong friends in memory of Abby's generous spirit, supports attendance of a graduate student and a postdoctoral fellow that self-identify as women, and whom are researching substance use disorders at the annual meeting of Behavior, Biology, and Chemistry: Translational Research in Substance Use Disorders.

Predoctoral
2022 – Kimberly M Holter
2023 – Gwendolyn Burgess

Postdoctoral
2022 – Renata Christina Nunes Marchette

Travel Awardees

Danya Aldaghma
Mohammad Alkhatib
Mia Allen
Nina Ardabili
Jasmin Beaver
Nina Beltran
Carter Bierbaum
Jade Bose
Rachel Burrichter
Gisela Camacho Hernandez
Astrid Cardona-Acosta
Yi-Hua Chiang
Adelis Cruz
Selen Dirik
Michelle Doyle, M
William Doyle, W
Darby Durbin
Harrison Elder
Veronkika Espinoza
Laura Ferguson
Troy Fort
Lindsey Galbo-Thomma
Karla Galvan
Brett Gelino
Priscilla Giner
Tiffany Gonzalez-Gutierrez
Rachel Herman
Rachel Heueisen
Kalee Holloway
Kimberly Holter
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Kwang-Hyun Hur
Jared James
Alaina Jaster
Haila Jiddou
Julia King
Drew Kwitchoff
Kayleigh LaMalfa
Dylan Laux
Kaitlyn Little
Miguel Luján
Sanjana Mada
Indu Mithra Madhuranthakam
Madison Marcus
Yorkiris Marmol Contreras
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Jaela Melton
Riley Merkel
Hadley Mills
Amarachi Okorom
Sebastian Ortegon
Yuma Ortiz
Tanya Pareek
Alyssa Parra
Marina Peveto
Loc Pham
Bethany Pierce
Ran Qiao
Jaren Reeves-Darby
Hailey Rizk
Elizabeth Saab
Nadia Said
Rebekah Schlitzer
Evan Smith
Celsey St. Onge
Kaitlyn Steck
Anapaula Themann
Justin Van Heukelom
Nathan Vardeleon
Caleb Vogt
Brandon Wallroff

Program Overview

FRIDAY 24 MARCH 2023

3:30 PM – 6:00 PM	Pathways to Careers in Science Workshop
4:00 PM – 7:00 PM	Registration – Embassy Landmark
7:00 PM – 9:00 PM	BBC Opening Reception and Networking - Embassy Landmark

SATURDAY 25 MARCH 2023

8:00 AM – 8:05 AM	Welcome and Opening Remarks	
8:05 AM – 10:05 AM	Plenary Symposium:	Chair: Gregory T Collins and Briana Mason
	Neuroimmune systems as therapeutic targets for mental health and substance use disorders **Amari Carter** | National Institutes of Health *Inflammatory markers in substance use and mood disorders: a neuroimaging perspective* **Irma (Lisa) Cisneros** | University of Texas Medical Branch *Danger-associated molecular patterns (DAMPS) and mitochondrial antiviral protein (MAVS) trigger neuroinflammatory networks in substance use disorder* **Saadet Inan** | Temple University *Chemokine and cytokine receptor antagonists as potential therapeutics for psychostimulant use disorder* **Marisa Roberto** | Scripps Research Institute *Targeting neuroimmune mechanisms in alcohol use disorder*	
10:05 AM – 11:35 AM	Poster Session and Refreshments	
11:35 AM – 12:50 PM	Lunch & Learn with **Yu (Woody) Lin** | Division of Neuroscience and Behavior, NIDA, NIH *Strategies to succeed research career transition and independence*	
12:50 PM – 2:20 PM	Open Oral Communications I	Chairs: Justin Strickland and Lindsey Galbo
2:20 PM – 3:50 PM	Poster Session II and Refreshments	
3:50 PM – 5:20 PM	Open Oral Communications II	Chairs: Dustin Stairs and Nina Beltran
5:20 PM – 5:30 PM	Refreshment Break	
5:30 PM – 6:30 PM	Special Lecture	Chair: Justin Strickland
	William Stoops | University of Kentucky College of Medicine *Offering alternatives: translational research on the use of non-drug reinforcers to reduce cocaine use*	
6:30 PM – 7:30 PM	Cocktail Hour and Poster Viewing	
7:30 PM – 9:30 PM	Dinner and Science Trivia	

SUNDAY 26 MARCH 2023

7:45 AM	Travel Awardee Group Photo	
8:00 AM – 9:30 AM	Open Oral Communications III	Chairs: Jenny Wilkerson and Gwendolyn Burgess
9:30 AM – 9:40 AM	Refreshment Break	
9:40 AM – 10:55 AM	Open Oral Communications IV	Chairs: Arturo Zavala and Gisela Camacho Hernandez
10:55 AM – 11:05 AM	Refreshment Break	
11:05 AM – 12:05 PM	Special Lecture	Chair: Mike Nader
	Carrie Jones | Vanderbilt University *Developing muscarinic receptor allosteric modulators for neuropsychiatric disorders*	
12:05 PM – 12:20 PM	Travel and Presentation Awards	
12:20 PM – 1:30 PM	Lunch and Adjournment	

Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee

Abby Loudermilk Travel Awardee

BBC Travel Awardee

Program Details

Friday 24 March 2023

Pathways to Careers in Science Workshop	3:30 PM – 6:00 PM	*UT Health Campus*
Registration	4:00 PM – 7:00 PM	*Bluebonnet Foyer*
Opening Reception	7:00 PM - 9:00 PM	*Lantana Ballroom*

Saturday 25 March 2023

Welcome and Opening Remarks	8:00 AM - 8:05 AM	*Bluebonnet AB*
Plenary Symposium	8:05 AM – 10:05AM	*Bluebonnet AB*

Neuroimmune systems as therapeutic targets for mental health and substance use disorders
(Chairs: Gregory T Collins and Briana Mason)

8:05 AM – 8:35 AM **Amari Carter** | National Institutes of Health
Inflammatory markers in substance use and mood disorders: a neuroimaging perspective

8:35 AM – 9:05AM **Irma (Lisa) Cisneros**| University of Texas Medical Branch
Danger-associated molecular patterns (DAMPS) and mitochondrial antiviral protein (MAVS) trigger neuroinflammatory networks in substance use disorder

9:05 AM – 9:35AM **Saadet Inan** | Temple University
Chemokine and cytokine receptor antagonists as potential therapeutics for psychostimulant use disorder

9:35 AM – 10:05AM **Marisa Roberto** | Scripps Research Institute
Targeting neuroimmune mechanisms in alcohol use disorder

Poster Session I and Refreshments (odd posters judged)	10:05 AM – 11:35 AM	*Bluebonnet C/Foyer*
Lunch & Learn Session: Yu (Woody) Lin	11:35 AM – 12:50 PM	*Bluebonnet AB*

Strategies to succeed research career transition and independence

Oral Communications I	12:50 PM – 2:20 PM	*Bluebonnet AB*

(Chairs: Justin Strickland and Lindsey Galbo)

12:50 PM – 1:05 PM **Mia Allen** | Wake Forest School University of Medicine
A comparison of the reinforcing efficacy of cocaethylene and cocaine in rhesus monkeys responding under a progressive-ratio schedule of reinforcement

1:05 PM – 1:20 PM **Justin Van Heukelom** | University of North Carolina Wilmington
Oxycodone and sensitivity to reinforcement magnitude in female and male rats: Implications for impulsive and risky choice

1:20 PM – 1:35 PM **Gwendolyn Burgess** | University of Michigan
The reinforcing effects of fentanyl or cocaine in a state of chronic neuropathic pain

1:35 PM – 1:50 PM **Riley Merkel** | University of Pennsylvania
The role of central amygdala GLP-1 receptor-expressing circuits in cocaine abstinence-mediated behaviors

1:50 PM – 2:05 PM **Alice McQueney** | University of Nebraska at Omaha
Effect of serotonin 2A receptor activation by 2,5-dimethoxy-4-iodoamphetamine on fentanyl self administration and reinforcer value in female and male rats: a behavioral economic approach

2:05 PM – 2:20 PM **Jacques Nguyen** | Baylor University
Elucidating behavioral effects using opioid and cannabinoid self-administration and related models

Poster Session II and Refreshments (even posters judged) 2:20 PM – 3:50 PM *Bluebonnet C/Foyer*

Oral Communications II 3:50 PM – 5:20 PM *Bluebonnet AB*
(Chairs: Dustin Stairs and Nina Beltran)

3:50 PM – 4:05 PM **Yuma Ortiz** | University of Florida, Texas Tech University Health Sciences Center
Cannabidiol and mitragynine, both alone and in combination, attenuates mechanical allodynia in a mouse paclitaxel chemotherapy-induced peripheral neuropathy model

4:05 PM – 4:20 PM **William Doyle** | University of Mississippi Medical Center
Resistance of cocaine and food reinforcement to extinction and punishment under fixed vs. variable schedules of reinforcement

4:20 PM – 4:35 PM **Madison Marcus** | Virginia Commonwealth University
Concurrently available negative reinforcement decreases cocaine self-administration in male and female rats

4:35 PM – 4:50 PM **Troy Fort** | Kansas State University
N-acetylcysteine is ineffective in attenuating cue-induced relapse to amphetamine following extended- or short-access amphetamine self-administration

4:50 PM – 5:05 PM **Hannah Shaw** | University of Arkansas for Medical Sciences
Pro-social effects of 3,4-methylenedioxymethamphetamine (MDMA), its enantiomers, and a non-racemic mixture of S-MDMA and R-MDMA (ALA-002) in C57BL/6 and BTBR T+Itpr3tf/J mice

5:05 PM – 5:20 PM **Justin Strickland** | Johns Hopkins University School of Medicine
Interaction of cigarette nicotine dose and dose expectancy in health perceptions and behavioral economic demand

Refreshment Break 5:20 PM – 5:30 PM

Special Lecture: William Stoops 5:30 PM – 6:30 PM *Bluebonnet AB*
Offering alternatives: translational research on the use of non-drug reinforcers to reduce cocaine use
(Chair: Justin Strickland)

Cocktail Hour and Poster Viewing 6:30 PM – 7:30 PM *Bluebonnet C/Foyer*

Dinner 7:30 PM – 9:30 PM *Bluebonnet AB*

Science Trivia *Bluebonnet AB*
Join us for an hour of fun, science, trivia, and prizes!

Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee
Abby Loudermilk Travel Awardee
BBC Travel Awardee

Sunday 26 March 2023

Travel Awardee Group Photo — 7:45 AM — *Bluebonnet AB*

Oral Communications III — 8:00 AM – 9:30 AM — *Bluebonnet AB*

(Chairs: Jenny Wilkerson and Gwendolyn Burgess)

8:00 AM – 8:15 AM — **Miguel Luján** | University of Maryland, School of Medicine
A multivariate regressor of patterned dopamine release predicts relapse to cocaine

8:15 AM – 8:30 AM — **Caleb Vogt** | National Institute on Drug Abuse
Development of cariprazine analogs for the treatment of psychostimulant use disorders

8:30 AM – 8:45 AM — **Nadia Said** | National Institute on Drug Abuse Intramural Research Program
Sex differences in the neuroimmune response to heroin withdrawal in rats

8:45 AM – 9:00 AM — **Brett Gelino** | Johns Hopkins University School of Medicine
Acute pain moderates analgesic valuation in a behavioral economic choice task

9:00 AM – 9:15 AM — **Michelle Doyle** | University of California San Diego / Scripps Research Institute
Alcohol use disorder-related phenotypes in nondependent and dependent heterogeneous stock rats

9:15 AM – 9:30 AM — **Raj Desai** | McLean Hospital/Harvard Medical School
Fentanyl-targeting monoclonal antibodies block fentanyl-induced respiratory depression

Refreshment Break — 9:30 AM – 9:40 AM

Oral Communications IV — 9:40 AM – 10:55 AM — *Bluebonnet AB*

(Chairs: Arturo Zavala and Gisela Camacho Hernandez)

9:40 AM – 9:55 AM — **Loc Pham** | University of Mississippi Medical Center
The kappa-opioid receptor agonists, U50,488 and triazole 1.1, reduce oxycodone choice in rhesus macaques

9:55 AM – 10:10 AM — **Shawn Flynn** | UT Health Science Center at San Antonio
Effects of gabapentinoids on heroin and cocaine self-administration in rats

10:10 AM – 10:25 AM — **Bethany Pierce** | Wake Forest School of Medicine
Effects of non-contingent oxycodone and buprenorphine on sleep and quantitative EEG in rats

10:25 AM – 10:40 AM — **Harrison Elder** | Virginia Commonwealth University
Monoamine receptors differentially affect basal and fentanyl-depressed respiration

10:40 AM – 10:55 AM — **Tommy Gunawan** | NIH/ NIAA
Resilience factor from the addictions neuroclinical assessment buffered against the risk of comorbid alcohol use disorder with trauma disorder in individuals with a history of childhood trauma

Refreshment Break — 10:55 AM – 11:05AM

Special Lecture: Carrie Jones — 11:05 AM – 12:05 PM — *Bluebonnet AB*

Developing muscarinic receptor allosteric modulators for neuropsychiatric disorders
(Chair: Mike Nader)

Travel and Presentation Awards — 12:05 PM – 12:20 PM

Lunch and Adjournment — 12:20 PM – 1:30 PM

See you at BBC 2024!

Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee | Abby Loudermilk Travel Awardee | BBC Travel Awardee

Oral Communications

Oral Communication 1-1

A comparison of the reinforcing efficacy of cocaethylene and cocaine in rhesus monkeys responding under a progressive-ratio schedule of reinforcement

Allen, Mia[1] and Nader, Michael[1]

[1] Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC 27157

In the clinical setting, individuals who use cocaine have high rates of co-morbid alcohol abuse and estimates suggest that up to 90% of cocaine users also consume alcohol. Although the mechanistic basis of co-abuse is still poorly understood, the pharmacokinetic interactions between cocaine and alcohol may underlie the prevalence of this co-abuse. When administered concurrently, the metabolite cocaethlyene is formed. This metabolite is equipotent to cocaine in the inhibition of dopamine reuptake and substitutes for cocaine in drug discrimination studies. However, to our knowledge, no previous work has directly compared the reinforcing efficacy of cocaine to cocaethylene. In this study, three individually-housed male rhesus macaques were trained to self-administer cocaine under a progressive-ratio (PR) schedule of reinforcement. Under PR schedules of reinforcement, the primary dependent variable is break point (BP), defined as the number of injections received prior to the 1-hr limited hold or over the 4 hr session. Full cocaine dose-response curves (saline, 0.001-0.3 mg/kg per injection) were determined in each monkey, with doses available for at least 5 consecutive sessions and until stable (± 20% variability in BP). Next, doses of cocaethlyene (saline, 0.001-0.3 mg/kg per injection) were substituted for the dose of cocaine that resulted in peak BPs; each cocaethylene dose was available for at least 5 consecutive sessions. Preliminary findings suggest that cocaethylene has equal reinforcing strength to cocaine and that cocaethylene is more potent than cocaine. Thus, it is possible that individuals co-abuse alcohol and cocaine because cocaethylene promotes synergistic interactions and may elongate the subjective rewarding effects of cocaine given that cocaethylene is eliminated from the body more slowly than cocaine. In order to better model the human condition, future studies will examine how alcohol drinking affects the reinforcing strength of cocaine.

Oral Communication 1-2

Oxycodone and sensitivity to reinforcement magnitude in female and male rats: Implications for impulsive and risky choice

Van Heukelom, Justin T[1]; Hughes, Christine, E[1]; Langford, Jeremy S[1,2], and Pitts, Raymond C[1]

[1]Department of Psychology, University of North Carolina Wilmington, Wilmington, NC, USA and [2]Department of Psychology, University of West Virginia, Morgantown, WV, USA

Given recent trends in prescription opioid (e.g., oxycodone) misuse, many preclinical and translational research studies are needed to investigate effects of opioids on impulsive choice (choice of smaller, immediate reinforcers over larger, delayed reinforcers) and risky choice (choice of larger reinforcers associated with probabilistic consequences over smaller, certain/safer reinforcers). Additionally, investigations of potentially unique processes between female and male subjects are warranted, given reported sex differences in regard to (1) opioid misuse and (2) impulsive and risky choice. The current preclinical research study sought to investigate oxycodone's acute effects on choice controlled by reinforcement magnitude in females and males; that is, the contribution of reinforcement magnitude to impulsive and risky choice was of interest. Female (n = 6) and male (n = 8) rats chose between two alternatives within each session. The magnitude for one alternative varied across blocks within sessions (1, 3, or 9 dipper presentations of a sucrose solution), while the magnitude for the other alternative remained consistent (3 dipper presentations). Choice under non-drug conditions was more sensitive to magnitude in females than in males. Acute administration of oxycodone (0.1 - 1.0 mg/kg) decreased sensitivity in both sexes. While this effect was comparable between groups, drug effects primarily seemed to be a function of sensitivity during baseline (i.e., oxycodone's effects were somewhat baseline-dependent). These findings have important implications for understanding effects of opioids on impulsive and risky choice and suggest some critical considerations for future preclinical and translational research.

Oral Communication 1-3

The reinforcing effects of fentanyl or cocaine in a state of chronic neuropathic pain

Burgess, Gwendolyn E and Jutkiewicz, Emily M

Department of Pharmacology, University of Michigan, Ann Arbor, Michigan, USA

MOR agonists produce pain relief and have high abuse potential; this complicates thier use in treating chronic pain. The goal of this study was to test the effect of chronic neuropathic pain on the reinforcing effects of fentanyl or cocaine in a within-subjects design to evaluate behavior over several weeks of chronic pain. Male and female Sprague-Dawley rats were trained to self-administer 0.01 mg/kg/inf fentanyl or 0.32 mg/kg/inf cocaine under a fixed ratio (FR) 5 schedule of reinforcement, and dose effect curves (fentanyl: 0.32-32 mg/kg/inf; cocaine: 0.032-0.56 mg/kg/inf) were evaluated in daily, multicomponent sessions. After 5 days of stable responding on the multidose procedure, rats underwent sham or spared nerve injury (SNI) surgery. The SNI model induces life-long neuropathic pain in all animals. Prior to sham surgery, the ED50 for fentanyl was 0.80 (in males and 0.89 (mg/kg/inf in females. Prior to sham surgery, the ED50 for cocaine in males was 0.078 (mg/kg/inf and 0.079 (mg/kg/inf in females. After sham or SNI surgery, drug intake decreased in all groups for 3-5 days, shown by a downward shift in the dose effect curve. However, by 1 week, all animals resumed pre-surgical levels of intake. 4-6 weeks after sham or SNI surgery, the ED50s for fentanyl were mostly unchanged. The ED50s for cocaine were slightly shifted to the right (1.23-fold in males and 1.15-fold in females) at 4-6 weeks after SNI surgery, but sham surgery did not alter cocaine ED50s. These data indicate that the reinforcing effects of fentanyl or cocaine were unaltered by chronic neuropathic pain.Further, acute pain may suppress operant responding, but prolonged neuropathic pain does not increase the abuse liability of fentanyl or cocaine.

Oral Communication 1-4

The role central amygdala GLP-1 receptor-expressing circuits in cocaine abstinence-mediated behaviors

Merkel, Riley; Herman, Rae; Zhang, Yafang, and Schmidt, Heath D

Department of Biobehavioral Health Sciences, School of Nursing; Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Activation of glucagon-like peptide-1 receptors (GLP-1Rs) reduces the rewarding effects of cocaine and attenuates cocaine-seeking behavior during abstinence in rats. However, the neural mechanisms mediating the effects of GLP-1R agonists on cocaine seeking have not been fully characterized. GLP-1Rs are expressed abundantly in the central amygdala (CeA). However, the role of CeA GLP-1Rs in cocaine seeking is unclear. Our hypothesis was that activation of GLP-1Rs in the CeA would attenuate cocaine seeking in male rats. We showed that intra-CeA administration of the GLP-1R agonist exendin-4 (Ex-4) dose-dependently attenuated cocaine primed (n=15; $p<0.0001$) and cue primed (n=18; $p<0.0001$) drug seeking without producing adverse malaise-like effects. Neural tracing and fluorescent *in situ* hybridization approaches were used to determine the downstream targets of GLP-1R-expressing CeA neurons. We identified GLP-1Rs expressed on CeA GABA neurons that project to the nucleus accumbens (NAc). We then used viral-mediated chemogenetic techniques in transgenic rats to explore the cell type-specific functional role of CeA->NAc GABA neurons in cocaine abstinence-mediated behaviors. Activation of CeA->NAc GABA neurons was sufficient to attenuate cocaine reinstatement in rats (n=5; $p<0.005$). Next, *in vivo* calcium imaging was used to characterize the effects of cocaine and Ex-4 on CeA GABA neuronal dynamics. Our pilot data show that Ex-4 pretreatment reversed cocaine-induced increases in activity of GABA neurons in the CeA (n=3). Finally, we explored the role of CeA GLP-1Rs in cocaine withdrawal-induced anxiety. Our preliminary findings suggest that Ex-4 pretreatment produces anxiolytic effects in cocaine-experienced rats. Taken together, these findings highlight a novel GLP-1R-expressing circuit that could be targeted to reduce cocaine use disorder.

Oral Communication 1-5

Effect of serotonin 2_A receptor activation by 2,5-dimethoxy-4-iodoamphetamine on fentanyl self-administration and reinforcer value in female and male rats: a behavioral economic approach

McQueney, Alice J[1] and Garcia, Erik J[1,2]

[1]Department of Psychology, University of Nebraska Omaha, Omaha, NE USA and [2]Neuroscience and Behavior, University of Nebraska Omaha, Omaha, NE, USA

Synthetic opioids like fentanyl account for most opioid-related deaths, and while currently available treatments do have a significant positive impact, rising rates of synthetic opioid overdoses highlight the necessity to pursue novel treatment options. The serotonin system innervates many nodes within the mesocorticolimbic pathway and modulates reward and reinforcement through the serotonin 2A and 2C receptors (**5-$HT_{2A/2C}$R**). Historically, agonists aimed at the 5-HT_{2A}R have been ignored due to their hallucinogenic effects, but recent empirical evidence suggests a possible therapeutic role. In the current study, we examined the action of the 5-HT_{2A}R in fentanyl self-administration using a behavioral economic approach in female and male Sprague-Dawley rats (n=28), with an overarching hypothesis that 5-HT_{2A}R activation can attenuate fentanyl reinforcing value. Rats were trained to self-administer fentanyl on a fixed ratio 1 (**FR1**) schedule until stable behavior was reached (<10% variability in infusion number for three consecutive days). Then rats completed a 2hr within-session threshold procedure where the dose of fentanyl was decreased by ¼ log every 10 minutes (11 doses ranging from 0.0100-3.200µg). Consumption was transformed to 'price' (response/µg) and exponentiated demand curve analysis was completed to extract the parameters **α** and Q_0, which summarize consumption/demand. Pretreatment with 5-HT_{2A}R agonist DOI dose-dependently (saline, 0.01, 0.03, 1.0 mg/kg; s.c.) altered **α** and Q_0 suggesting that fentanyl reinforcement value was reduced. The effect of DOI was blocked by selective 5-HT_{2A}R antagonist M100907 (0.01 mg/kg; i.p.), but not 5-HT_{2C}R antagonist SB-242084 (0.5 mg/kg; i.p.) These results indicate that the 5-HT_{2A}R modulates opioid reward and is a novel therapeutic target to control the rewarding components of opioid analgesics.

Oral Communication 1-6

Elucidating behavioral effects using opioid and cannabinoid self-administration and related models

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Substance use disorders, including opioid and cannabis use disorder, are a significant global problem. Recently developed animal models of self-administration have been useful for researchers to investigate behavioral and neurobiological mechanisms underlying drug-consumption via different routes of administration (e.g. intravenous or intrapulmonary). In the following studies, we investigated the escalation of intravenous self-administration of oxycodone, one of the most commonly prescribed medications (OxyContin® or as part of Percocet®), and the behavioral and neurophysiological effects of cannabinoid vapor inhalation using electronic nicotine delivery devices (ENDS; e-cigarettes). We hypothesized that the dysphoric, or negative affective, state that is experienced during the abstinence of *oxycodone* self-administration potentiates escalation behavior. We also hypothesized that training of self-administration of *cannabinoids* via vapor inhalation may result in relatively fewer responses and below 80% drug-appropriate responding. Male Wistar rats were trained to self-administer oxycodone (0.15mg/kg, i.v.) under long access (LgA, 12 h) conditions. In separate studies, groups of male and female Wistar rats were permitted to respond on nose-poke manipulanda for deliveries of propylene glycol (PG) vapor adulterated with Δ9-tetrahydrocannabinol (THC; 50-100 mg/mL). Results confirmed mean oxycodone intake was escalated following 60-hour discontinuation. Mean THC vapor deliveries were not systematically changed across 50 sessions, with more infusions of the 12.5 mg/mL concentration and responses on the drug-associated manipulandum below 80% of responses. Overall, these data provide behavioral and mechanistic insight into opioid and cannabinoid self-administration and confirm the developmental progress of new experimental approaches using rodent subjects.

Oral Communication 2-1

Cannabidiol and mitragynine, both alone and in combination, attenuates mechanical allodynia in a mouse paclitaxel chemotherapy-induced peripheral neuropathy model

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In chemotherapy-treated patients, chemotherapy-induced peripheral neuropathy (CIPN) is a side effect. Mitragyna speciosa (kratom) contains the alkaloid mitragynine (MG), which produces analgesic-like properties in preclinical pain models. In humans, anecdotal reports suggest cannabidiol (CBD) may enhance kratom-related analgesia. The underlying pharmacological mechanisms of MG as a potential CIPN pain therapeutic are not well understood. We sought to assess the potential capacities for both CBD and MG to attenuate mechanical allodynia associated with CIPN. Male and female C57BL/6 mice received a cycle of intraperitoneal (i.p.) paclitaxel injections (cumulative dose 32 mg/kg). The von Frey assay was utilized to assess CIPN-induced allodynia. In separate paclitaxel-naïve mouse cohorts, schedule-controlled responding for food was conducted under a fixed ratio (FR)-10, and hot plate antinociception was examined. CBD attenuated allodynia but did not decrease schedule-controlled response rates or produce antinociception. Isobolographic analysis revealed 1:1, 3:1 MG+CBD mixture ratios additively attenuated CIPN-induced allodynia, with all combinations decreasing schedule-controlled responding and producing antinociception. MG attenuated allodynia but did reduce schedule-controlled responding and produced acute antinociception. The attenuating effects of MG were antagonized with naltrexone and yohimbine pretreatment. CBD+MG may be further optimized to yield novel CIPN therapeutics

Oral Communication 2-2

Resistance of cocaine and food reinforcement to extinction and punishment under fixed vs. variable schedules of reinforcement

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Uncertainty in the time and effort required to obtain a drug may be a significant determinant of the reinforcing effects of illicit substances and in the inability of legal restriction and negative consequences to deter substance use. The goal of this study was to determine whether behavior maintained by a variable-ratio (VR) schedule of cocaine reinforcement would be more resistant to extinction and punishment compared with a fixed-ratio (FR) schedule.
A group of male (n=5) and female (n=6) rhesus monkeys self-administered cocaine (0.03 or 0.1 mg/kg/infusion) or food (4 pellets/delivery) under a FR or VR 200 schedule of reinforcement. During extinction, saline was substituted for cocaine or food, and during punishment, cocaine (0.03 or 0.1 mg/kg/infusion) or food (4 pellets/delivery) was administered in combination with a known drug punisher (histamine; 0.001-0.1 mg/kg/infusion).
The number of sessions required to meet extinction criteria were greater during VR compared with FR conditions, particularly with food and the lower cocaine dose. Similarly, resistance to punishment was greater during VR compared with FR conditions, indicated by higher response rates. The effect was more robust with cocaine than food and in females compared with males. Our findings suggest that uncertainty in the time and effort required to obtain a drug may contribute to perseverative substance use and decreased sensitivity to negative consequences associated with drug seeking and taking. These results support the use of therapeutic efforts aimed at reducing the uncertainty of illicit drugs that exists in the environment, perhaps through an agonist-medication approach.

Oral Communication 2-3

Concurrently available negative reinforcement decreases cocaine self-administration in male and female rats

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Aim: Drug-taking despite negative consequences is a prevalent behavioral characteristic of addiction, but few studies have examined behavioral allocation between concurrently available self-administered drug or escaping/avoiding an aversive stimulus (i.e., negative reinforcement, NR). The goal of this study was to establish a cocaine-vs-NR choice procedure in male and female rats and determine sensitivity to environmental and pharmacological manipulations. Methods(0–0.7mA)
Results: NR was chosen over all cocaine doses. Decreasing shock intensities decreased NR trials completed; however, cocaine trials did not significantly increase. Increasing the response requirement for NR only increased omitted trials. Acute diazepam pretreatment failed to alter behavioral allocation between NR and cocaine up to doses that eliminated operant responding. EA cocaine increased daily cocaine intake but did not alter choice behavior.
Conclusions: Concurrently available NR decreased cocaine self-administration across a range of doses that we have previously shown were chosen over nondrug positive reinforcers. The demonstrated insensitivity to environmental manipulations suggests that cocaine and NR may be economic independents. Lastly, the failure of EA cocaine to increase cocaine choice does not provide empirical evidence for the theory of drug-taking despite negative consequences. Future studies will investigate neural mechanisms underlying interactions between positive and negative reinforcers.

Oral Communication 2-4

***N*-acetylcysteine is ineffective in attenuating cue-induced relapse to amphetamine following extended- or short-access amphetamine self-administration**

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Relapse is a significant barrier to treating substance-use disorder (SUD) and is associated with decrements in glutamate homeostasis. The therapeutic *N*-acetylcysteine (NAC) has been shown to lower cocaine cue-induced relapse by restoring glutamate homeostasis due to improvements in the function of the of the cysteine-glutamate exchanger (xCT). In separate studies, we tested the efficacy of NAC on lowering cue-induced amphetamine (AMP) relapse following 2-hr or 6-hr AMP self-administration (SA). We also evaluated the expression of xCT within the nucleus accumbens (ACb) and medial prefrontal cortex (mPFC). We predicted that NAC would lower relapse following both 2-hr and 6-hr access SA. We also predicted that AMP would lower xCT expression for rats that did not receive NAC. 68 male Sprague-Dawley rats were subjected to 14 days of FR-1 AMP SA (0.1 mg/kg per infusion) or saline for either 2 or 6 hrs per session. Following SA, rats entered a 14-day forced abstinence period. During abstinence, animals received daily injections of either NAC (100 mg/kg; ip) or a saline vehicle. On Withdrawal Day 14, a cue-induced relapse test was conducted where active lever responses resulted in the presentation of drug cues but no delivery of the drug itself. Our results indicate that NAC treatment was ineffective at lowering cue-induced relapse to AMP following abstinence to 2-hr or 6-hr AMP SA. Following the cue-test, rats were perfused, and brains were extracted for immunohistochemical staining of xCT. IHC results indicate that, for the 2-hr AMP access group, abstinence from AMP did not decrease xCT expression in the ACb or mPFC relative to the saline SA group. However, NAC treatment decreased xCT expression. Though 6-hr xCT data collection is ongoing, our preliminary results to date suggest that abstinence from AMP does decrease xCT expression as predicted. Together, these results suggest that AMP alters glutamate function via different mechanisms than cocaine.

Oral Communication 2-5

Pro-social effects of 3,4-methylenedioxymethamphetamine (MDMA), its enantiomers, and a non-racemic mixture of S-MDMA and R-MDMA (ALA-002) in C57BL/6 and BTBR T^{+}Itpr3^{tf}/J mice

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Autism spectrum disorder (ASD) is a complex neurodevelopmental condition defined by deficits in social communication and social interaction, as well as repetitive and inflexible patterns of behaviors, interests, and thoughts. Existing pharmacological treatments for social withdrawal secondary to ASD are of limited effectiveness. The BTBR T^{+}Itpr3^{tf}/J (BTBR) mouse is an inbred strain generated from the C57BL/6 (C57) strain, exhibiting an ASD-like phenotype including deficits in reciprocal social interactions and social approach, unusual patterns of ultrasonic vocalization, and high levels of repetitive self-grooming. We conducted novelty and social preference studies using purpose-built 2-compartment chambers containing empty cups (habituation phase), an empty cup vs a dummy mouse (novelty preference test), a stranger NIH Swiss mouse vs a dummy mouse (sociability test), or a stranger NIH Swiss mouse vs a familiar NIH Swiss mouse (social novelty test.) Time spent in each compartment and compartment entries were tracked in 15 min sessions conducted 30 min after injection of saline or various doses of S-methamphetamine (S-METH), S-MDMA, R-MDMA, racemic MDMA or a non-racemic mixture of S-MDMA and R-MDMA (ALA-002). In C57 mice, S-METH and S-MDMA had no systematic effects in any of the preference tests, but elicited stimulant-like dose-dependent increases in compartment entries. In contrast, R-MDMA, racemic MDMA and ALA-002 dose-dependently increased sociability and social preference, without altering novelty preference, and did so at doses which did not increase compartment entries. BTBR mice exhibited the expected decrements in sociability and social preference, but R-MDMA, racemic MDMA and ALA-002 normalized social behavior in this strain. These studies illustrate that MDMA-like drugs may be useful in the treatment of social avoidance in ASD.

Oral Communication 2-6

Interaction of cigarette nicotine dose and dose expectancy in health perceptions and behavioral economic demand

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Regulatory efforts to reduce public health harms of tobacco have focused on mandates of cigarette nicotine content. Data are needed on how the interaction of (a) expectations of nicotine content and (b) actual nicotine content affect consumer response and subsequent regulatory success. The purpose of this within-subject, human laboratory study was to evaluate reduced nicotine expectancy effects using a balanced placebo design. Participants who smoke daily (*N*=18; 44.4% female) completed four experimental sessions in which expectancy (label "average" or "very low" nicotine) and nicotine dose (15.8 mg/g or 0.4 mg/g) were manipulated. Participants smoked a session's assigned cigarette with puff topography and subjective effects collected. Participants then completed an incentivized demand procedure to measure demand for session cigarettes. Analyses evaluated main and interactive effects of expectancy and nicotine dose. Effective manipulations were used with lower perceived nicotine in reduced nicotine expectancy and reduced dose conditions. Full nicotine cigarettes increased heart rate independent of expectancy indicating that pharmacologically relevant doses were included. Lower demand intensity (consumption when free) was observed for reduced nicotine cigarettes in both expectancy conditions. Lower health harm attributed to reduced nicotine expectancy was observed regardless of actual nicotine dose. These data indicate that nicotine content may alter the reinforcing and physiological effects of cigarettes independent of dose expectancy while dose expectancy may alter the perceived health harms of cigarettes independent of actual nicotine dose. Future chronic exposure designs are needed to explore the durability of these effects to inform impacts for regulatory efforts.

Oral Communication 3-1

A multivariate regressor of patterned dopamine release predicts relapse to cocaine

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Drug addiction is characterized by sustained vulnerability to relapse even after long periods of abstinence. A deeper understanding of the brain systems underlying this state could inform therapeutic strategies with novel prognostic biomarkers aimed at preventing renewed drug seeking. Most drugs of abuse, in particular psychostimulants such as cocaine, lead to long-lasting mesolimbic dopamine system adaptations, that ultimately facilitate drug seeking following exposure to drug-paired cues. This "dopaminergic hypothesis" of relapse has been previously addressed, but technical limitations in measuring *in vivo* dopamine release have precluded the assessment of its sufficiency without introducing pharmacological, electrical, or optogenetic confounds. Using a dopamine receptor-based fluorescent sensor in freely moving mice, we show that long-lasting dopamine recordings in the nucleus accumbens (NAc), throughout the animal's entire history of cocaine self-administration, are strong predictors of relapse as well as the time to extinguish drug seeking behavior. Moreover, we reveal previously unseen sex-specific trajectories of cocaine-related phasic dopamine responses from acquisition to relapse. We show that males exhibit higher-amplitude phasic dopamine responses, a trait accompanied by greater resistance to extinguish their cocaine seeking, compared to females. Furthermore, we show that a semi-parametric model of the transition to extinction – using only multivariate patterns of dopamine release and sex as covariates – faithfully recapitulates male-specific vulnerability to persistent cocaine seeking. In conclusion, we present a predictive model of reinstatement behavior that uses information exclusively conveyed by NAc phasic dopamine responses, thus confirming, and actuating the sufficiency of the dopaminergic hypothesis of relapse.

Oral Communication 3-2

Development of cariprazine analogs for the treatment of psychostimulant use disorders

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Psychostimulant use disorder (PSUD) remains a major public health problem that contributes to death by overdose. Currently, there are no approved medications for PSUD, which severely limits the number of available treatment options. As part of ongoing efforts to address this immediate medical need, highly selective dopamine D_3R receptor (D_3R) antagonists/partial agonists have been developed as PSUD pharmacotherapeutics. However, none have reached the clinic due to either insufficient potency/efficacy or possible cardiotoxicity. Interestingly, cariprazine, an atypical antipsychotic marketed for schizophrenia and bipolar disorder, has been shown to reduce cocaine-seeking behavior in animal behavioral models. This drug, unlike many in its class, is a high affinity D_3R partial agonist (K_i = 0.22 nM) with 3.6-fold selectivity over the homologous dopamine D_2 receptor (D_2R). We hypothesized, therefore, that analogs of cariprazine may be effective as treatments for PSUD. By modifying the parent drug, we discovered partial agonists/antagonists that bind to D_3R with high affinity (K_i = 0.14–50 nM) and moderate selectivity over D_2R (<100-fold). In rats, cariprazine and two of our lead compounds decreased cocaine self-administration (fixed-ratio schedule of 2, 1–10 mg/kg, i.p.), demonstrating the potential of partial agonists/antagonists with modest D_3R/D_2R-selectivity in treating PSUD.

Oral Communication 3-3

Sex differences in the neuroimmune response to heroin withdrawal in rats

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Opioid overdose has become the leading cause of accidental death in the United States, causing nearly 500,000 deaths from 1999 to 2019. Evidence suggests that opioids have an impact on the neuroimmune system in humans and rodents. However, only a few studies have focused on the immune response to opioid withdrawal. Therefore, our objective is to assess the effect of heroin withdrawal on the neuroimmune system by determining brain cytokine/chemokine levels and potentially identify cytokines/chemokines that modulate withdrawal-related behavior. To address this objective, we first measured hyperalgesia and the aversive effects of heroin withdrawal in adult male and female Wistar rats. After two weeks of repeated heroin administration, we performed a battery of behavioral tests: Von Frey and Hargreaves tests (hyperalgesia), Conditioned place Aversion (CPA; hyperkatifeia), sucrose test (anhedonia-like responses), novelty-suppressed feeding test (anxiety-like behavior) and somatic signs of withdrawal. Then, we quantified brain levels of monocyte chemoattractant protein-1 (MCP-1), Interleukin-10 (IL10), Interleukin 17A (IL17A), tumor necrosis factor α (TNFα), and chemokine (C-X-C motif) ligand 1 (cxcl1) in both heroin-dependent and nondependent rats by a FirePlex immunoassay. These behavioral observations were confirmed by a significant increase in MCP-1 and CXCL1 and IL-10 levels in male rats that received heroin, but not in females. In summary, these data suggest a sex-dependent proinflammatory effect of heroin withdrawal in the rat brain and that MCP1, CXCL1 and IL10 may serve as novel biomarkers of opioid withdrawal. This work is supported by NIDA IRP/NIH.

Oral Communication 3-4

Acute pain moderates analgesic valuation in a behavioral economic choice task

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Prescription opioids are a gold-standard treatment for acute and chronic pain, yet our ability to predict non-medical opioid use motivations and transitions to opioid use disorder remains limited. Research underscores the importance of biological and contextual factors such as pain as predictors of substance use decision-making. In contrast to conventional views that pain increases opioid analgesic value via negative reinforcement processes, preclinical research reveals that the reinforcing effects of opioids are reduced in non-human animals following experimentally induced pain. This study was designed as a first step clinical translation of these findings by evaluating behavioral economic demand for analgesics under varied pain states among people with self-reported chronic pain. We recruited respondents (N=97) using crowdsourcing methods to complete operant demand hypothetical purchase tasks for intentions to purchase and consume over-the-counter analgesics under varying degrees of simulated acute pain. We evaluated data using a field-standard non-linear demand model from which we derived metrics of analgesic valuation. Results indicated a significant main effect of acute pain level on metrics of consumption at unconstrained cost (p < .01, d = -0.27) and demand persistence (p < .001, d = 1.18). Responding also reflects a visually apparent (but not statistically significant) interaction between acute pain conditions and history of chronic pain, wherein respondents with a self-reported history of chronic pain reported elevated demand intensity and persistence from low to high acute pain conditions. These results are among the first to demonstrate the role of acute and chronic pain as predictors of opioid demand in human participants. Next steps include translation to validated laboratory models of acute and chronic pain to experimentally test the effect of pain on analgesic use.

Oral Communication 3-5

Alcohol use disorder-related phenotypes in nondependent and dependent heterogeneous stock rats

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Over 175 million Americans use alcohol each year, but only ~16% of those people develop an alcohol use disorder (AUD), suggesting there are significant individual differences on to the development of problematic drinking, which could be related to genetic factors. Heterogeneous stock rats are genetically and phenotypically diverse rats that may be useful for investigating individual differences in AUD related behaviors. In this study, male and female heterogeneous stock rats self-administered oral ethanol (10% v/v) on a fixed ratio 1 schedule of reinforcement until a stable baseline of intake was achieved. Multiple AUD-related behaviors (i.e., preference for ethanol over water, progressive ratio responding, level of quinine-adulterated ethanol intake) were measured. Dependence was then induced using the chronic intermittent ethanol vapor exposure (14 hours/day, achieving blood ethanol levels of 150-250 mg%) and the same AUD-related behaviors were evaluated during acute withdrawal (6-8 hours after vapor) from ethanol. We computed an Addiction Index using Z scores from each of the behaviors. Female rats had higher levels of ethanol intake before and after induction of dependence. Females also showed higher motivation and compulsivity (as demonstrated by the higher breakpoint in the progressive ratio test and the lower sensitivity to quinine adulteration), compared to males, and were significantly less sensitive to alcohol in the loss of righting reflex task. The individual differences in the Addiction Index suggest heterogeneous stock rats exhibit diverse AUD-like phenotypes that are likely related to genetic factors influencing the development of AUD and highlight the importance of pharmacogenetic studies when treating AUD. Research supported by R01 AA029688 and T32 AA007456.

Oral Communication 3-6

Fentanyl-targeting monoclonal antibodies block fentanyl-induced respiratory depression

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Fentanyl is a synthetic opioid that is routinely abused for its pleasurable psychoactive effects, which can lead to substance use disorder (SUD) and subsequent overdose. Although treatments for fentanyl overdose exist, they can be ineffective and are short-acting. Thus, antibody-based therapeutics have emerged as a new approach to prevent fentanyl overdose. Here, we examined the ability of a novel fentanyl-targeting monoclonal antibody, CSX-1004, to block fentanyl's respiratory depressant effects. Eight squirrel monkeys were treated with either 10 or 40 mg/kg CSX-1004 via IV infusion and received fentanyl challenge up to 28 days post-infusion to determine the time course and magnitude of fentanyl antagonism. Respiratory depression was examined using a ventilation chamber in which subjects were exposed to air and air with 5% CO_2 in 10-minute alternating increments. Results show that CSX-1004 successfully blocked fentanyl's respiratory depressant effects in both a dose- and time-dependent manner. Fentanyl challenge on Day 0 post-CSX-1004 resulted in no fentanyl-associated reductions in minute volume, and these effects continued through Day 28, although efficacy gradually diminished starting at Day 14. Subjects that received the 10 mg/kg dose returned to baseline levels faster than those that received the 40 mg/kg dose, with efficacy beginning to diminish at day 7. Both 40 and 10 mg/kg CSX-1004 also produce, respectively, a ~14- and ~5-fold rightward shift in the fentanyl dose-response function but did not block the effects of other mu-opioid agonists. These initial studies suggest that monoclonal antibodies could be a promising treatment in preventing fentanyl overdose while not disrupting the efficacy of other opioids that are often prescribed for pain relief. (NIDA: 1U01DA051071)

Oral Communication 4-1

The kappa-opioid receptor agonists, U50,488 and triazole 1.1, reduce oxycodone choice in rhesus macaques

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We recently reported that the biased kappa opioid receptor (KOR) agonist, triazole 1.1, functioned as a punisher of oxycodone choice in rhesus macaques as effectively as the prototypical KOR agonist, salvinorin A. Given that the studies of triazole 1.1 on other behavioral endpoints have typically used the prototypical KOR agonist, U50,488, as a comparator, the current study compared the relative potencies of triazole 1.1 and U50,488, as punishers of oxycodone choice, to facilitate comparability with the other reports. Using a food vs. drug choice design, four rhesus macaques (3 male, 1 female) were trained to self-administer a fixed dose of oxycodone that was consistently preferred over food (0.01 mg/kg/inf; i.v.) across 5 components consisting of 10 choice trials each. The doses of co-injections of triazole 1.1 or U50,488 were increased in successive components. Both KOR agonists functioned as punishers of oxycodone choice, with the average ED_{50} values for U50,488 and triazole 1.1 being 0.95 and 35.9 µg/kg, respectively. Triazole 1.1 was most potent in the female subject, but this subject's ED_{50} fell within the distribution of the potency series for U50,488. Notably, reductions in oxycodone choice were associated with increased choice of food and no reductions in choice trials completed, indicating that the KOR agonists produced selective punishing effects. Consistent with prior reports in other measures in different species, triazole 1.1 was less potent in behavioral effect than U50,488. Given that triazole 1.1 has been reported to produce fewer adverse effects than U50,488 in prior reports, this compound or derivations from its scaffolding are reasonable candidates for further investigation as abuse-mitigating agents for co-formulation with prescription opioids.

Oral Communication 4-2

Effects of gabapentinoids on heroin and cocaine self-administration in rats

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A growing body of epidemiological evidence suggests increasing prevalence of misuse of gabapentinoids in people with opioid use disorder. Prevalence of gabapentinoids (gabapentin and pregabalin) in opioid overdose deaths has increased similarly over the past decade. Despite these trends, little research has evaluated interactions between gabapentinoids and opioids related to misuse. The aim of this study was to determine the effects of gabapentinoids on self-administration of heroin and cocaine in rats. Male Sprague-Dawley rats were trained to self-administer heroin or cocaine under a progressive ratio schedule of reinforcement. Dose-effect curves for heroin (0.0032-0.1 mg/kg/inf) and cocaine (0.1-1 mg/kg/inf) were determined following pretreatment with saline, gabapentin (1-32 mg/kg) or pregabalin (1-10 mg/kg). The effects of gabapentinoid pretreatment were determined by comparing the number of infusions earned at each dose of heroin or cocaine across pretreatment conditions. Rats self-administered heroin in a dose-dependent manner with the greatest number of infusions (~8) earned at a unit dose of 0.032 mg/kg. Self-administration of cocaine was also dose-related with the greatest number of infusions (~15) earned at a unit dose of 1 mg/kg. Pretreatment with gabapentin or pregabalin dose-dependently increased the number of infusions earned at the two smallest doses of heroin tested. Pretreatment with gabapentin or pregabalin did not alter the number of infusions earned for any cocaine dose tested. These findings are consistent with reports suggesting that gabapentinoids can enhance the reinforcing effects of opioids and demonstrate the need for further evaluation of interactions between these drug classes. Future studies will determine the reinforcing effects of gabapentinoids alone, as well as the effects of gabapentin on the reinforcing effects of buprenorphine. Funding: Welch Foundation AQ-0039, Texas Research Society on Alcoholism McGovern Fellowship, NIDA 1F31DA057832

Oral Communication 4-3

Effects of non-contingent oxycodone and buprenorphine on sleep and quantitative EEG in rats

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As sleep disturbances during opioid use are common and are a major contributor to drug use and relapse, it is essential to characterize how different opioid affect sleep. The present study utilizes electroencephalography (EEG) to characterize sleep and oscillatory brain activity after non-contingent administration of full (oxycodone) and partial (buprenorphine) mu agonists. Adult male Sprague Dawley rats (n=10) were surgically implanted with subcranial leads placed in contact with the frontal and contralateral occipital lobe and subcutaneous transmitters that record EEG, electromyography (EMG), temperature, and activity wirelessly from within the home cage. Rats were administered saline, oxycodone (1-5.6 mg/kg, i.p.), or buprenorphine (0.05-0.5 mg/kg, s.c.) during the light or dark phase. EEG was recorded for 24 hours per treatment condition: 2 hours pre-dosing (BL), and 22 hours post-dosing. Following sleep staging, custom MATLAB scripts averaged power within frequency bands Delta, Theta, Alpha, Sigma, Beta, Low Gamma, and High Gamma separated by state (Wake, REM, and NREM sleep). Duration of each sleep/wake state and relative power was calculated and analyzed. Oxycodone and buprenorphine produced dose-dependent decreases in NREM and REM sleep, although effects were longer lasting following buprenorphine administration than oxycodone. Sleep disturbances following opioid administration were most prominent during light cycle administration. This study provides evidence that time of administration and sleep cycle should be taken into consideration when prescribing oxycodone, and that sleep treatments may be beneficial in combination with buprenorphine treatment given buprenorphine's long-lasting effects on sleep.

Oral Communication 4-4

Monoamine receptors differentially affect basal and fentanyl-depressed respiration

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Rationale: Fentanyl remains the primary driver of opioid-induced respiratory depression (OIRD) and its associated increasing number of fatal overdoses. The incidence of methamphetamine (METH) and fentanyl co-use is following a similar trajectory. Previous studies from our lab demonstrate that METH dose determines whether it enhances or mitigates OIRD. Monoaminergic activity mediates METH's effects, understanding how those pathways underlie METH's bidirectional respiratory effects may illuminate targets for future non-opioid adjuvants for treating OIRD when antagonists are inadequate.
Methods: Six monoamine (MA) receptor agonists implicated in METH's activity were tested in adult male Swiss Webster mice (N = 8) to determine their effects on minute volume (MVb; i.e., *respiratory frequency x tidal volume*) using whole-body plethysmography. Dose ranges of phenylephrine (PNE; a_1), clonidine (CLON; a_2), SKF-82958 (SKF; D_1), quinpirole (QPR; D_2), 8-OH-DPAT (8-OH; $5HT_{1A}$), and DOI ($5HT_2$) were first evaluated to determine their basal effects. Agonists that did not depress basal MVb were subsequently tested under fentanyl (0.3 mg/kg)-depressed conditions. Data were analyzed using two-way ANOVAs followed by Holm-Šídák post-hoc tests to compare treatment conditions across time.
Results: Under basal conditions, PNE and SKF dose-dependently ($p<0.05$) increased while CLON and QPR decreased MVb. Neither 8-OH nor DOI altered basal MVb. Under fentanyl-depressed conditions, SKF transiently elevated MVb significantly compared to controls, while PNE increased MVb over a longer duration. Interestingly, DOI transiently increased depressed MVb, while 8-OH significantly decreased it.
Conclusions: Selective activation of MA receptors differentially alters basal respiration and OIRD, with D_1 and a_1 receptors representing potential targets for respiratory stimulants, while a_2, D_2, and $5HT_{1A}$ receptors may mediate the enhancement of OIRD by METH.

Oral Communication 4-5

Resilience factor from the Addictions Neuroclinical Assessment buffered against the risk of comorbid alcohol use disorder with trauma disorder in individuals with a history of childhood trauma

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PURPOSE: AUD and trauma disorders (TD) often co-occur. Negative Emotionality (NE), one of the neurofunctional domains of the Addictions Neuroclinical Assessment, is integral to the etiology of AUD and TD. Childhood trauma (CT) increases the risk of AUD and TD, and causes disruption in NE. The present study investigates how NE factors mediate the relationship between CT and risk of comorbid AUD and TD.
METHODS: Participants (N=300) completed the ANA battery, which includes assessments of NE. CT was measured using the Childhood Trauma Questionnaire (CTQ). Participants were classified into Healthy controls (HC; n=84), AUD only (n=131), or AUD with comorbid TD (AUD+TD; n=79). Factor analyses were used to elucidate NE factors. Structural equation models were used to evaluate relationships between CT, NE factors, and psychiatric groupings.
RESULTS: Three factors of NE were found: Internalizing, Externalizing, and Resilience. HC exhibited lower Internalizing and Externalizing than AUD only and AUD+TD, and AUD+TD showed higher Internalizing than AUD only (p's<.003). Resilience was higher among HC relative to AUD only (p=.03). CT was associated with both Internalizing and Resilience (p's<0.002). Internalizing mediated the relationship between CT and risk of AUD and AUD+TD (p's=0.001). Resilience mediated the relationship between CT and risk of AUD+TD (p=0.047) but not AUD only.
CONCLUSION: Internalizing, Externalizing, and Resilience underlie the NE domain. CT conferred risk of AUD (regardless of TD) through Internalizing. Effect of CT on risk of AUD+TD was buffered by Resilience, but no effect were detected for risk of AUD only. Resilience-based interventions may be especially effective for individuals with history of CT to reduce the risk of comorbid AUD+TD.

Poster Presentations

Poster 1

Uncovering the role of neuropeptide receptor GPR83 in nociception

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Nociception, the sensation of pain, is mediated by various nociceptors. GPR83 is a deorphanized G-protein coupled receptor that has a critical neurobiological function activated by its endogenous ligand, neuropeptide PEN. Studies have shown that GPR83 is expressed in a specific ascending spinal tract and is highly sensitive to mechanical stimuli. GPR83 agonist (CPD1) and antagonist (CPD25) have been used to study the therapeutic effect of GPR83 receptors. By using these compounds, we identified that the GPR83 agonist reduced the nociceptive effect of morphine while the antagonist enhanced it, indicating the involvement of GPR83 in pain pathways. However, it is still unknown whether GPR83 has a direct effect on nociception and whether targeting this receptor can alleviate chronic pain. Our data suggested that GPR83 antagonist increased sensitivity to mechanical stimuli, and had no effect on chronic pain, whereas GPR83 agonist attenuated the chronic inflammatory pain caused by Complete Freud's Adjuvant (CFA). Our study aims to further characterize the role of GPR83 in nociception and whether this receptor has a direct impact on pain pathways.

Poster 2

Bioisosteric replacement of amide linkers with 1,2,3-Triazoles for improved pharmacokinetics without losing dopamine D4 receptor potency or selectivity

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The neurotransmitter dopamine signals through G protein-coupled receptors that regulate a variety of neurophysiological functions, including movement, emotional regulation, motivation, and cognition. Dopamine D4 receptors (D_4Rs) are enriched in the hippocampal and prefrontal cortical regions of the brain that are critical to attention, cognition, memory formation, and decision-making. While the physiological relevance of D_4R signaling in the brain is not fully understood, preclinical studies indicate that D_4R-selective ligands can improve outcomes in animal models of neuropsychiatric disorders with deficits in cognition and behavioral control, including Alzheimer's disease, ADHD, and SUD. We have recently reported a library of novel D_4R-selective ligands of varying efficacies, based on a phenylpiperazine scaffold, to investigate D_4R function in preclinical models. However, the *in vivo* utility of some of these ligands was limited by rapid phase I metabolism, which invariably cleaved an amide bond in the molecular template. Herein we report the development and structure-activity relationship of novel ligands featuring a bioisosteric replacement of the amide linker with a 1,2,3-triazole moiety using click chemistry methods. Comprehensive *in vitro* analyses indicate that this substitution is well tolerated and 1,2,3-triazole compounds maintain binding and functional profiles similar to their matching amide analogs. The 1,2,3-triazole moiety should be more resistant to drug metabolism; studies evaluating analog stability in rat and human liver microsomes are presently underway.

Poster 3

Effect of high-fat diet consumption on the rewarding and aversive effects of morphine

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The interaction of high fat diets (HFD) and opiates is well documented; however, little is known about changes in the rewarding and aversive effects of opiates in animals with a history of high fat diet consumption. Given the well characterized interaction of HFD and opiates and the common effects of each on reward substrates, it was hypothesized that HFD exposure would significantly impact the affective properties of morphine. To address this issue, in the present experiment 64 experimentally naïve, male Sprague-Dawley rats were given ad-libitum access to a western-style diet (high in saturated fat and sugar) or a control chow diet beginning in adolescence and continuing into adulthood at which point they were trained in a combined conditioned taste avoidance (CTA) / conditioned place preference (CPP) procedure in which they were given access to a novel saccharin solution, injected intraperitoneally with morphine and then placed on one side of a place preference chamber to assess the aversive and rewarding effects of morphine, respectively. A mixed model ANOVA revealed that under these conditions, all subjects injected with morphine displayed significant avoidance of the morphine-associated solution (CTA; all ps < 0.05) and preferred the side associated with the drug (CPP; all ps<0.05). There were no differences between the two diet groups (all ps>0.05), indicating that chronic exposure to the western diet had no impact on the affective properties of morphine (despite increasing body weight, food consumption and fat deposition; all ps<0.05). These results will be discussed in terms of previously reported increases in drug intake in animals with a history of HFD (as evident with nicotine, cocaine and amphetamine) and the possible mechanisms involved in such increases (e.g., loss of response inhibition instead of functional changes in the rewarding or aversive effects of the drugs).

Poster 4

The effects of differential rearing on sucrose preference

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It is hypothesized that social isolation increases incentive motivation. In operant paradigms, rats reared in social isolation self-administer more for a variety of rewards than rats reared in an enriched environment. However, we recently demonstrated that in taste reactivity paradigms, enriched rats display more hedonic responses for sucrose than isolated rats. Therefore, social isolation increases incentive salience and decreases hedonic responding. There is limited research on how differential rearing effects preference and reward sensitivity to varying concentrations of sucrose. To better understand the impact of differential rearing on incentive motivation, the current experiment examined sucrose preference. We hypothesized that rats in the enriched condition (EC) will have a higher sucrose preference than rats raised in the isolated condition (IC). Twenty-four male Long Evans rats (Charles Rivers Laboratories) arrived on PND 21 and were randomly assigned to the standard condition (SC), IC, or EC for 30 days. SC rats were pair housed in a shoe box cage with weekly handling and no novelty, IC rats were single housed in hanging wire cages, and EC rats were communally housed with daily handling and novel objects. This study used a within-subjects two-bottle design to examine preference for a 32% sucrose solution compared to tap water, 0.7%, and 10% sucrose. After rearing, each rat was given access to a 32% sucrose solution and tap water, a 0.7% or 10% sucrose solution for one hour

Poster 5

Effects of a mAChR1 positive allosteric modulator (VU0364572) on methamphetamine-vs-food choice in rats

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Methamphetamine use disorder is a significant public health issue for which there is currently no Food and Drug Administration-approved pharmacotherapies. Recent evidence suggests that positive allosteric modulation of the muscarinic acetylcholine receptor (mAChR)1 might be a potential pharmacotherapy target. For example, administration of the mAChR1 positive allosteric modulator VU0364572 (VU'72) decreased cocaine-vs-food choice in male rats that was sustained for several weeks. The goal of the present study was to extend these promising findings on cocaine by determining the effectiveness of VU'72 to alter methamphetamine self-administration in a methamphetamine-vs-food choice procedure in male and female rats. Male and female Sprague-Dawley rats (n=8; 4F/4M) were implanted with intravenous (IV) catheters and trained to self-administer IV methamphetamine (0.032-0.18 mg/kg/inf) and 32% vanilla flavored ensure under a concurrent fixed-ratio 5 schedule of reinforcement during daily 2h behavioral sessions. Once methamphetamine choice behavior was stable as defined by the smallest unit methamphetamine dose maintaining greater than 80% methamphetamine choice did not vary by more than 0.25 log units over three consecutive days, VU'72 (1-1.8 mg/kg, IP) was administered as a 30min pretreatment to the behavioral session and choice behavior was tracked for at least two weeks. At baseline, food was chosen over small methamphetamine doses. Larger methamphetamine doses were chosen over food. 1.8 mg/kg VU'72 decreased methamphetamine choice and increased food choice in a lead rat without depressing overall rates of operant behavior. This profile of behavioral reallocation away from methamphetamine and towards food supports the further evaluation of VU'72 as a candidate medication for methamphetamine use disorder.

Poster 6

Preliminary biological evaluations of the first brain-penetrant GPR119-based radiotracer in rodents and non-human primates

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Cannabinoids (CB) have long been associated with multiple pharmacological benefits. However, abuse of CB leads to cannabis use disorder and recent studies shows 3 in 10 people using CBs suffer with this disorder. CBs exert their biological activity through two important receptors, called cannabinoid receptors 1 and 2 (CB1 and CB2). Both these receptors are G protein-coupled receptors (GPCRs) that are abundantly expressed in brain tissue and neuronal cells and whose characterizations significantly improved the therapeutic opportunities to treat the cannabis use disorder. Modulation of a few important GPCRs are implicated with improving pharmacological effects of CB1 and CB2 and one such GPCR is GPR119, which plays a key role in direct stimulation of glucagon-like peptide-1 (GLP1) to regulate insulin release in glucose metabolism. While GLP1/GPR119 agonists primarily regulate glucose metabolism, they also showed promising activity on improving neurologic and cognitive functions in cannabis use disorder subjects. However, the neuroprotective effects of these agonists remain largely unknown and PET imaging of GPR119 levels will significantly benefit any clinical therapeutic interventions to treat cannabis use disorder. Our lab synthesized a series of novel triazole-substituted piperidine analogs as GPR119 agonists and identified two analogs (T1 and T2) with high GPR119 binding potency (2-5 nM) for [^{18}F]-radiochemistry for the first time. Here we present the chemistry, radiochemistry, preliminary in vitro cell uptake, and in vivo imaging in rodents and vervets.
The combination of selective binding and favorable pharmacokinetics with excellent brain uptake makes [^{18}F]T2 a suitable PET ligand for imaging GPR119 in monkey models of cannabis use disorder.

Poster 7

Sex of social stimulus mouse influences behavioral responses to social conditioning

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Social stress is most commonly studied in male rodents using acute or chronic social defeat paradigms. However, using social defeat can introduce some variability in the amount of stress experienced by each experimental rodent due to varying aggressor rodent behaviors. We sought to develop a modified paradigm in mice by integrating a uniform aversive stimulus with a social cue to enable study of social stress responses in a more controlled manner across both sexes. We hypothesized mice experiencing an unpleasant stimulus in the presence of another (target) mouse would have reduced social behavior when tested in social interaction with that same mouse. Adult male and female F1 C57BL/6J × 129S1/SvlmJ experimental mice underwent a social conditioning paradigm that involved pairing five foot shocks with the presence of a specific age-matched C57BL/6J target mouse. Experimental mice were tested for social interaction and contextual fear. Four control groups were included to evaluate the impact of social encounter timing and foot shock exposure on social conditioning outcomes. Paradigm assessment was pursued through two studies: one used same-sex target mice, the other used different-sex targets. Results indicated that socially conditioned males exhibited reduced social interaction with their same-sex target relative to males conditioned in the absence of a same-sex social stimulus. This suggests that males associate their social target with the aversive experience. Female mice that were exposed to the target mouse before (not during) aversive stimulus presentation had increased social behavior relative to females not exposed to any target mouse. No differences were seen in social interaction across sexes when using different-sex targets. These data suggest that associations between unpleasant stimuli and social targets are sex-dependent, both upon the sexes of the experimental animal and the social stimulus. This paradigm may be useful for identifying sex-specific social behavior changes in multiple research areas, including substance use and stress responsivity

Poster 8

The effects of eating a high fat or a ketogenic diet on withdrawal following discontinuation of morphine treatment

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Opioid medications are prescribed at higher rates to individuals with obesity as compared to the general population; however, it remains unknown if dietary intake of high fat foods impacts withdrawal severity following morphine discontinuation. To test the hypothesis that eating a high fat diet would increase withdrawal following discontinuation of morphine administration, 24 female Sprague-Dawley rats (*n*=8/diet) eating standard chow (17% kcal from fat), a ketogenic genic chow (90.5% kcal from fat), or a traditional high fat/high fat carbohydrate chow (60% kcal from fat) were injected twice-daily with morphine for 19 days (increasing in ¼ log increments every 3 days: 3.2-56 mg/kg, IP) to induce tolerance. Following chronic administration, morphine was discontinued and body weight, feeding and observable withdrawal signs were measured. For 5 days, several observable signs of withdrawal (including but not limited to: ptosis, teeth chattering, lacrimation, abdominal withering, wet dog shakes) were recorded and scored as present or absent 30, 60 and 90 min after morphine discontinuation. Observable withdrawal sign scores and percent change in body weight were analyzed using two-way mixed model ANOVAs with diet and day as factors, linear regression, and Tukey multiple comparisons tests where appropriate. Observable withdrawal signs were not different among rats eating different diets. However, rats eating ketogenic chow experienced less withdrawal-induced weight-loss as compared to rats eating standard or high fat chow and recovered back to pre-withdrawal weight at a faster rate. These results suggests that while many aspects of non-precipitated withdrawal are not altered by dietary intake, some aspects of withdrawal severity might be mitigated by the consumption of a ketogenic diet.
Funding provided through NIH award numbers R25DA033613, and 3U54MD007592-29S4

Poster 9

Effects of 3,4-methylenedioxymethamphetamine (MDMA) and its enantiomers on place conditioning in C57BL/6 and BTBR T^{+}Itpr3^{tf}/J mice

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3,4-methylenedioxymethamphetamine (MDMA) elicits psychostimulant-like and psychedelic-like effects, and it and its analogues are being explored as potential treatments for numerous psychiatric disorders. The BTBR T^{+}Itpr3^{tf}/J (BTBR) mouse is an inbred strain generated from C57BL/6 (C57) stock, and is the "gold standard" model for autism research. We used place conditioning to investigate abuse-related effects of MDMA and its enantiomers in C57 and BTBR mice. Chambers consisted of two boxes differentiated by floor texture (rough black plastic vs steel punch plate) and wall pattern (vertical vs. horizontal stripes), and connected to one another by a PVC T-junction. An infrared photobeam emitter / detector array mounted at each intersection of the T-junction started or stopped a counter on an interfaced computer, allowing automated collection of time spent in each compartment. After a 30 min preference / habituation test, mice were assigned to receive saline in one compartment and drug in the other. Saline pairings occurred in the morning (~10:00) while drug pairings occurred in the afternoon (~16:00). After 3 saline and drug pairings, mice were assessed in a 30 min preference test in which time in each compartment and compartment entries were recorded. Mice administered saline in both compartments showed no change in preference, regardless of strain, while racemic MDMA and S-MDMA elicited strong place preferences. Interestingly, BTBR mice displayed greater preferences than C57s, perhaps indicating an increased sensitivity to rewarding effects of MDMA. At the doses tested, R-MDMA did not elicit place preference in either stain. These studies further emphasize differences in the effects of the MDMA isomers, and suggest that genetic models for various neuropsychiatric conditions may also alter susceptibility to abuse-related effects.

Poster 10

Exosomal-adeno-associated virus for substance-abuse treatment

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Substance abuse and addiction are harmful conditions that alter the brain's natural reinforcement circuitries to reinforce drug-seeking behaviors. Understanding the genetics and brain circuits involved in addiction are necessary to develop new and better therapies. Our laboratory has worked to develop tools to better understand how the brain is altered with substance use and we do this using targeted genetic manipulations in the brain. One genetic manipulation tool is an adeno-associated viral (AAV) vectors which can turn on or off different circuits, neuronal populations, or signal transduction components. AAV is a naturally harmless virus that can be engineered to replace deliver genes to targeted brain regions and circuits and is the most effective virus for gene therapy. Nonetheless AAVs are limited in part due to immune responses and AAV antibodies that are produced which limits the effectiveness. The goal of this project is to use a new formulation of AAV as a biological tool effectively study the neural mechanisms underlying substance abuse, identify targets for treatment, and potential develop AAV-based gene therapies therapies. This new formulation consists of AAVs contained with exosomes (exo-AAV), which offer increased engineering possibilities that will allow us to develop AAVs that bypass the blood brain barrier, target specific brain regions or neuronal subtypes, and avoid neutralization by antibodies which will allow multiple treatments. We have developed new protocols for generating exo-AAV and characterized the nature of the exosome, their packaging capacity, and their ability to deliver their genetic payloads. We have determined that exo-AAVs represent a new formulation of AAV with increased efficiency in gene deliver that will help in both basic research and clinical gene therapy applications.

Poster 11

Effects of remifentanil/ketamine mixtures in rats responding under a choice procedure

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Mu opioids are the "gold standard" for treating moderate to severe pain despite the adverse effects of these drugs, and safer options for pain management are needed. One such option for avoiding adverse effects might be opioid mixtures such that smaller doses of each constituent are needed for antinociception compared with either drug alone. Our laboratory showed that morphine in mixtures with the NMDA receptor antagonist ketamine has additive antinociceptive effects. It is important to determine whether ketamine might enhance abuse-related effects of opioids. This study compared the effects of the mu agonist remifentanil (0.001-0.01 mg/kg/infusion) and ketamine (0.1-0.32 mg/kg/infusion), alone and in mixtures to test the hypothesis that remifentanil/ketamine mixtures are less reinforcing compared with remifentanil alone. Rats (n=16) chose (100 trials/session) between a pellet alone and a pellet + an intravenous infusion. When choosing between a pellet and a pellet + saline, rats responded approximately equally on both levers. When choosing between a pellet and a pellet + remifentanil, rats responded predominantly for the pellet + remifentanil; conversely, when choosing between a pellet and a pellet + ketamine, rats responded predominantly for the pellet alone. Both doses of ketamine attenuated the reinforcing effects of the largest dose of remifentanil. That is, the effects of a mixture containing 0.01 mg/kg/infusion remifentanil and 0.1 or 0.32 mg/kg/infusion ketamine were different from the effects of the constituent doses but not saline. Reinforcing doses of remifentanil combined with ketamine can yield mixtures that are neither reinforcing nor punishing, offering "proof-of-principle" for using drug mixtures to avoid adverse effects of opioid agonists. Support: Center for Undergraduate Research and Scholarship as well as the Department of Psychological Science at Creighton University

Poster 12

High selective fluorescently labeled ligand allows detection of DAT in human peripheral immune cells via flow cytometry.

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The dopamine transporter (DAT) is the primary regulator of dopamine (DA) signaling in the central nervous system (CNS) and in the periphery. Dysregulation of DAT function has been established as a key contributor of several neurodegenerative diseases and disorders, including Parkinson's disease and substance use disorder (SUD). Moreover, recent reports support the concept that DAT alteration occurs in both, the CNS and in the periphery as a neurological disorders and diseases progress. Fluorescently tagged small molecules have proven useful as pharmacological tools to visualize protein expression, localization and distribution in distinct live cell systems avoiding genetic modifications of the native protein. We have developed rhodamine-labeled and diSulfoCy5 fluorescently labeled ligands (FLL), with high binding affinities and selectivity for DAT, by utilizing two modafinil-like atypical DAT inhibitors as the parent ligands. DiSulfoCy5 FLL, **GC04-38** was utilized to labeled DAT in peripheral blood mononuclear cells (PBMCs) and, mice and human PBMCs DAT-labeled samples were analyzed via flow cytometry. Overall, our studies provided a novel selective fluorescent tool and a more efficient method that will increase our understanding of the relationship of DAT levels in human PBMS in health and its association with neurological diseases and disorders.

Poster 13

Alprazolam exposure during adolescence exacerbates spontaneous morphine withdrawal

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Alprazolam (Xanax; ALP) use and abuse has increased in recent years, fueling the opioid drug epidemic. Concomitant ingestion of ALP and opioids has been reported in the adolescent population, resulting in a heightened risk for developing substance use disorders (SUDs). Surprisingly little is known about ALP-opioid interactions and the potential negative effects that come with their co-ingestion during this critical period of development. We hypothesize that ALP exposure during adolescence enhances spontaneous morphine (MOR) withdrawal symptoms thus contributing to the development of SUDs. Adolescent C57BL/6J male mice (postnatal day [PD] 35) were pretreated with either vehicle (VEH) or ALP (0.5 mg/kg) once daily from PD35-49. The mice were then treated twice daily with either saline (SAL) or escalating doses of MOR for 6 consecutive says. On day 7, the mice received a challenge dose of MOR (20 mg/kg), and spontaneous withdrawal signs were observed 2, 4, 8, and 24 hours after the last MOR injection. Mice pretreated with ALP exhibited significant weight loss during MOR treatment. Twenty-four hours after discontinuation of MOR treatment, ALP pretreated mice showed significant weight loss when compared to the VEH-MOR-treated controls. Moreover, ALP pretreated mice exhibited a significant increase in total withdrawal signs (i.e., jumping, chewing/licking, paw tremors, headshakes) when compared to the VEH-MOR-treated controls. These results suggest that ALP exposure during adolescence can have detrimental effects as its pretreatment worsens MOR withdrawal symptoms. Our findings have critical implications for the perpetuation of SUD's during adolescence as potentiated withdrawal symptoms can drive the continuation of drug use.

Poster 14

Sex differences in behavioral and physiological responses to chronic ethanol intake

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Ethanol experience causes functional plasticity of nucleus accumbens (NAc) dopamine D1 receptor-expressing medium spiny neurons (D1MSNs). Our prior work in this area demonstrated significant behavioral and physiological differences between ethanol-dependent and non-dependent male mice, but we hypothesized that there are sex differences in the behavioral and physiological expression of ethanol dependence. In the present study, behavioral studies assessed ethanol intake of male (n=11) and female (n=11) mice using a 2-bottle choice model (2BC, 15% EtOH vs H2O, 2 h/day). After 21 days of drinking, 11 mice were treated with chronic intermittent ethanol (CIE) vapor for 4 days, 16 h/day, followed by 3 days of no treatment, then 5 days of 2BC testing, with this 12-day cycle repeated 4 times to induce ethanol dependence. Mice in the Air Control condition (n=11) were treated with air, rather than CIE. Following a 5th cycle of CIE/air, brain slices were prepared (24 hours into withdrawal) for whole cell patch clamp electrophysiological recordings to measure membrane properties and excitability of NAc D1MSNs. Effects of Condition and Sex were analyzed by 2-way ANOVA. As expected, male CIE mice demonstrated an escalation of ethanol drinking, relative to both air controls and their own baseline, while the two female groups both escalated drinking compared to baseline and did not differ from each other. In regard to physiological parameters, no main effects of Condition or Sex were found, but there were significant Condition by Sex interactions for two measures of membrane excitability. Male CIE mice had significantly increased input resistance and decreased rheobase relative to air controls, while, in females, these measures did not differ between conditions. Although these findings seem to suggest that females are more prone to ethanol-induced behavioral and physiological plasticity, interpretation will be aided by ongoing studies that compare physiology with ethanol-naïve groups.

Poster 15

Alcohol consumption mediates the relationship between incentive salience and systemic inflammation

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Introduction: Incentive Salience (IS), whereby alcohol-related cues are instilled with motivational value, is one of the neurofunctional domains of the Addictions Neuroclinical Assessment (ANA) thought to underlie alcohol use disorder. IS drives alcohol consumption (AC). Excessive AC causes systemic inflammation, an indicator of allostatic load. The aim of this study was to examine whether IS increases systemic inflammation (SI) through increased AC.
Methods: 300 participants completed the NIAAA natural history protocol and the ANA battery. IS was measured by self-report questionnaires and a behavioral task. SI was quantified using serum C-Reactive Protein levels (CRP). AC was assessed with the Alcohol Use Disorder Identification Test-Consumption scale. Factor analyses were conducted to identify subfactors of IS. Structural equation modeling was used to examine pathways between IS, AC, and CRP, with smoking status, age, race and sex as covariates.
Results: Two subfactors of IS were identified: alcohol motivation (AM) and alcohol insensitivity (AI). The relationship between AM and CRP was mediated by AC (indirect effect=0.23, p<0.001). The association between AI and CRP was also mediated by AC (indirect effect=0.08, p<0.01). No direct association between AM or AI and CRP were detected.
Discussion: These results suggest that IS-related processes can increase SI through increased AC. These findings can help inform the clinical treatment of SI by way of targeting IS-related processes to reduce alcohol consumption. Future studies will evaluate the other domains of ANA and their relationship with biomarkers of allostatic load.

Poster 16

Steady-state pharmacokinetics and safety of mitragynine, the main alkaloid of *Mitragyna speciosa*, in rats

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Kratom (*Mitragyna speciosa*), is a tropical evergreen tree from Southeast Asia which produces opioid- and stimulant-like effects. It is used as a self-treatment for pain and has shown the potential to treat opioid-withdrawal symptoms. Among the alkaloids in kratom, mitragynine (MTG) is thought to be responsible for the pharmacological effects. Although single-dose pharmacokinetic (PK) study has been reported, there are no multiple-dose studies available describing the steady-state PK studies of MTG. Therefore, a multiple-dose PK study of MTG in both male and female rats (n=4) was conducted. Plasma concentration of MTG and its metabolites (7-hydroxymitragynine, mitragynine pseudoindoxyl, 9-hydroxycorynantheidine, and mitragynine acid) were quantified using ultra-performance liquid chromatography-tandem mass spectrometry. Pre- and post-study blood samples were also analyzed for clinical chemistry and hematological tests. The results showed that there were no abnormal hematological findings. The PK study showed the sex differences between male and female rats, provided the reference to determine the dosing interval, and quantified the metabolites of MTG. The MTG systemic exposure is significantly higher in female rats than in male rats. The accumulation index indicated that MTG has a weak accumulation, and the results of fluctuation are also included to determine the dosing interval. The major metabolites were mitragynine acid and 9-hydroxycorynantheidine. This study includes toxicological results and the PK parameters of multiple-dose MTG which can be referenced in further clinical settings.

Poster 17

Investigating the roles of the intralaminar thalamus, prefrontal cortex, and dorsal striatum in punished cocaine seeking in rats

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Compulsive drug seeking that continues despite negative consequences may result from a loss of behavioral flexibility, which is the ability to update behavior in response to changes in environmental conditions. The intralaminar thalamus (ILN), prefrontal cortex (PFC), and striatum (STR) have been implicated in behavioral flexibility and regulation of compulsive behaviors. We hypothesized that ILN, PFC, and STR may be recruited to control drug seeking when faced with negative consequences (i.e. punishment). First, we examined punishment-induced c-Fos expression in ILN (parafascicular, PF; centromedial, and paracentral thalamus), PFC (prelimbic and orbitofrontal cortex) and STR (dorsomedial and dorsolateral STR; nucleus accumbens, NAc). To assess c-Fos expression, male Sprague Dawley rats trained to self-administer cocaine were sacrificed and brains were collected 30 min after 1 or 2 sessions of footshock punishment (0.7 mA, 0.3 s, randomly 1/3 trials) or after a self-administration session. We found increased c-Fos on day 2 of punishment in PF and NAc, but no change in PFC, indicating thalamostriatal interactions may be required to regulate punished cocaine seeking. We then tested the effects of post-training NMDA lesions of PF in another group of rats receiving footshock punishment. Rats were given two types of punishment during cocaine self-administration: 4 sessions of footshock at 0.4 mA (0.3 s, randomly 1/3 of trials) and 3 sessions of footshock with ramped amplitude (0.32, 0.56, 1.0 mA, 0.3 s, every trial). Regardless of the type of punishment testing, we observed no difference in punishment sensitivity in rats that received PF lesions as compared to sham lesions, indicating that global inactivation of PF does not affect punished cocaine seeking. Together, our findings expand the current understanding of the neural mechanisms driving compulsive drug seeking.

Poster 18

Intermittent sucrose drinking in male and female C57BL/6J mice

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Alcohol use disorder is often characterized by compulsive drug seeking to avoid the negative effects associated with abstinence. This often results in episodes of hedonic consumption driven by both craving and relief in withdrawal. There is considerable overlap between the behaviors observed and brain regions activated when consuming palatable food or drugs of abuse. Some animal models have been developed with the aim of understanding these cycles of binging for both drugs of abuse and food rewards. Our aims were to develop intermittent access sucrose consumption in male and female C57BL/6J mice and to determine which areas of the brain play a role in binge-like behaviors. Mice were divided into two groups: intermittent access (IA) and continuous access (CA) . IA access mice received two bottle choice access to 4% sucrose for 24 hours on alternating days for a total of 12 drinking days. CA mice had two bottle choice access to 4% sucrose for 12 consecutive days. IA to 4% sucrose increases sucrose consumption in males. However, escalation of sucrose intake under IA was not observed in females. This suggests that males may be more vulnerable to escalation of voluntary drinking behavior under episodic/restricted schedule of 4% sucrose access. To determine which neuronal populations, play a role in sucrose consumption under different access conditions, we performed whole c-Fos immunohistochemistry after the initial 2 hour consumption period. We focused on the nucleus accumbens, hippocampus, amygdala and cingulate cortex hypothesizing that some regions of interest may exhibit higher neuronal activation in the intermittent access sucrose condition. Ongoing studies are comparing c-Fos expression in these limbic regions of interest between intermittent and continuous sucrose drinkers and examining whether a lower concentration of sucrose may produce sucrose binge-like behavior in female mice. These experiments provide insight into whether schedules of availability are an important environmental variable in the development of binge consumption behavior.

Poster 19

Preclinical assessment of the effects of chronic cannabidiol treatment over the different stages of alcohol dependence

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Cannabidiol (CBD), a non-psychoactive constituent of the cannabis plant, has received attention for its potential to decrease drug and alcohol use given its anti-inflammatory, antioxidant, and neuroprotective effects. Here we used a multidisciplinary approach, combining state of the art behavioral models, immunohistochemistry, and electrophysiology to evaluate the effects of chronic (60 mg/kg/day) CBD treatment in several alcohol-related behaviors and on the alcohol-induced neurodegeneration in alcohol dependent rats. We used two different animal models to induce alcohol dependence in rats: the recently developed ethanol vapor self-administration model (EVSA) and the chronic intermittent ethanol vapor exposure (CIE). The new EVSA model highlights the volitional aspects of alcohol dependence. We found that chronic CBD treatment hindered the development of alcohol dependence in the EVSA model and reduced alcohol-induced neurodegeneration in the nucleus accumbens shell and the dorsomedial striatum. In animals treated after the alcohol dependence was established using the CIE model, CBD reduced alcohol drinking, as well as somatic and emotional signs of withdrawal. Finally, the treatment was also effective in reducing alcohol seeking and stress-induced reinstatement, possibly by reversing the reduction of neuronal excitability induced by alcohol in the basolateral amygdala. These results extend to the current literature and indicate a profile of potential benefit of CBD for the treatment of alcohol dependence.
This research was supported by the UCSD Center for Medicinal Cannabis Research Grant P6401004 to GDG.

Poster 20

Behavioral effects of vaped delta-3-tetrahydracannabinol (Δ6a-10a) in male rats

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The popularity and diversity of cannabis derivatives are on the rise due to the recent federal legalization of the production of hemp products with less than 0.3% of Delta-9 tetrahydrocannabinol (THC). While some recent research has evaluated the abuse potential of Delta-9 THC, there is not much data available for the more novel minor cannabinoids. These include compounds such as the less potent and frequently marketed secondary compound, Delta-8 THC. Similar to Delta-8 in potency and molecular structure, the minor cannabinoid Delta-3 THC (also known as Δ6a10a) is promoted for recreational use most commonly as a vaped substance. The current study investigated the effects of exposure to vaporized Delta-3 THC (0, 5, 10 and 15 mg/300□l) on locomotor activity and antinociception using a warm water tail withdrawal assay. Overall, Delta-3 THC did not significantly alter locomotor behavior in the 2-hour session, but locomotor activity tended to decrease across the session. When split into 30-minute bins, the 5mg dose of Delta-3 THC caused an increase in activity (p= 0.06) during the 60-90 min block. In terms of analgesic effects, Delta3 THC increased tail withdrawal latencies immediately post vaporization and 30 min postvapor exposure compared to vehicle. At the 0-time point, both the 10 and 15mg doses resulted in significantly higher tail withdrawal latencies compared to PG. This study indicates that exposure to vaporized Delta-3 THC can alter an analgesic response, although higher concentrations might be necessary for more robust analgesic effects and more a pronounced locomotor effect. Contemporary minor cannabinoids that are emerging in the hemp industry should continue to be evaluated for classic cannabinoid effects and abuse potential.

Poster 21

Adolescent sex differences in the brain mechanisms underlying the behavioral effects of nicotine vapor

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The epidemic rise in electronic cigarette use is a major public health problem, particularly in adolescent females who are more susceptible to nicotine use. Preclinical studies are needed to provide a deeper understanding of the underlying mechanisms that promote age and sex differences in nicotine use, particularly with rodent models that mimic nicotine use patterns in humans. Evidence in male rodents has revealed that the interpeduncular nucleus (IPN) modulates the behavioral effects of nicotine withdrawal. There are unanswered questions regarding age and sex differences in the role of the IPN in modulating nicotine withdrawal. Therefore, this study compared neuronal activation within the IPN during withdrawal from nicotine vapor in adolescent female and male rats. The present study employed methods involving passive exposure to nicotine vapor for 14 days. Adolescent sex differences in approach behavior were assessed in a port that delivered nicotine plumes on Day 1 and 14 of our exposure regimen. Controls received ambient air. After the final exposure session, rats received an injection of the nicotinic receptor antagonist mecamylamine to precipitate withdrawal. Physical signs were assessed before rats were euthanized, and blood was collected to assess cotinine levels across conditions. Afterwards, brain sections containing the IPN were processed for Fos immunofluorescence. The results revealed that females displayed a larger increase in approach behavior to the nicotine port than males. Adolescents exposed to nicotine vapor displayed more physical signs of withdrawal compared to controls, an effect that is likely related to higher levels of approach behavior. Adolescent females also displayed higher cotinine levels and greater withdrawal induced Fos expression in the IPN compared to males. These results are an important first step in our understanding of the mechanisms that modulate age differences produced by nicotine withdrawal.

Poster 22

Thermoregulatory and locomotor effects of 3,4-methylenedioxymethamphetamine (MDMA), its enantiomers, and a non-racemic mixture of S-MDMA and R-MDMA (ALA-002) in C57BL/6 and BTBR $T^{+}Itpr3^{tf}/J$ mice

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Hyperthermic and locomotor stimulant effects of 3,4-methylenedioxy-methamphetamine (MDMA) have been demonstrated in multiple species, and these effects may be treatment-limiting in a therapeutic context. MDMA and its analogues are being explored as potential treatments for social withdrawal secondary to Autism spectrum disorder (ASD), but the effects of these drugs in the BTBR $T^{+}Itpr3^{tf}/J$ (BTBR) mouse – the "gold standard" model for ASD research – have not previously been characterized. These studies used implantable radiotelemetry probes to simultaneously monitor changes in core temperature and locomotor activity within a home cage environment elicited by injection of MDMA, its enantiomers, and a non-racemic mixture of S-MDMA and R-MDMA (ALA-002) in C57 and BTBR mice. MDMA and S-MDMA elicited dose-dependent locomotor stimulant effects in both mouse strains, but dose-effect curves were shifted upwards in BTBR mice, suggesting increased sensitivity to stimulant effects of these drugs. Interestingly, dose-effect curves for locomotor effects of methamphetamine did not reveal a strain difference between C57 and BTBR mice. In contrast, R-MDMA and ALA-002 elicited minimal effects on motor activity in either strain. In the same animals, S-MDMA elicited greater hyperthermia than all other MDMA formulations in C57 mice, but in BTBR mice, racemic MDMA and S-MDMA had similar hyperthermic effects. Neither R-MDMA nor ALA-002 elicited significant hyperthermia in either strain, at any dose. These studies show that various formulations of MDMA elicit locomotor stimulant and hyperthermic effects that are dependent on the presence of the S-enantiomer. Importantly, these studies suggest that ALA-002 elicits reduced abuse-related stimulant effects and is devoid of hyperthermic effects.

Poster 23

Biological signatures of acute and chronic alcohol exposure in whole blood transcriptome

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Brain gene expression patterns can classify subjects as AUD or non-AUD and predict treatments that reduce drinking in rodents. It is not possible to access the brain in patients, so a more accessible tissue is required for clinical use. Here we present findings regarding whole blood transcriptional signatures of alcohol exposure in mice and humans.

We analyzed whole blood transcriptome profiles from C57BL/6J mice exposed to chronic intermittent ethanol vapor (CIE) or air. Machine learning models classified subjects as CIE or Air-exposed with a high degree of accuracy based on blood mRNA predictors (maximum AUC of 90.4% for the regularized logistic regression model). We compared the blood CIE signature to those of pharmaceuticals in the NIH Connectivity Map database (CMap). The top drug candidate reduced voluntary alcohol consumption in CIE-exposed C57BL/6J mice by ~50% in males and ~70% in females. We also analyzed whole blood transcriptome profiles from healthy human subjects with and without a family history of AUD at four time points after iv ethanol infusions. There was a much larger blood transcriptional response to acute ethanol in family history positive participants than in family history negative.

We conclude that there is a transcriptional signature of ethanol exposure in blood in mice and humans. These findings support the utility of blood as an accessible tissue that can be used for transcriptome-based drug repurposing to identify therapeutics for AUD and potentially personalize AUD treatment.

Poster 24

Reversal of a scopolamine-Induced cognitive deficit in group-housed monkeys who drink ethanol

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Individuals who experience chronic stress are vulnerable to developing problematic drinking behaviors that can impair cognitive flexibility, ultimately contributing to the development of an alcohol use disorder (AUD). Interestingly, the cholinergic modulation of activity in the prefrontal cortex (PFC), which mediates cognitive flexibility, is sensitive to stress and alcohol. Thus, there is interest in the putative pro-cognitive effects of cholinergic drugs to remediate alcohol-induced cognitive deficits in vulnerable individuals. In the present study, we examined the efficacy of the M1/4 muscarinic receptor agonist xanomeline (XML) and the a4b2 nicotinic receptor partial agonist varenicline (VAR) to reverse a scopolamine (SCOP)-induced deficit of a PFC-mediated task in group-housed monkeys with ethanol self-administration histories. Twelve male dominant- or subordinate-ranked cynomolgus monkeys self-administered ethanol for one year and performed a serial stimulus discrimination and reversal task. Subsequently, sensitivity to SCOP-induced cognitive impairment was determined, as was the putative pro-cognitive potential of XML and VAR. We hypothesized that subordinates, who had greater mean daily ethanol intakes ($p=0.014$), would be more sensitive to SCOP and require greater doses of XML and VAR to reverse the SCOP-induced deficit. SCOP ED_{50}s did not indicate differences in sensitivity. XML and VAR dose-response curves (alone or with SCOP) are presently being collected, and SCOP ED_{50}'s will be redetermined. These findings characterize the role of cholinergic receptor subtypes involved in reversal learning in individuals with varying social experiences and ethanol-drinking histories and may help identify potential pharmacotherapeutic targets for AUD.

Poster 25

Distress tolerance and impulsivity share a common neuronal ensemble in the prelimbic cortex that predicts drug- and water-seeking behavior

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Literature has established that there are certain behaviors that are predictive of drug seeking and relapse such as impulsivity, distress tolerance (DT), and Pavlovian conditioned approach (PCA). However, few studies have examined behavioral interactions among these tasks and drug-seeking, and none have examined neural interactions among these tasks and drug-seeking. We hypothesize that there are certain common or unique neuronal activation patterns present that are involved between these behaviors and drug-seeking.
We used female (n=6) and male (n=6) Sprague Dawley rats that were subjected to a viral infusion of GCAMP6s and lens implantation in the prelimbic area. After a recovery period, rodents went through a training period. Once rats exhibited stable behavior, they were implanted with intrajugular catheters and miniscope baseplates. Once recovered, we recorded PrL activity with in vivo calcium imaging during the behavioral tasks. Afterward, rats were placed into cocaine or water self-administration for two weeks and on the 15th day, an extinction task was used to measure reward seeking. Subsequently, neurons were classified as 'common' or 'unique' depending on their shared activity patterns across the tasks.
Low reward seekers (for either cocaine or water) had higher neuronal excitability in the DT and impulsivity tasks. This effect was driven by neurons with common patterns of activity across both DT and impulsivity. Conversely, neurons with unique patterns of activity present solely in one or the other task did not differentiate low and high reward seekers. Understanding and targeting these common and unique neuronal populations could assist in specific therapeutics for individuals that exhibit one or more of the behaviors that predict drug seeking and relapse.

Poster 26

Evaluation of serotonin 2C and dopamine D3 receptor ligands as candidate medications for opioid and stimulant use disorder in rats

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Rates of substance use disorder (SUD) are at an all-time high. Despite this, there are few FDA approved drugs to treat SUDs and none that are approved for stimulant use disorders. Drugs targeting serotonin 2C receptors (5-HT2CR) and dopamine D3 receptors (DAD3Rs) show promise for inhibiting drug-taking across multiple classes of drugs. However, the clinical utility of currently approved drugs with actions at these receptors are limited by off-target effects (e.g., 5-HT2AR mediated hallucinations). The current studies evaluated the potency and effectiveness of highly selective ligands targeting 5-HT2CRs (CP809101; 0.32-10 mg/kg) and DAD3Rs (VK4-40 and VK4-116; 3.2-32mg/kg) to reduce the self-administration of fentanyl (0.0032 mg/kg/inf), cocaine (0.32 µg/kg/inf), methamphetamine (0.056 mg/kg/inf) (and sucrose; 1 pellet) in male and female Sprague-Dawley rats (n=8-10/group). Rats were trained to respond under a progressive ratio schedule of reinforcement with pretreatments of CP809101, VK4-40, and VK4-116 administered via IP injection, 15 min prior to the start of the session. All treatments dose-dependently decreased drug-taking, with CP809101 producing the greatest decrease in drugtaking. The potency and effectiveness of each of the pretreatment drugs was comparable across drugs (i.e., fentanyl, cocaine, and methamphetamine) and did not differ as a function of sex. These data suggest that agonists acting at 5-HT2CR, and partial agonists or antagonist acting at DAD3R might have broad spectrum effectiveness as novel treatments for (poly)substance use disorders.

Poster 27

Characterization of nicotine withdrawal across the estrous cycle

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During abstinence from chronic nicotine use, the magnitude of withdrawal severity fluctuates across the menstrual cycle in women. Female rodents have a 4-day estrous cycle that can be subdivided into a follicular (estrus and proestrus) and luteal phase (metestrus and diestrus). The follicular phase is characterized by peak increases in estradiol (E2) and progesterone. Our prior work has revealed that the removal of ovarian hormones abolishes the negative affective states produced by withdrawal. Also, the magnitude of withdrawal severity is correlated with high E2 and low progesterone levels. Ongoing mechanistic studies in our laboratory have revealed that the interpeduncular nucleus (IPN) plays a central role in modulating anxiety-like behavior (but not physical signs) of nicotine withdrawal. Previous work in our laboratory has demonstrated that E2 promotes and progesterone reduces anxiety-like behavior produced by nicotine withdrawal in female rats. The goal of the present study was to compare neuronal activation, by observable Fos expression in the IPN of nicotine vapor-dependent females that were tested in the follicular or luteal phase of the estrous cycle. Female rats were exposed to 12mg/mL of nicotine vapor for fourteen days. Rats then received administration of the nicotinic receptor antagonist, mecamylamine (3.0 mg/kg), and physical signs and anxiety-like behavior were assessed. Also, vaginal lavage procedures were used to assess the phase of the estrous cycle they were tested in. The rats were then euthanized and brain sections containing the IPN were processed for Fos immunofluorescence to infer the possible IPN subnuclei displaying differential activation. The results revealed an increase in Fos activation in the IPN of female versus male rats. The magnitude of neural activation in female rats was correlated with anxiety-like behavior (but not physical signs). The activation of the IPN in males was not correlated with either anxiety-like behavior or physical signs. This work suggests that the magnitude of anxiety-like behavior and activation of the IPN is greater during the follicular phase of the estrous cycle.

Poster 28

Cocaine diminishes consolidation of cued fear expression in female rats through interactions with dopamine D2 receptors

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In addition to cocaine's addictive properties, cocaine use may lead to heightened risk-taking behaviors in individuals despite potentially aversive or fatal consequences. One possible reason for this may be cocaine's disruptive effect on memory formation, particularly aversive memories. The purpose of the present study was to investigate the effects of cocaine on fear memory consolidation using a cued fear conditioning paradigm in female Sprague Dawley rats. On day 1 animals received tone-shock pairings and on day 2 (24 hours later) were returned to the fear chamber and tested for recall of fear memory. In Experiment 1 (n = 32), cocaine (15mg/kg; i.p.) was administered immediately after the conditioning trials. To determine whether cocaine's effects on memory consolidation are mediated by D2 receptors the D2 receptor antagonist eticlopride (0.1mg/kg; i.p.) was administered concurrently with cocaine (15mg/kg; i.p.). No cocaine or eticlopride was administered on test day. A one-way ANOVA and Dunnett's multiple comparison post hoc test revealed that immediate post-conditioning cocaine administration resulted in diminished fear expression during test. Concurrent D2 antagonism attenuated the impairing effect of cocaine on fear consolidation, with animals showing increased fear expression relative to animals receiving cocaine alone. In Experiment 2 (n = 16), animals received direct infusions of eticlopride (0.05 µl/min) into the ventral hippocampus (VH), a structure involved in cued fear conditioning and a target region of ventral tegmental area dopaminergic neurons. Intra-VH eticlopride (0.05 µl/min) or saline was directly infused into the VH immediately after conditioning concurrent to cocaine (15mg/kg; i.p.) administration. Results from Experiment 2 suggest that the antagonism of VH D2 receptors may disrupt the impairing effects of cocaine on fear memory consolidation, suggesting the VH as a potential region mediating this effect.

Poster 29

5-HT1B receptor activation attenuates the acquisition of nicotine reward in adolescent male rats

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Activation of serotonin (5-HT)1B receptors decreases the rewarding and reinforcing effects of stimulant drugs, such as cocaine and methamphetamine. In the present study, we examined the hypothesis that administration of CP 94,253, a 5-HT1B receptor agonist, would reduce nicotine preference in adolescent male rats using a 10-day Conditioned Place Preference (CPP) procedure, a well-established animal model of drug reward. On postnatal day (PD) 28, baseline preference for a two-sided apparatus was assessed during a 15 min session. In two-day cycles, rats received an injection of CP 94,253 (0 or 5.6 mg/kg) 15 min before the administration of nicotine (0, 0.2, or 0.6 mg/kg) on one day and saline administration on the other day before being confined to one side of the two-chamber apparatus for 15 min. This two-day cycle was repeated over the next 6 days. On day 10, the preference for the nicotine-paired chamber was assessed for 15 min. Rats exhibited nicotine-induced CPP when conditioned with either 0.2 or 0.6 mg/kg of nicotine. Administration of CP 94,253 (5.6 mg/kg) before nicotine (0.2 or 0.6 mg/kg) resulted in a decreased preference for the nicotine-paired compartment. The present findings demonstrate that activation of 5-HT1B receptors with CP 94,253 attenuated the acquisition of nicotine-induced CPP in male adolescent rats. Overall, these findings further add to a growing body of literature that points to the 5-HT1B receptor as a pharmacological target for treating psychostimulant addiction.

Poster 30

GLP-1 receptor agonism in the interpeduncular nucleus decreases fentanyl reinstatement in male and female rats

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Uncovering the neural mechanisms of opioid seeking will facilitate the development of novel treatments for opioid use disorder that may help to decrease or prevent opioid overdose deaths. Our previous studies showed that systemic administration of the glucagon-like peptide-1 receptor (GLP-1R) agonist Exendin-4 (Ex-4) decreased voluntary fentanyl taking and seeking in rats, but the neural mechanisms mediating these effects are unknown. We hypothesized that activation of GLP-1Rs in the interpeduncular nucleus (IPN), a brain region known to regulate the mesolimbic dopamine system, would attenuate fentanyl reinstatement. We trained male and female rats to self-administer intravenous fentanyl (1.25 µg/kg/infusion) for 21 days on a fixed-ratio 5 schedule of reinforcement. Drug taking was then extinguished by replacing the fentanyl solution with saline and turning off the contingent light cue. Once fentanyl taking was extinguished, the reinstatement of opioid seeking was assessed following an acute priming injection of fentanyl and re-exposure to conditioned light cues. We showed that intra-IPN infusion of Ex-4 (0.1 µg) decreased drug- + cue-induced reinstatement of fentanyl seeking in male and female rats without affecting body weight, chow intake, or pica. Additionally, we found that GLP-1Rs and mu opioid receptors are co-expressed on IPN neurons that project to the LDTg, providing a potential mechanism for the suppressive effects of Ex-4 on opioid seeking. We are currently investigating whether chemogenetic activation of the IPN→LDTg pathway attenuates fentanyl reinstatement to confirm a role of this circuit in fentanyl-seeking behavior. Overall, these results support a functional role of IPN GLP-1R activation in Ex-4's effect on opioid seeking and support the use of GLP-1R agonists as a potential treatment for fentanyl use disorder.

Poster 31

Additive antinociceptive effects of morphine:ketamine mixtures in rats with hindpaw inflammation

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Prescription opioids are the "gold standard" for treating moderate to severe pain despite their well-documented adverse effects (dependence, respiratory depression, constipation). There is a need for safer, more effective treatments for pain. One strategy for improving the margin of safety of opioids is combining them with other analgesic drugs to decrease the opioid dose needed for pain relief, thereby avoiding adverse effects that occur with larger doses. The NMDA receptor antagonist ketamine has been used safely and effectively to treat pain, but only under a narrow range of conditions (e.g., emergency departments, post-operative recovery, combat casualty). The current studies used a model of chronic pain by inducing hindpaw inflammation with Complete Freund's Adjuvant to determine the antinociceptive effects of morphine and ketamine alone and in mixtures (in 3:1, 1:1, and 1:3 ratios) in 40 male Sprague Dawley rats (n=8 per group). Given alone, both morphine (0.56-5.6 mg/kg) and ketamine (3.2-32 mg/kg) dose-dependency increased force required to elicit a paw withdrawal response, with morphine having greater potency and effetiveness as compared to ketamine. ED_{50} values were used to determine the doses for mixtures. In mixtures, the potency of morphine or ketamine to produce antinociception was enhanced 2-3 fold as compared to either drug given alone. Dose-equivalence and dose-additivity analyses showed that the effects of morphine:ketamine mixtures were additive. Morphine:ketamine mixtures might have greater therapeutic potential than opioids alone for treating moderate to severe pain, but only if adverse effects of each drug are not enhanced.

This work was supported by the Center for Undergraduate Research and Scholarship as well as the Department of Psychological Science at Creighton University.

Poster 32

Locomotor and discriminative stimulus effects of three synthetic cannabinoids

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Aims: Synthetic cannabinoids are manufactured as "legal" alternatives to delta-9-tetrahydrocannabinol (THC). These synthetic compounds act on cannabinoid receptors (Type 1 & 2) and can cause major side effects such as hallucinations and death. Governmental control of these compounds prompts the creation of new synthetic cannabinoids in the underground markets. The DEA has identified three synthetic cannabinoids of concern 4F-ABUTINACA, ADB-4-en-PINACA, and MDA-19. The investigators tested them in vivo to determine the locomotor and, discriminative effects, and potency compared to THC.

Methods: Swiss-Webster mice were tested for locomotor activity in a standard apparatus to compare behaviorally active dose ranges of each compound with THC. Discriminative stimulus effects were tested in male Sprague-Dawley rats trained to discriminate THC (3 mg/kg, 30-minute pretreatment) from vehicle (ethanol/Cremophor EL/0.9% saline (1:1:18)).

Results: In the locomotor activity tests, THC (ED_{50}=3.3 mg/kg) produced a 90-120-minute depressant phase, 4F-ABUTINACA (ED_{50}= 0.19 mg/kg) produced a 50-minute depressant phase, while ADB-4-en-PINACA (ED_{50}= 1.9 mg/kg) produced an 80-minute depressant phase. In the drug discrimination assay, 4F-ABUTINACA (ED_{50}= 0.14 mg/kg) and ADB-4-en-PINACA (ED_{50}= 0.039 mg/kg) fully substituted for the discriminative stimulus effects produced by THC (ED_{50}= 0.84 mg/kg). ADB-4-en-PINACA decreased the response rate. However, MDA-19 from 5 to 100 mg/kg failed to substitute for the discriminative stimulus of THC.

Conclusion: Two of the synthetic cannabinoids tested in the locomotor activity assay had locomotor effects similar to THC, but were more potent. In the drug discrimination assay, two of the three synthetic cannabinoids fully substituted for THC, suggesting they have a similar subjective effect. These results support evidence that 4F-ABUTINACA and ADB-4-en-PINACA have substantial abuse liability as substitutes for THC, whereas MDA-19 may not.

Support: Supported by NIDA contract N01DA-18-8936

Poster 33

Comparison of methocinnamox (MCAM) and naloxone to reverse and prevent the ventilatory depressant effects of fentanyl, heroin, and carfentanil in rats

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Mu-opioid receptor (MOR) agonists produce life-threatening hypoventilation and the short duration of action of the MOR antagonist naloxone, the only medication for treating opioid overdose limits its effectiveness to reverse and protect opioid overdose. The MOR antagonist methocinnamox (MCAM) antagonizes hypoventilation by the non-morphinan fentanyl and the morphinan heroin in laboratory animals with an unusually long duration of action. We compared the potency and effectiveness of MCAM to naloxone for reversing and preventing hypoventilation by fentanyl, the longer-acting fentanyl analog carfentanil, and heroin in eight rats in a within-subjects design. Whole-body plethysmography was employed (normal air) to assess ventilation (minute volume, V_E). Drugs were infused i.v. through catheters. When administered 5 min after opioid administration, both MCAM (0.1-100 µg/kg) and naloxone (0.1-10 µg/kg) significantly reversed hypoventilation by fentanyl (0.1 mg/kg), heroin (3.2 mg/kg), or carfentanil (0.01 mg/kg) compared with vehicle control. MCAM (ED_{80} values: 0.059, 0.056, and 0.007 mg/kg, respectively) was less potent than naloxone to reverse hypoventilation by fentanyl, heroin, and carfentanil (potency ratios: 2.7, 8.2, and 6.5, respectively). When administered 22 hr prior to opioid administration, MCAM (0.1-1.0 mg/kg) but not naloxone (1.0 mg/kg) prevented hypoventilation by fentanyl, heroin, and carfentanil compared with vehicle control (ED_{80} values: 0.69, 0.70, and 0.69 mg/kg, respectively). The present study demonstrates the effectiveness of MCAM to reverse as well as prevent
hypoventilation by various MOR agonists. Supported by USPHS grants UG3DA048387, UG3DA048387-S1, and R01 DA048417, and the Welch Foundation (Grant AQ-0039).

Poster 34

Cardiovascular effects of methamphetamine, 3,4-methylenedioxymethamphetamine, and other entactogens in C57BL/6 and BTBR T$^+$Itpr3^{tf}/J mice

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Hypertensive effects of substituted amphetamines including methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA) have been demonstrated in multiple species, and these effects may be treatment-limiting in a therapeutic context. MDMA and its entactogenic analogues are being explored as potential treatments for a range of neuropsychiatric conditions, but the effects of these drugs in the BTBR T$^+$Itpr3^{tf}/J (BTBR) mouse – the "gold standard" model for autism research – have not previously been characterized. These studies used a tail-cuff volume pressure recording system to simultaneously monitor changes in systolic and diastolic pressure elicited by injection of saline, METH, MDMA or the novel entactogen-like compounds 1-(benzofuran-5-yl)-N-ethylpropan-2-amine (5-EAPB) and 1-(benzofuran-6-yl)-N-ethylpropan-2-amine (6-EAPB) in restrained C57 and BTBR mice. All mice were habituated to restraint and tail cuff pressure monitoring for at least three days before drug administration. As compared to saline administration, METH and MDMA elicited dose-dependent increases in systolic, diastolic and mean arterial pressures in both mouse strains, with the pressor effects of METH being more potent than those of MDMA in both strains. Interestingly, the effects of MDMA in all measures were greater in magnitude in C57 mice than in BTBR mice, perhaps suggesting decreased sensitivity to pressor effects of MDMA in BTBR mice. The effects of 5-EAPB and 6-EAPB on all pressure parameters will be compared to those of METH and MDMA in both strains. These studies show that BTBR mice are relatively insensitive to cardiovascular effects of MDMA, as compared to C57 mice, and further suggest that drug development efforts should focus on minimizing the acute adverse cardiovascular effects of new entactogenic amphetamine analogues.

Poster 35

Novel full and partial $mGlu_5$ negative allosteric modulators attenuate cocaine-induced increases in accumbal dopamine concentrations and cue-induced reinstatement

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Metabotropic glutamate receptor subtype 5 ($mGlu_5$) negative allosteric modulators (NAMs) have demonstrated therapeutic potential in preclinical models of cocaine use disorder (CUD). However, one factor hindering progression of these compounds to clinical trials is the narrow therapeutic window. Approaches to combat this issue include the development of more selective $mGlu_5$ NAMs as well as partial $mGlu_5$ NAMs, which demonstrate ~50% inhibition of maximal glutamate response. Here, we compared the efficacy of novel full (VU0424238) and partial (M-5MPEP) $mGlu_5$ NAMs in attenuating cocaine-induced increases in accumbal dopamine concentrations using *in vivo* microdialysis and cocaine-mediated behaviors using cue- and cocaine-induced reinstatement. Male Sprague Dawley rats (n=32) were implanted with probes in the nucleus accumbens shell. Dialysate samples were collected every 20 minutes with vehicle, VU0424238 (30 mg/kg, i.p.), or M-5MPEP (56.6 mg/kg, i.p.) administered 2 hours into sampling; vehicle or cocaine (10 mg/kg, i.p.) was administered 30 minutes later. Dopamine concentrations were then quantified using high performance liquid chromatography (HPLC). A separate group of rats (male (n=55) and female (n=27)) were trained to self-administer cocaine (0.5 mg/kg/infusion) in the presence of a vanilla-odor and light cues. After a 5-day extinction period, cues were reintroduced in a cue-induced reinstatement session followed by a cocaine-induced (10 mg/kg, i.p.) reinstatement session 3 days later. Both VU0424238 and M-5MPEP reduced increases in accumbal dopamine concentrations and attenuated cue-induced reinstatement. However, only VU0424238 attenuated cocaine-induced reinstatement. Together, the association between behavioral and neurochemical findings support the development of both novel full and partial compounds for CUD.

Poster 36

Chronic morphine impairs interoceptive control: Implications for dysregulated drug intake

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We have previously established that using an interoceptive drug state to signal aversive outcome is particularly efficient for training animals to avoid an otherwise rewarding stimulus. This signaling function of interoceptive drug state may be important in regulating drug intake by disambiguating whether additional consumption will be rewarding or aversive. Given that control over drug intake often goes awry with extended use, the current study tested the hypothesis that chronic drug exposure (via drug tolerance) would impair the function of interoceptive drug states to signal aversive contingencies. In a serial feature positive discrimination (FP), male Sprague-Dawley rats (n=49) were trained to use an internal morphine state (10 mg/kg, IP) to predict that a saccharin solution would be followed by the illness-inducing agent LiCl, while the saline vehicle signaled that saccharin would not be followed by LiCl. FP-trained rats were then exposed to a chronic, escalating-dose regimen of morphine (CM; n=24) or saline (CS; n=25). We assessed the retention of discrimination at three doses of morphine (0, 5, 10 mg/kg) in different groups of rats (ns=8 or 9) following chronic exposure and a 3-week washout (dissipation of tolerance). Analysis of variance was performed on the data. All animals acquired the discrimination, avoiding saccharin when it was preceded by morphine and consuming saccharin when it was preceded by saline. While CS-exposed rats displayed a dose-dependent avoidance, CM-exposed rats displayed no avoidance at any dose of morphine after chronic exposure. Following dissipation of tolerance, both CM- and CS-exposed rats injected with 10 mg/kg morphine avoided saccharin. These findings provide a baseline for the detrimental effect of chronic exposure on the drug's interoceptive control of inhibitory responding and, by demonstrating that discrimination recovered after dissipation of tolerance, suggest that tolerance may contribute to such impairment.

Poster 37

Brain volumetric differences in distinct amygdala-prefrontal circuitry predict sensitivity to the reinforcing effects of d-methamphetamine or MDMA

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Reward sensitivity to drugs can serve as a predictor of vulnerability to substance abuse. However, the specific brain structural mechanisms responsible for reward sensitivity to specific drugs have not yet been elucidated. Here, we investigated whether subregions of amygdala-prefrontal circuitry are related to reward sensitivity to d-methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA). Adult rhesus monkeys responded for intravenous injections of METH (3 males; 3 females) or MDMA (3 males; 3 females) under a fixed ratio schedule of reinforcement. ED50 values, which are inversely proportional to reward sensitivity, were determined through dose-response analysis (0.001-0.1 mg/kg/inj) for each drug. In the METH group, the maximal response occurred at the same dose (0.003 mg/kg/inj) for all subjects, and ED50 values were positively correlated with the number of injections earned across the dose range. Conversely, in the MDMA group, the maximal response occurred at either 0.03 or 0.01 mg/kg/inj depending on the subject, which was related to ED50 value. Correlations between individual ED50 values determined in dose-response analysis and the volumes of subregions of the amygdala-prefrontal circuitry determined using magnetic resonance imaging were evaluated for each drug group. In the METH group, ED50 values were positively correlated with the volume of cortical amygdaloid complex (R=0.86, P=0.03) and dorsolateral prefrontal cortex (R=0.94, P<0.01). In contrast, in the MDMA group, ED50 values were positively correlated with the volume of orbito-medial prefrontal cortex (R=0.85, P=0.03) and negatively correlated with the volume of basolateral amygdaloid complex (R=-0.85, P=0.03). These results suggest that the sensitivity to the reinforcing effects of METH and MDMA may be mediated by different subregions of the amygdala-prefrontal circuitry, resulting in different response tendencies to each drug.

Poster 38

Respiratory depressant effects of synthetic cannabinoid receptor agonists alone and in combination with fentanyl in NIH Swiss mice

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Cannabinoids and opioids elicit similar *in vivo* effects, and CB1 cannabinoid receptors and μ-opioid receptors exhibit significant "cross-talk" *in vitro*. The respiratory depressant effects of μ-opioids are well known, but there is limited evidence from human case reports and preclinical animal studies that synthetic cannabinoid receptor agonists (SCRAs) may also depress respiration. In these studies we used whole body plethysmography to characterize respiratory depressant effects of the μ-opioid fentanyl and the SCRAs JWH-018 and 5F-ADB-PINACA in NIH Swiss mice. Mice were habituated to the plethysmography pods for at least 3 days prior to testing. All mice received saline injections during habituation, and drug data were expressed as percentages of the final saline control. Fentanyl and both SCRAs elicited acute respiratory depressant effects at similar doses, and the magnitude of the effects of the SCRAs was similar to those of fentanyl. Naloxone attenuated respiratory depressant effects of fentanyl, but not those of the SCRAs, while rimonabant attenuated the effects of the SCRAs, but not those of fentanyl. As expected, daily administration of fentanyl for 4 consecutive days produced similar effects each day, consistent with slow or no tolerance to fentanyl-elicited respiratory depression. Surprisingly, mice receiving daily JWH-018 were completely tolerant to its respiratory depressant effects on the 2nd day, but expressed partial tolerance to fentanyl when that drug was injected on the 3rd day. In contrast, daily injection of 5F-ADB-PINACA resulted in a fentanyl-like lack of tolerance. Combining fentanyl with JWH-018 produced an additive respiratory depressant effect. Attempts to "rescue" mice treated with the combination with 30 mg/kg naloxone only partially reversed respiratory depression to the same level as JWH-018 alone. Similarly, "rescuing" mice with 10 mg/kg rimonabant only partially reversed respiratory depression to the same level as fentanyl alone.

Poster 39

Differences across sexes in psychedelic modulation of the opioid reward system

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Opioid use disorder effects over two million people in the United States and SUDs overall have a relapse rate of 40-60%, with current pharmacotherapies being insufficient. Mechanistically, it is clear that all psychedelics induce most of their hallucinogenic effects through the 5-HT_{2A} receptors in the frontal cortex, despite their differences in pharmacology and structure. It is unclear how these compounds may be potentially therapeutic. Recent survey data has suggested psilocybin was associated with a 30% decrease in odds of developing an opioid use disorder. Using a conditioned place preference (CPP) model to focus on the rewarding aspects of drugs through context-related conditioning associated with drug use, the present study aimed to assess the ability of psilocybin to reduce oxycodone-CPP in adult male and female mice and whether the reduction is due to specific 5-HT_{2A}R activation on pyramidal neurons projecting to the nucleus accumbens. We have found that female have increased acute response to psychedelics, but when tested in CPP male but not female mice have a reduction in the expression of oxycodone-CPP 24 h following psilocybin administration. This warrants future studies on psychedelics in female subjects.

Poster 40

Low Dose 1-(Benzofuran-5-yl)-N-methylpropan-2-amine (5-MAPB) Does Not Alter Anxiety-Like Behaviors in a Rodent Elevated Plus Maze

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3, 4-methylenedioxymethamphetamine (MDMA) is an amphetamine derivative with demonstrated clinical efficacy for the treatment of post-traumatic stress disorder (PTSD). As a popular recreational drug, MDMA also poses a public health risk. Benzofurans comprise a group of synthetic phenethylamines with similar pharmacological actions to MDMA that may be a safer therapeutic alternative. No published studies have investigated these drugs in animal models of anxiety. Preclinical screening for anxiety in the mouse elevated plus maze (EPM) indicated MDMA exerts anxiogenic effects at low doses but may have anxiolytic effects at higher doses. The current study employed the EPM to assess behavioral effects of acute low dose treatment with 1-(Benzofuran-5-yl)-N-methylpropan-2-amine (5-MAPB) in rats. Twenty-four experimentally naïve adult male Sprague-Dawley rats were randomly assigned to three treatment groups (0, 0.31 mg/kg, 1.24 mg/kg 5-MAPB, N=8). The rats received an injection of saline of 5-MAPB 30 min prior to a 5 min placement in the EPM while an overhead camera recorded maze activity. Three independent observers scored video recordings for number of entries, explorations, and time spent in open and closed arms. A two-way repeated measures ANOVA (arm type, dose) indicated a statistically significant difference between open and closed arms for all dependent variables, though no significant treatment effect. A one-way ANOVA yielded a significant treatment effect only on closed-open arm time. Tukey multiple comparisons revealed statistical significance only between the 0.31 mg/kg and 1.24 mg/kg treatment groups. These results indicate that at low doses, 5-MAPB does not alter anxiety-like behaviors in the rat EPM.

Poster 41

Acquisition of cocaine reinforcement using fixed-ratio and concurrent choice schedules in socially housed female and male monkeys

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Using socially housed monkeys, we previously showed that while becoming dominant resulted in increases in dopamine D2/D3 receptor availability, as determined with PET, there was an inverse relationship between these measures and vulnerability to cocaine abuse in males, but the opposite relationship in females. We recently extended this characterization to the kappa opioid receptor (KOR) system and found significant interactions between sex and social rank in KOR availability. The overall lowest KOR availability across all brain regions was observed in dominant (dom) females and subordinate (sub) males, the two most vulnerable phenotypes to cocaine reinforcement, based on earlier research. To replicate Nader et al. (2012) in female monkeys (N=5/social rank), Exp. 1 assessed cocaine acquisition using a fixed-ratio (FR) 30 schedule of reinforcement; KOR availability had previously been assessed in 8 of these monkeys. Exp. 2 examined cocaine acquisition in the male monkeys (N=3/social rank) using a concurrent food vs. cocaine choice schedule of reinforcement. In females (Exp. 1), while sub monkeys appeared slightly more sensitive to cocaine reinforcement compared with dom, there were no statistically differences. In males (Exp. 2), no dom monkeys (0/3) acquired cocaine reinforcement, whereas 2/3 subordinates chose cocaine relative to food pellets. In monkeys that had not acquired, giving them access to cocaine under an FR 30 schedule of reinforcement and then re-exposing them to the concurrent schedule, resulted in cocaine being chosen over food at high enough doses. These data support the use of concurrent food vs. cocaine choice schedules of reinforcement to assess drug vulnerability. In males, a relationship between KOR availability and vulnerability to cocaine reinforcement was apparent.

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Poster 42

Behavioral assessments and neurochemical assays differentiate the effects of 1-(1-benzofuran-5-yl)-2-(methylamino) propan-1-one hydrochloride (BK-5-MAPB) enantiomers

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Aims: This study characterized the locomotor stimulant and discriminative stimulus effects of 1-(1-benzofuran-5-yl)-2-(methylamino) propan-1-one hydrochloride (BK-5-MAPB) enantiomers and differentiated their pharmacokinetics and neurochemical actions.
Methods: Drug discrimination methods were employed to characterize S- and R-BK-5-MAPB (0.32, 0.64, 1.27 mg/kg IP) in 16 male Sprague-Dawley (SD) rats trained to discriminate 1.5 mg/kg MDMA from saline. Locomotor activity was assessed in three separate cohorts of male SD rats (N=6) following a single injection of saline or each enantiomer; doses (0, 0.32, 0.64, 1.27 mg/kg IP) were assessed once per week in ascending order. In a separate set of experiments, monoamine release and uptake inhibition at SERT, DAT, and NET were assayed using rat synaptosomes and [^{3}H]5-HT or [^{3}H]MPP+ as substrate. In separate cohorts of male SD rats (N=4), plasma concentrations were assayed after 1.27 and 3.81 mg/kg IP and pharmacokinetics were estimated.
Results: S--BK-5-MAPB produced dose-dependent increases in MDMA-lever responses and full substitution at 0.64 and 1.27 mg/kg; R-BK-5-MAPB produced less than 30% MDMA-lever responding. Both enantiomers increased distance traveled in a dose-dependent manner that was statistically significant compared to saline-treated controls. Both enantiomers were substrate-type releasers at all three transporters. The S-enantiomer displayed an MDMA-like profile with greater potency at SERT than DAT (DAT/SERT ratio of 0.6), while R-BK-5-MAPB had a typical stimulant profile (DAT/SERT ratio of 18). Both enantiomers had higher potency at DAT than NET (DAT/NET ratios of 2.7 and 1.9 for the S- and R- enantiomer, respectively). Pharmacokinetics differed between the enantiomers, with R-BK-5-MAPB showing a lower Cmax and higher clearance than the S-enantiomer.
Conclusions: S- and R- BK-5-MAPB produce behavioral and neurochemical actions similar to MDMA and stimulants, likely through monoamine transporters. Because they have reduced potency at NET, these novel substances may have utility in elucidating the contributions of NET to MDMA-like and typical stimulant effects.

Poster 43

Rewarding effects of D8-Tetrahydrocannabinol, cannabidiol and a mixture following of vapor exposure in male rats

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Delta-8-Tetrahydrocannabinol (Delta-8) has the largest growth in sales in the 2021 cannabinoid market. The current study was designed determine if exposure to vaporized Delta-8, CBD and a mixture of the two drugs result in rewarding effects using the conditioned place preference (CPP) procedure. Forty-eight male Sprague Dawley (PND 56; N=12/drug group) rats were exposed for 10 min to vaporized concentrations of either Delta-8 distillate (10 mg/300 ml), CBD isolate (30 mg/300 ml) and a mixture of CBD/Delta-8 (30mg/10mg per 300 ml) or the vehicle propylene glycol (PG). Using a biased three-chamber CPP design, animals first had a 15 min pretest with access to all three chambers in order to determine their initial side preference. On the next day, the animals started daily conditioning trials where they received a vaporized exposure of either active cannabinoid drug or PG. Following the 10 min exposure, animals were immediately confined to one of the pairing chambers of the CPP apparatus for a 30 min conditioning trial. Conditioning trials were repeated across 16 daily conditioning trials. After the 8th and 16th conditioning session non-vapor exposed rats were tested for CPP during a 15 min test session. Results indicated that relative to a PG only group neither the active concentration of Delta-8, CBD or the mixture of the two drugs results in a significant CPP response after the first 8 conditioning trials. Although, after the 16th conditioning trial, both Delta-8 and the mixture of CBD/Delta-8 resulted in a significant CPP response compared to PG, while CBD alone did not result in a CPP response and a trend towards aversion. The current results indicate vaporized exposure to Delta-8 THC can result in rewarding effect while CBD alone does not. Also, the combination of vaporized exposure to delta-8 THC and CBD results in rewarding effects.

Poster 44

Retesting hexamethonium antagonism in rats trained to discriminate fading doses of nicotine

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The drug discrimination paradigm has been crucial to understanding mechanisms of nicotine addiction and in comparing the interoceptive effects of nicotine to other compounds. Hexamethonium, a non-lipid soluble nicotinic receptor antagonist, has been used in many studies to show that nicotine dependence is solely centrally mediated. Following preliminary model optimization studies in our lab, we hypothesized that the standard training dose of nicotine (0.4 mg/kg) may be too large and thus decrease the overall sensitivity of the model to hexamethonium. Our goal was to gradually fade the training dose of nicotine to 0.1 mg/kg and reassess hexamethonium antagonism of nicotine. Using a two-bar drug discrimination operant chamber, 6 of 12 rats initially trained to discriminate 0.4 mg/kg of nicotine tartrate at a pretreatment time of 15 min were trained with decreasing doses of nicotine in steps of 5 training sessions (0.3®0.2®0.1 mg/kg). On test days, hexamethonium (1, 3, 10, 25, and 50 mg/kg) at a pre-treatment time of 30 min was administered prior to nicotine 0.4 mg/kg in the standard-trained group, and nicotine 0.1 mg/kg in the faded group. Percentage of drug lever responses were recorded to measure antagonism and analyzed using repeated measures ANOVA. In both the standard-trained and the faded training dose-trained groups, drug lever responses stayed above 80% at all doses of hexamethonium tested. These findings show that increasing the sensitivity of the drug discrimination model by fading the training dose does not increase the propensity of hexamethonium to block nicotine's discriminative stimulus effect. It may also strengthen the argument that the peripheral effects of nicotine do not contribute to nicotine's overall discriminative stimulus effect. Further hexamethonium antagonism studies in naïve rats trained with low dose nicotine need to be conducted.

Poster 45

From drug of abuse to preclinical potential: evaluating the prohedonic efficacy and cognitive deficits associated with MDMA

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In recent years, drugs traditionally associated with abuse potential have increasingly been evaluated for medicinal applications. However, pursuits of this sort demand assessment of their undesirable effects that may dampen clinical utility. Notably, the potential of 3,4-methylenedioxymethamphetamine (MDMA) has been reconsidered due to the promising applications of MDMA-assisted psychotherapy to treat PTSD. With the above in mind, it is vital to understand the potential of cognitive deficits following acute MDMA administration. Anhedonia, the loss of pleasure from previously rewarding stimuli, is a prominent feature that poses a significant challenge across a host of neuropsychiatric disorders, including PTSD. Therefore, the aim of the present study is two-fold: 1) examining the prohedonic efficacy of MDMA and 2) assessing MDMA's potential cognition-disruptive effects at the same doses. Three groups of female and male rats were assigned to either the Probabilistic Reward Task (PRT; n=12, 6/sex), an assay of reward responsivity, the Titrating Vigilance Task (TVT; n=8, 4/sex), an assay of attentional processes, or the Titrating Delay Matching-to-Position task (TDMTP; n=8, 4/sex), an assay of short-term spatial memory. Following steady-state task performance, doses of MDMA (1-10 mg/kg) were administered prior to select test sessions. 3.2 and 10 mg/kg MDMA was shown to significantly increase reward sensitivity in the PRT. Dose-dependent performance deficits were noted in sustained attention and short-term spatial memory using TVT and TDMTP, respectively. Importantly, however, all subjects across all tasks fully returned to baseline performance levels 24 hours post-MDMA administration. The present findings provide a compelling preclinical profile of MDMA as a promising novel prohedonic treatment, notwithstanding some evidence of short-lived cognitive impairment following acute administration.

Poster 46

Effects of voluntary ingestion of low-dose THC on locomotor behavior and cannabinoid receptor 1 expression

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Due to the recent surge in legalization and trending methods of ingesting THC, preclinical models have attempted to investigate the behavioral and neurobiological changes that occur from ingesting THC. The present experiment was designed to investigate behavioral (locomotor) and neurobiological (cannabinoid receptor 1 (CbR1)) changes resulting from ingestion of low doses of THC comparative to human use. We hypothesized that low doses of edible THC would dose dependently increase locomotor behavior and decrease CbR1 expression in the hippocampus (CA1). 47 male Sprague-Dawley rats had access to voluntarily eat THC (low=0.625mg/kg, medium=1.25mg/kg, high=2.5mg/kg) or control (sesame oil) Mini-Oreo wafer cookies every other day. For 8 consecutive trials (every other day for 16 days), rats were placed in locomotor chambers 1-hour after eating their cookies and locomotor behavior was recorded for 2-hours. Immediately after the final session brains were processed for immunohistochemistry staining of CbR1. ANOVA revealed a dose-dependent increase in total distance traveled (cm) for THC rats. Similarly, repeated voluntary ingestion of THC at high doses significantly reduced CbR1 expression in the hippocampus (CA1) compared to the control group. These results suggest that lower edible doses of THC can alter locomotor behavior and CbR1 expression in the CA1 region. Importantly, these results suggest that the development of preclinical edible models of low dose THC consumption translatable to human use can be developed to further our understanding of exogenous cannabinoids

Poster 47

Avoidance learning dysfunction in problem drinking – behavioral and imaging evidence

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Drinking as a pain-avoidance coping behavior plays a central role in problem drinking. Specifically, problem drinkers seek alcohol to alleviate or avoid painful physical and emotional states. As drinking escalates, consumption is progressively driven by individuals' heightened sensitivity to the painful consequences of alcohol intake cessation. Paradoxically, chronic alcohol use heightens pain reactivity which further motivates drinking as an avoidance coping strategy. Over time, this maladaptive behavior becomes increasingly less amenable to cognitive control, trapping drinkers in a spiraling cycle of drinking and distress. Yet, the underlying circuits of avoidance learning in problem drinkers are poorly understood. We acquired fMRI and behavioral data that assessed avoidance learning in 35 human problem drinkers and 40 social drinkers who performed a probabilistic learning go/no-go task. The task involved learning to associate visual cues with outcomes to avoid painful electric shocks and gain monetary reward. We hypothesized that relative to social drinkers, problem drinkers would exhibit (1) poorer avoidance learning, (2) weakened prefrontal cortical activation during avoidance learning; and (3) a link between prefrontal deactivation, impaired avoidance learning rates, drinking-to-cope motive, and drinking severity. Our findings confirmed the hypotheses. Specifically, problem drinkers showed lower learning rates during pain avoidance conditions, coupled with reduced dorsolateral prefrontal cortical activity. Path analysis showed significant relationships between behavioral, neural, and drinking metrics. The current work sheds light on the neural and cognitive processes underlying avoidance learning dysfunction in problem drinking. The characterization of these processes offers further understanding of negative reinforcement drinking in humans, thus bridging the gap with preclinical research.

Poster 48

Exploring substance use in the NIH All of Us research program

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Background/Rationale: The All of Us (AoU) Research Program (NIH) is a public health database that contains data from over 300,000 individuals in the United States, including electronic health records (EHRs), surveys, and genetic information. This program gives researchers access to data from a diverse sample of participants for greater generalizability. Methods: Using the AoU Researcher Workbench, we created a sample of participants (including a matched control sample, N = 45,198) between January 1, 2012, and January 1, 2022, that contained demographic variables and their most recent diagnosis of substance use (including alcohol, cannabis, psychoactives, cocaine, opioids, stimulants, inhalants, and others). SNOMED and ICD-9-CM codes were translated to their equivalent ICD-10-CM codes. Chi-square tests of association were used to explore relationships between nominal variables and regression models will be used to explore the ability of various demographic and health-related variables to predict substance use diagnosis. Results: Those diagnosed with substance use (M = 53.13, SD = 14.0) were significantly younger than those not diagnosed with substance use (M = 55.69, SD = 16.8), t = 17.606, $p < 0.0001$. Significant associations were seen between diagnosis of substance use and physical health ($X^2(5, N = 45,198) = 2,015.7$, $p < 0.0001$, Cramer's V = 0.211), mental health ($X^2(5, N = 45,198) = 2,920$, $p < 0.0001$, Cramer's V = 0.254), and quality of life ($X^2(5, N = 45,198) = 2,772.7$, $p < 0.0001$, Cramer's V = 0.248). Participants diagnosed with substance use rated physical health, mental health, and quality of life as "Poor" more often than those not diagnosed with substance use. Conclusions: Exploring substance use through large, diverse datasets such as AoU allows researchers and health professionals to consider where resources may be placed to better serve those seeking help for substance use.

Poster 49

Fundamental focus on fentanyl in females: sex differences in the behavioral pharmacology of fentanyl

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Aim: Fentanyl (FEN), a synthetic opioid and highly effective mu-opioid receptor agonist, is a major contributor to the growing rates of opioid-related overdoses and deaths. Sex differences in behavioral responses to morphine (MOR) have been reported previously. We now examine whether there are sex differences in behavioral responses to FEN. Findings would provide evidence of a potential driver of FEN addiction vulnerability in women.
Methods: Separate sets of male and female Sprague-Dawley rats were tested for: 1) analgesic responses in hot plate and tail flick tests; 2) locomotor activity in an open field (30-m); and 3) schedule-controlled responding under a fixed-ratio 15 (FR15) schedule of food pellet delivery (30-m). Analgesia responses and locomotor activity were assessed 30-m after administration of saline, 0.05 and 0.1 mg/kg (SC). Several doses of both FEN (0.003- 0.1 mg/kg) and morphine (0.3-10 mg/kg) were assessed in the schedule-controlled responding study 30-m after administration. Results: Analgesic responses showed significant Sex, Dose, and Sex X Dose effects for both tail flick and hot plate tests (P's< 0.01). Latencies were lower in females compared to males across FEN doses, but no differences were seen at baseline. No sex differences were found in distance traveled. Schedule-controlled responding rates decreased across FEN and MOR doses but there were no sex differences.
Conclusions: While FEN has a high analgesic potency, females uniquely showed increased analgesic responses compared to males. Yet, FEN did not alter activity effects differently between the sexes. These results mirror those reported from MOR behavioral responses in rats.

Poster 50

A novel DSM-V based model of alcohol use disorder in mini pigs

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Alcohol Use Disorder (AUD) is a chronic, relapsing condition characterized by lost control over alcohol intake despite adverse social, occupational, or health consequences. Preclinical AUD research has predominantly used rodent models. A gap in the field is there are no non-primate animal models that satisfy the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) criteria for diagnosis of AUD. Ideally, safety of therapeutics should be evaluated in multiple mammalian models before FDA approved clinical trials in humans. Given the significant biological and physiological similarities of pigs to humans, including drinking to intoxication, we developed DSM-V based diagnostic tools with good face validity and hypothesized that minipigs would reach criteria for AUD. Using a within-subject design, 11 custom-made DSM-V criteria-based tests of AUD were established. To date, 7 of 11 measures have been evaluated, and all 5 pigs meet AUD criteria. Every animal drank to intoxication (p=0.0001) with a blood alcohol concentration higher than 0.8 mg/ml and showed greater than 80% preference at all concentrations (p<0.002). As predicted, as ethanol concentration increased, all pigs showed impaired motor coordination on the agility test (p=0.0013). However, four of five pigs showed craving after deprivation (>50% increase upon reinstatement). Pig 2 and Pig 5 had decreased home pen recreational activity by ~65%. Pig 2 and Pig 4 showed physiological withdrawal symptoms. A full severity assessment will be completed when the remaining 4 criteria are tested. Our results highlight that the minipig may be a highly translationally relevant model species for pre-clinical evaluation of therapeutic strategies for AUD.

Poster 51

Hair cortisol levels among individuals seeking prenatal health care in the US-Mexico border region.

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Maternal stress is associated with a range of adverse health outcomes (e.g., gestational diabetes, preeclampsia). Pregnant individuals living in border communities might further experience unique instances of heightened stress due to complexities related to immigration and border policies. To explore this in the present study, medical information (obtained following the signing of a HIPPA release) for 113 pregnant individuals in the El Paso region were explored. Participants also had the voluntary opportunity to provide hair samples (collected during the first trimester) and self-reported surveys assessing sociodemographic variables, health history and measures of emotional distress. A subset of 62 participants with viable hair samples were assessed, and of this group, five had a diagnosis of type 2 diabetes, and 13 individuals developed gestational diabetes during pregnancy. Medication use was reported for 14 participants, and this included medication used for type 2 diabetes (among 5 participants), as well as medication for anxiety or depression (among 8 participants). While no illicit drug use was reported, one individual was taking a prescription stimulant during the study. A total of 14 of these 62 individuals developed preeclampsia during pregnancy, and a total of 6 patients contracted COVID-19 while pregnant. This study is ongoing, and hair cortisol levels (which serve as a biomarker of long-term stress) are being analyzed using an ELISA kit. This project will provide insight into the relationship between stress and other health outcomes among pregnant individuals living in a US-Mexico border community. This work is funded by a National Science Foundation Senior Researcher Grant #1947551.

Poster 52

The role of dorsal striatum dopamine D1 receptors in Methamphetamine (METH) self-administration in male and female Long Evans rats is METH experience-dependent

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The role of dorsal striatum dopamine D1 receptors in the mechanism of methamphetamine self-administration (METH SA) is not very clear. We hypothesised that METH experience might regulate the role of striatal dopamine D1 receptors in METH SA. To test this, we designed experiments to examine the relationship between prior methamphetamine intake (0.1 mg/kg/injection) and the effects of dopamine D1 receptor inhibition, using chemogenetic-mediated methods (Clozapine-N-Oxide, CNO, 1 mg/kg i.p.), on subsequent methamphetamine self-administration in male and female dopamine D1 transgenic rats. We defined methamphetamine experience as cumulative intake during training and measured the effect of inhibition on weekly intake using normal mixtures clustering, regression analysis and ANOVA. Normal mixtures cluster analysis identified groups with low and high METH experience. Regression analysis revealed that the effect of CNO on METH SA was related to prior METH experience with no sex differences. One-way ANOVA revealed that the effect of CNO in the high METH, but not the low METH group was significantly different from the control group. We conclude that Dopamine D1 receptors in the rat dorsal striatum play a role in controlling METH SA in a METH experience-dependent but sex-independent fashion.

Poster 53

Effects of serial polydrug use on the rewarding and aversive effects of the novel synthetic cathinone eutylone

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The affective properties of drugs are impacted by a host of experiential and subject factors, consequently influencing their abuse vulnerability. One such factor is drug history (i.e., serial interactions), a factor especially relevant to the use and abuse of the synthetic cathinones which are often used with other drugs. The consequences of such polydrug use, however, are not well characterized. In this context, the goal of the present study was to investigate the impact of a history with cocaine or MDMA on the aversive and rewarding effects of the novel synthetic cathinone eutylone. Given the neurochemical actions of these compounds (dopamine reuptake inhibition and/or serotonin substrate releaser), it was predicted that both cocaine and MDMA would affect eutylone's rewarding and aversive effects. Male C57BL/6 mice (n = 96) were exposed to 32 mg/kg of cocaine or 3.2 mg/kg of MDMA every 4th day (for a total of five injections) prior to undergoing a combined conditioned taste avoidance/conditioned place preference design with 3.2, 10 or 32 mg/kg of eutylone. Subjects injected with 10 and 32 mg/kg of eutylone during conditioning displayed significant taste avoidance and place preferences ($p < 0.05$), indices of eutylone's aversive and rewarding effects, respectively. While eutylone-induced place preferences were not impacted by cocaine or MDMA pre-exposure at any dose ($p > 0.05$), eutylone-induced taste avoidance (at 32 mg/kg) was significantly attenuated by both cocaine and MDMA pre-exposure ($p's < 0.05$). Given the importance of the balance of aversion and reward in use and abuse liability, these results suggest that both cocaine and MDMA history could impact vulnerability to eutylone. These findings also argue that serial drug use may be an important factor to examine in populations heavily associated with polydrug use, e.g., those using and abusing synthetic cathinones.

Poster 54

Knocking down orphan G-protein-coupled receptor Gpr12 in the nucleus accumbens shell decreases motivation for cocaine by differentially affecting frustration-related behavior

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The orphan G-protein-coupled receptor (GPCR) GPR12 is a highly understudied protein, but one with tremendous potential for neuropsychiatric conditions. Despite expression of Gpr12 in a limited number of brain regions, suggesting highly specific function, research exploring the role of GPR12 in regulating neuronal activity and behavior is extremely limited. Though endogenous ligands are unclear, some reports have suggested involvement of Gpr12 in regulating brain function via its high constitutive G_s-coupled activity. The combination of multiple transcriptomic analyses led us to identify Gpr12 as a target of interest in the context of substance use disorders (SUDs). The use of electrophysiological assays revealed that Medium Spiny Neurons of shGpr12 rats exhibit lower intrinsic excitability compared to controls, which would predict a protective behavioral phenotype. We confirm the involvement of shNAc Gpr12 in regulating motivation-related behaviors in operant tasks, likely by increasing frustration-related behavior (as measured via barpress durations). We find specifically that Gpr12 knockdown differentially increases reinforced and non-reinforced frustration-related behavior (i.e. progressive ratio and extinction procedures, respectively) during cocaine self-administration. Exploration of the effect of Gpr12 knockdown in the shNAc on depression-related and anxiety-related behavior is ongoing.

Poster 55

Organic Cation Transporter (OCT3) is crucial for the reinforcing effects of amphetamine

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Rates of stimulant misuse and overdose are continuing to rise, yet there are no targeted or FDA-approved pharmacotherapies to assist individuals with a stimulant use disorder. Recent data suggests that uptake 2 (low affinity, high capacity) transporters such as the organic cation transporter 3 (OCT3) mediate the rewarding effects of amphetamine. However, it is unknown whether OCT3 also mediates the reinforcing effects of amphetamine. Here, wild-type (WT) and OCT3 knockout (KO) mice of both sexes were trained to lever press for presentation of liquid food prior to being surgically prepared with indwelling venous catheters. Mice were then tested in daily, 90 min fixed ratio (FR) 1 sessions in which responding resulted in an infusion of 0.32 mg/kg cocaine. Amphetamine dose response curves were then generated by dose substitution (0.0032-0.32 mg/kg/inf) from a cocaine baseline. Compared to WTs, the dose-response curve for amphetamine was shifted down and to the right in KOs. Separate groups of WT and KO mice were then trained to respond for 0.32 mg/kg/inf cocaine and 0.032 mg/kg/inf amphetamine to evaluate the effects of an uptake 2 inhibitor, decynium-22 (D22, 0.1 mg/kg) on the self-administration of cocaine and amphetamine. Though D22 reduced responding for amphetamine (but not cocaine) in WT mice, it was without effect in KO mice. Finally, WT and KO mice were tested under a progressive ratio (PR) schedule and showed similar levels of responding for 0.32 mg/kg/inf cocaine, but OCT3 KO mice responded significantly less than WT mice when 0.032 mg/kg/inf amphetamine was available. Overall, these data suggest that OCT3 plays a key role in the reinforcing effects of amphetamine and may be a viable target for pharmacotherapies for stimulant abuse.

Poster 56

Medication assisted treatment and sobriety outcomes in child welfare

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Caregiver substance use is a concern for child protection agencies due to the increased risk for child maltreatment. Many Ohio counties have adapted the Ohio START child protection model to address the problem of caregiver substance use and reduce the risk of ongoing trauma for children and families. This study examined the factors affecting sobriety for caregivers participating in Ohio START. Multiple regression analysis was used to explore the relationship between the use of medication-assisted treatment (MAT) and the timeliness of Ohio START referrals with the length of caregiver sobriety at case closure. It was hypothesizing that faster referrals and longer use of MAT would result in increased sobriety at case closure.
Statistical analysis for this project was completed using data from the Ohio START Needs Portal, the primary data collection tool for the Ohio START model. Data is entered into the Needs Portal throughout the life of the case by the child protection caseworker, supervisor, or family peer mentor. The current dataset with the chosen variables included 127, predominantly female, participants. The participants were parents who completed a child protection case plan with an Ohio START team between October 2020 and August 2022.
The combination of days to START referral and months of MAT treatment contributed to the variance in the number of months of sobriety at case closure. Adjusted R-square (.060) indicated that six percent of the variability in months of sobriety at case closure is explained by the combination of months of MAT use and timeliness of the START referral. Additionally, prolonged use of MAT treatment was found to be predictive of extended months of sobriety at case closure when controlling for the timeliness of the START referral (p=.002). For every additional month of MAT use, the months of sobriety at case closure increased by .119 (B=.119), controlling for the number of days to the START referral. This finding has important implications for counties implementing Ohio START. Ensuring access to MAT services should be a consideration as the child protection agencies develop relationships with SUD treatment providers during model implementation. Additionally, child protection agencies may benefit from education regarding the impact of MAT to better understand the benefits of this service for caregivers affected by SUD.

Poster 57

Repeated alprazolam exposure during adolescence induces a stress-resistant phenotype

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Reports show that alprazolam (Xanax; ALP) is the most abused benzodiazepine (BDZ) among adolescents. Studies using adult rodents have demonstrated that repeated exposure to BDZs can lead to adverse effects, including a rebound of anxiety during periods of abstinence. Given that adolescence is a sensitive period of development characterized by enhanced vulnerability to stress and drugs of abuse, we hypothesized that repeated exposure to ALP during adolescence would dysregulate mood-related behaviors in mice. Adolescent male C57BL/6J mice (postnatal day [PD] 35) were pretreated with either vehicle (VEH) or ALP (0.5 mg/kg) once daily from PD 35-49. Twenty-four hours (short-term) after the last ALP treatment, mice were tested on various behavioral assays (i.e., open field test [OFT], three-chamber sociability test, elevated-plus maze [EPM], and the forced swim test [FST]) to assess their sensitivity to stressful circumstances. Mice pretreated with ALP showed a significant increased time spent in the center of the OFT when compared to the VEH- pretreated controls. No differences were observed in locomotor activity. In the sociability test, these mice showed an increase in frequency and time spent in the chamber with a stranger ("stranger side") social target mouse when compared to the opposite chamber ("empty side"), along with a significant decrease in latency to interact with the social target when compared to the VEH-pretreated controls. No significant differences were observed in the EPM test. When exposed to the FST, ALP-pretreated mice showed a significant decrease in time spent immobile, and significantly more time swimming, struggling/wall-climbing when compared to controls. Overall, our results indicate that repeated ALP treatment during adolescence does not induce negative behavioral consequences for up to 24-hours after cessation of treatment.

Poster 58

Age and sex-specific differences in spatial dependent learning in male and female C57BL/6J mice

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Spatial-dependent learning requires functional cognitive ability and is a hippocampal-dependent task. Adolescents and adults likely use different strategies for spatial and nonspatial dependent learning. The Barnes Maze is a cognitive, learning, and memory test used to measure the ability to navigate an environment using spatial cues in rodents. The Barnes maze can also be used to measure cognitive flexibility maintained by the frontal cortex. Previous research in adult animals has shown sex-related differences in spatial learning and navigation. The present study was designed to determine age- and sex-specific differences in spatial learning and memory and cognitive flexibility in adolescent and adult male and female C57BL/6J mice. Adolescent (postnatal day (PNS 28-46) and adult (PND 96-114) were trained for 20 acquisition trials over 10 days, 1 probe memory trial, 6 reversal trials over 3 days, and 1 reversal probe trial. Results indicate that during the initial acquisition trials, there is a clear separation of spatial-dependent learning between female adolescent and adult mice, with adolescent females learning to navigate to the escape tunnel faster than their adult counterparts. A similar, but less robust effect was observed in adolescent and adult male mice. During the reversal learning task, adolescent females continued to show better performance compared to their adult female counterparts. However, in males the differences in performance were not present. Together, these data indicate contrasting manifestations of age-related differences based on sex in both spatial-dependent learning and cognitive flexibility. We will use these data from naive mice as a baseline to continue our work in sex and age-specific alterations in learning and memory following binge alcohol exposure.

Poster 59

Effect of toll-like receptor 3 antagonist on heroin-induced analgesia and hyperalgesia during spontaneous withdrawal in mice

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Although opioids are potent analgesics when taken acutely, chronic use results in the development of hyperalgesia during withdrawal, which may contribute to continued drug taking. Increasing evidence indicates that opioid use activates neuroimmune pathways that promote the expression of inflammatory mediators, which in turn can lead to increased nociceptive states that may further drive continued drug taking. Toll-Like-Receptor 3 (TLR3) is a component of one such pathway, and its potential role in opioid-related changes in nociceptive states remains unknown. Thus, in our study we utilized a novel TLR3 antagonist, CuCPT4a, to investigate the role of TLR3 in a mouse model of heroin-induced analgesia and hyperalgesia during withdrawal. First, we performed a pharmacokinetic study and determined that CuCPT4a crosses the blood-brain barrier and that its half-life is approximately 2 h. Acute administration of CuCPT4a had no significant effect on heroin-induced analgesia as assessed using a hotplate test. Similarly, acute CuCPT4a administration did not cause an effect on thermal hyperalgesia during heroin withdrawal as measured by a coldplate test. Using a schedule of repeated CuCPT4a administration, we observed a trend towards a decrease in hyperalgesia during heroin withdrawal in both the cold plate test of thermal hyperalgesia and the Von Frey test of mechanical hyperalgesia. Finally, we observed in a pilot experiment that the continuous administration of CuCPT4a via subcutaneously implanted osmotic minipumps may attenuate hyperalgesia. Ongoing work is focused on replicating these findings, exploring potential molecular markers of these effects, and characterizing the dynamics of CuCPT4a in both the brain and plasma.

Poster 60

Locomotor depressant effects of four novel hallucinogens

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Despite the efforts of the Drug Enforcement Administration (DEA) to safeguard the public from hazardous analogs of synthetic hallucinogens, they have increasingly been observed in the illicit drug market. As an initial step in characterizing their safety and abuse liability, we evaluated 4 substituted phenethylamine hallucinogens (25B-NBOH, 25C-NBOH, 25E-NBOH and 25I-NBOH) for their ability to modify spontaneous locomotor activity in mice, in comparison to a known abused hallucinogen, 2,5-dimethoxy-4-methylamphetamine (DOM). Separate groups of 8 male Swiss-Webster mice were tested for the time-course of their locomotor activity following intraperitoneal injections of vehicle (deionized water) or different doses of each compound, within Digiscan locomotor activity testing apparatus housed in sound-attenuating chambers. Within 10 minutes following injection, the abused hallucinogen DOM produced dose-dependent locomotor depression lasting up to 100 minutes (ED_{50} = 4.8 mg/kg). Each of the substituted phenethylamines produced maximal depression of locomotor activity equivalent to DOM, with similar onset and time course. The compounds differed in potency for this effect, with 25B-NBOH, 25C-NBOH, and 25E-NBOH having potency slightly lower than DOM (ED_{50} = 8.1, 8.6, and 8.7 mg/kg respectively) whereas 25I-NBOH was markedly less potent (ED_{50} = 20.0 mg/kg). The locomotor depressant effects were similar in magnitude and potency to the 25X-NBOMe phenethylamines established as hazardous synthetic hallucinogens. Funding for this study was provided by NIDA contract N01DA-18-8908.

Poster 61

Respiratory effects of the novel $GABA_A$ modulator TPA023B in combination with opioids using whole-body plethysmography in rats

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Opioids and benzodiazepines are commonly prescribed medications to treat pain and anxiety disorders, respectively, but both drugs are associated with clinically significant respiratory depression. Moreover, opioid-benzodiazepine combinations have been reported to result in enhanced respiratory depression relative to the drugs alone. We evaluated the effects of the novel $GABA_A$ positive modulator, TPA023B, alone and combined with opioid agonists, on respiratory function using whole body plethysmography (WBP). TPA023B is an a2/3/5$GABA_A$ selective partial allosteric modulator, and it is a potential candidate for the long-term treatment for anxiety disorders. Adult male Sprague-Dawley rats were implanted with chronic catheters into the internal jugular vein under isoflurane anesthesia. Rats were habituated to the WBP apparatus, and respiratory parameters (frequency, tidal volume, and minute volume) were recorded for 50 min. TPA023B (0.03-1.0 mg/kg), buprenorphine (0.3-10 mg/kg) or oxycodone (0.3-5.6 mg/kg) were tested alone, with the latter two drugs re-tested following pretreatment of TPA023B (1.0 mg/kg). TPA023B and buprenorphine alone had no significant effects on respiratory parameters compared to vehicle, whereas oxycodone suppressed both frequency and minute volume parameters. Pretreatment with TPA023B did not alter respiration parameters when combined with buprenorphine and did not alter the respiratory depressant effects of oxycodone. These results provide support for development of TPA023B as a safe and effective medication for treatment of anxiety disorders and provide evidence that this compound may have reduced respiration-associated overdose risk in combination with opioids.

Poster 62

The effects of Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, on the expression of methamphetamine preference in adolescent male rats

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Methamphetamine (METH) use is especially damaging in adolescence as early initiation leads to poorer treatment outcomes. Currently, there are no FDA-approved treatments for stimulant use disorder. Preclinical studies have shown that Liraglutide, an FDA-approved drug that activates glucagon-like peptide-1 (GLP-1) receptors, lessens the rewarding effects of cocaine, heroin, and oxcyodone. However, the role of activating GLP-1 receptors on METH reward has not been examined, nor has it been examined in adolescent rats. Thus, the present study investigated whether stimulating GLP-1 receptors with Liraglutide, decreases METH-seeking behavior in adolescent male rats. Male Sprague-Dawley rats underwent a 10-day conditioned place preference (CPP) procedure, a validated animal model of drug reward. During day 1, baseline, rats were assessed for initial side preference in a two-chamber-sided box. Conditioning days took place over the next 8 days, during which rats had alternating drug and saline treatment sessions. Rats were administered METH (0.0, 0.3, or 1.0 mg/kg) or saline on their respective days and immediately confined to one side of the CPP box for 30 min. On day 10, testing, the rats were pretreated with Liraglutide (1.0 mg/kg) or saline 60 min before being placed into the box with free access to both sides for 15 min. A prefrence score was computed by taking the time spent in the drug-paired side during testing minus the time spent in the same compartment during baseline. Moreover, changes in the time spent on the METH-paired side between baseline and testing wtihin each group was also examined. Overall, rats exhibited a preference for the METH-paired side during testing, and this preference was not attenuated by pretreatment with Liraglutide. Additional studies examining the effects in females and the effects of Liraglutide on the acquisition of METH are needed, given the feasability of Liraglutide, an FDA-approved drug, in the treatment of substance use disorder.

Poster 63

Modifications to DAT-inhibiting bis(4-fluorophenyl)methyl)sulfinyl)alkyl alicyclic amines that improve metabolic stability and retain an atypical profile

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Atypical dopamine transporter (DAT) inhibitors have shown therapeutic potential in preclinical models of psychostimulant use disorders. In rats, 1-(4-(2-((bis(4-fluorophenyl)methyl)sulfinyl)ethyl)-piperazin-1-yl)-propan-2-ol (**JJC8-091)** was effective in reducing the reinforcing effects of both cocaine and methamphetamine but did not exhibit psychostimulant behaviors itself. Improvements in DAT affinity and metabolic stability were desirable for discovering pipeline drug candidates. Thus, a series of bis(4-fluorophenyl)methyl)sulfinyl)alkyl alicyclic amines were synthesized and evaluated for binding affinities at dopamine and serotonin transporters. Replacement of the piperazine with either a homopiperazine or piperidine ring system was well tolerated at DAT (K_i range = 3-180 nM). Importantly, several analogues (**TCK-3-2, AVO-01-32, TCK-3-60,** and **AVO-01-61**) showed improved metabolic stability in rat liver microsomes as compared to previously reported compounds. In addition, lead compounds **TCK-3-2** and **TCK-3-60** also appeared to retain an atypical DAT inhibitor profile, evidenced by negligible locomotor activity in mice at doses up to 30 mg/kg and molecular simulations that predict the binding of these two compounds to a more inward-facing conformation of DAT, similar to **JJC8-091**.

Poster 64

Retrieval+Extinction prevents alcohol seeking behavior in female rat model of alcohol dependence

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During alcohol consumption, discrete cues precede alcohol availability. These discrete cue-alcohol pairings can lead to a conditioned behavior over time. Cue-elicited alcohol-seeking behavior can promote relapse. Extinction-based therapies reduce behavioral cue reactivity but extinguished behaviors return under certain conditions a phenomenon that may be due to the formation of a new competing memory rather than modifying the original one. A proposed alternative approach is the retrieval+extinction (R+E) paradigm in which extinction is conducted after the original memory is retrieved and the reconsolidation process has begun. We previously showed that R+E reduces the return of alcohol-seeking behavior in male rats with a history of alcohol dependence. The aim of the present study is to test the R+E paradigm in a female rat model of alcohol dependence. Female Long-Evans rats (n=42) were induced to consume unsweetened alcohol (15%, 15E) over 15 sessions with the choice of two bottles (one 15E and one water) on a MWF schedule. Then, they were either exposed to chronic intermittent ethanol vapor (CIE) over 10 days to induce physical dependence or control air. After withdrawal recovery, rats received 12 Pavlovian conditioning sessions where a light-cue was paired with a sipper containing unsweetened 15E. Rats were then assigned to either standard extinction (Ext) or R+E groups and underwent appropriate 14 extinction sessions resulting in 4 experimental groups: air-R+E (n=12), air-Ext (n=9), vapor-R+E (n=10), vapor-Ext (n=11). Relapse-like return of cue-elicited alcohol-seeking behavior was tested after 48hrs. A two-way ANOVA was performed and showed rats in the R+E groups, regardless of history of ethanol exposure, did not show significant return of sipper site approach behavior. Therefore, the R+E paradigm is effective at preventing return of conditioned alcohol-seeking behavior in female rats with a history of alcohol dependence.

Poster 65

Assessing the efficacy of pharmacotherapeutic agents on reducing the excessive nicotine intake observed in diabetic rats

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Diabetes and nicotine use are major public health concerns that lead to compounded health consequences. Clinical evidence suggests that individuals with diabetes often continue to smoke despite negative health effects and they have more difficulty quitting than their non-smoking counterparts. This problem appears to be worse in women with diabetes who report more anxiety during withdrawal and lower cessation rates as compared to their male counterparts. Diabetes is characterized by a disruption in insulin signaling that results in the development of insulin resistance (IR). A major goal of our laboratory is to employ rodent models to study the complex interaction between insulin resistance and nicotine use. The goal of this project was to examine the efficacy of clinically approved medications for diabetes on excessive nicotine intake observed in IR rats. To address this issue, female and male Wistar rats received a high-fat diet (HFD) or a regular diet (RD) for 4 weeks. At the end of the feeding period, the rats received a low dose of streptozotocin (STZ) at a dose that damages pancreatic beta cells and rapidly induces IR. Rats were then given extended (23-hour) access to self-administration of increasing doses of nicotine with 3 intermittent days of abstinence. We then tested the efficacy of 3 different medications used clinically to alleviate IR. Specifically, nicotine self-administration behavior and blood glucose levels were assessed following repeated administration of bromocriptine (10 mg/kg, IP), then dapagliflozin (10 mg/kg, IP) and finally insulin (0.75 U/kg, IP). The injections were administered at 6 pm at the onset of their night cycle. The results revealed that the highest level of nicotine self-administration was evident in a cohort of HFD female rats that displayed IR as compared to obese female and male rats that did not display IR. Our results also revealed that both bromocriptine and dapagliflozin increased nicotine self-administration behavior. Interestingly, the increase in nicotine intake observed in the IR rats was normalized to control levels following insulin administration. This work suggests that a disruption in insulin signaling promotes nicotine intake in a sex-dependent manner. Also, our findings highlight the possibility that certain medications used to treat diabetes may have an unexpected consequence of increasing nicotine use.

Poster 66

Pharmacokinetic profile of the reinforcement enhancing effects of THC in rats

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Cannabis use has increased as prohibition is repealed at the state level, but establishing a pre-clinical THC self-administration model has been difficult. We hypothesized that THC would have reinforcement enhancing effects comparable to caffeine and nicotine. To test this hypothesis, we investigated the effects of experimenter-administered THC in male and female rats. Rats were shaped to respond at a nose key for saccharin under a progressive ratio (PR) schedule to measure motivation. Rats were pretreated with THC (0, 0.05, 0.1, 0.3, or 0.5 mg/kg, IP) 15 min before testing; a 72 h washout period was enforced between repeated THC injections. There were no differences in M and F nose pokes or saccharin reinforcers earned. THC injections (0.1, 0.3, 0.5 mg/kg) increased motivation for saccharin from baseline for both M and F rats ($p<0.05$). To further characterize the time course of the reinforcement enhancing effects of THC we injected rats with 0.5 mg/kg (peak dose) at different intervals before testing. Enhancing effects were measurable when rats were injected 15, 30, or 60 min before testing, but not 120 min before testing. The peak of this time-response curve was approximately 30 min. In a previous pilot study, we identified a reduction in the enhancing effects of THC when injections were repeated every 24 h, therefore we directly tested the hypothesis that this procedure could reduce motivation for SACC. To test this hypothesis male and female rats were injected with the peak dose (0.5 mg/kg) at the peak interval (30 min) every 24 h, over 8 consecutive days; data were converted to (2-session blocks). After a 72 h washout period the rats received an additional 4 tests with 0.5 mg/kg, separated by a 72 h washout period. Daily testing caused a define in motivation that was statistically significantly during the last 4 test sessions ($p<0.05$). These studies detail important parametric and pharmacological considerations for measuring the reinforcement enhancing effect of THC. These parameters and the enhancing effects of THC may aide in development of volitional models of THC intake.

Poster 67

Medication development for alcohol use disorder: evaluation of a minocycline analog

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Alcohol Use Disorder (AUD) is prevalent worldwide, yet less than 10% of patients receive medication for treatment. We modified minocycline to remove antimicrobial activity while retaining reduction in alcohol consumption and anti-inflammatory activities. Results of the evaluation for the lead analog, butylether minocycline (BEM) were: BEM reduced alcohol consumption in a dose responsive manner with no significant reduction in water intake or change in ethanol metabolism. MTT assays indicated BEM had an IC_{50} of 125 µM compared to minocycline at 50 µM (2.5 fold reduced cytotoxicity). Lack of mutagenic potential was confirmed using an AMES test. *In vitro* Caco-2 permeability studies revealed high permeability. *In vitro* intestinal and microsomal stability assays identified that BEM is stable in the GI and had a half-life of over 1hr. Protein binding assays identified no significant hERG channel binding, but showed affinity for several neurotransmitter receptors that participate in addiction processes and other psychological conditions. Overall, BEM showed preferred drug-like characteristics in terms of efficacy, solubility, permeability, stability, and half-life. High hydrophilicity and permeability of BEM makes it a class 1 drug according to Biopharmaceutical Classification System, the most desirable class of pharmaceuticals. Our results confirmed that BEM is an excellent lead candidate for AUD and additional pharmacokinetic and toxicity tests are ongoing for submission of an IND to the FDA.

Poster 68

Molecular signaling pathways in the hippocampus of rhesus monkeys with chronic alcohol use

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Context-induced relapse is a major problem limiting recovery from alcohol use disorder (AUD), with the hippocampus being critically involved in contextual reward memories. The present study is examining the molecular pathways altered following chronic alcohol use in hippocampus samples from rhesus monkeys. RNAseq analysis was conducted on frozen hippocampal samples from adult, male rhesus monkeys with a history of chronic alcohol use (n=7) or no alcohol use (n=5) to assess changes in the molecular signaling pathways in the hippocampus. Differential gene expression analysis and gene ontology pathway analysis were conducted. A targeted pathway analysis was utilized on L-type calcium channel signaling pathways and GABA receptor signaling pathways. We identified 796 differentially expressed genes including several genes implicated in GWAS studies such as GLP2R and GABBR2. Targeted pathway analysis identified downregulated expression of several GABA receptor genes including the GABAA receptor β2 subunit and GABBR2 but lack of changes in L-type calcium channel genes. The current results identify molecular pathways that may serve as future targets for development of pharmacotherapies for context-induced relapse and point to pathways involved in GABA signaling, mitochondrial function, synaptic regulation and genetic factors associated with AUD.

Poster 69

The effects of eating a traditional high fat or a ketogenic diet on sensitivity of rats to the antinociceptive effects of morphine

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Patients with obesity are prescribed opioid medications at a higher rate than the general population; however, it is not known if eating a high fat diet might impact sensitivity of individuals to these medications. To explore the hypothesis that eating a high fat diet would increase sensitivity of rats to the effects of morphine, 24 female Sprague Dawley rats (n=8/diet) ate either a standard laboratory chow (17% kcal from fat), a ketogenic chow (90.5% kcal from fat), or a traditional high fat/high carbohydrate chow (60% kcal from fat). Morphine-induced antinociception was assessed using a warm water tail withdrawal procedure, during which latency (in seconds) for rats to remove their tail from warm water baths (40, 50, or 55°C) following saline or morphine (0.32-56 mg/kg, IP) injections was measured. Morphine was administered under acute conditions as well as following chronic exposure (e.g., to induce tolerance), which involved 19-days of twice daily injections (increasing in ¼ log dose increments every 3 days: 3.2-56 mg/kg). Warm water tail withdrawal latencies were analyzed using a two-way mixed model ANOVA with diet and dose as factors. ED_{50} values determined from individual antinociception dose-response curves were also examined and analyzed using a two-way mixed model ANOVA with diet and week as factors. When tested under acute conditions, morphine induced comparable antinociception in rats eating different diets, and all rats developed tolerance after chronic morphine exposure. However, tolerance was greater among rats eating standard chow and high fat chow, as compared to rats eating ketogenic chow. These results indicate that eating a ketogenic diet could reduce the severity of the tolerance development among patients taking opioid medications.

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Poster 70

Locomotor effects of ring-substituted arylcyclohexylamine analogues of phencyclidine, eticyclidine and ketamine in NIH Swiss mice

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Several arylcyclohexylamine drugs (ACXs) were developed as anesthetics in the 1950s, but became widespread drugs of abuse by the mid-1960s. Phencyclidine (PCP) was the first synthetic psychoactive drug to be abused, and as the popularity of PCP waned, its analogue ketamine became associated with 1990s dance culture and remains a common "club drug" to this day. More recently, novel ACXs have appeared on the illicit market, driven by their relative ease of synthesis and the chemical scaffold's versatility, allowing clandestine chemists to tailor the pharmacological profile of each analogue. In these studies, we determined dose-effect curves for locomotor effects of PCP and 4 ring-substituted analogues, eticyclidine (PCE) and 2 ring-substituted analogues, and ketamine (KET) and 2 novel analogues in NIH Swiss mice. Because locomotor effects of the ACXs are less well-characterized than those of dopaminergic stimulants, we compared their effects to those of methamphetamine (METH), MDMA, and two novel MDMA analogues. PCP and 3-Cl-PCP elicited robust locomotor effects which were of larger magnitude than those of METH and MDMA, but –OH and –MeO analogues of PCP had reduced locomotor effects as compared to the parent drug. PCE and its –OH and –MeO analogues elicited similar dose-dependent locomotor effects which were less than those observed with PCP, but similar to those of METH and MDMA. Ketamine elicited motor incoordination, but no locomotor stimulant effects were observed at any dose. In contrast, deschloroketamine and 2F-deschloroketamine elicited dose-dependent locomotor stimulant effects which were less than those observed with PCE and its analogues, METH and MDMA.

Poster 71

Medial prefrontal and insular cortex activity during a distress tolerance task using in vivo electrophysiology in male and female rats which undergo cocaine self-administration

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Distress tolerance (DT) is the behavioral ability to persist in challenging, goal-directed activity while experiencing stress-inducing factors. Individuals with low DT exhibit heightened drug-seeking behavior and a tendency to relapse. The medial prefrontal (mPFC) and insular (INS) cortex are brain regions that have been implicated in drug-seeking. However, no preclinical studies have examined the neural activity of these brain regions in tandem during DT and linked this activity to drug seeking. We hypothesize that mPFC cell firing and INS-mPFC connectivity during the DT task will correlate with subsequent cocaine seeking and taking and that a history of cocaine self-administration will disrupt this activity and connectivity. To investigate this, a Neuropixel dual-probe fixture implanted in the INS and the infralimbic (IL), prelimbic (PrL), and anterior cingulate cortex (ACC) regions of the mPFC was used to record neuronal activity in freely behaving male (n=1) and female (n=1) Long Evans rats during a DT task. Subsequently, rats underwent an elevated plus maze (EPM) test and 2 weeks of cocaine self-administration for 6 hr/day. Animals then began a 1-month period of experimenter-imposed abstinence after which DT, EPM, and neural activity were reassessed. We used chi-square analyses to assess differences in neural activity across brain regions and experimental groups. Our data suggest a trend for IL neurons to have a more excited profile than PL neurons during the DT task. Collectively, these data support existing research demonstrating a role for the mPFC in DT and future work will expand upon these findings by assessing drug-seeking and INS-mPFC connectivity.

Poster 72

Rat strain differences in opioid addiction-like behaviors

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Due to the growing concerns of the opioid crisis in the U.S., there is an urgent need to develop better treatments for opioid use disorder (OUD), which requires a better understanding of its biological basis. Genetic variation is one of the most important factors that may contribute to individual differences in susceptibility to OUD, which also has huge implications for clinical practices. Here, we performed a behavioral screening in four inbred rat strains (ACI/N, BN/SsN, WKY/N, and F344/N) to identify strain differences in motivation to seek oxycodone during abstinence and other behavioral traits relevant to OUD. We used extended access to intravenous oxycodone self-administration (12 h/day, 150 μg/kg/inj) as a model of OUD. We used a fixed ratio schedule of reinforcement to measure the escalation of oxycodone self-administration and a progressive ratio schedule of reinforcement to measure the motivation in drug-taking. Moreover, we included additional behavioral assays to measure traits associated with opioid use in humans, including tolerance to the analgesic effects of oxycodone (tail immersion test), withdrawal-induced hyperalgesia (von Frey test), and oxycodone-induced respiratory depression (pulse oximeter). Finally, we measured oxycodone seeking during protracted abstinence (4 weeks) by re-exposing the animals to the same environment and cues previously associated with oxycodone self-administration, but without oxycodone availability. The results showed strain differences in most of the measures including oxycodone metabolism. Interestingly, BN/NHsd and F344/N had similar drug intake and metabolism but showed significantly different behaviors in response to opioids. Overall, these findings offer a foundation for the identification of genetic and molecular variants that underlie different aspects of the opioid addiction process not related to metabolism or intake.

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Poster 73

Prefrontal neural signals of opioid-induced risk-taking or risk-avoiding behavior in rats

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Opioid use disorder occurs alongside impaired risk-related decision-making, but a causal neural mechanism is unclear. In a conditioned place preference protocol, rats received alternating morphine or saline injections for 10 days (5 pairings each). Rats underwent a preference test followed by a conflict test in which aversive cat odor was placed in the drug-paired side. In the preference test, the morphine group showed increased time spent in the drug-paired side. In the conflict test, the saline group avoided the side of the apparatus containing cat odor. In contrast, the morphine group continued to prefer the drug-paired side despite the presence of cat odor. K-means clustering identified two subsets of morphine-treated rats that exhibited either persistent drug seeking (risk-takers, RT) or increased avoidance (risk-avoiders, RA) during conflict. Single-unit recordings from the prelimbic (PL) cortex revealed decreased neuronal firing rates upon acute morphine exposure in both RAs and RTs. However, the final injection failed to suppress firing rates. Preference test recordings uncovered subpopulations of neurons that were either excited or inhibited when rats in all groups entered the paired side. Interestingly, while cells inhibited during paired side entries in the preference test did not respond during conflict in saline or RA rats, these inhibitory responses persisted in RTs. Additionally, RTs showed greater proportions of neurons that responded differently to paired-side entries in the preference vs. conflict tests. Our results suggest that a loss of PL inhibition after opioid conditioning is associated with the formation of contextual reward memory. Furthermore, persistent inhibitory signaling of the drug-associated context in PL during conflict may underlie increased risk taking following opioid exposure.

Poster 74

Effects of self-administered alcohol on actigraphy-based sleep measures in rats

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Alcohol causes sleep disruptions, and sleep disruptions can increase relapse risk in individuals with Alcohol Use Disorder (AUD). This study used actigraphy-based sleep measures and alcohol self-administration in rats to investigate the relationship between alcohol and sleep disruption. Wistar rats (5 per sex) were surgically implanted with E-mitter transponders to track activity then were trained to orally self-administer alcohol under a fixed-ratio schedule of alcohol delivery using a sucrose fading procedure. On the final stable day of each step of the sucrose fade, actigrams for each rat were generated. Total activity and parameters associated with inactivity (i.e., <10% of the maximum activity count) were determined in 5 min epochs during the acute dark phase (first 5h after self-administration), the light phase (12h), and the extended dark phase (6h before next session). Data analysis included a two-way RMANOVA for total activity (Phase x Step) and one-way RMANOVAs for parameters of inactivity. Alcohol primarily affected the inactive (i.e., light) phase by increasing activity counts compared to sucrose alone. The increase in activity was not alcohol dose-related. In the light phase, exposure to alcohol decreased the time spent inactive and shortened the longest bout of inactivity. These significant effects appeared to reflect days of exposure, rather than dose. However, in the extended dark phase, dose was negatively correlated with # of inactive bouts and positively correlated with latency to first inactive bout. The results indicate that alcohol alters actigraphy-based sleep measures in phase and time-related ways. The net effect of the alterations is a disruption of inactivity parameters that suggests alcohol disturbs normal sleep patterns. Our results corroborate and extend clinical findings and reinforce the need for addressing alcohol-induced sleep problems as an aspect of AUD treatment.

Poster 75

Behavioral economics of polysubstance use involving cocaine, fentanyl, and mixtures of cocaine + fentanyl in Sprague-Dawley rats

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The co-use of stimulants and opioids has become increasingly evident in recent years, yet few studies have systematically investigated the reinforcing effects of cocaine-fentanyl mixtures. Behavioral economic demand analyses provide a translational approach to quantify the relative value of drug reinforcers across different classes (stimulant vs opioid), making it a viable method to help ascertain factors which promote polysubstance use in humans. The current study used a multiple component schedule of drug self-administration to assess economic demand for cocaine (0.032, 0.1, 0.32, 1.0 mg/kg/inf), fentanyl (0.00032, 0.001, 0.0032, 0.01 mg/kg/inf), and mixtures of cocaine:fentanyl (in 10:1, 3:1, 1:1, 1:3, 1:10) in rats. Available unit-doses of drug increased across each of 4, 20-min drug components, increasing the response requirement (fixed ratio) across sessions. Demand curves for cocaine, fentanyl, and their respective mixtures were generated once consumption (number of infusions earned) was normalized to Q_0 (estimate of unconstrained demand) and plotted as a function of standardized price (FR X Q_0). Elasticity coefficients (α) generated from demand curve analyses were used to assess the relative value of each drug and mixture preparation. The elasticity coefficient of fentanyl was greater than that of cocaine. Similarly, demand for the 10:1 mixture of cocaine + fentanyl was found to be greater than demand for fentanyl alone but comparable to cocaine. Mixtures of 1:3 and 1:10 cocaine + fentanyl produced alpha values that were greater than that of cocaine but not that of fentanyl, further suggesting that interactions may be strictly additive in respect to essential value. Further studies are warranted for a more comprehensive interpretation of the interaction and reinforcing effectiveness of cocaine-fentanyl mixtures.

Poster 76

Impact of chronic neuropathic pain on sucrose-maintained responding in rats

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Chronic pain affects ~20% of the U.S., and opioid analgesics are used, at times, to treat chronic pain. It is unknown if chronic pain alters the potency and efficacy of mu-opioid receptor (MOR) agonists. Thus, the current project evaluated the effects of MOR agonists on food-maintained operant responding in male and female Sprague-Dawley rats in the presence or absence of 6 mo of chronic neuropathic pain induced by spared nerve injury (SNI). Rates of responding were evaluated under a FR10 schedule of reinforcement for 45 mg sucrose pellets in daily, multiple component sessions, each comprised of three, 18-min components. Fentanyl (0.01-0.1 mg/kg), morphine (1-10 mg/kg), and nalbuphine (3.2-100 mg/kg) were evaluated before SNI or sham surgery and 2 and 5 mo post-surgery. Fentanyl dose-dependently decreased rates of responding prior to sham surgery (IC_{50}: 0.022 mg/kg 0.001) and SNI surgery (IC_{50}: 0.019 mg/kg 0.001). Five months after sham surgery, there was no change in the fentanyl IC_{50}s, but there was a small 1.6-fold shift in the fentanyl dose effect curve following SNI surgery. Morphine dose-dependently decreased rates of responding prior to sham surgery (IC_{50}: 3.97 mg/kg 0.24) and SNI surgery (IC_{50}: 4.06 mg/kg 0.58). There was a 1.4-fold shift in the morphine dose effects curve 5 mo after SNI surgery (IC_{50}: 5.37 0.001) but no shift following sham surgery. Nalbuphine decreased rates of responding in a dose-dependent manner prior to sham surgery (IC_{50}: 26.78 mg/kg 2.11) and SNI surgery (IC_{50}: 23.91 2.76 mg/kg). Nalbuphine was less effective at suppressing rates of responding 2 months after either surgery, but this effect was more robust in the SNI condition. Doses up to 100 mg/kg nalbuphine did not suppress responding 5 mo after SNI surgery. Changes in the effects of nalbuphine over time may be due to repeated drug exposure and/or age of the rats. These findings suggest that the presence of chronic neuropathic pain may alter the behaviorally disrupting effects of MOR partial agonists to a greater extent than full agonists.

Poster 77

Altering responding for cocaine-paired cues in the new response acquisition procedure

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One contributor to relapse is the ability of environmental cues that have been associated with drug-taking behavior to evoke drug-craving and -seeking behaviors. Various drugs can increase responding maintained by drug-paired cues following contingent drug self-administration and during reinstatement procedures. We sought to evaluate whether compounds that induce drug-seeking behavior also increase responding for cocaine-paired cues in a stringent test of cocaine conditioned reinforcement (New Response Acquisition). We hypothesized that indirect dopamine agonists and other drugs that induce cocaine-seeking behavior would increase responding for cocaine-paired cues in the New Response Acquisition procedure. This procedure begins with Pavlovian Conditioning in which subjects receive five infusions of cocaine (320 ug/kg/inf) and either simultaneous (Paired) or separate (Unpaired) presentations of a light+tone stimulus per day for 10 days. Then, novel operant manipulanda are introduced into the chamber, and responses produce presentations of cues formerly associated with cocaine (Acquisition). On the fourth day of Acquisition, a drug pre-treatment was administered acutely before the start of the session and responding was evaluated. Consistent with previous findings, subjects in the Paired group make more active responses than inactive responses for cue presentations than Unpaired subjects. Interestingly, drugs that increase responding during reinstatement (cocaine, amphetamine, or nicotine) do not acutely increase responding for cocaine-paired cues under the New Response Acquisition procedure. These data suggest the two behavioral assays to measure the conditioned reinforcing properties of drug-paired cues may evaluate different aspects of conditioned reinforcement with potentially different underlying mechanisms.

Poster 78

Pharmacological and physicochemical properties optimization for dual-target dopamine D_3 (D_3R) and m-opioid (MOR) receptors ligands as potentially safer analgesics

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A new generation of ligands with optimized physiochemical properties were obtained, based on previously characterized dual-target mu opioid receptor (MOR) agonists/dopamine D3 receptor (D3R) antagonists/partial agonists. We identified new structural scaffolds that achieved high affinity and agonist/antagonist potencies for MOR and D3R, respectively, improved the dopamine receptor subtype selectivity (e.g. D3R/D2R), and significantly enhanced the physiochemical properties (MPO scores) of our lead compounds. We identified the substituted trans-phenylcyclopropyl amine scaffold as a key dopaminergic moiety around which we designed this new series of MOR-D3R ligands by tethering it to different opioid scaffolds. We synthesized new pharmacological entities with the potential of maintaining the analgesic effects through MOR agonism, combined with reduced opioid-abuse liability because of D3R antagonism. The new leads have the desired dual-pharmacology. Metabolic studies in rodent liver microsomes showed high stability and current in vivo experiments are underway to measure analgesic properties with reduced addictive liability profiles, for the centrally active compounds. In addition, the derivatives that are more peripherally limited will be evaluated for reduction of opioid induced hyperalgesia, or neuropathic pain via peripheral MOR mechanisms.

Poster 79

Investigating the impact of opioid dependence and withdrawal on economic demand for opioids and stimulants in rats

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Currently, there is an increased prevalence of co-use of opioids and stimulants, highlighted by the increased number of overdose deaths wherein both opioids and stimulants were in the individual's system. However, the impact of opioid dependence and withdrawal on the reinforcing effects of opioids and/or stimulants remains poorly understood. The current study evaluated the effects of opioid dependence and withdrawal on economic demand for fentanyl, methamphetamine, and cocaine. Twenty-four male rats were trained to self-administer fentanyl (3.2 µg/kg/inf), cocaine (0.32 mg/kg/inf), or methamphetamine (0.1 mg/kg/inf) under a fixed ratio 1 schedule of reinforcement. Subsequently, rats were injected with escalating doses of morphine (10-40 mg/kg) twice per day for four days, and thereafter once daily with 40 mg/kg morphine to maintain opioid dependence. Rats were then allowed to self-administer fentanyl (3.2, 10 µg/kg/inf), cocaine (0.32, 1 mg/kg/inf), and methamphetamine (0.1, 0.32 mg/kg/inf) in sessions occurring either 12- or 20-hrs after morphine injections. Response requirements were incremented across sessions until no infusions were earned. Economic demand for fentanyl was greater in rats deprived of morphine for 20-, but not 12-hrs, relative to non-dependent rats. Economic demand for cocaine was reduced in rats deprived of morphine for 12-hrs, whereas demand for methamphetamine was unchanged. In contrast, demand for both cocaine and methamphetamine were reduced in rats deprived of morphine for 20-hrs. Taken together, these data suggest that motivation to use opioids increases as a function of opioid withdrawal, whereas motivations to use stimulants are differentially impacted. Future work will utilize drug-drug choice procedures to investigate the relationship between opioid withdrawal and the reinforcing effects of opioids and/or stimulants.

Poster 80

Intensive momentary assessment of inpatient treatment dynamics in opioid use disorder

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Real-time monitoring methods in which participants are randomly sampled several times a day over an extended period of time offer an effective and efficient means to understand dynamic variations in mood and behavior. Despite the potential to inform a fine-grained view of treatment dynamics, applications within treatment settings are scarce and their value for predicting long-term treatment success all but unknown. This pilot trial was designed to evaluate the feasibility of incorporating intensive, real-time monitoring methods among patients in residential treatment for opioid use disorder (OUD). Participants with OUD completed brief surveys evaluating mood, craving, and decision-making 4 times daily during a 28-day inpatient treatment episode. Participants also wore a wristworn actigraphy and photoplethysmography (PPG) device to continuously monitor heart rate, heart rate variability, sleep, blood oxygen saturation, and respiratory rate. Long-term treatment outcomes include standardized assessment of relapse, mood, and quality of life following treatment discharge. To date, 8 participants have completed the protocol. Feasibility was supported with good compliance (70% of assessments completed; range: 34% to 100%). Analysis of clinical data suggested time-dependent decreases in behavioral economic demand for opioids and opioid craving during the treatment episode. Notably, opioid demand and craving were not closely correlated across treatment consistent with prior studies showing a mechanistic separation between drug use motivation and drug craving. These proof-of-concept data support the feasibility of implementing intensive momentary assessment methods in residential treatment settings. Future studies may use these methods to identify risk phenotypes that may be used to provide just-in-time interventions and triage to higher levels of care.

Poster 81

The intoxicating pathway from incentive salience to cardiovascular dysfunction

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Introduction: Excessive alcohol consumption (AC) is a risk factor for cardiovascular dysfunction (CD). Incentive Salience (IS), the process in which drug-related cues are imbued with motivational salience due to changes in the brain reward circuitry, is a neurofunctional domain in the Addictions Neuroclinical Assessment (ANA) thought to underlie unhealthy AC. Our study seeks to examine if AC mediates the relationship between IS and CD.
Methods: 300 participants with various alcohol consumption behaviors completed the NIAAA natural history protocol and the ANA battery. IS was measured by self-report questionnaires and a behavioral task. CD was quantified using heart rate and both systolic and diastolic blood pressure. We assessed AC with the Alcohol Use Disorders Identification Test-Consumption scores. Factor analyses were conducted to identify the latent factors of the IS and CD. Structural equation modeling was used to model the direct and indirect relationships between IS, AC, and CD. Smoking status, age, race and sex were used as covariates.
Results: A two-factor structure of IS provided the best fit to the data. Those two factors were alcohol motivation (AM) and alcohol insensitivity (AI). The relationship between AM and CD was mediated by AC (indirect effect=0.28, p<0.001). Mediation by AC was also observed in the relationship between AI and CD (indirect effect=0.1, p<0.001).
Discussion: Our results highlight the contribution of IS in the development of CD as a result of AC. These findings can help inform clinical management of CD by way of reducing alcohol consumption. In the future, we will direct our attention towards the pathological effects AC may have on metabolic and neuroendocrine systems.

Poster 82

Physiological effects of binary mixtures of common "bath salts" constituents: studies with MDPV, methylone, and caffeine in rats

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It is becoming increasingly clear that polysubstance abuse is the norm rather than the exception, particularly highlighted by the popularity of "bath salts" mixtures. These mixtures often comprise at least one synthetic cathinone (e.g. MDPV, methylone), in addition to other stimulants (e.g., caffeine). "Bath salts" use has garnered much attention in the popular press due to frequent reports of adverse psychiatric (paranoia, hallucinations) and physiological (tachycardia, hypertension) events leading to large numbers of emergency room visits and/or death. The current studies aimed to characterize the cardiovascular and locomotor effects of MDPV, methylone, and caffeine, and subsequently, to determine the nature of the interactions between binary mixtures of these drugs. Male rats were implanted with an intravenous (IV) catheter and a radio-telemetric probe capable of recording heart rate, blood pressure, and locomotion. Rats were habituated to the test chamber for 1-h before receiving an IV infusion of either MDPV (0.032-3.2 mg/kg), methylone (0.32-10 mg/kg), caffeine (0.32-32 mg/kg), or binary mixtures of these drugs. Recordings continued for 3-h following drug administration. MDPV, methylone, and caffeine produced dose-dependent increases in blood pressure (MDPV > caffeine > methylone), heart rate (methylone > MDPV > caffeine), and locomotion (MDPV > caffeine = methylone). Binary mixtures produced largely additive interactions across all endpoints, with possible departures from additivity observed at the largest dose-pairs evaluated. Taken together, these data are consistent with the physiological effects reported in "bath salts" users. Future work will determine whether the physiological effects of these drug mixtures are mediated by pharmacokinetic interactions between individual constituents.

Poster 83

Effects of Cannabinoid CB_1 agonists on extracellular levels of dopamine in the nucleus accumbens shell of male mice

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While mounting evidence suggests that actions at CB1 receptors modulate dopamine (DA) within the nucleus accumbens shell (nAcc shell)–a key brain region involved in the abuse-related neurobiological actions of most drugs of abuse, the full range of effects CB1 agonist have within the system have not been fully characterized. We utilized in vivo microdialysis and liquid chromatography-mass spectrometry to quantify changes in DA within the nAcc shell of mice administered (i.p.) the synthetic full CB1 agonist AM8936 (0.01-1.0 mg/kg), the synthetic partial CB1 agonist AM11101 (0.1-3.2 mg/kg), or the phytocannabinoid partial CB1 agonist Δ9-THC (0.1-3.2 mg/kg). At lower doses, AM8936, AM11101, and Δ9-THC administration increased extracellular levels of DA within the nAcc shell reaching a maximum of 134%, 140%, and 161% of baseline levels after 0.032, 0.32, and 0.32 mg/kg, respectively. AM11101 and Δ9-THC produced peak increases in DA at 20 minutes post-injection, while AM8936 produced peak DA increases at about 140 minutes post-injection. At 10-fold higher doses, AM8936, AM11101, and Δ9-THC decreased DA to 62%, 72%, and 62% of baseline levels; these decreases persisted until the end of the experiment. The calculated area under the curve for during the peak DA increase for each agonist showed that low doses of AM8936 (0.01-0.032 mg/kg) AM11101 (0.1-0.32 mg/kg) and Δ9-THC (0.1-0.32 mg/kg) increased DA levels, whereas higher doses of AM8936 (0.1-1.0 mg/kg) AM11101 (1.0-3.2 mg/kg) and Δ9-THC (1.0-3.2 mg/kg) decreased extracellular levels of DA. Together, while AM11101 and Δ9-THC DA effects have quicker onset and shorter duration compared to AM8936, CB1 partial and full agonists have similar, biphasic effects on DA within the nAcc shell.

Poster 84

Development of dual KOR/MOR modulators and their effects on fentanyl/cocaine mixture vs. food choice in rats

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Already one of the worst public health crises in history, the opioid epidemic is exacerbated by the rising prevalence of concomitant stimulant/opioid use. Furthermore, there are currently no approved treatment options for patients with stimulant or polysubstance use disorders. We hypothesized that ligands acting as bifunctional kappa opioid receptor (KOR) agonists/mu opioid receptor (MOR) low-efficacy partial agonists will serve as effective medications to treat co-occurring opioid and stimulant use disorders. Novel chemical entities that fit this pharmacological profile were designed, synthesized, and evaluated. Competitive radioligand and [^{35}S]GTPγS binding assays were used to determine binding affinity, selectivity, efficacy, and functional activity for the KOR, MOR, and delta opioid receptor (DOR); identified hits were further tested for their opioid agonism, dose-response, and time-course using warm-water tail immersion assays in male mice (n=6/group). The most promising compound was characterized through self-administration assays to determine effectiveness to reduce fentanyl/cocaine self-administration in male and female rats (n=6-11) using a drug-food choice procedure. Data were analyzed using one-way or two-way ANOVA with the Geisser-Greenhouse correction as appropriate, and significant ANOVA results were followed by post hoc testing. Although the lead compound did not significantly attenuate fentanyl/cocaine choice, fundamental information was obtained to guide future research developments towards polysubstance use disorder treatments.

Poster 85

Mechanisms of Phosphatidylethanol (PEth) formation and degradation

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Phosphatidylethanol (PEth) is a phospholipid used as a biomarker for ethanol consumption, but the mechanisms underlying its formation and elimination are not understood. Current interpretation of PEth is limited by inter-individual variability in detected PEth levels – likely due to heterogeneity of mechanisms of PEth formation/degradation. Phospholipase D (PLD) is the primary enzyme responsible for PEth formation. PEth degradation is thought to occur through different actions of several enzymes including phosphatidylinositol-specific phospholipase C (PI-PLC) and phosphatidic acid phosphohydrolase (PAH). However, the relative role of each isoform (PLD1 and PLD2) in PEth formation and the relative roles of the enzymes involved in PEth degradation is unknown. This study was to determine the relative roles of several enzymes in the formation and degradation of PEth in erythrocytes following ethanol exposure. Enzymes were systematically inhibited in whole blood samples obtained from an alcohol abstaining volunteer. Samples were incubated with physiologically relevant concentrations of ethanol. PEth (homolog 16:0 18:1) concentration was measured using high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS), and Emax and IC50 were determined for each inhibitor. Nonselective PLD inhibition dose dependently prevented formation of PETH. Conversely, PI-PLC inhibition prevented degradation of PEth at moderate inhibitor concentrations, but not at greater inhibitor concentrations. PAH inhibition did not greatly affect PEth degradation. The results support a role of PLD in PEth formation and suggest PI-PLC has more of a role in PETH elimination than PAH. Therefore, PI-PLC activity may underly inter-individual variability observed in PEth elimination.

Poster 86

Dietary probiotic supplements attenuate rate suppressant effects of MDMA in male rats trained on a DRL 18 reinforcement schedule

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The recent emergence of research focused on gut microbiome connections to mental health offers an exciting new prospect for the development of complementary treatments for substance use disorders. Reduced executive functioning and increased impulsivity is associated with psychostimulant abuse. The current study implemented a DRL 18 reinforcement schedule to evaluate whether probiotic supplements would alter drug effects on impulsive action in rats. Eight adult male Sprague-Dawley rats were trained five days a week for several months on a DRL 18 schedule of food reinforcement until responding was stable. Rats were subsequently assigned to two treatment groups, matched on performance measures, and fed daily supplements of an Align® probiotic/Nutella® mixture or Nutella® alone for three months, while training continued three days a week and fecal samples were collected weekly. All rats were assessed following acute injections of saline or MDMA (3 mg/kg) at week 7, 24 hours after binge dosing (5 mg/kg x 4) at week 8, and again after acute injections at week 11. Performance measures remained stable and equivalent between groups throughout dietary treatment prior to injections. In probiotic-fed animals, acute MDMA treatment shifted the interresponse time distribution to the left compared to saline injections, whereas animals fed the control diet displayed an overall response suppression following MDMA injections. These effects did not persist 24 hours after acute or binge treatment at weeks 7 and 8, but response rate suppression did persist in the control diet rats 24 hours after MDMA injection in week 11. While fecal sample analysis is currently ongoing, these behavioral results indicate MDMA's effects on impulsive action may be attenuated by probiotic treatments. In conclusion, the DRL 18 schedule shows promise as a predictive tool to evaluate the effects of gut microbiome manipulations as a means of attenuating drug-induced behavioral changes.

Poster 87

Adolescent fluoxetine exposure increases ERK-related signaling within the prefrontal cortex of adult male sprague-dawley rats

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There has been a disproportionate increase in fluoxetine (FLX) prescription rates within the juvenile population. Thus, we evaluated how adolescent FLX exposure alters expression/phosphorylation of proteins from the extracellular signal regulated kinase (ERK)-1/2 cascade within the adult prefrontal cortex (PFC). Male Sprague-Dawley rats were exposed to FLX (20 mg/kg) for 15 consecutive days (postnatal-day [PD] 35-49). At PD70 (adulthood), we examined protein markers for ERK1/2, ribosomal S6 kinase (RSK), and mammalian target of rapamycin (mTOR). FLX-pretreatment decreased body weight, while increasing PFC phosphorylation of ERK1/2 and RSK, as well as total mTOR protein expression, in adulthood. We provide first-line evidence that juvenile FLX-pretreatment induces long-term decreases in body weight-gain, along with neurobiological changes in the adult PFC – highlighting that early-life antidepressant exposure increases ERK-related signaling markers in later life.

Poster 88

Methylphenidate exposure during adolescence dysregulates second messenger signaling in the prefrontal cortex

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Aim. Methylphenidate (MP) is an amphetamine commonly prescribed to treat attention deficit hyperactivity disorder (ADHD) in adolescents. Research suggests that adolescents with ADHD are at a significantly higher risk of developing substance use and other mood-related disorders such as major depressive disorder (MDD). Evidence indicates that MP pre-treatment enhanced cocaine drug seeking and reward behavior in adolescent and adult rodents, and potentiates addiction related gene regulation. Therefore, the present study was designed to investigate the molecular effects of MP treatment on second messenger signaling within the rodent brain across varying ages and sexes.
Methods. C57BL/6J male and female mice ranging from postnatal day (PD) 21-70 (i.e., 3-, 6-, and 9-weeks old) were treated with either vehicle (VEH) or a clinical dose of MP (2 mg/kg) twice a day for 14 days. The mice were then sacrificed 24 hours after their last drug treatment, and tissue punches from the prefrontal cortex (PFC) were collected for RT-qPCR analysis of mRNA expression. The PFC was selected because it is innervated by neural projections from the mesolimbic dopamine reward system that are essential for mediating reward and mood related behaviors under normal conditions.
Results. The 6-weeks old group of both males and females showed a significant decrease ($p<0.001$; $p<0.01$) of extracellular signaling regulated kinase (ERK2 – a protein kinase modulated by stress and drugs of abuse) gene expression when compared to the VEH-treated controls. Across all age groups, both sexes showed a significant decrease ($p<0.01$) in ERK2.
Conclusions. These data suggest that the repeated MP exposure resulted in similar ERK-related gene expression observed after stress exposure in animal models for depression.

Poster 89

Effects of oral hormonal contraceptives on amphetamine extinction learning in female rats

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Prevailing evidence suggests that increased levels of gonadal hormones, such as estrogens and progestins, play an important role in the maintenance of female substance use disorders; however, little research has been devoted to understanding external factors that alter the natural fluctuation of gonadal hormones in females with substance use disorders. One such factor is the use of hormonal contraceptives (HCs). Previous research in our lab has demonstrated that hormonal implants containing Levonorgestrel (LNG), a synthetic progestin commonly used in HCs, led to a rapid reduction in preference for the amphetamine (AMPH)-associated context (A-AC) over the course of extinction; yet HC implanted females showed reinstatement to the A-AC after a challenge dose of AMPH. The current experiment investigated whether oral administration of LNG during different phases of AMPH-extinction learning would lead to a reduction in extinction and reinstatement of A-AC. To investigate this, female rats underwent AMPH-conditioned place preference and tested for their AMPH-preference for three sessions (served as extinction learning) after receiving either oral administration of LNG (n=7) or tested during an estrous cycle stage associated with higher levels of gonadal hormones (i.e., proestrus/estrus) (n= 8). While both groups initially showed preference for the A-AC regardless of hormonal treatment, females who received LNG showed a non-significant trend towards a decrease for AMPH-preference by the third extinction session. In addition, females who received LNG did not display a disruption of their estrous cycle, unlike what had been previously shown after administration of LNG. Future directions include an increase in LNG dose that leads to a persistent estrous stage associated with lower gonadal hormone levels (i.e., metestrus/diestrus) and a new mode of preparation of LNG to better mirror the administration in humans.

Poster 90

Differential effects of naloxone on reversal of the respiratory depressant effects of fentanyl and fentanyl + methamphetamine mixtures in rats

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Overdose deaths from the concurrent use of opioids (e.g., fentanyl) and stimulants (e.g., methamphetamine) have been increasing in the United States. In 2021, there were over 70,000 overdose deaths attributed to synthetic opioids; almost half of these also involved a stimulant. Though naloxone (NarCan®) is highly effective at reversing the respiratory depressant effects of opioids, it is unclear whether it is equally potent and/or effective at reversing an overdose related to the co-use of opioids and stimulants. Using a collar-based pulse oximetry system, the current study characterized the effects of intravenous (IV) fentanyl (0.0056-0.56 mg/kg), methamphetamine (0.1-1 mg/kg), or a mixture of 0.56 mg/kg fentanyl + 1 mg/kg methamphetamine on measures of SpO2 and heart rate in male and female Sprague-Dawley rats. In order to evaluate the capacity of naloxone to reverse these effects, naloxone (0.01-3.2 mg/kg; IV) or vehicle was administered 5 min after fentanyl, methamphetamine, or the fentanyl + methamphetamine mixture. The effects of fentanyl on SpO2 and heart rate were dose-dependently reversed by naloxone, with larger doses recovering baseline levels of SpO2 and heart rate sooner than smaller doses. The two largest doses of naloxone also produced a rebound tachycardia indicative of a sympathetic overshoot. There was no effect of naloxone treatment on SpO2 or heart rate when it was administered after methamphetamine. Naloxone was less effective at reversing the cardiorespiratory effects of fentanyl + methamphetamine, regardless of dose. Ongoing efforts are evaluating mixtures of fentanyl + cocaine and heroin + methamphetamine in order to determine if similar interactions are observed when fentanyl is combined with other stimulants, and when non-fentanyl opioids are combined with methamphetamine.

Poster 91

The dose-dependent relationship between DOI treatment and food self-administration in rats

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Similar to many drugs of abuse, palatable foods activate the mesocorticolimbic pathway, making them highly reinforcing; this can lead to overconsumption and poor health outcomes. Serotonin (5-HT), a monoamine neurotransmitter, projects widely throughout the same mesocorticolimbic pathway and transduces its signal through a range of G protein-coupled receptors. Multiple 5-HT receptor subtypes regulate reinforcing behaviors, such as the activation of the 5-HT2C, which reduces palatable food consumption but is associated with increased instances of cancer. It is unclear if other 5-HT receptors regulate these behaviors without undesirable effects. We examined the effects of 5-HT2A receptor activation in sucrose and high fat food (HFF) self-administration to determine the extent to which its activation affects motivated behavior. Male and female Sprague-Dawley rats (n=64) were trained to self-administer sucrose or HFF pellets (45% fat, 35% carbohydrate, 20% protein) on a fixed ratio 5 schedule of reinforcement in daily 30-minute sessions. Once stable, rats were pretreated with saline or the 5-HT2A agonist DOI (0.03, 0.1, 0.3 mg/kg; s.c.) before performing the self-administration task in a within-subjects counterbalanced design. Rats were then trained to extinction and tested in a cue-induced reinstatement procedure. DOI treatment dose-dependently decreased sucrose and HFF self-administration, as well as cue-induced reinstatement for both reinforcers. There was a modest difference in the ED_{50} between sucrose and HFF overall. Our data suggest that 5-HT2A activation reduces palatable food consumption and the drive to pursue reinforcers activated by associate cues. Future experiments should further isolate these effects with selective blockade of 5-HT2 receptor subtypes.

Poster 92

Characterization of buprenorphine antagonism at human mu opioid receptors

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Opioid overdose deaths in the USA have increased by over 50% since 2017. Medications such as buprenorphine can facilitate a reduction of opioid use by reducing cravings and withdrawal. Buprenorphine is characterized as a low-efficacy (partial) agonist of the mu opioid receptor (MOR). Thus it can behave as either an agonist or an antagonist depending upon cellular context, such as the amount of MOR functionally expressed. The antagonist properties of buprenorphine are complex and incompletely understood. We have rigorously characterized the pharmacological actions of buprenorphine at the human MOR using a genetically encoded biosensor to monitor cAMP levels in real time in HEK293 cells. In these cells, which express a low density of human MOR, buprenorphine acted as a competitive antagonist to reduce the potency of the MOR agonist DAMGO in a concentration dependent manner. Additionally, buprenorphine acted as a non-competitive antagonist to decrease the maximal response to DAMGO, which saturated at higher buprenorphine concentrations. Molecular modeling and experimental blockade of buprenorphine by the antagonist naloxone suggested that both of these effects were mediated by the orthosteric site. To explain the competitive and non-competitive actions of buprenorphine, we considered that the observed effects were kinetically mediated. Calculations using equations that allow for incomplete re-equilibration support the hypothesis that the non-competitive antagonist effects of buprenorphine are due to hemi-equilibrium. This hypothesis was further supported when buprenorphine antagonism became surmountable with longer coincubation time (4 hrs). As a frontline treatment for opioid use disorder, understanding the unique properties of buprenorphine may facilitate treatment improvements and drug discovery efforts. This work is supported by the Institutional NRSA (T32, DA031115) Postdoctoral Training in Drug Abuse Research at UT Health San Antonio and a grant from NIH/NIDA (RO1 DA038645).

Poster 93

Combination therapy with morphine and the imidazodiazepine KRM-II-81 in adult rats for pain control: lack of tolerance

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Opioid analgesics, such as morphine, have been widely used to treat chronic pain despite side effects such as respiratory depression, constipation, and development of tolerance and addiction. Tolerance to the analgesic effects of opioids necessitates increasing doses to maintain therapeutic efficacy, which thereby increases the likelihood of side effects, since tolerance to the respiratory depressant and gastrointestinal motility effects develops more slowly. The imidazodiazepine KRM-II-81 acts specifically at subunits of the $GABA_A$ receptor found to mediate analgesia, has demonstrated antinociceptive effects in chronic pain models, and does not develop analgesic tolerance following repeated treatment. However, the potential of KRM-II-81 to reduce the extent to which tolerance develops to opioids has not been determined. Therefore, this study systematically examined the antinociceptive effects of KRM-II-81 in combination with morphine before and after repeated treatment in a rat model of chronic inflammatory pain. Nociceptive thresholds were measured using von Frey filaments before (day 0) and after (days 4, 8, 12, 13) twice-daily treatment with combinations of KRM-II-81 and morphine at different fixed ratios. Twice-daily treatment with KRM-II-81 and morphine combined at ratios of 3:1, 1:1, and 1:3 did not lead to significant antinociceptive tolerance after 11 days in either male or female rats. Furthermore, dose addition analysis indicated that KRM-II-81 and morphine produced additive interactions at all fixed ratios. These findings suggest KRM-II-81 could be used not only to maintain the same level of therapeutic efficacy with lower doses of morphine, but also to reduce the extent to which tolerance develops to opioids like morphine.

Poster 94

Novel small molecule antioxidant reduces psychostimulant-induced oxidative stress and inflammation in neural cells

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Background: Psychostimulant use disorder (PSUD), such as with methamphetamine (METH) and cocaine, causes oxidative-stress (OS) induced cell death leading to addiction neuropathies. These conditions promote reactive-oxygen species (ROS) accumulation and chronic activation of the inflammatory response. Our laboratory has synthesized a novel antioxidant small molecule, SA-31, previously shown to increase cell viability and activity of the endogenous antioxidant superoxide dismutase in neural cells. We predict SA-31 to increase activity of glutathione peroxidase (GPx) and total antioxidant status, and to reduce pro-inflammatory cytokines in cells treated with METH and cocaine. Methods: Compound SA-31 was synthesized and characterized in our lab. Human neuroblastoma SH-SY5Y cells were cultured and exposed to t-butyl hydrogen peroxide (TBHP, 200μM), cocaine hydrochloride (1.5mM), or METH (3.5mM) followed by co-treatment with SA-31 (1, 10, 100μM) for 24 hours. Lysate and supernatant were collected for assessing levels of GPx, total antioxidant status, and IL-1β using ELISA. Results: SA-31 (100μM) significantly increased GPx activity in cells treated with cocaine. No significant changes in total antioxidant status were observed in cells co-treated with cocaine and SA-31 (100 μM). Cells treated with TBHP showed increased IL-1 β levels and SA-31 (10μM) significantly reduced IL-1β compared to TBHP alone. Conclusion: Our results demonstrate neuroprotective potential of SA-31 to alleviate psychostimulant-induced ROS accumulation and pro-inflammatory cytokine release. Future studies will address the potential of SA-31 to progress further in pre-clinical drug development for future application in the treatment of PSUD.

Poster 95

Dose effects of oral Δ8-tetrahydrocannabinol and comparison to Δ9-tetrahydrocannabinol in healthy adults

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The expansion of cannabis legalization has led to the proliferation of novel cannabis products that are legally available to consumers. Recently, a number of novel products have become available in a variety of retail outlets for which the primary chemical constituent is Δ8-tetrahydrocannabinol (Δ8-THC). However, little is known about the behavioral and pharmacokinetic effects of Δ8-THC in humans. The aim of the present study was to characterize the acute effects of oral Δ8-THC, compared with a positive control dose of Δ9-THC and placebo, on subjective drug effects, cardiovascular effects, cognitive performance, and pharmacokinetics. Seven healthy adults completed five outpatient drug administration sessions to examine the acute effects of oral Δ8-THC (0 mg, 10 mg, 20 mg and 40 mg) and oral Δ9-THC (20 mg). Outcome assessed before and for 8 hours following drug administration included: vital signs, blood, urine and oral fluid samples, self-reported drug effects and performance on a battery of cognitive tasks. Following administration of active Δ8-THC, the pharmacodynamic assessments show a dose orderly effect of Δ8-THC on all assessments. The 20 mg Δ9-THC dose showed a qualitatively stronger drug effect than all 3 doses of Δ8-THC on most measures. Pharmacokinetic testing of biological samples is pending. Acute doses of oral Δ8-THC produced pharmacodynamic drug effects that overlap almost completely with the acute drug effects of Δ9-THC. However, Δ8-THC produces significantly lower magnitude of effects compared with Δ9-THC at the same dose, which is consistent with prior research on binding affinity between the 2 isomers.

Poster 96

Contrasting effects of mitragynine and morphine on respiratory parameters in unrestrained rats

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Kratom (*Mitragyna speciosa*) is a natural product ubiquitously available in most US states. Many use kratom to self-treat pain and opioid use disorder (OUD). Indeed, kratom is being studied as a potential OUD therapeutic. As respiratory depression is the direct cause of death due to opioid overdose, a great need exists to determine kratom-related respiratory effects alone and in the presence of opioids. For the current study we examined the effects of prototypical opioid, morphine, and mitragynine, the most abundant alkaloid in kratom. Adult male (n=4) and female (n=4) Sprague Dawley rats arrived pre-implanted with jugular catheters. Experiments were conducted using a within-subjects experimental design with a 7-day drug washout period between sessions. Respiratory frequency, tidal volume, minute ventilation, and % expiratory pause were measured, both pre- and post-drug administration, using whole body plethysmography in unrestrained animals. Morphine (10 - 32 mg/kg, i.v.) dose-relatedly produced robust respiratory depression as indicated by decreased frequency, tidal volume, minute ventilation and increased the % expiratory pause. Mitragynine (5.6 – 17.8 mg/kg, i.v.) dose-relatedly increased respiratory frequency and minute ventilation but did not alter tidal volume. All doses of mitragynine decreased the % expiratory pause. Taken together these findings demonstrate that at relatively low, 'therapeutic' doses intravenous morphine had no effect on respiratory parameters. However, at a higher dose, morphine produced robust respiratory depression symptoms, whereas mitragynine, at all studied doses, did not. These findings have important implications in OUD and opioid overdose medication development.
Supported by National Institute on Drug Abuse grants DA25267 and DA048353.

Poster 97

Widening the opioid analgesia therapeutic window with a dual pharmacotherapeutic strategy

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Opioid analgesics often produce profound side effects, including respiratory depression, abuse liability, and tolerance. Given that said analgesics are the standard of care for acute and chronic pain management, new pharmacotherapeutic strategies are needed to improve patient safety. Central and peripheral μ-opioid receptors (MORs) mediate opioid analgesia and antinociception. Enhanced activation of ionotropic $GABA_A$ receptors also produces antinociception, which can be selectively enhanced via $GABA_A$ positive allosteric modulators (PAMs). Our lab tested a novel imidazodiazepine PAM selective for the α-2/α-3 subunits of $GABA_A$, MP-III-024. Previous studies determined that MP-III-024 produces antinociceptive effects with minimal behavioral disruptions. Co-administration of morphine and MP-III-024 (1.0:0.94 ratio), produces synergistic antinociceptive effects. In this study, we determined that co-administration of morphine and MP-III-024 produces only additive/sub-additive effects in morphine-induced hyperlocomotion, conditioned place preference, and measures of behavioral disruption in food-maintained operant responding. MP-III-024 does not potentiate morphine tolerance. Ongoing studies are evaluating the effects of morphine and MP-III-024 co-administration on respiratory depression. These results indicate that a dual pharmacotherapy strategy may provide analgesia with reduced risk of side effects, including opioid addiction.

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Notes

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Poster Index

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 Substance Use Disorders***.

Maharaj Ticku Memorial Travel Fellowship for New Investigators

2012 – Jun-Xu Li	2013 – Kevin B Freeman	2014 – Christopher W Cunningham
2015 – Brian D Kangas	2016 – Clinton E Canal	2017 – Thomas M Keck
2018 – Comfort A Boateng	2019 – Stephen J Kohut	2020 – T Lee Gilman
2022 – Corinde E Weirs	2023 – Justin C Strickland	

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