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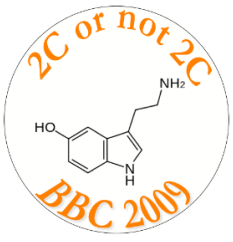

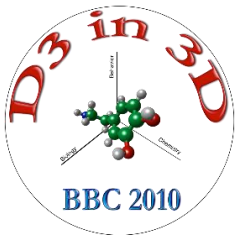

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Program Overview

FRIDAY 1 MARCH 2019

1:45 PM – 3:45 PM	**Pathways to Careers in Science Workshop** – UT Health Campus
4:00 PM – 5:00 PM	**San Antonio Substance Use Symposium Panel Discussion** – UT Health Campus
2:00 PM – 6:00 PM	Registration – Omni Colonnade
5:15 PM	Bus departs from UT Health to the Omni Colonnade
6:00 PM	Busses depart from Omni Colonnade to Opening Reception at La Vista Terrace on the Riverwalk
6:00 PM – 9:00 PM	**BBC Opening Reception, La Vista Terrace on the Riverwalk**

SATURDAY 2 MARCH 2019

7:00 AM – 5:00 PM	Registration
8:00 AM – 9:05 AM	Poster Session I
9:05 AM – 9:10 AM	Welcome and Opening Remarks
9:10 AM – 11:30 AM	Plenary Symposium: *Imaging Addiction* **Deborah C Mash**; *Mapping cocaine addiction circuitry in postmortem human brain* **Congwu Du**; *Advanced optical imaging of the neurotoxic and functional consequences of cocaine self-administration in rats* **David Matuskey**; *Utilizing PET to image neurotransmitter systems in substance abuse* **Nelly Alia-Klein**; *Imaging disease and recovery in addicted individuals* (Chairs: David Matuskey and Gregory T Collins)
11:30 AM – 1:15 PM	Lunch
11:50 AM – 1:05 PM	Panel Discussion: *How scientists can be more visible and impactful in their communities* **T Celeste Napier** **Wendy Rigby** **David Martin Davies** **Will C Sansom**
1:15 PM – 3:05 PM	Open Oral Communications I (Chairs: T Celeste Napier and Alessandro Bonifazi)
3:05 PM – 3:20 PM	Coffee Break
3:20 PM – 5:20 PM	Open Oral Communications II (Chairs: Katherine M Serafine and Samantha J McClenahan)
5:20 PM – 5:35 PM	Coffee Break
5:35 PM – 6:35 PM	Special Lecture: **Stephen M Husbands**; The *orvinols and close analogs: from opioid maintenance to relapse prevention* (Chair: James H Woods)
6:35 PM – 7:35 PM	Poster Session and Cocktail Hour
7:35 PM – 9:25 PM	Dinner After Dinner Speaker: **Alan Frazer**; *Making it in modern science* (Chair: William P Clarke) Hospitality and entertainment

SUNDAY 3 MARCH 2019

7:45 AM	Travel Awardee Group Photo
8:00 AM – 9:05 AM	Poster Session II
9:10 AM – 11:10 AM	Open Oral Communications III (Chairs: Stephen J Kohut and E Andrew Townsend)
11:10 AM – 11:25 AM	Coffee Break
11:25 AM – 12:25 PM	Special Lecture: **Sharon L Walsh**; *The opioid crisis: leveraging science to change hearts and minds* (Chair: Richard J Lamb)
12:25 PM	Presentation of travel awards and awards for oral and poster presentations
12:30 PM – 1:30 PM	Adjournment and Lunch

Maharaj Ticku Memorial Travel Fellowship for New Investigators

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Program Details

Friday 1 March 2019

1:45 PM – 3:45 PM Pathways to Careers in Science Workshop – UT Health Campus

4:00 PM – 5:00 PM San Antonio Substance Use Symposium Panel Discussion – UT Health Campus
Harm reduction strategies and other cutting-edge approaches for substance use disorders

Opening Reception

La Vista Terrace on the Riverwalk

6:00 PM Busses depart from Omni Colonnade

6:30 PM - 9:00 PM Welcome Reception –La Vista Terrace on the Riverwalk

8:30 PM – 9:00 PM Buses depart for Omni Colonnade

Enjoy the Alamo and beautiful San Antonio Riverwalk. Buses will depart from Omni Colonnade at 6:00 PM to La Vista Terrace for dinner and drinks. Buses will return to Omni Colonnade 8:30 PM - 9:00 PM. A badge is required to board the bus and for dinner. Additional tickets can be purchased in advance or at the registration desk for $50.00.

Saturday 2 March 2019

Poster Session I 8:00 AM - 9:05 AM *La Joya*

Welcome and Opening Remarks 9:05 AM - 9:10 AM *Ballroom*

Plenary Symposium 9:10 AM – 11:30 AM

Imaging Addiction (Chairs: David Matuskey, and Gregory T Collins)

Drug addiction is a chronic disorder characterized by compulsive drug use that is thought to arise from, and induce, dysregulation in brain circuits important for reward, motivation, and memory. Imaging techniques provide a powerful approach to studying the effects of drugs on the brain, and this symposium brings together leading experts on the use of postmortem analysis of human brain tissue, multi-modal in vivo optical imaging, positron emission tomography (PET), and functional MRI to better define the antecedents and consequences of substance use disorders.

9:10 AM – 9:45 AM **Deborah C Mash**
Mapping cocaine addiction circuitry in postmortem human brain

9:45 AM – 10:20 AM **Congwu Du**
Advanced optical imaging of the neurotoxic and functional consequences of cocaine self-administration in rats

10:20 AM – 10:55 AM **David Matuskey**
Utilizing PET to image neurotransmitter systems in substance abuse

10:55 AM – 11:30 AM **Nelly Alia-Klein**
Imaging disease and recovery in addicted individuals

Lunch 11:30 AM – 1:15 PM

Panel Discussion 11:50 AM – 1:05 PM

How scientists can be more visible and impactful in their communities

Attendees are invited for a frank and friendly moderated panel discussion on how scientists can be more visible and impactful in their communities. Significant time will be provided for audience questions and participation.

T Celeste Napier, Rush University (*Moderator*)
Wendy Rigby, Texas Biomedical Research Institute
David Martin Davies, Texas Public Radio
Will C Sansom, UT Health San Antonio

Oral Communications I 1:15 PM – 3:00 PM

(Chairs: T Celeste Napier and Alessandro Bonifazi)

1:15 PM – 1:30 PM **Jennifer Betts**, University at Buffalo, SUNY
Comparing the reward value of cigarettes and food during tobacco abstinence and nonabstinence

1:30 PM – 1:45 PM **Daniel Gabriel**, The University of Memphis
Risky decision-making predicts dopamine release dynamics in nucleus accumbens

1:45 PM – 2:00 PM **Aboagyewaah Oppong-Damoah**, Mercer University
Caryophyllene oxide is more potent than beta caryophyllene in attenuating the abuse-related effects of ethanol

2:00 PM – 2:15 PM **Eric Wold**, The University of Texas Medical Branch
Towards characterizing a serotonin (5-HT) 5-HT_{2C} receptor allosteric binding site via compound design and synthesis, in vitro characterization, and in silico docking of 5-HT_{2C} receptor PAMs

2:15 PM – 2:30 PM **Omar Sial**, Texas A&M University
Early-life adversity followed by western-style diet leads to physiological dysregulation, depressive phenotype, decreases in reward sensitivity, and treatment resistance in adulthood

2:30 PM – 2:45 PM **Sean Duke**, University of Mississippi Medical Center
Development of a novel anxiolytic medication: the behavioral pharmacology of KRM-II-81

2:55 PM – 3:00 PM **Alessandro Bonifazi,** NIH-NIDA
Novel and potent dopamine D_2 receptor (D_2R) Go-protein biased agonists

Coffee Break 3:05 PM – 3:20 PM

Maharaj Ticku Memorial Travel Fellowship for New Investigators

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Oral Communications II 3:20 PM – 5:20 PM

(Chairs: Katherine M Serafine and Samantha J McClenahan)

3:20 PM – 3:35 PM **Andrea Dimet**, The University of Texas Medical Branch
PARγ agonism drives structural, functional, and behavioral changes in a rodent cocaine-seeking model

3:35 PM – 3:50 PM **Trent Bullock**, Temple University
A three-lever drug discrimination method differentiates the stimulus effects of 3,4-methylenedioxypyrovalerone (MDPV) and 4-methylmethcathinone (4-MMC) in rats

3:50 PM – 4:05 PM **Michael Leonard**, Tufts University
Corticotropin releasing factor modulates dopamine in the nucleus accumbens core to invigorate cocaine-seeking via CRF-R_2

4:05 PM – 4:20 PM **Samantha McClenahan**, University of Arkansas for Medical Sciences
Active vaccination reduces reinforcing effects of MDPV in Sprague-Dawley rats trained to self-administer cocaine

4:20 PM – 4:35 PM **Veronica Campbell**, The University of Texas Medical Branch
Cocaine cue reactivity and impulsivity are linked processes underlying relapse-related behavior

4:35 PM – 4: 50 PM **William Hyatt**, University of Arkansas for Medical Sciences
Effects of repeated 5-HT_{2A} agonist 2,5-dimethyoxy-4-iodoamphetamine (DOI) on increases in motor impulsivity elicited by 3,4-methylenedioxypyrovaleron (MDPV)

4:50 PM – 5:05 PM **Jianfeng Liu,** University of Buffalo, SUNY
Activation of TAAR1 attenuates extended access of cocaine self-administration and the stress- induced reinstatement of cocaine-seeking

5:05 PM – 5:20 PM **Stephen Kohut,** McLean Hospital/Harvard Medical School
Resting-state fMRI connectivity in awake nonhuman primates: Modulation by cocaine self-administration

Coffee Break 5:20 PM – 5:35 PM

Special Lecture: Stephen M Husbands 5:35 PM – 6:35 PM (Chair: James H Woods)

The orvinols and close analogs: from opioid maintenance to relapse prevention

Cocktail Hour and Poster Session 6:35 PM – 7:35 PM

Dinner 7:35 PM – 9:25 PM

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

After Dinner Speaker: Alan Frazer (Chair: William P Clarke)

Making it in modern science

Hospitality and Entertainment

Maharaj Ticku Memorial Travel Fellowship for New Investigators

Travel Awardee

Sunday 3 March 2019

Travel Awardee Group Photo 7:45 AM *Ballroom*

Poster Session II 8:00 AM – 9:05 AM *La Joya*

Oral Communications III 9:10 AM – 11:10 AM
(Chairs: Stephen J Kohut and E Andrew Townsend)

9:10 AM – 9:25 AM **Lisa Wooldridge**, McLean Hospital/Harvard Medical School
The antiemetic and cognition-impairing effects of delta-9-tetrahydrocannabinol and methanandamide in nonhuman primates

9:25 AM – 9:40 AM **Austin Zamarripa**, University of Mississippi Medical Center
Kappa-opioid agonists: assessment of signaling bias on antinociception and oxycodone self-administration reduction in rats

9:40 AM – 9:55 AM **Justin Strickland,** University of Kentucky
Utilizing the purchase task procedure to evaluate non-medical prescription opioid demand: Incremental validity and temporal reliability.

9:55 AM – 10:10 AM **Ruyan Wu**, University of Buffalo, SUNY
The role of interleukin-1 receptor-associated kinase 4 in drug addiction

10:10 AM – 10:25 AM **Drew Townsend**, Virginia Commonwealth University
Vaccine decreases choice of fentanyl over food and blocks expression of opioid withdrawal- associated increases in fentanyl reinforcement in male and female rats.

10:25 AM – 10:40 AM **Jenny Wilkerson**, University of Florida
Opioid, $GABA_B$, and 5-HT_{1A} receptor agonist combinations in a mouse model of neuropathic pain

10:40 AM – 10:55 AM **Victoria Taylor,** University of Florida
Pharmacological characterization of mitragynine, the primary constituent in kratom (mitragyna speciosa): discriminative stimulus effect

10:55 AM – 11:10 AM **David Maguire,** UT Health San Antonio
Long-lasting effects of methocinnamox (MCAM) on opioid self-administration

Coffee Break 11:10 AM – 11:25 AM

Special Lecture: Sharon L Walsh 11:25 AM – 12:25 PM (Chair: Richard J Lamb)
The opioid crisis: leveraging science to change hearts and minds

Presentations of Awards for Travel, Oral and Poster Presentations 12:25 PM

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

See you at BBC 2020!

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Oral Communications

Oral Communication 1-1

Comparing the reward value of cigarettes and food during tobacco abstinence and nonabstinence

Betts, Jennifer M[1] and Tiffany, Stephen T HD[1]

[1]Department of Psychology, University at Buffalo, SUNY, Buffalo, NY USA

Some addiction theories propose that nicotine dependence is characterized by an imbalance between motivation for cigarettes compared to nondrug primary rewards, such as food. This imbalance is thought to become increasingly polarized during abstinence, which motivates smoking. The present study evaluated motivation for cigarettes and food during abstinence and nonabstinence in heavy smokers using the Choice-Behavior-Under-Cued-Conditions (CBUCC) procedure to examine cue- specific reactions to cigarettes and food. Fifty daily, dependent cigarette smokers underwent two study sessions using the CBUCC procedure under nonabstinent and overnight abstinent conditions. During the CBUCC procedure, participants were presented with cigarettes, food, or water across multiple trials. On each trial, participants rated their craving for both tobacco and food and indicated the amount of money they would spend to access the cue. The amount spent directly determined the probability that the cue could be accessed and sampled on each trail. Multiple variables were collected from CBUCC to evaluate motivational factors and drug use behaviors such as reward value, craving, seeking, choice time, and consumption. As an index of reward value, participants spent significantly more money to access cigarettes than food or water, and spent significantly more for food relative to water, regardless of abstinence status. Abstinence significantly increased the reward value of cigarettes but did not significantly affect the reward value of food or water. Participants also demonstrated clear cue-specific craving for cigarettes and food, although craving was overall higher for cigarettes than for food. This study indicated that motivation for cigarettes was generally greater than motivation for food. Overnight abstinence selectively increased motivation for cigarettes but had little impact on motivation for food. This suggests that, during abstinence, heavy smokers do not reallocate motivational resources from nondrug rewards towards cigarettes; rather, motivational processes for food remain constant from nonabstinent to abstinent sessions.

Oral Communication 1-2

Risky decision-making predicts dopamine release dynamics in nucleus accumbens

Gabriel, Daniel B K[1]; Freels, Timothy G[2], Caughron, William B. [1], Lester, Deranda B[1], and Simon, Nicholas W[1]

[1]Department of Psychology, University of Memphis, Memphis, TN USA; [2]Department of Integrative Physiology and Neuroscience, Washington State University, WA USA

Excessive risky decision-making is a hallmark of addiction, promoting ongoing drug seeking despite the risk of social, financial, and physical consequences. Therefore, elucidating the neural mechanisms underlying risky decision-making may have utility for identifying vulnerability to substance abuse disorders. The risky decision-making task (RDT) measures risk-taking in a rat model by assessing preference between a small, safe reward and a large reward with increasing risk of punishment (mild foot shock). It is well-established that dopaminergic drugs modulate risk-taking; however, little is known about how differences in baseline phasic dopamine signaling drive individual differences in risk preference. Here, we used in vivo fixed potential amperometry in male Long-Evans rats (n=17) to test the hypothesis that biologically relevant nucleus accumbens (NAC) dopamine dynamics are associated with risk-taking. We observed that a positive correlation between phasic dopamine release in the NAC and risky decision-making, suggesting that risk-taking is associated with elevated dopamine sensitivity. Furthermore, a one-way ANOVA showed greater evoked dopamine efflux in “risk-takers”, rats with greater than 75% preference for risky rewards, vs. the rest of the population. Risky decision-making also predicted enhanced sensitivity to nomifensine, a dopamine reuptake inhibitor, quantified as elevated latency for dopamine to clear from the synapse. Importantly, the hyperdopaminergic phenotype of risk-takers was not due solely to a preference for larger rewards, as delay discounting performance did not predict any NAC dopamine parameters. These data suggest that individual differences in risk-taking predict dopamine release dynamics in the NAC. Furthermore, baseline risk-based decision-making is more closely associated with NAC dopamine sensitivity than delay based decision-making. This suggests that NAC dopamine may provide a therapeutic target for combatting pathological risk-taking seen in addiction.

Oral Communication 1-3

Caryophyllene oxide is more potent than beta caryophyllene in attenuating the abuse-related effects of ethanol

Oppong-Damoah, Aboagyewaah[1]; Wood, Bo J[1]; Blough, Bruce[2] and Murnane, Kevin S[1]

[1]Department of Pharmaceutical Sciences, Mercer University College of Pharmacy, Mercer University Health Sciences Center, Atlanta, GA USA; [2]Center for Drug Discovery, Research Triangle Institute, Research Triangle Park, NC, USA

17 million adults in the United States had an alcohol use disorder (AUD) in 2012 and current treatments yield disappointing remission rates. In recent years, the endocannabinoid system has been shown to modulate the abuse-related effects of ethanol. In this study, we used the loss of righting reflex (LORR) assay to assess the direct pharmacodynamic interactions between beta-caryophyllene (BCP), its derivative caryophyllene oxide (BCPO), and ethanol. We investigated the effects of BCPO in two widely accepted animal models of AUD: two bottle choice ethanol consumption and ethanol-induced conditioned place preference (CPP). Finally, we determined whether there is any pharmacokinetic interaction between BCPO and ethanol using blood and brain ethanol analysis. BCPO augmented the ethanol-induced LORR at a dose tenfold lower than BCP. This effect was reversed by pretreatment with a selective CB_2 antagonist, AM630. BCPO significantly decreased ethanol intake and preference without any effect on total fluid intake in mice that consumed high amounts of ethanol. In mice that consumed low amounts of ethanol, BCPO had no effect on ethanol intake, preference, or total fluid intake. BCPO significantly attenuated the expression of an ethanol-induced CPP. Our findings show that BCPO is more potent than BCP *in vivo* and that its attenuation of the abuse-related effects of ethanol is likely mediated through pharmacodynamic rather than pharmacokinetic interactions. This study expands the support for the CB_2 receptor as a viable target for the treatment of AUD.

Oral Communication 1-4

Towards characterizing a serotonin (5-HT) 5-HT_{2C} receptor allosteric binding site via compound design and synthesis, *in vitro* characterization, and *in silico* docking of 5-HT_{2C} receptor PAMs

Wold, Eric A[1]; Wild, Christopher T[1]; Chen, Jianping[1]; Pazdrak, Konrad[1]; Garcia, Erik J[1]; Anastasio, Noelle C[1]; Cunningham, Kathryn A[1]; Zhou, Jia[1]

[1]Center for Addiction Research, Department of Pharmacology and Toxicology, University of Texas Medical Branch, TX USA.

The serotonin (5-HT) 5-HT_{2C} receptor (5-HT_{2C}R) is a member of the G protein-coupled receptor (GPCR) super-family and is one of 14 genetically encoded 5-HT receptor subtypes through which 5-HT binds an orthosteric site to mediate cellular physiology. Accumulating evidence suggests a modulatory role for the 5-HT_{2C}R in significant human diseases, such as substance use disorders (SUDs), obesity, and various neuropsychiatric disorders. Pharmacological modulation of the 5-HT_{2C}R has been shown to yield beneficial clinical outcomes in obesity, but the clinical scope is still extremely limited due to off-target effects, and no drug targeting the 5-HT_{2C}R is available for SUDs. We propose that increasing the chemical space available for the design of 5-HT_{2C}R agonists and positive allosteric modulators (PAMs) may provide preferential receptor selectivity and enable diversity in ligand-target engagement. In this study, we rationally designed a series of potential 5-HT_{2C}R PAMs with diverse substituents and performed primary functional screening in-house to identify active 5-HT_{2C}R PAMs and secondary competition binding studies via the Psychoactive Drug Screening Program (PDSP; PI: Bryan Roth). To further illuminate PAM-receptor interactions, we performed *in silico* modelling studies with the ergotamine-bound, active-state 5-HT_{2C}R crystal structure (PDB: 6BQG) and generated a 5-HT-bound active-state 5-HT_{2C}R model. This model generation process was repeated for 5-HT_{2C}R agonists WAY-163909 and lorcaserin. Active 5-HT_{2C}R PAMs were then docked to different active-state models via Schrödinger computational chemistry software to render a consensus putative 5-HT_{2C}R allosteric binding site. Our results are suggestive of a 5-HT_{2C}R PAM binding site within the extracellular-facing transmembrane domain bundle and provide additional compound design criteria that may improve the 5-HT_{2C}R ligand chemical space.

Oral Communication 1-5

Early-life adversity followed by western-style diet leads to physiological dysregulation, depressive phenotype, decreases in reward sensitivity, and treatment resistance in adulthood

Sial, Omar K[1]; Parise, Lyonna F[1]; Skansi, Peyton N[1]; Cardona, Astrid M[1]; Vieregg, Emily L[1]; Gnecco, Tamara[1] and Bolaños-Guzmán, Carlos A[1]

[1]Texas A&M University, Department of Psychological and Brain Sciences: Behavioral and Cellular Neuroscience. College Station, TX.

There has been a striking increase in the prevalence and comorbidity of major depressive disorders, obesity, and drug addiction in adolescents. Elucidating the interaction between these disorders may lead to crucial implications for adolescent health and sociocultural patterns of behavior. Exposure to western-style high fat diet (HFD) has been linked to metabolic syndrome and mood and reward dysregulation in rodents as similarly seen in the human condition. Because adolescence is highlighted by vulnerability to stress, poor diet, and drugs of abuse, it is pivotal to understand the mechanism(s) underlying the negative effects of HFD on mood, natural and drug reward, and future adult functioning. Adolescent male C57bl/6J mice were exposed to HFD (14 days) before chronic social defeat stress (CSDS) and were subsequently tested for their ability to regulate mood, sucrose and morphine preference. Mice given HFD showed increased sensitivity to stress and decreased preference for both sucrose and saccharin (i.e., anhedonia) when compared to control mice. When tested in the conditioned place preference, chronic HFD-exposed mice showed decrease sensitivity to morphine (1mg/kg). We also show here that mice stressed during adolescence and then exposed to HFD show decreased responsivity to the antidepressant fluoxetine (Prozac). Surprisingly, this phenotype was still prevalent when the mice were tested in adulthood. These novel findings indicate that exposure to HFD during adolescence blunts reward sensitivity, and that stress exposure followed by consumption of HFD induces neurobiological changes that lead to physiological and mood related deficits which, in turn, could lead to the development of maladaptive behaviors and negative health outcomes in adulthood that may be treatment resistant. Biochemical and optogenetic manipulations are currently being conducted to establish causality.

Oral Communication 1-6

Development of a novel anxiolytic medication: the behavioral pharmacology of KRM-II-81

Duke, Sean M[1], Davis, Patrick G[1], Slone, Austin N[1], Rüedi-Bettschen, Daniela[1], Methuku, Kashi Reddy[2], Cook, James M[2] and Rowlett, James K[1]

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Since their introduction in the 1960s, benzodiazepines (BZs) have been the most commonly used type of anxiolytic medication due to their rapid and robust ability to curb anxiety. These anti-anxiety effects, however, coincide with less desirable effects such as sedation, ataxia and abuse potential. Current BZs bind to several forms of $GABA_A$ receptors ($GABA_ARs$) at the interface between the α and γ subunits. It has been shown that BZ binding to $GABA_ARs$ containing different isoforms of the α subunit underlie the behavioral effects of BZs. For instance, increased ion flux through $GABA_ARs$ with the α 1 isoform can cause sedation, an effect exploited by the hypnotic drug zolpidem. Likewise, α 2/3-$GABA_ARs$ are thought to mediate the anxiolytic effects of BZs. Therefore, selectivity for α 2/3-$GABA_AR$ subtypes may represent a target for anxiolytic development while minimizing the sedative and ataxic effects associated with "non-selective" BZs. KRM-II-81 is a second generation α 2/3-$GABA_AR$-selective compound that avoids first-pass metabolism, making it a great candidate for the study of the anxioselective nature of this class of compounds. In this study, we sought to characterize KRM-II-81's behavioral effects in rodents and non-human primates (NHPs). In the elevated zero maze, a measure of anxiolysis, rats injected with KRM-II-81 spent similar amounts of time in the open arm as those given chlordiazepoxide (CDP), a typical BZ, without attenuating overall motor activity. Rats also associated KRM-II-81 with CDP rather than zolpidem in a drug-discrimination paradigm. Finally, a dose-related sedative effect was observed in the rat open field test and in an NHP observational measure, along with some ataxic effects. These findings suggest that by targeting α 2/3-$GABA_ARs$, KRM-II-81 may function as an anxioselective BZ at specific doses, warranting further study.

Oral Communication 1-7

Novel and potent dopamine D_2 receptor (D_2R) Go-protein biased agonists

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Dopamine D2-like receptors (D2Rs) can signal through G-protein dependent (cAMP) or independent pathways, with the latter involving beta-arrestin recruitment, resulting in receptor internalization and additional downstream signaling. Thus, development of D2R biased agonists can provide molecular tools that can disentangle which pathways are involved in motor and/or psychiatric disorders associated with altered dopaminergic transmission. We hypothesized that bivalent ligands that bind in both the orthosteric binding site (OBS) and the secondary binding pocket (SBP) might enhance biased activation by stabilizing unique receptor conformations. Building on our previously developed G- protein selective biased leads (Bonifazi A. and Yano H. et al. J. Med. Chem. 2017), new bivalent Sumanirole (D2R balanced full agonist) analogues were prepared by introducing novel secondary pharmacophore fragments inspired by recently published D2-like positive allosteric modulators (Wood M. et al. Mol. Pharmacol. 2016) and by increasing linker rigidity and chirality. The compounds were evaluated in hD2R, hD3R and hD4R binding assays and in 4 different functional bioluminescence energy transfer constructs (BRET): Gi protein and Go protein activation, adenylyl cyclase inhibition, and beta-arrestin2 recruitment. We discovered agonists with highly selective D2R G-protein biased profiles, identifying new leads able to selectively activate the Go protein with picomolar EC50's and unprecedented selectivities >100-1000 fold over Gi-protein activation and beta-arrestin recruitment (using an operational model for calculating bias factors). Extensive intracellular electrophysiology recordings from midbrain dopamine neurons confirmed that these new Go-protein selective agonists induce sustained GIRK activation, exclusively via D2Rs, highlighting new potential therapeutic approaches for the treatment of dopamine system dysfunctions, especially in the central nervous system where the Go-proteins are highly expressed.

Oral Communication 2-1

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

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Cocaine use disorder (CUD) causes structural and functional changes in white matter (WM) and gray matter (GM) which drive behavioral phenotypes, including cocaine-seeking behavior. Cocaine-seeking can be modeled in rats with a cue reactivity task after self-administration (SA) and forced abstinence (FA). We discovered that the FDA-approved peroxisome proliferator-activated receptor gamma (PPARγ) agonist pioglitazone (PIO, ActosTM) attenuates cocaine cue reactivity when PIO is administered during FA. Importantly, this effect of PIO is reversed by pretreatment with the irreversible PPARγ antagonist GW9662. Phosphorylated extracellular signal-regulated kinase (pERK) is a protein we identified in complex with PPARγ, and thus a potential co-regulator. **We hypothesized** that PPARγ agonism counteracted the cocaine-mediated alterations in WM and GM underlying persistent cocaine- seeking behavior through induction of markers for structural and functional integrity via downstream transcriptional or pERK-related mechanisms. We tested our hypothesis using RNA sequencing and bioinformatics analyses, protein expression studies with the Protein Simple Wes™, and Luxol Fast Blue myelin staining. We statistically analyzed our data using Fisher's exact test, student's t-test, two-way ANOVA, and multivariate ANOVA with posthoc analyses where appropriate. We discovered that 1) PIO alters prefrontal cortex regenerative or neuroprotective gene expression pathways that are enriched for PPAR- and ERK-dependent genes, 2) PIO changes hippocampal protein expression suggestive of WM restructuring, and 3) PIO increases WM in the medial anterior CC, recapitulating diffusion tensor imaging results in human CUD subjects undergoing PIO treatment. In conclusion, our work further supports PIO as a CUD treatment and suggests that it likely attenuates cocaine cue reactivity via large- scale neurocircuit restructuring and neuro-regenerative or neuroprotective mechanisms.

Oral Communication 2-2

A three-lever drug discrimination method differentiates the stimulus effects of 3,4-Methylenedioxypyrovalerone (MDPV) and 4-Methylmethcathinone (4-MMC) in rats

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Drug discrimination is a widely used preclinical behavioral assay with pharmacological specificity. This assay has been utilized to characterize the discriminative stimulus effects of two common constituents of illicit "bath salts", 3, 4-methylenedioxypyrovalerone (MDPV) and 4- methylmethcathinone (4-MMC). Traditional two-lever (drug vs no drug) discrimination studies have demonstrated stimulus generalization between these substances and other psychostimulants, such as cocaine and MDMA. However, asymmetrical substitution patterns between 4-MMC and MDPV have been noted. The current study employed a three-lever discrimination method to determine if the interoceptive stimulus effects of 4-MMC and MDPV could be differentiated. Twelve male Sprague- Dawley rats were trained to discriminate 0.5 mg/kg MDPV, 2.0 mg/kg 4-MMC, and saline vehicle.

Once discrimination was established, a range of doses of each training stimulus as well as MDMA (0.75-3.0 mg/kg), cocaine (2.5 -10 mg/kg) and methamphetamine (0.1-1 mg/kg) were assessed for stimulus generalization. The discrimination was established within 39.8 (± 3.9) training sessions. Both MDPV and 4-MMC produced reliable stimulus control and dose-dependent increases in responding on the condition-appropriate lever. Following all cocaine test doses (N=6), responses were predominantly on the MDPV-lever and full substitution for MDPV was observed with 5 and 10 mg/kg cocaine. In contrast, MDMA (N=5-8) produced responding predominantly on the 4-MMC-lever, with full substitution for 4-MMC observed with 1.5 mg/kg MDMA. Methamphetamine was assessed in only three animals, and all doses produced 100% responding on the MDPV-lever. Inasmuch as drug discrimination is a model of subjective drug effects, the present results indicate that 4-MMC and MDPV produce distinct subjective effects, likely due to their differential mechanisms of action. Further studies with selective dopamine and serotonin antagonists will serve to further elucidate these differences.

Oral Communication 2-3

Corticotropin releasing factor modulates dopamine in the nucleus accumbens core to invigorate cocaine-seeking via CRF-R_2

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Adverse life events often precipitate the initiation of– and relapse to– cocaine use in drug-dependent individuals. Exposure to acute stress can potently exacerbate the extent to which drug-stimuli elicit craving to seek and procure drug, perhaps via peptidergic modulation of mesolimbic dopamine transmission. The present studies examine the site-specific actions of the stress peptide corticotropin releasing factor (CRF) within the nucleus accumbens core (NAcc) as a putative substrate for stress-potentiated arousal. First, we assessed the extent to which pharmacological manipulation of CRF within the NAcc alters instrumental responding for cocaine; secondly, we begin to characterize the conditions under which CRF modulates local dopamine transmission. Long-Evans rats self-administered cocaine under a chain schedule of reinforcement (FI-FR) in order to dissociate appetitive ('drug-seeking') from consummatory ('drug-taking') behavior. Completion of a fixed interval (5min) was followed by 5 min of continuously reinforced responding (0.4mg/kg cocaine; FR1) on another lever. After training, rats were microinjected with CRF (50 or 500ng) into the NAcc prior to self-administration sessions. Microinfusion of CRF dose-dependently increased responding during the fixed-interval link of the chain schedule ('seeking'), but did not affect subsequent cocaine consumption. These effects were determined to be CRF-R_2-dependent, as CRF-potentiated responding was prevented by pretreatment with Astressin-2B, but not the CRF-R_1 antagonist CP376395. Parallel microdialysis studies revealed that CRF is endogenously released into the NAcc during acute stress exposure (i.e. social defeat), and that CRF can produce a robust increase in extracellular dopamine in the NAcc. These data suggest a role for CRF-R_2 in modulating appetitive drug-seeking behavior – perhaps via interactions with NAcc dopamine – and may offer insight into the substrates of stress-induced relapse. CRF-R_2 may therefore represent a worthy therapeutic target for cocaine use disorder.

Oral Communication 2-4

Active vaccination reduces reinforcing effects of MDPV in Sprague-Dawley rats trained to self-administer cocaine

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3,4-Methylenedioxypyrovalerone (MDPV) is a psychoactive synthetic cathinone that has a similar mechanism of action as cocaine, but dramatically less affinity for serotonin transporters. Previous studies showed that active vaccination with an MDPV-like vaccine could significantly decrease concentrations of MDPV in the brain and reduce MDPV-induced locomotor effects in rats. The goal for these studies was to test the capacity of active vaccination to reduce the reinforcing effects of MDPV. In the present studies, we hypothesized that treatment with this vaccine would shift MDPV self-administration curves to the right compared to non-vaccinated rats. Rats were trained to administer 0.32 mg/kg/inf of cocaine under a fixed-ratio 1 with a 10 s time out (FR1/TO10), then subsequently transitioned to an FR5/TO10. Cocaine (0.032-1 mg/kg/inf) was substituted to obtain a full dose-response curve before substituting MDPV (0.001-0.32 mg/kg/inf). Rats then transitioned to a progressive ratio schedule to establish breakpoints for cocaine (0.1-1.0 mg/kg/inf) and MDPV (0.01-0.1 mg/kg/inf). Acquisition of IV cocaine self-administration and transition to an FR5/TO10 did not differ between vaccinated and non-vaccinated rats. The ED50 for cocaine under FR5/TO10 was not different between vaccinated and non-vaccinated rats. In non-vaccinated rats, MDPV was more potent than in vaccinated rats, but there was no difference in effectiveness between treatments. Results from progressive ratio testing will also be discussed. Active vaccination did not alter rats' ability to acquire cocaine self-administration indicating the vaccine did not affect learning or produce antibodies that bind to cocaine. Furthermore, despite the vaccine being surmounted with no differences in effectiveness of MDPV between treatments, higher doses of MDPV were required to produce similar effects in vaccinated rats than non-vaccinated rats. Funded by NIH grants DA039195, F31 DA046121, T32 GM106999.

Oral Communication 2-5

Cocaine cue reactivity and impulsivity are linked processes underlying relapse-related behavior

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The trajectory from drug use to substance use disorders (SUDs) begins against a background of vulnerability based upon genetic and environmental factors and progresses as neuronal plasticity in key brain circuits. The cycling progressive nature of SUDs stymies efforts to stay abstinent with vulnerability to abuse and relapse during abstinence often precipitated by impulsive behavior. Impulsive action (behavioral disinhibition) and impulsive choice (decision-making) are two dimensions of impulsivity that have been associated with addictive behaviors in humans and laboratory animals. Cocaine-dependent subjects often present with high levels of impulsive action, which is negatively correlated with treatment retention in cocaine-dependent individuals. Impulsive action has been shown to positively correlate with cue reactivity (attentional bias to drug-associated cues) in cocaine-dependent subjects. Preclinical models have shown that impulsive action and cocaine cue reactivity are interlocked phenotypes but the exact nature of the relationship between these behaviors is not well understood. It has not been established whether phenotypic differences in impulsive action is a factor leading to and/or resulting from withdrawal from cocaine use. Therefore, the objective of the current study was to determine whether high inherent impulsive action is a factor that predisposes vulnerability to cocaine- associated cues or arises as a result of exposure and withdrawal from cocaine. We examined the effects of extended abstinence from cocaine self-administration on expression of impulsive action and cocaine cue reactivity in an outbred rat population. Levels of inherent impulsive action were not altered by the dynamic state of abstinence from cocaine. High impulsive action associated with high cocaine cue reactivity after 30 days of forced abstinence from cocaine. Thus, high inherent impulsive action appears to be a critical antecedent leading to higher relapse-like behaviors.

Oral Communication 2-6

Effects of repeated 5-HT2A agonist 2,5-dimethyoxy-4-iodoamphetamine (DOI) on increases in motor impulsivity elicited by 3,4-methylenedioxypyrovaleron (MDPV)

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Previous studies from our lab have demonstrated that both acute and chronic administration of the synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV) increases motor impulsivity. Evidence is accumulating that acute administration of serotonin 5-HT_{2A} antagonists, such as M100907, decreases motor impulsivity, while 5-HT_{2A} agonists, such as DOI, have been demonstrated to cause acute increases in motor impulsivity. Further, recent evidence has indicated that repeated exposure to DOI, but not M100907, may cause long-term down regulation of 5-HT_{2A} receptors, potentially resulting in protracted decreases in motor impulsivity. Thus, in the current experiments, we investigated both acute and chronically administered M100907 and DOI, individually or in combination, to alter impulsivity elicited by MDPV. Twenty four drug-naïve, adult male Sprague- Dawley rats were split into four groups of six: a control group that received MDPV and a saline treatment, an MDPV group with DOI treatment, an MDPV group with M100907 treatment, and an MDPV group that received both DOI + M100907 treatment. Impulsivity was measured using a differential reinforcement of low rate of responding (DRL 20 sec) task. Following stabilization, each animal received once daily subcutaneous doses of 1mg/kg MDPV paired with escalating doses of their respective group treatment, prior to assessment in the DRL20 task. Following testing of acute, pre- session treatment, each animal was moved into a 'chronic' administration phase where they received 10 injections of the highest dose of their respective treatment, followed by a washout, then a reassessment of pre-session acute MDPV. At the end of the experiment, animals will be sacrificed and brains will be dissected into prefrontal cortex, motor cortex, hippocampus, and striatum in order to determine concentrations of dopamine, serotonin, norepinephrine, and their metabolites, as well as the absolute protein concentrations of 5-HT_{2A} and 5-HT_{2C} receptors. These studies were supported in part by DA039195 and T32DA022981.

Oral Communication 2-7

Activation of TAAR1 attenuates extended access of cocaine self-administration and the stress-induced reinstatement of cocaine-seeking

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Trace amine-associated receptor 1 (TAAR1) is the best-characterized sub-family of receptors of trace amines. As a modulator of dopaminergic system, TAAR1 plays a critical role in regulating the rewarding properties of drugs of abuse such as cocaine. In our previous studies, we demonstrated that TAAR1 agonists were able to reduce cocaine intake and the cue- and drug-induced reinstatements of cocaine-seeking under short-access conditions. However, the short-access self-administration model could not mimic some core properties of addiction such as escalation, compulsive motivation, and incubation of cocaine-seeking. In contrast, these behaviors can be mimicked in the extended access cocaine self-administration model. Stress could also induce reinstatement of drug-seeking, however, it remains unclear whether activation of TAAR1 would affect stress-induced reinstatement of cocaine- seeking. Here, we investigated the effects of TAAR1 partial agonist RO5263397 on the extended access of cocaine self-administration. We also assessed the effects of the selective TAAR1 full agonist RO5166017 on the alpha 2-adrenoceptor antagonist yohimbine-induced reinstatement of cocaine- seeking. We found that RO5263397 attenuated the escalation, breakpoint, and cue-seeking behavior in the extended access of cocaine self-administration model. We also found that RO5166017 reduced yohimbine-induced reinstatement of cocaine-seeking and yohimbine-potentiated cue-induced reinstatement of cocaine seeking. These results indicated that activation of TAAR1 attenuated extended access of cocaine self-administration and the stress-induced reinstatement of cocaine- seeking. Our results suggest that TAAR1 is a promising therapeutic target for the treatment of cocaine addiction.

Oral Communication 2-8

Protein kinase Cβ inhibition selectively decreases the reinforcing effects of amphetamine

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Several resting-state functional magnetic resonance imaging (fMRI) studies have documented altered cortico-striatal activity in long-term cocaine abusers. To investigate this further, functional neuroimaging during IV cocaine self-administration in nonhuman primates was used to examine potential changes in resting state fMRI connectivity, employing a seed-based approach from the dorsal striatum, i.e., putamen. This brain region has been associated with reinforcement learning and is thought to play a key role in drug-seeking and relapse-related behaviors. Three adult rhesus macaques (2 male, 1 female) were trained to self-administer intravenous cocaine in a mock MRI scanner under a fixed ratio 3 schedule of reinforcement, in which holding down a lever for 1-sec constituted a single response. All subjects underwent three scan sessions on a 3.0 Tesla TIM Trio MRI scanner; in each session, they could earn two injections of 0.1 mg/kg/inj cocaine/session. Functional connectivity maps were derived from a seed region placed in bilateral putamen and data from a 10-min timeout period before cocaine was compared with the 10-min timeout period following the second self-administered dose of cocaine (total intake: 0.2 mg/kg). Following cocaine self-administration, alterations in resting-state connectivity were identified in regions associated with motor control, reward, and cognitive processing, e.g., primary motor cortex, nucleus accumbens, insula, thalamus, and anterior/posterior cingulate cortex, respectively. A number of circuits previously identified in human cocaine abusers were found to be disrupted in the present study, suggesting that this protocol may be a translationally relevant means to characterize functional changes to brain networks in response to self-administered drugs. This approach may allow us to characterize the development of altered neural systems as a consequence of drug self- administration and to understand how such neural changes are modulated by candidate medications.

Oral Communication 3-1

The antiemetic and cognition-impairing effects of delta-9-tetrahydrocannabinol and methanandamide in nonhuman primates

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Emesis is one of the most common adverse symptoms associated with both disease and medical treatments of disease. Cannabinoid agonists have shown antiemetic effectiveness, but few preclinical studies have expressly examined the antiemetic effects of cannabinoids alongside their well-known cognition-impairing effects, limiting the translational value of antiemetic findings. In the present studies, we characterized both the antiemetic and cognition-impairing effects of delta-9- tetrahydrocannabinol (THC), the primary psychoactive phytocannabinoid in marijuana, and methanandamide (mAEA), the metabolically stable synthetic analog of the endocannabinoid anandamide. Adult male squirrel monkeys were administered THC (0.032-0.1 mg/kg) or mAEA (3.2- 10 mg/kg) prior to treatment with emetic doses of nicotine (0.1-0.56 mg/kg) or lithium chloride (LiCl; 200 mg/kg). A separate group of subjects was administered the same doses of THC or mAEA prior to a touchscreen-based task designed to assay learning (Repeated Acquisition), cognitive flexibility (Discrimination Reversal), or short-term memory (Delayed Matching-to-Sample). Administration of THC blocked both nicotine- and LiCl-induced emesis in a dose-related manner. Administration of 0.1 mg/kg THC fully blocked emesis produced by 0.32 mg/kg nicotine. However, this dose was associated with moderate impairment of Repeated Acquisition and Discrimination Reversal task performance and significant impairment of Delayed Matching-to-Sample task performance. Administration of mAEA also dose-dependently blocked nicotine- and LiCl-induced emesis; however, no dose tested blocked emesis in all subjects. Importantly, no dose of mAEA tested affected performance in any cognitive task. Taken together, although mAEA produced a less robust emetic effect than did THC, its more favorable cognitive profile indicates that each cannabinoid offers potential therapeutic benefits depending on specific treatment goals.

Oral Communication 3-2

Kappa-opioid agonists: Assessment of signaling bias on antinociception and oxycodone self-administration reduction in rats

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RATIONALE: Mu-opioid receptor (MOR) agonists are highly effective for the treatment of pain but have significant abuse liability. Combinations of MOR/kappa-opioid receptor (KOR) agonists have been shown to reduce the reinforcing effects of MOR agonists without decreasing their therapeutic benefits. However, it is unknown if biasing signaling at the KOR affects the ability of KOR agonists to modulate the reinforcing effects of MOR agonists. METHODS: We assessed the relative reinforcing effects of oxycodone alone or combined with a series of KOR agonists that spanned the bias spectrum in self-administration under a progressive-ratio (PR) schedule of reinforcement. In addition, we assessed the relative potency of each KOR agonist in thermal antinociception (hot plate). For self-administration, male Sprague-Dawley rats (n=6) received intravenous (i.v.) oxycodone (0.056 mg/kg/inf), or oxycodone combined with U50488H (0.032-0.1 mg/kg/inf), nalfurafine (0.32-3.2 ug/kg/inf), or Triazole 1.1 (0.32-1.0 mg/kg/inf). For the hot-plate tests, male rats (n=3; study ongoing) received i.v. injections of oxycodone (0.032-3.2 mg/kg), nalfurafine (0.0032-0.1 mg/kg), U50488H (0.032-10 mg/kg), or Triazole 1.1 (0.1-10 mg/kg) alone, and response latencies were measured. For the PR test, maximum injections were analyzed with a repeated-measure ANOVA, and means across subjects were compared using Bonferroni tests. For the hot-plate tests, relative potencies were determined with linear regression, and ED50 values were averaged and analyzed with a repeated- measures ANOVA and Bonferroni tests. RESULTS: Oxycodone functioned as a reinforcer. Nalfurafine and U50488H produced dose-dependent decreases in the reinforcing effects of oxycodone while Triazole 1.1 did not. In the hot-plate test, all drugs were equieffective, but varied in potency: nalfurafine > oxycodone > U50,488H = Triazole 1.1. CONCLUSION: This study demonstrates that G-protein biased KOR agonists are less effective at decreasing the reinforcing effects of a MOR

Oral Communication 3-3

Utilizing the purchase task procedure to evaluate non-medical prescription opioid demand: Incremental validity and temporal reliability

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Non-medical prescription opioid use and opioid use disorder (OUD) present a significant public health concern. Identifying behavioral mechanisms underlying OUD will assist in developing improved prevention and intervention approaches. Behavioral economic demand has been extensively evaluated as a measure of reinforcer valuation for alcohol and cigarettes, whereas prescription opioids have received comparatively little attention. The purpose of the present study was to utilize a purchase task procedure to measure the incremental validity and test-retest reliability of opioid demand in human participants. Individuals reporting past year non-medical prescription opioid use were recruited using the crowdsourcing platform Amazon Mechanical Turk. Participants completed an opioid purchase task (Experiment 1; N = 40) as well as measures of cannabis demand, delay discounting, and self-reported pain (Experiment 2; N = 83). Participants in Experiment 2 also completed a follow-up assessment one month later to evaluate test-retest reliability. More intense and inelastic opioid demand was associated with OUD in these two independent samples. Multivariable models indicated that higher opioid intensity and steeper opioid delay discounting rates each significantly and uniquely predicted OUD above and beyond use frequency. Increased opioid intensity was associated with higher self-reported pain, but not with perceived pain relief from opioids. Opioid demand showed good test-retest reliability (intensity r = .75; elasticity r = .63) as did OUD classifications based on a brief DSM-V assessment (r = .76). Taken together, opioid demand was incrementally valid and test-retest reliable as measured by the purchase task procedure. These findings support behavioral economic demand as a clinically useful measure of drug valuation that is sensitive to individual difference variables (e.g., pain, OUD).

Oral Communication 3-4

The role of interleukin-1 receptor-associated kinase 4 in drug addiction

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Drug addiction remains an unmanageable and costly disease. Apart from neuronal adaptation, growing recognition arises that glial proinflammatory activation importantly contributes to the rewarding effects of multiple drugs of abuse. Recent studies suggest the central role of Toll-like receptor 4 (TLR4), a candidate neuroimmune therapeutic target for drug addiction. While Interleukin- 1 receptor associated kinase 4 (IRAK4) plays a crucial role in TLR4 mediated innate immunity, there are few further studies support its functioning in drug addiction. We hypothesized that IRAK4 mediates drug-induced reinforcing effects, and disruption of IRAK4 signaling attenuates the addictive behaviors. In the present study, IRAK4 and IRAK1 phosphorylations after morphine and cocaine self- administration were evaluated using western blotting. The role of IRAK4 in morphine self- administration and cue-induced reinstatement was examined with its inhibitor, PF06650833. Moreover, local pharmacological manipulation was conducted to determine the role of IRAK4 in the nucleus accumbens (NAc) core in the cue-induced reinstatement of morphine seeking. We found that morphine self-administration significantly increased the phosphorylation of IRAK4, but not IRAK1, both in NAc and VTA. However, neither cocaine short access (2h/d) nor long access (6h/d) self-administration had any effect on the phosphorylation of IRAK4. Systemic administration of PF06650833 significantly attenuated cue-induced reinstatement of morphine seeking without affecting the spontaneous locomotion in rats, and microinjection of PF06650833 into NAc core sufficiently decreased cue-induced morphine reinstatement. These results demonstrated that modulation of IRAK4 activity regulates the cue-induced morphine reinstatement, and suggested it as a novel candidate target in treating drug addiction.

Oral Communication 3-5

Vaccine decreases choice of fentanyl over food and blocks expression of opioid withdrawal-associated increases in fentanyl reinforcement in male and female rats

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The current opioid crisis is a significant public health issue and there is a critical need for biomedical research to develop effective and easily deployable candidate treatments. One emerging treatment strategy for opioid use disorder may be immunopharmacotherapies or opioid-targeted vaccines. The present study determined the effectiveness of a fentanyl-tetanus toxoid conjugate vaccine to alter fentanyl self-administration using a fentanyl vs. food choice procedure in adult rats (n= 9 male, 10 female) under three conditions. First, fentanyl vaccine administration significantly blunted fentanyl reinforcement and increased food reinforcement for 15 weeks in non-opioid dependent rats. Second, surmountability experiments empirically determined that the fentanyl vaccine produced an approximate 22-fold potency shift in fentanyl vs. food choice that was as effective as the clinically approved treatment naltrexone. Lastly, fentanyl vaccine administration prevented the expression of withdrawal-associated increases in fentanyl vs. food choice following introduction of extended 12 h fentanyl access sessions. Overall, these results support the potential and further consideration of immunopharmacotherapies as candidate treatments to address the current opioid crisis.

Oral Communication 3-6

Opioid, $GABA_B$, and 5-HT_{1A} receptor agonist combinations in a mouse model of neuropathic pain

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Rationale: Chronic pain is a serious and common complaint, carries a large economic burden, and has an unmet need for better therapeutics. The prescription of opiates has been a major strategy for managing pain but carries a major risk in the form of abuse and overdose. One way to reduce this liability is through the combination with other drugs that selectively enhance the analgesic effects of opioids, without increasing the side effects of opioids. Here, morphine, the $GABA_B$ receptor agonist baclofen, and the 5-HT_{1A} receptor agonist buspirone were studied alone and in combination in a mouse model of neuropathic pain: chronic constriction injury (CCI) of the sciatic nerve.

Hypothesis: Baclofen and buspirone will enhance the effects of morphine in the CCI model of neuropathic pain.

Methods: CCI of the sciatic nerve or sham surgeries were performed in a total of 62 male and female C57BL/6J mice. Mechanical sensitivity was assessed with von Frey filaments of differing intensities and thermal sensitivity was assessed on a hotplate set at 52 degrees C with a 30-s cut-off.

Results: CCI produced significant increases in sensitivity to mechanical stimuli (i.e., allodynia) and decreases in response latency to the thermal stimulus (i.e., hyperalgesia). By themselves baclofen, buspirone and morphine reversed CCI-induced mechanical allodynia and thermal hyperalgesia. A 1:1 combination of these drugs, prepared based upon their respective ED_{50} values, produced dose dependent anti-allodynia and anti-hyperalgesia. Naltrexone antagonized the effects of morphine, as well as the effects of drug combinations that included morphine. The $GABA_B$ receptor antagonist CGP34358 antagonized the effects of baclofen, as well the effects of drug combinations that included baclofen.

Conclusions: These findings suggest that $GABA_B$ and 5-HT_{1A} agonists may be useful adjunctive therapies when combined with opioid agonists for the treatment of neuropathic pain.

Oral Communication 3-7

Pharmacological characterization of mitragynine, the primary constituent in Kratom (Mitragyna Speciosa): Discriminative stimulus effect

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Mitragynine is the primary alkaloid constituent of kratom (Mitragyna Speciosa). Mitragynine is known to have affinity for mu-opioid receptors, and lesser affinity for alpha2-adrenergic receptors. The present study characterized the discriminative-stimulus effects of mitragynine under a standard two-lever operant conditioning procedure using a food reinforcer. In rats trained to discriminate morphine (3.2 mg/kg, i.p.) from vehicle, morphine (0.56-3.2 mg/kg) and the mu-opioid receptor agonist fentanyl (0.0032-0.056 mg/kg) produced dose-dependent increases in morphine-lever responding (ED50s: 1.74 and 0.0201 mg/kg, i.p.). Mitragynine produced a maximum of 74% morphine-lever responding up to a dose (56 mg/kg) that markedly decreased response rate. In rats trained to discriminate mitragynine (32 mg/kg, i.p.) from vehicle, mitragynine (3.2-56 mg/kg) dose-dependently increased mitragynine-lever responding (ED50: 16.9 mg/kg). Morphine (up to 32 mg/kg) and fentanyl (up to 0.178 mg/kg) produced a maximum of 75% mitragynine-lever responding. The opioid antagonist naltrexone (0.032 mg/kg) significantly antagonized both training drugs. The alpha2-adrenergic receptor agonist clonidine (0.0178-0.32 mg/kg) produced a maximum of 22% and 43% drug-lever responding in morphine- and mitragynine-trained rats, respectively. The alpha2-adrenergic receptor antagonist yohimbine (1-10 mg/kg, i.p.) produced a maximum of 5% and 51% drug-lever responding in the respective discriminations. Yohimbine (3.2 mg/kg) significantly antagonized only mitragynine. The current results suggests that mitragynine functions as a low efficacy mu-opioid receptor agonist with discriminative stimulus effects that are overlapping yet distinct from those of morphine. These data suggest that alpha2-adrenergic receptors represent a component of mitragynine's pharmacological mechanism of action in vivo. Supported by NIDA DA25267 and DA48353.

Oral Communication 3-8

Long-lasting effects of methocinnamox (MCAM) on opioid self-administration

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Methocinnamox (MCAM) is a pseudo-irreversible mu opioid receptor antagonist that suppresses heroin self-administration in rhesus monkeys for several days following a single administration, demonstrating the potential of MCAM for treating opioid abuse. However, the selectivity of MCAM for decreasing drug versus non-drug (e.g., food) reinforced behavior has not been well characterized. This study compared effects of MCAM with those of naltrexone on responding under a food versus drug choice procedure, which is more selective for changes in reinforcing effectiveness as compared to single-response procedures. Three male rhesus monkeys served as subjects. Responding on one lever delivered a 300-mg sucrose pellet and responding on the other lever delivered an i.v. infusion of remifentanil; the unit dose of remifentanil increased across blocks within the session. Naltrexone or MCAM was administered i.v. prior to a test session. Remifentanil dose-dependently increased choice of remifentanil over food and dose-effect curves were stable across days. Naltrexone and MCAM decreased choice of remifentanil and increased choice of food, shifting the remifentanil dose-effect curve rightward, and, in some cases (i.e., following MCAM) downward, with monkeys choosing food exclusively. Effects of naltrexone were short-lived, lasting less than one day, while effects of a single injection of MCAM lasted for several days. The number trials completed was not significantly altered, indicating that effects were the result of reallocation of behavior rather than a generalized suppression of behavior. Selective attenuation of opioid-maintained behavior coupled with a long duration of action indicates that this novel drug could be superior to currently available treatments for opioid abuse. This work was supported by the National Institutes of Health [Grants R01DA005018 and R01DA007315] and the Welch Foundation [Grant AQ-0039].

Poster Presentations

Poster 1

Individual differences in high levels of MDPV self-administration: interactions with nicotine

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A subset of rats that self-administer synthetic cathinones, such as 3,4-methylenedioxypyrovalerone (MDPV), develop compulsive-like patterns of responding that result in high levels of drug intake that may be related to the patterns of synthetic cathinone use reported in humans. Although previous studies suggest that the MDPV "high-responder" phenotype transfers to other stimulants, and is absent in rats with a prior history of responding for cocaine, it is unknown if: 1) prior histories with drugs from other classes (e.g., nicotine) would similarly inhibit the development of high levels of MDPV self-administration; and 2) if the high-responders for MDPV exhibit similarly high levels of nicotine self-administration. Male Sprague-Dawley rats (n=20) initially self-administered MDPV (0.032 mg/kg/inf) or nicotine (0.032 mg/kg/inf) under a fixed ratio (FR) 1 schedule for 10 sessions and then a FR5 schedule for 10 sessions. Consistent with previous studies, ~40% of the rats responding for MDPV developed a high-responder phenotype; however, none of the rats responding for nicotine rats did. The nicotine group was then allowed to self-administer MDPV for 20 additional sessions. Subsequently, full FR5 dose response curves were generated for MDPV and nicotine in both groups. These studies found that, unlike with a cocaine self-administration history, a history of responding for nicotine failed to prevent the transition to high levels of MDPV self-administration. Additionally, though there are no differences in the descending limb of the nicotine dose response curve, there is a leftward/upward shift in the ascending limb in high-responder rats compared to low-responder rats, suggesting only some aspects of the high-responder phenotype transfer to nicotine self-administration. These findings suggest that the neurobiological mechanisms mediating the high levels of dysregulated self-administration of MDPV and other stimulants may be different than those mediating dysregulated intake of nicotine.

Poster 2

Characterization of the DOR-mediated effects of MMP2200, a mixed efficacy opioid agonist

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Mixed efficacy opioid ligands are being considered as a potential alternative to the mu opioid receptor (MOR) agonists used clinically for analgesia. It has been shown that pharmacological manipulation of the delta opioid receptor (DOR) in conjunction with a MOR agonist can lead to a better side effect profile. MMP2200 is a CNS permeable, glycosylated peptide and an agonist at both MORs and DORs. Previous reports characterized the MOR agonist effects of MMP2200, however, the DOR agonist effects of MMP2200 in vivo have not been explored. The purpose of this study was to determine whether or not MMP2200 acts as a DOR agonist in male C57BL6 mice. We hypothesize that MMP2200 will produce DOR-mediated convulsions and antidepressant-like effects in male C57BL6 mice. Convulsions were evaluated by observation and assessed qualitatively using a modified Racine scale. Antidepressant like effects were evaluated in the mouse forced swim test. Administration of MMP2200 produced convulsions in mice in a dose-dependent manner. These convulsions were short and non-lethal and followed by catalepsy period and a quick recovery— similar to that produced by SNC80, a prototypical DOR agonist. MMP2200-induced convulsive activity was prevented by pretreatment with naltrindole, a DOR selective antagonist or genetic deletion of DOR. In the forced swim test, SNC80, was able to produce dose-dependent decreases in immobility, and MMP2200 produced modest effects. This is the first study to demonstrate that MMP2200 produces some DOR agonist effects in vivo, in particular DOR-mediated convulsions. In addition, this work further identifies that DOR activation by structurally different DOR agonists induces convulsions in mice.

Poster 3

HIV-1 Gag protein nanoparticle systems: assembly and viral inhibition strategies

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Current drug therapies available to individuals infected with the HIV-1 virus work to target reverse transcriptase and the viral protease with a drug cocktail. It is known that during the process of maturation in HIV-1 viral protease cleaves Gag and initiates conformational changes in CA proteins which foster its assembly into the capsid, a fullerene shaped shell composed of ~1500 copies of CA. This capsid houses the viral genetic information and poses as a viable target for treatment to combat the virus. Current knowledge of the mechanisms and processes of this conformational shift is very limited. To enhance and further our mechanistical understanding of the process of maturation we studied the effects of protein crowding by constructing Gag virus-like particles (VLP's) alone (control), in the presence of C-terminal capsid, cytochrome-c, lipids, and ribonucleic acid to study the effects their presence may have on Gag's ability to self-assemble. Our results indicate that Gag retains its ability to self-assemble into VLP's despite protein crowding effects and competitive inhibition of its dimerization interface. Future work will be centered around 3D-NMR spectroscopy utilizing methods involving magic angle spinning (MAS) analysis. (Supported by the NSF Grant 1757365 to University of Puerto Rico-Rio Pierdas)

Poster 4

Role of KCNQ ("M-type") K+ channels of dopaminergic neurons as key regulators of cocaine addiction

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Dopamine neurons in the ventral tegmental area (VTA) fire bursts of action potentials in response to the presentation of rewarding stimuli, producing a learning signal that plays a central role in the development of addiction. It has been shown that dopamine neurons of the VTA express "M-type" K+ ion channels, which play dominant roles in control of excitability, action-potential firing and neurotransmitter release throughout the nervous system. In VTA neurons, the neurophysiological role of M channels is still little understood, nor is it known how manipulating the activity or expression of these channels could affect drug-related behaviors. We hypothesize that up-regulation of M current activity in VTA dopaminergic neurons could oppose the reinforcing properties of psychostimulants by countering increased dopamine neuron firing, a finding that could have far-reaching implications for drug abuse treatment. Our preliminary results are in accordance with this hypothesis. Experiments with whole-cell slice patch clamp show that VTA neurons do present a M current-like outward current in response to changes in voltage. We have also shown that pharmacological inhibition of M current, with XE991, increases the number of spikes in response to a large current. Furthermore, in cell attached mode, the M channel opener Flupirtine decreases D-aspartic acid-induced neuronal spikes and XE991 increases spontaneous firing in VTA dopaminergic neurons. In future experiments we will investigate, in VTA slices, how M current manipulation alters cocaine-induced neuronal firing and test the roles of different M channel subunits. We will also perform cocaine self-administration behavioral experiments in M channel knockdown mice and quantify cocaine-induced dopamine release in these animals. These findings could elucidate important neuro-adaptive mechanisms associated with psychostimulant use and point toward novel therapeutic targets to alleviate the devastating effects of chronic psychostimulant addiction.

Poster 5

Effects of ambient temperature and social housing on 3,4-methylenedioxypyrovalerone (MDPV) oral self-administration and locomotor activity

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Novel "designer" drugs are inexpensive to synthesize and mimic the effects of traditional drugs of abuse. Synthetic analogues of plant-derived cathinone are active constituents in abused "bath salts" products, and are commonly reported adulterants of popular party drugs like MDMA, leading to widespread unintentional use of these substances. Few studies have attempted to characterize the *in vivo* effects of synthetic cathinones under party-like environmental conditions typical of the settings in which they are used by humans. To address this knowledge gap and perhaps establish a more translatable model of synthetic cathinone abuse liability and toxicity, we assessed the oral self-administration and locomotor stimulant effects of the synthetic cathinone MDPV under conditions of increased ambient temperature, and social housing. To first assess the effects of increased ambient temperature on oral self-administration, singly housed mice were maintained at either 20ºC or 28ºC, water deprived for 21-hr, then allowed a 3-hr period to orally self-administer 0.3 mg/ml MDPV for 10 consecutive days. There was no initial difference in MDPV intake as a function of ambient temperature, but consumption escalated more rapidly at the 28ºC condition. In separate studies, mice implanted with a radio telemetry probe were housed singly or in social groups of 3 or 6 at either 20ºC or 28ºC, then administered saline, 1.0, 3.0, or 10.0 mg/kg MDPV *via* intraperitoneal injections every 2 hours for a total of 4 injections. Locomotor activity and core temperatures were recorded throughout the drug regimen, and body weights were also tracked. The effects of social housing at both ambient temperatures on MDPV-elicited locomotor activity, weight loss, and thermoregulation will be presented. These experiments suggest that, similar to structurally-related psychostimulants like MDMA, the pharmacological actions of MDPV are also impacted by environmental variables associated with the settings in which the drug is commonly abused in humans. These studies supported by DA039195, DA022981 and the UAMS CTN.

Poster 6

Behavioral, cardiovascular, and thermoregulatory effects of IV MDPV, Methylone, and caffeine in rats

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Abuse of synthetic cathinones ("bath salts") remains a significant global health concern. The constituents of bath salt preparations are typically at least one synthetic cathinone (e.g. 3,4-methylenedioxypyrovalerone [MDPV] or 3,4-methylenedioxy-N-methylcathinone [methylone]), in addition to other stimulants such as caffeine. Acute toxicity following synthetic cathinone ingestion typically comprises psychosis, sympathomimetic effects, tachycardia, and hyperthermia. The goal of the current study was to characterize behavioral, cardiovascular, and thermoregulatory effects of MDPV, methylone, and caffeine. Male Sprague Dawley rats were implanted with an intravenous catheter and a radio-telemetric probe capable of recording core body temperature, heart rate, blood pressure, and locomotor activity. 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 (0.1-10 mg/kg), or caffeine (0.32-32 mg/kg). Recordings continued for 6 hours following drug administration. All trials were video recorded to allow for quantification of rearing and stereotypy. MDPV, methylone, and caffeine produced dose-dependent increases in core body temperature (caffeine > MDPV > methylone), blood pressure (MDPV > caffeine > methylone), heart rate (methylone > MDPV > caffeine), and locomotor activity (MDPV > caffeine = methylone) relative to baseline measurements. MDPV was more potent than methylone, which was more potent than caffeine. MDPV and methylone also dose-dependently increased stereotypy. These data show that intravenous administration of either MDPV, methylone, or caffeine alters temperature, heart rate, blood pressure, and locomotor activity in a dose-dependent manner. Though these data provide evidence regarding the physiological effects of synthetic cathinones, future studies will determine the degree to which these effects are enhanced when administered as "bath salts" mixtures.
Research supported by R01DA039146 (GTC), and the NIDA/NIAAA IRP (KCR)

Poster 7

The impact of opioids on maternal-infant interaction, stress response, and attunement

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The quality of early primary relationships, such as the one between a mother and her infant, are critical to early childhood development. The mental and behavioral health of the mother plays a key role in this process, and is supported by the reciprocal behavioral responses between a mother and infant, known as physiologic attunement. Physiological attunement has been studied with term and preterm infants however, studies with infants who are prenatally opioid-exposed are indicated. Therefore, the purpose of this prospective, cohort study is to gain a better understanding of the impact of prenatal opioid use on: 1) maternal diurnal cortisol patterns during pregnancy, 2) maternal-infant stress reactivity and recovery, and 3) maternal-infant physiologic attunement. Data collection and analysis is ongoing. Women (N=160) are being enrolled either prenatally or shortly after the birth of their infants. Infants (N=160) are being enrolled shortly after birth. Physiological data are being non-invasively collected from mothers and infants at several time-points. To assess diurnal cortisol patterns, we are collecting four saliva samples over two consecutive days from women during the third trimester of pregnancy. When infants are approximately six months old, we are assessing the mother-infant dyad for stress reactivity, recovery and physiological attunement using an established behavioral paradigm, the Still Face Paradigm (SFP). We are collecting physiological data (heartrate and saliva) at baseline, during the emotion suppression phase, and following completion of the experiment. The SFP is being video-recorded and will be coded for mother-infant behavior to analyze maternal and infant interaction patterns. Physiological samples are being stored in a repository for future analysis. To date, data has been collected on a total of 30 mother-infant dyads. Study findings will provide a better understanding of the impact of prenatal opioid use on early mother-infant interactions that could lead to the development and implementation of interventions that improve stress response and support the maternal-infant relationship.

Poster 8

Engaging paramedicine support services to provide post opioid overdose follow-up and referral to treatment

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Overdose is now the leading cause of injury death in the United States. As overdose rates have steadily risen at the national level, Texas has also experienced a dramatic increase in overdose deaths. For example, in 2016 the state reported 1,375 overdose deaths, almost doubling the number reported in 2010. To positively impact this crisis and save lives, novel and new approaches are needed. Therefore, with funding from the Texas Health & Human Services Commission (HHSC), the School of Nursing at UT Health San Antonio is partnering with the San Antonio Fire Department's Integrated Mobile Health Unit and the San Antonio Council on Alcohol & Drug Awareness (SACADA) to design, implement, and evaluate an opioid overdose survivor follow-up pilot program. Through this new program, paramedicine is providing overdose follow-up services to include peer recovery coaching services provided by SACADA. This community informed program is filling an identified gap in our current behavioral healthcare infrastructure by offering a "warm handoff" of overdose survivors to available treatment and recovery services. Launched in November of 2018, our team is conducting continuous program evaluation as the future goal of HHSC is to disseminate this program statewide.

Poster 9

Evaluating the acute drug effects on food intake in rats

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Decreased appetite or food intake is a major adverse effect of many drugs, including drugs of abuse. The acute effects of drugs on food intake may be difficult to discern by 24 h home cage food intake or body weight measurements. Therefore, the current study aims to establish an assay that can be used to evaluate acute drug effects on food intake or appetite. As part of the assay validation process, we hypothesized that the cannabinoid receptor 1 (CB1) antagonist Rimonabant (SR141617A) would decrease acute food intake in a dose dependent manner following a brief period of food restriction. Single-housed male Sprague-Dawley rats were food deprived in their home cage an hour prior to the start of the dark cycle. Thirty minutes into the dark cycle each rat was given a single i.p. injection of vehicle or drug. Food pellets were pre-weighed and put in bowls in the rat's home cage an hour after injection. Food intake was measured twice: one hour after and approximately 14 h after pre-weighed food was placed in the home cage. Food intake was measured repeatedly once per week using a within subjects design to evaluate the consistency of the assay. Rats consistently ate between 9-11g of food within the first hour of food access and 11-14g over a 14 h period, demonstrating the majority of food was consumed at the start of the dark cycle. Rimonabant (1-10 mg/kg, i.p.) dose-dependently decreased food intake 1 hr after drug administration; however, the magnitude of these effects was greatly diminished when measured over 14 h. Overall, these data suggest this experimental design could be an effective screening tool to determine if compounds have an acute or prolonged effect on food intake.

Poster 10

MJN110 enhancement of operant responding to reward predictive cues is not affected by acute appetite stimulation

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Cannabinoids have potent and well documented appetite stimulating effects. However, the complex contribution of endocannabinoid regulation to hedonic and homeostatic feeding is increasingly appreciated. MJN110 enhances 2-arachidonyl (2-AG) levels by inhibiting its primary degradative enzyme monoacyl glycerol lipase (MAGL). Recently it has been shown that MJN110 produces an anorexigenic effect characterized by decreased food intake over a 4-hour period. However, we demonstrate that MJN110 enhances both the choice and vigor of responding in an operant task reinforced by a highly palatable reward outcome (10% sucrose), indicating that MJN110 increases motivation for food rewards. To better understand these contradictory results, we determined whether MJN110 alters free intake of 10% sucrose within the parameters of our operant results (i.e., volume and time). Pretreatment with 10 mg/kg (i.p.) of MJN110 significantly increased cumulative sucrose consumption compared to vehicle after one hour of freely available sucrose. However, there was no change in consumption early in the session, which reflects the volume normally obtained in our standard operant task (~5-7 ml). Analysis of drinking bout parameters and additional doses of MJN110 over different session lengths are being explored. Together these data suggest that the enhancement of operant responding for sucrose is most readily be explained by changes in motivation rather than appetite.

Poster 11

Locomotor stimulant effects and sensitization following cumulative administration of MDMA and its putatively safer deuterated form in mice

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Locomotor activity was monitored by 8 clear acrylic chambers equipped with photocell beam detectors sensitive to infrared light (43.2 x 43.2 x 29.8 cm; Med Associates Inc., St. Albans, VT USA). Cages of pair-housed mice (*N*=16) were randomly assigned to MDMA (*n*=8) or deuterated (*n*=8) treatment groups. Following two 60 min habituation sessions and a 150 min session wherein mice received five injections of saline, a 150 min session (day 1) was conducted during which mice received cumulative doses of deuterated or MDMA (cumulative doses of 0, 3.2, 10, 32, 56 mg/kg; ip; injections spaced 30 min apart). For the next six consecutive days, mice received either 10 mg/kg deuterated or 10 mg/kg MDMA according to their grouping assignments. Conditioning sessions were 60 min long. On day eight, deuterated and MDMA dose-effect curves were determined using procedures identical to day 1, and was followed by a six-day drug-free break during which mice remained untouched in their home cages. On day 15, cumulative dose-effect curves were re-determined as described above. On day 16, deuterated and MDMA dose-effect curves were determined according to a crossover design, in which the deuterated-conditioned mice were tested with MDMA and the MDMA-conditioned mice were tested with deuterated. Cumulative doses of deuterated or MDMA increased horizontal distance traveled and stereotypy counts within the dose range of 3.2-56 mg/kg. MDMA more potently increased locomotor activity compared to deuterated. Horizontal activity and stereotyped movements sensitized as a result of the cumulative dosing procedure in both groups. Compared to our previous experiment that compared the locomotor stimulant effects and sensitization of deuterated to MDMA following acute administration, the findings of the present study indicate that the relative safety advantage of deuterated may be reduced following cumulative administration. These studies supported by NIH T32 DA022981

Poster 12

One of a dozen phenylmorphans: optimization of the key oxide-bridge closure in the synthesis of an important narcotic receptor for pharmacological evaluation

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Over the last decade, the misuse of synthetic opioids in the United States has led to a rapid increase in overdose mortalities. As a result, President Trump signed an executive order in 2017 that recognized the current opioid epidemic in the US as a Nationwide Public Health Emergency. In order to combat the opioid crisis, the National Institute on Drug Abuse (NIDA) has identified key areas for chemical development, which includes the creation of safe, effective, and nonaddictive pharmacotherapies for managing chronic pain. Toward this goal, our group has synthesized and pharmacologically characterized twelve structurally rigid a-through f-oxide-bridged phenylmorphans– whose chemical structures are related to morphine. Of the dozen compounds surveyed, one racemic *N*-phenethyl *ortho*-c oxide-bridged phenylmorphan was found to contain the highest μ-opioid receptor (MOR) affinity (K_i = 1.1 nM). This promising *in vitro* result has augmented our interests in further studying individual enantiomers and analogs thereof. In order to provide sufficient amounts of these materials, efforts are being made to optimize the synthesis of our lead compound. In particular, the key ring closure step to form the *trans*-fused dihydrobenzofuran skeleton is being investigated and our recent findings will be discussed.

Poster 13

The significance of chirality in drug design and synthesis of bitopic ligands as D_3R selective agonists

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The development of selective dopamine receptor agonists is a subject of increasing interest due to the potential therapeutic applications in neurological disorders. Due to the large degree of homogeneity among the D_2-like family of dopamine receptors, achieving ligands capable of discrimination among them remains a significant challenge. Previous work from our lab has shown the use of bitopic ligands to be a powerful strategy in achieving increased D_2R or D_3R selectivity for agonists and antagonists alike. Inspired by the potential for chemical modification of the D_3 preferential agonists (+)-PD128,907 and PF-592379, we sought to synthesize and test a variety of bitopic structures to further improve their D_3R selectivity. When in a bitopic configuration, the (S,S) conformation of the PF-592379 scaffold resulted in a privileged architecture with increased affinity and selectivity for the D_3R orthosteric binding site. Driven by an earlier finding (Kumar *et al.*, 2017) revealing the inclusion of a cyclopropyl moiety in the linker of the bitopic molecule may induce a structural orientation favorable for D_3R selectivity we proceeded to synthesize the bitopic compounds of the privileged (S,S) PF-592379 primary pharmacophore with a cyclopropyl ring in the linker. Incorporation of the ring in the linker and full resolution of the chiral centers present allowed us to analyze the effect of the stereochemistry of the linker on the final affinity and selectivity of the bitopic molecules synthesized. Lead compound FOB-02-04A (D_2R K_i: 87.8 nM, D_3R K_i: 1.85 nM, D_2R/D_3R: 47.5), may have the highest D_3R to D_2R selectivity reported for an agonist, to date. The high structural complexity of these compounds may inspire future computational studies to better understand ligand-receptor interactions, as well as underscore potential biased agonism as a consequence of specific receptor conformations.

Poster 14

Novel muscarinic antagonists with anti-depressant-like effects in rodents

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Scopolamine, a non-selective muscarinic antagonist, is a rapidly effective antidepressant compound in humans likely mediated through an antimuscarinic effect. Unfortunately, scopolamine can produce cognitive impairment including memory disturbances in humans. It is our goal to identify a muscarinic antagonist that may be able to relieve depression without disrupting cognitive effects. The 3-*exo*-1-azabicyclo[2.2.1]heptane, 1-azabicyclo[2.2.2]octane, and N-methyltetrahydropyidine 3-substituted-1,2,4-oxadiazoles appear to be excellent chemical scaffolds for the generation of potent muscarinic agonists/antagonists. The addition of a methyl group to the 3-position of the 1,2,4-oxadiazole yields some of the most potent muscarinic agonists currently known. Yet, addition of a cyclopropyl group appears to reduce efficacy and confer antagonist action at muscarinic sites. Herein we show the pharmacological profiles of multiple pairs of methyl/cyclopropyl analogues we have designed in the anticipation of separating antidepressant-like activity from cognitive impairment. (Supported by NIMH Grant 107499).

Poster 15

Metabolic stability assessment of cannabinoid receptor negative allosteric modulators

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Activation of the cannabinoid receptor 1 (CB1R) contributes to the rewarding effects of drugs of abuse and CB1R agonists produce orexant effects that are useful as adjuvants for chemotherapy. Conversely, inhibitors of CB1R activity have potential therapeutic use as treatments for obesity and substance use disorders; however, CB1R inverse agonists such as rimonabant (Acomplia) cause suicidal ideation that limit their use as pharmacotherapies. CB1R negative allosteric modulators (CB1R-NAMs) are a potential alternative to CB1R inverse agonists because the "ceiling effect" limits their potential to cause such dangerous side effects. Two CB1R-NAMs (PSNCBAM-1, 1; and Org27569, 2) have produced variable results in both *in vitro* and *in vivo* studies. We have discovered a novel CB1R-NAM, CWC-1-002 (3), that may be a viable alternative lead. The goal of this study is to evaluate the aqueous solubility, potential to inhibit CYP2D6 and CYP3A4, and metabolic stability of 1-3 using human liver microsomes (HLMs). Aqueous solubility was determined by nephelometry over 7 dilutions for 1, 2, and the HCl salt and free base forms of 3. The free base and HCl salt forms of 3 were approximately 2-3-fold more soluble than 1 and 2, though the limit of solubility for each was < 1 mg/mL. The CYP inhibition studies (P450 Glo, Promega, Inc., Madison, WI) suggest modest potential for 1 to inhibit CYP2D6 (IC50 15.63 ± 5.15 μM) and CYP3A4 (IC50 2.772 ± 0.603 μM), and low potential for 2 to inhibit either enzyme (IC50 > 62.5 μM). It is highly unlikely that 3 would inhibit the activity of CYP3A4 (IC50 56.8 ± 4.23 μM), but a CYP2D6 interaction is possible (IC50 4.26 ± 0.58 μM). In the HLM study, test compounds (2 and 3, 10mM; 1, 5mM) were incubated with HLMs, extracted at 8 time points over 120 minutes, and analyzed by high performance liquid chromatography (HPLC). Metabolic half-life values were calculated. The order of increasing stability was found to be 1 (37.15 min) < 3 (163.39 min) < 2 (356.49 min). These findings add to our understanding of the solubility and stability of 1 and 2, and demonstrate the potential of 3 as an improved lead for developing CB1R-NAMs as therapeutics.

Poster 16

Juvenile combination treatment with fluoxetine and aripiprazole does not alter cocaine-seeking behavior in adulthood

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Major depressive disorder (MDD) is a highly debilitating illness that affects millions of people across the globe. Interestingly, the first reported incidence of MDD occurs during the adolescence stage of development. Because fluoxetine (FLX) is the only antidepressant medication approved by the Food and Drug Administration (FDA) for the treatment of pediatric MDD, the prescriptions rates of this antidepressant are very high within populations younger than 20 years of age. Unfortunately, FLX does not alleviate MDD symptoms in most patients – with close to 50% being resistant to this pharmacotherapeutic treatment. An alternative approach for treatment resistant-MDD is the prescription of FLX in combination with the atypical antipsychotic aripiprazole (ARIP). This is surprising, given that the long-term consequences of this combination treatment (FLX+ARIP) have not been thoroughly assessed at either the clinical or preclinical level. Thus, the purpose of this study is to examine for potential long-term consequences of juvenile combination therapy with FLX+ARIP on sensitivity to drugs of abuse in adulthood. To achieve this, adolescent (postnatal day [PD] 35) male C57BL/6 mice were administered with either vehicle (DMSO) or FLX (10 mg/kg) with aripiprazole (0.03 mg/kg) for 15 consecutive days (PD35-49). Twenty-one days later, once the mice reached adulthood (PD70), they were tested for cocaine (5 mg/kg) sensitivity using the conditioned place preference test (CPP). The results of this experiment show that when tested in adulthood, animals pretreated with FLX+ARIP during adolescence did not differ in the time spent in the cocaine-paired side when compared to VEH-treated controls. Together, our results suggest that no long-lasting reward-related deficits become apparent in male C57BL/6 mice exposed to FLX+ARIP during the adolescent stage of development.

Poster 17

Sex differences in affective behaviors following adolescent intermittent ethanol exposure.

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More than 90% of alcohol consumed by young people is in the pattern of binge drinking. This pattern of alcohol consumption occurs during a critical developmental period when the adolescent brain is undergoing dramatic maturational changes that can influence long-lasting changes in behavior control and affective behaviors in adulthood. Sex differences in the influence of adolescent binge alcohol exposure have been observed in rodent models. This study's focus is to investigate the long-term impact of binge alcohol exposure during adolescence in males and females. Specifically, we aimed to determine changes in affective behaviors in adulthood following adolescent intermittent ethanol (AIE) exposure as a model of binge alcohol exposure. We exposed fifty-seven C57BL/6J male and female mice to AIE vapor inhalation exposure from postnatal day (PND) 28-41. Specifically, on PND 28-29, 32-33, 36-37, and 40-41, adolescent mice were exposed to vapor inhalation of volatized ethanol, or air as a control, for 16 hr a day/overnight. Each cycle consisted of two consecutive days of ethanol, or air, exposure followed by two days of non-exposure. Mice were introduced to the inhalation chamber at 1600 hr and removed the following morning at 0800, followed by eight hours in the home cage. After the two days of each exposure cycle, mice remained in the home cage. Mice underwent an abstinence period from PND 42 until testing in adulthood. From PND 70-80, we assessed behavior in the light/dark test and forced swim test to examine changes in affective behaviors of anxiety-like behavior and stress reactivity, respectively. Data were analyzed by two-way ANOVA for Sex and Exposure. Blood ethanol concentrations during AIE ethanol exposure were 295.8 ± 23.3 mg/dl for females and 269.1 ± 25.0 mg/dl for males. Preliminary data indicate that females entered the light side more quickly and more frequently in the light/dark test compared to males. There were no differences in time spent immobile in the forced swim test as a measure of stress reactivity. Together, these data indicate the presence of sex differences in affective behaviors in adulthood.

Poster 18

Locomotor effects of repeated 3,4-methylenedioxypyrovalerone administration in male Sprague-Dawley rats

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Over the past decade, the recreational use of synthetic cathinones ("bath salts") has increased worldwide. 3,4-methylenedioxypyrovalerone (MDPV) is a common constituent of many "bath salt" mixtures, and although a number of studies have described its acute behavioral effects, less is known about how these effects change with repeated administration. Accordingly, the primary goal of this study was to characterize the locomotor effects of MDPV across 9 weeks of repeated dosing, in 4 adult male Sprague-Dawley rats. Cumulative dose response curves (0.1 mg/kg – 10 mg/kg) were generated weekly (Monday), with bolus doses of 10 mg/kg of MDPV also administered weekly (Thursday); locomotor activity and rearing were recorded for a total of 3 hours. During initial tests, the dose-response curves for MDPV-induced activity and rearing peaked at 3.2 mg/kg, with a bolus dose of 10 mg/kg stimulating activity and rearing for the duration of the observation period. However, with repeated dosing, the peak of the dose-response curves gradually shifted leftward. Although slight increases in activity and rearing were observed at small doses (ascending limb), much of this effect was driven by an increase in stereotypy (e.g., head movements) at larger doses of MDPV, resulting in a leftward shift of the descending limb, and a suppression of activity and rearing following bolus doses. Thus, unlike the sensitization to locomotor stimulatory effects often observed with cocaine, repeated administration of MDPV primarily resulted in an increased sensitivity to the stereotypic behavioral effects with little evidence for increases in locomotor activity.

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Poster 19

MAGL inhibition in the ventral tegmental area and nucleus accumbens enhances responding to reward predictive cues.

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The endocannabinoids (eCBs) 2-arachidonoyl glycerol (2-AG) and anandamide (AEA) are metabolized by the degradative enzymes monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH), respectively. Using an operant model of reward-seeking, in which animals are trained to respond to discrete incentive cues (ICs), we have demonstrated that antagonizing eCB tone at the CB1 receptor disrupts responding to ICs. Conversely, MAGL inhibition with MJN110 enhanced both the choice to respond to reward-predictive ICs, and the vigor of the response. In the current study, our lab sought to determine whether these effects are centrally mediated, specifically in the ventral tegmental area (VTA) and nucleus accumbens (NAc), two regions critically involved in reward-seeking. In the IC task, rats must nosepoke during an 8-sec audiovisual cue to receive 64 µl of 10% sucrose. In a variant of this task, the reward delivered progressively decreases every 15 mins from 64 µl to 48 µl, 32 µl and 16 µl. The percentage of ICs responded to progressively decreases proportionately with the volume of sucrose, while the latency to respond to the IC and the latency to enter the reward cup both increase. MJN110 (2, 4 ug) and rimonabant (3ug) were microinfused into the VTA or NAc of male Long Evans rats, 30 mins prior to start of the IC task. MAGL inhibition in the VTA and NAc enhanced responding to the IC, and decreased the latencies to respond and obtain the reward. However, the CB1 antagonist rimonabant decreased responding when microinfused in the NAc, but not the VTA. Our results suggest that enhancing 2-AG levels in both the VTA and NAc increases responding to reward predictive incentive cues, while disrupting normal eCB signaling in the NAc but not VTA attenuates responding. Together these data demonstrate heterogenous regulation of reward seeking by eCBs.

Poster 20

In vivo pharmacology of 1-Benzyl-3-aminopyrrolidine enantiomers in mice

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1-benzylpiperazine (BZP) is an abused research chemical with psychostimulant effects. In the early 2000s, its usage become widespread in New Zealand as a legal alternative to MDMA, and abuse throughout the western world soon followed. 1-benzyl-3-aminopyrrolidine (BZAP) is a chiral molecule with two stereoisomers, and is currently being used as a precursor in medications development efforts, but there are concerns that therapeutics based on the BZAP structure may themselves have BZP-like abuse potential. The abuse potential of the BZAP enantiomers has not been previously assessed in any models, but given structural similarities to BZP, locomotor stimulant and hyperthermic effects were predicted in mice. Therefore, these studies used radiotelemetry to track core temperature and locomotor activity in mice following treatment with saline or various doses of BZP, (*R*)-BZAP or (*S*)-BZAP. As compared to saline, BZP dose-dependently elicited locomotor stimulant effects, but neither BZAP enantiomer significantly altered motor activity up to doses with lethal effects. Interestingly, both BZAP enantiomers induced dose-dependent hypothermic effects in mice. Because BZAP is being used as a precursor for the development of novel cannabimimmetics, we hypothesized that these hypothermic effects were mediated by CB1 receptors. To test this, the CB1 antagonist / inverse agonist rimonabant was administered prior to hypothermic doses of (*R*)-BZAP and (*S*)-BZAP. Rimonabant failed to block hypothermic effects for either enantiomer. The results of these experiments suggest that neither BZAP enantiomer has psychostimulant-like effects, but that both compounds elicit hypothermic effects via an as-yet undiscovered mechanism. Novel therapeutics based off the BZAP structure are perhaps unlikely to display psychostimulant-like abuse liability.

Poster 21

The 5-HT$_{1B}$ receptor agonist, CP 94,253, attenuates the reinforcing effects of cocaine post-abstinence and after resumption of cocaine self-administration during the estrus phase in female rats

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Previous research from our lab found that a selective 5HT$_{1B}$R agonist, CP 94,253 (CP), facilitates cocaine intake during daily maintenance of self-administration, while attenuating cocaine intake and drug-seeking behavior after 21 days of protracted abstinence. In this study, we examined if CP produces the same abstinence-dependent effects during the estrus phase of the rat estrous cycle. Female Sprague-Dawley rats were tested for the effects of CP on cocaine self-administration during estrus after 21 days of abstinence. We chose to examine the estrus phase because previous research has shown that female rats are more sensitive to the effects of cocaine during this phase. All rats were first trained to self-administer 0.75 mg/kg, IV cocaine on a fixed ratio (FR) 5 schedule of reinforcement. Once reinforcement rates stabilized, rats were given 21 days of abstinence during which daily vaginal smears were taken starting in the last week. Once rats were in the estrus phase on day 22 or later, they underwent pretreatment with CP or vehicle and were tested for cocaine self-administration 15 minutes later. Cocaine was available on an FR5 schedule for one hour at the training dose, and then the dose of cocaine was reduced to 0.075 mg/kg for the second hour of testing. After the test, rats resumed cocaine self-administration and were retested as outlined above to determine whether effects of CP observed after abstinence persisted once rats resumed self-administration. This study is ongoing and thus far, findings indicate that CP attenuates cocaine intake and response rates post-abstinence and after the resumption of cocaine self-administration. This has important implications for developing treatments for cocaine dependence in women.

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Poster 22

Genetic influences on distinct forms of impulsivity and cocaine sensitivity

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Selective differences in behavior can shape vulnerability to substance use disorder. Understanding the genetic basis of these traits may be effective for identifying and treating addiction prone individuals. One such behavioral pattern is impulsivity, defined broadly as deficits in self-regulation. Impulsivity is a multi-faceted construct, with two elements that are readily quantifiable in rodent models: impulsive action, the inability to withhold a prepotent response, and impulsive choice, a preference for immediate gratification over larger, delayed rewards. We hypothesized that subtle differences in genetic patterns drive different factors associated with addiction vulnerability, including impulsivity, cocaine locomotor sensitivity, and cocaine reinforcement. To investigate this, we compared genetically similar subpopulations within different inbred rat strains. We compared both Lewis and Fischer rats between two vendors (Charles River and Envigo), for a total of 46 subjects. Critically, the genetic similarity between substrains from different vendors enhances the ability to identify unique candidate genes underlying any heritable or comorbid behaviors of interest. One-way between-subjects ANOVAs revealed heritable phenotypic differences specific to each strain. Impulsive action (but not choice) was enhanced in Lewis rats from Envigo but not from Charles River, and enhanced cocaine locomotor sensitivity was evident in Fischer rats from Charles River but not from Envigo. No differences between groups were observed in cocaine CPP, an indirect measure of cocaine reinforcement. Critically, the observed phenotypic differences were not comorbid across any substrains, which suggests that cognitive (impulsive action) and pharmacological (cocaine sensitivity) factors related to substance abuse arise from unique genetic origins. Further genotyping research of these strains may reveal discrete genetic factors that drive these traits, providing preventative and therapeutic targets for substance use disorder.

Poster 23

Investigating the effects of nicotine vapor exposure on impulsive choice

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Background: Studies with humans have shown that nicotine cigarette smokers exhibit increased impulsive choice relative to non-smokers. Pre-clinical studies investigating the effects of nicotine injections on impulsive choice have also demonstrated that nicotine increases impulsive choice. Importantly, research investigating the effects of nicotine vapor exposure on impulsivity has not been conducted. An increased understanding of the effects of nicotine vapor on the brain and behavior is critical, as electronic cigarette use has now surpassed traditional cigarette use in adolescents. Objective: The goal of this study is to investigate the effects of nicotine vapor exposure on impulsive decision-making, using the delay discounting task. Methods: Twenty-four adult male rats trained in the delay discounting task, in which rats are allowed to choose between a small immediate food reward or a larger food reward with delayed deliveries. After training in the discounting task, rats were passively exposed to vapor containing either 0, 12, or 24 mg/ml of nicotine, daily for 10 days. On the first day of vapor exposure, blood samples were collected, and ELISA was used to assess plasma cotinine levels. Eight days after nicotine vapor exposure, the effects of nicotine vapor on choice preference in the discounting task was assessed. Results: Analysis of blood plasma levels revealed plasma cotinine in the 12 and 24 mg/ml groups, but not the 0 mg/ml group. Testing in the discounting task after nicotine vapor exposure showed that exposure to 24 mg/ml nicotine vapor shifted choice preference towards the large delayed reward (decreased impulsive choice), when compared to 0 mg/ml controls. Conclusions: Initial findings suggest that contrary to that seen following nicotine injections, testing in the discounting task after nicotine vapor exposure decreases impulsive choice. Findings from this study suggest that nicotine effects on decision making may differ by administration method and highlights the need for additional research assessing the effects of nicotine vapor on the brain and behavior.

Poster 24

Latent growth curve analyses of adolescent substance use, peer alcohol use, and individuation

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Adolescent substance use continues to be a major health problem in many areas. An important factor in adolescent development and substance use is the development of individuation (Baer & Bray, 1999). This includes intergenerational individuation, which is associated with autonomy and positive relationships with family (Baer & Bray, 1999), and separation, which is associated with detrimental detachment from parents and susceptibility to peers. The associations of adolescent individuation, alcohol use, and peer alcohol use, have been examined longitudinally across the middle school years (Bray, Adams, Getz, & McQueen, 2003), but less is understood about how these relationships occur across the high school years. We hypothesized that initial adolescent substance use and peer alcohol use would be associated bidirectionally with decreases in adolescent and peer usage over the high school years. We also hypothesized that greater intergenerational individuation would be associated with decreases in adolescent and peer alcohol usage over time, whereas separation would be associated with increases over time. Data were collected as part of the larger Baylor Adolescent Alcohol Project. Adolescents in the Houston, TX area completed a survey about their behaviors, substance use, family life, and peer relationships each semester for seven semesters, beginning in the spring of their freshman year until the spring of their senior year. Two latent growth curve models were used to model the data (N=4067) on substance use (alcohol, marijuana, tobacco) and peer alcohol use with intergenerational individuation (Model 1) and separation (Model 2). Both models showed good fit. A bidirectional relationship emerged as higher initial adolescent substance use was associated with decreases in peer alcohol use over time, and higher initial peer alcohol use was associated with decreases in adolescent substance use over time ($p < .05$). Higher initial intergenerational individuation was associated with decreases in adolescent substance use over time, whereas higher initial separation was associated with increases in substance use and peer alcohol use over time. These results can inform clinicians and health researchers to understand the roles of individuation and peers in adolescent substance use in high school.

Poster 25

Mycobacterium vaccae immunization for cocaine addiction and relapse

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Cocaine addiction and relapse are major public health concerns that lack FDA-approved pharmacological treatments. We evaluated the translational potential of a novel immunotherapy—immunization with a heat-killed preparation of *M. vaccae*, a nonpathogenic environmental bacterium—for effects on the rewarding properties of cocaine and its potential to reduce relapse-like behavior. Supporting studies determined that *M. vaccae* immunization has profound immuno-regulatory effects that prevented stress-induced exaggeration of neuroinflammation and sensitization of hippocampal microglia, altered serotonin signaling in the dorsal raphe nucleus, and attenuated stress- and anxiety-like behavioral responses in animal models of PTSD and other anxiety disorders. Cocaine-induced neuroinflammation may contribute to the development of addiction, and stress and anxiety are major triggers for relapse, thus we hypothesized that *M. vaccae* immunization may be a useful anti-addiction treatment that could alter the rewarding properties of cocaine, reduce relapse-like responding, and attenuate cocaine-induced neuroinflammation. *M. vaccae* immunization did not alter acquisition of cocaine conditioned place preference (CPP) to 30 mg/kg cocaine, but it abolished stress-induced reinstatement of cocaine CPP. *M. vaccae* immunization also altered patterns of chronic cocaine-induced neuroinflammation as seen in immunofluorescence imaging of astrocytes and microglia in the nucleus accumbens and hippocampus. Future experiments will evaluate the effects of *M. vaccae* immunization in self-administration and reinstatement models. These data are the first assessment of the translational potential of *M. vaccae* immunotherapy to treat substance use disorders. Given the excellent safety record of *M. vaccae* immunotherapy in clinical trials, successfully demonstrating an anti-relapse effect in preclinical models would justify relatively rapid clinical evaluation of treatment efficacy.

Poster 26

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

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Eating a high fat diet can lead to obesity, type 2 diabetes, and dopamine system dysfunction. For example, rats eating high fat laboratory chow are more sensitive than rats eating standard chow to the behavioral effects of dopaminergic drugs. Specifically, drugs that act on dopamine systems (e.g., quinpirole and cocaine) produce unconditioned behavioral effects (e.g., yawning and locomotion) that are enhanced among rats eating high fat chow. Daily dietary supplementation with fish oil prevents this high fat diet-induced effect; however, doctors recommend that patients take fish oil only 2-3 times a week for beneficial health effects. To test the hypothesis that intermittent (e.g., 2/7 days per week) dietary supplementation with fish oil prevents high fat diet-induced effects (e.g., enhanced sensitivity to the behavioral effects of dopaminergic drugs) rats eating standard chow (free access, 17% kcal from fat), high fat chow (free or restricted access, 60% kcal from fat), or standard (free access) or high fat chow (free or restricted access) with 20% (w/w) intermittent (e.g., 2/7 days per week) dietary fish oil supplementation were tested once weekly with quinpirole (0.0032-0.32 mg/kg, i.p.) or cocaine (1-17.8 mg/kg, i.p.) using cumulative dosing procedures. Consistent with previous reports, free access to high fat chow enhanced the sensitivity of male rats to quinpirole-induced yawning. Further, restricted access to high fat chow enhanced sensitivity of female rats to cocaine-induced locomotor sensitization. Intermittent fish oil dietary supplementation prevented these effects among male rats, but not female rats eating high fat chow. Future experiments will focus on understanding the mechanisms by which fish oil produces these beneficial effects in males, as well as understanding the mechanisms driving the sex differences observed.

Poster 27

Phosphatidylethanol in whole blood of rhesus monkeys correlates with alcohol consumption

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The purpose of this study was to test whether phosphatidylethanol (PEth) 16:0/18:1 and 16:0/18:2 levels in whole blood samples varies proportionately with daily alcohol intake of rhesus monkeys to establish the basis of a non-human primate model. PEth homologs are ethanol metabolites used to identify and monitor drinking in humans. Rhesus animals were trained to consume either water or 4% ethanol in water (w/v). Ethanol dosing was increased in steps of 0.0, 0.5, 1.0 and 1.5 g/kg every 30 days. After the training induction, monkeys were allowed to drink ethanol and water ad libitum during 22-hour daily sessions for 12 months and blood ethanol concentration (BEC) was measured. The daily amount of ethanol consumed was quantified in every session. To assess PEth levels, whole blood was collected from each animal at the very end of the entire experimental procedure. PEth 16:0/18:1 and 16:0/18:2 homolog levels were analyzed by HPLC with tandem mass spectrometry. Our results show that 1) PEth levels in drinker monkeys were proportional to their ethanol drinking intake; 2) the correlation between the average daily of alcohol intake during 12 months and BEC was significant ($P < 0.0001$) as well as the correlation between BEC and PEth ($P = 0.0276$); 3) the strongest correlation between the time frame of recent ethanol consumption and PEth levels was the last 4 days of drinking, slope of 2.370 and R2 of 0.7492; and 4) When monkeys were categorized into three groups based on average daily consumption (< 1.9 g/kg; ≥ 2 < 3 g/kg; ≥ 3 g/kg), the mean (SD) levels of combined PEth were 47.3 (54.99), 356.0 (262.3) and 586.1 (259.1), respectively The results of this study confirm that PEth is a sensitive biomarker for ethanol consumption in a non-human primate animal model. This monkey model may prove useful to test for sources of variability previously demonstrated between alcohol consumption and PEth homolog levels. Studied funded by NIAAA R24 AA019431 and NIAAA R01AA022361.

Poster 28

Estradiol's potentiation of the acquisition of cocaine place preference may involve mTOR signaling

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Women show an increased vulnerability to drug abuse. There is an abundance of empirical data supporting the idea that the ovarian hormone estradiol is responsible for mediating and potentiating these sex-specific responses to psychostimulants. Interestingly, previous data from our lab demonstrated that acutely elevating estradiol (EB) levels in cocaine-conditioned, ovariectomized (OVX) rats prior to a test for conditioned place preference (cocaine-CPP) increased the magnitude of the dose required for the expression of cocaine-CPP. However, the direct effects of acute elevations of estradiol at different stages of cocaine-CPP and their molecular underpinnings remain virtually unknown. Recently, mTOR signaling has been shown to be a key molecular mechanism by which psychostimulant drugs of abuse, including cocaine, exhibit their effects within the mesolimbic reward circuit of male rodents. Moreover, inhibition of mTOR has been demonstrated to attenuate cocaine-CPP. Thus, the goal of the present study was - a) to determine if estradiol potentiates cocaine-CPP via enhancing the drug-cue associations and b) to determine the involvement of mTOR in this effect. We subjected 31 adult Long Evans rats to a cocaine-CPP paradigm over five days; we used a 3/3 (AM/PM) conditioning procedure with intraperitoneal injections of 10mg/kg of cocaine hydrochloride. Rats were treated with either EB (5 µg; s.c.) or peanut oil (PO; equal volume; s.c.) 30 minutes prior to the start of each daily conditioning session. Expression of cocaine-CPP was assessed under a drug- and hormone-free state 24h following the last conditioning session. Immediately after the CPP test, animals were euthanized and brain tissue comprising VTA, NAc and dorsal striatum was isolated. ANOVAs were used to statistically analyze all data. Results demonstrated that EB-treatment during the conditioning phase of CPP augmented the preference for the drug-paired compartment. Moreover, EB-treatment increased levels of mTOR protein expression in dorsal striatum and NAc after cocaine-CPP. In conclusion, our results demonstrated for the first time that drug-cue associations potentiated by estradiol are mediated by increased expression of mTOR. Funding support: NIH/NIDA R15DA040809 (LIP).

Poster 29

Acute ethanol consumption leads to imbalance in neuro-immune network in animal model

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Alcohol is by far the most harmful substance to the user and more importantly to others compare to other drugs such as heroin, cocaine, methamphetamine, and many more. It's excessive consumption attributes to the almost 90000 deaths yearly. The mechanisms of dependency are multifactorial and involve different physiological systems. In this study, we evaluated the role of specific cytokines in the pathology of the regular alcohol consumption in animal model. Two groups of NIH Swiss mice were treated IP with 1.8ml/kg or 3.0 ml/kg of ethanol (groups A and B correspondingly) for a period of 3 days. Animals, which served as controls (group C) were treated with saline. Study design was approved by the Mercer University IACUC. Gene expression of STAT(s) 1-6, Tbx21, GATA3, RORc, and FoxP3 signal transducers, pro- and anti-inflammatory cytokines, as well as their receptors (R) were evaluated in the brains and spleens of animals with qPCR technique. Systemic level of cytokines were evaluated in plasma with flow cytometry. Significantly higher gene expression of STAT1, -2, -5A, -5B, and -6 was observed in brain tissues of Group A animals compare to Group B. Alcohol treatment significantly increased gene expression of the Tbx21, IL1β, IL1R1, and CXCL2 in the brains of Group A animals compare to control animals. Further, alcohol treatment significantly decreased gene expression of STATs but increased gene expression of inflammatory cytokines TNFα and IL6 in spleens of treated groups. Plasma level of IL1α and CCL2 were significantly higher in the Groups A and B compare to control animals. This data suggest that alcohol consumption even with minimal doses leads to systemic inflammation and unequally affects systemic as well as tissue-specific cytokine equilibrium in different tissues. Specifically, the data demonstrate that acute alcohol may markedly stimulate production of pro-inflammatory cytokines in brain and spleen in vivo.

Poster 30

Subjective responses to MDMA are influenced by a history of childhood teasing in healthy human volunteers

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3,4-Methylenedioxymethamphetamine (MDMA) is a psychostimulant drug that is widely used in social contexts and produces "prosocial" effects in both laboratory animals and humans. These effects have led to increased interest in the use of MDMA in psychotherapeutic contexts in the treatment of PTSD. The subjective effects of the drug vary across individuals, however, and few efforts have been made to understand the factors that contribute to such individual variability. The present study investigates the association between differences in social connectedness and subjective effects of MDMA in healthy human volunteers. 36 Healthy men and women completed questionnaires specifically designed to measure loneliness, perceived social support, and childhood teasing. They then participated in four separate experimental sessions with double blind administration of a placebo, 0.75 mg/kg MDMA, 1.5 mg/kg MDMA, and 20 mg methamphetamine (active control) in randomized order. They reported subjective mood and drug effects before drug administration and at 30 minute intervals throughout the session. Subjects were divided into high and low scoring groups on the three baseline social questionnaires (median split) to compare responses to the drug. Responses were summarized using area under the curve and analyzed using ANOVA. MDMA produced expected subjective effects, increasing ratings of social adjectives, such as feeling "friendly," and increasing feelings of elation and anxiety on the Profile of Mood States (POMS). Participants with a history of childhood teasing experienced significantly more pronounced prosocial effects during the high-dose MDMA session, including increased ratings of "friendly," "loving," and "playful." They also experienced significantly less anxiety. Participants scoring high in baseline loneliness reported feeling more "loving," and those low in perceived social support experienced more elation. No interactions were observed for other doses administered, and no other significant effects were found. All effects were significant at the $p<0.05$ level.

Conclusions: In summary, individuals with both a history of social difficulties (such as childhood teasing) and current feelings of loneliness and low social support experience the positive prosocial effects of MDMA more strongly than others. These findings may have implications for predicting which individuals are most likely to abuse the drug in recreational settings, and which individuals may be most susceptible to the beneficial effects of MDMA in a therapeutic context.

Poster 31

Do pain and psychological flexibility explain continued substance use among adults receiving methadone treatment for opioid use disorder?

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Non-withdrawal physical pain is an important reason for continued substance use among patients treated for opioid use disorder (OUD). However, extant research does not adequately characterize how psychological flexibility may contribute to continued illicit substance use among individuals with OUD and co-occurring chronic pain. We explored this relationship in a cross-sectional analysis of 100 adults receiving methadone therapy for OUD who have co-occurring chronic pain. Chronic pain characteristics (severity, interference), psychological flexibility (mindfulness, acceptance, value success), and past 30-day illicit substance use were reported during an interviewer-facilitated assessment. We modeled a zero-inflated negative binomial regression to concurrently examine 1) the probability that an individual does not use illicit substances and 2) predict illicit substance use frequency (i.e., days of use) among those expected to use. Pain severity, mindfulness, age, and gender were predictors in the zero-inflated model. Pain interference, acceptance, value success, age, and gender were predictors in the negative binomial model. Overall, 64% of participants reported illicit substance use at least once in the past 30 days. After controlling for other variables in the zero-inflated model, pain severity did not predict continued illicit substance use; however, participants with a higher degree of mindfulness had a 1.59 greater probability of no illicit substance use compared to those who had a lower degree of mindfulness, $p < 0.05$, 95% CI [0.01, 0.92]. After controlling for other variables in the negative binomial model, substance use frequency was 0.72 times lower among individuals who believed their behaviors were congruent with their personal values $p < 0.01$, 95% CI [-0.54, -0.12]. Pain interference and acceptance did not predict substance use frequency. Findings suggest individuals' ability to adapt to their pain experience, but not necessarily the presence of pain itself, may influence treatment outcomes among adults treated for OUD who have co-occurring chronic pain. Study findings may have implications for how to address the treatment needs of this complex population.

Poster 32

Assessment of conditioned place preference following concurrent treatment with 3,4-methylenedioxypyrovalerone (MDPV) and methamphetamine in male and female Sprague-Dawley rats

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Synthetic cathinones gained initial popularity on the illicit drug market as a result of attempts to evade legal restrictions on other commonly abused psychostimulants. A body of published research has determined that the psychopharmacology of MDPV is comparable to cocaine and methamphetamine (METH). Few preclinical studies have systematically investigated concurrent use of synthetic cathinones with other psychostimulant drugs. The present study utilized conditioned place preference (CPP), a rodent model of conditioned drug reward, to evaluate the effects of concurrent treatment with MDPV and METH. Male (N=72) and female (N=105) Sprague-Dawley rats underwent a two-compartment biased conditioned place preference procedure, with one trial per day for eight consecutive days. Subjects were randomly assigned to the following treatment groups: METH (1 mg/kg), MDPV (1, 3.2, 5.6 mg/kg), a mixture consisting of METH (1 mg/kg) and MDPV (1, 3.2, 5.6 mg/kg), or saline. Difference scores were determined from time spent in the drug-paired compartment during post-conditioning and pre-conditioning trials. A two way ANOVA (treatment, sex) of difference scores indicated a statistically significant treatment effect. Although the level of CPP established by MDPV and MDPV+METH mixtures varied between males and females, sex was not statistically significant. MDPV appeared to produce CPP in males only at the highest dose, whereas all MDPV doses produced CPP in females. Although none of the MDPV+METH mixtures produced stronger CPP than METH alone, the lower dose mixtures of MDPV and METH produced higher increases in locomotor activity compared to either drug alone. Further studies with higher doses may be warranted to determine if concurrent use of MDPV and METH pose an enhanced risk for abuse.

Poster 33

Operant costs modulate dopamine release to self-administered cocaine

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The costs associated with obtaining illicit drugs can fluctuate depending upon the relative drug availability. As a consequence of the changing costs, the effort one must exert to obtain drugs is dynamic. Considerable evidence illustrates a critical role for dopamine in the ventral medial striatum in mediating drug reinforcement. However, little is known regarding how dopamine release is affected by changes in the costs associated with earning drugs. We utilized fast-scan cyclic voltammetry to determine how changes in the operant requirement affected dopamine release to self-administered cocaine in male rats. Dopamine release to cocaine infusions increased across trials during self-administration sessions using a fixed ratio reinforcement schedule with a low operant requirement. However, increasing the operant requirement abolished the within-session elevation in dopamine release to drug rewards. This effect was not due to underlying changes in pre-infusion dopamine levels and was not explained by cocaine levels in the brain. This within-session increase in dopamine release to cocaine infusions reemerged when the operant requirement was lowered. Under a progressive ratio reinforcement schedule there was no increase in dopamine release to drug rewards across trials, which contrasts with prior studies demonstrating an increase in dopamine release to food rewards. Collectively, these findings illustrate that the influence of operant costs on reward-evoked dopamine release depends upon type of reward that can be earned (e.g. food or drug).

Poster 34

Sex differences in the assessment of delayed consequences during decision-making

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Addiction is characterized by ongoing substance abuse despite physical, financial, and social consequences. Critically, these negative outcomes are often delayed relative to immediate drug reinforcement, resulting in myopic decision-making that fails to respond appropriately to delayed consequences. Discounting of delayed rewards has been well studied in human and animal models, but systematic discounting of delayed consequences, which is associated with substance abuse, remains largely unexplored. To address this gap in the literature, we have developed the Delayed Punishment Decision-making Task (DPDT). In this task, rats choose between a small, single pellet reward and a large, three pellet reward accompanied by a mild foot shock (.35 mA). As the task progresses, a delay precedes the shock that is systematically enhanced with each 12 trial block (0s, 4s, 8s, 12s, 16s), followed by a final block in which the shock and delay are no longer present. We hypothesized that rats would discount the shock as a function of delay. Furthermore, we predicted that this effect will be more pronounced in male rats, as females typically demonstrate elevated punishment avoidance behavior.

We trained male (n=10) and female (n=10) Long Evans rats in the DPDT. A two-way repeated measures ANOVA revealed that rats discounted the negative value of delayed punishment, as indicated by a significant increase in choice of the large, punished reward as delay preceding the shock increased. Moreover, a sex x block mixed ANOVA showed that male rats discounted delayed punishment significantly more than female rats. The addition of a cue light bridging the delay between large reward and punishment decreased the selection of the punished lever comparably for both male and female rats, as observed via two-way repeated measures ANOVA. Finally, there was no significant correlation found between the discounting of delayed rewards and the discounting of delayed punishment. These findings demonstrate that undervaluation of delayed consequences can be measured in a rat model, and that males are more likely to discount delayed punishment than females. Development of the rat DPDT is the first step toward understanding the neural mechanisms underlying the assessment of delayed punishment, as well as how this process may become pathological in substance abuse.

Poster 35

The development of impulsivity and sensation seeking predicting marijuana use among adolescents with or without a family history of substance use disorder

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Children who have a family history of a substance use disorder (SUD) are at increased risk for developing substance use problems themselves. The dual systems model posits that the early development of sensation seeking relative to the protracted development of impulse control is the impetus for the increased rates of risk taking behavior during adolescence, which may be furthered by an understanding of the relationship between familial risk and the SUD. We hypothesized that family history status would predict higher levels of sensation seeking through heightened levels of impulsivity, which in turn would predict marijuana use.

In an ongoing longitudinal study, 386 adolescents ages 10–12 (305 with a family history of SUD, 71 without) and their parents were recruited through the community. Participants completed a baseline assessment and follow-up assessments every six months. The measures used include family history status (0 = FH–, 1 = FH+), impulsivity (30-item Barratt Impulsiveness Scale) and sensation seeking (26-item Sensation Seeking Scale for Children) at ages 13–16, and frequency of marijuana use at age 16. A series of multivariate growth were conducted to address the hypothesis.

Results revealed that having a family history of SUD predicted higher initial levels of impulsivity at age 13 but not initial levels of sensation seeking at age 13 or rate of change in impulsivity or sensation seeking from ages 13–16. Higher initial levels of impulsivity predicted higher initial levels of sensation seeking. Lastly, FH status indirectly predicted marijuana use through initial levels of impulsivity to initial levels of sensation seeking. This study extends research on the dual systems model, by relating the relationship of sensation seeking and impulsivity to adolescent substance use. involvement and in a high risk group.

Poster 36

Design and synthesis of fluorescent nanoprobes for the imaging of the NET transporter

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Fluorescent ligands provide a class of valuable pharmacological tools for the identification of transporters trafficking pathways in living cells and for the study of their recycling and degradation mechanisms. Novel tropane-based fluorescent ligands that bind with high affinity to dopamine transporters (DAT) and serotonin transporters (SERT) have been successfully used for transporter visualization, colocalization and trafficking studies (Cha *et al., J Med Chem,* 2005; Eriksen *et al., J. Neurosci*, 2009; Kumar *et al., ACS Med Chem Lett,* 2014). Building on this strategy, we have focused on the design and synthesis of novel molecular probes with high affinity and selectivity for the norepinephrine transporter (NET) and on the evaluation of their binding affinities and NET selectivities over DAT and SERT. The general structure of the compounds is based on a ligand linked by a linker chain of variable length and atomic composition to a fluorescent dye. The parent ligands, Nisoxetine and Talopram, were selected taking into account affinity, selectivity and synthetic feasibility. Using previously described structure activity relationships (SAR) we chose two different positions on each of these parent molecules for "fluorescent tagging". The design, synthesis and binding affinities of this first set of novel fluorescent tools will be reported with a plan for further characterization.

Poster 37

Fluoxetine exposure in adolescent and adult female mice decreases cocaine and sucrose preference later in life

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Preclinical literature indicates that exposure to antidepressant medications, during early stages of development, results in long-term altered behavioral responses to drugs of abuse (Iñiguez et al., 2015, Sci Rep, 5:15009). However, to date, these studies have been conducted in male subjects primarily. This is surprising, given that females, when compared to males, are more likely to be diagnosed with mood-related disorders, and thus, be prescribed with antidepressants. Therefore, the objective of this study is to assess whether exposure to the selective serotonin reuptake inhibitor fluoxetine (FLX) results in long-lasting alterations in sensitivity to the rewarding properties of cocaine and sucrose, using female mice as a model system. To do this, adolescent (postnatal day [PD]-35) and adult (PD70) female C57BL/6 mice were exposed to FLX (in their drinking water, 250 mg/l) for 15 consecutive days. Twenty-one days later (PD70+ and PD105+, respectively), mice were assessed on behavioral responsivity to cocaine (0, 2.5, 5, 7.5 mg/kg) using the conditioned place preference paradigm, or their sensitivity to a 1% sucrose solution using the 2-bottle choice test. Our results indicate that female mice pre-exposed to FLX during adolescence or adulthood displayed reliable conditioning to the cocaine-paired compartment, in a dose-dependent manner. However, when compared to respective age-matched controls, antidepressant pre-exposure decreased the magnitude of conditioning at the 5 ($p<0.05$, $R2= 0.21$) and 7.5 mg/kg ($p<0.05$, $R2= 0.51$) cocaine doses. Similarly, independent of age of antidepressant pretreatment, FLX-pretreated mice also displayed a decrease in sucrose preference ($p<0.05$, $R2= 0.62$), without altering total liquid intake ($p>0.05$). Collectively, our results suggest that exposure to FLX, in adolescent and adult female C57BL/6 mice, leads to prolonged decreases in sensitivity to the rewarding properties of both drug- and natural-rewards. This data further highlight the need for investigations assessing the potential enduring neurobiological side effects that may arise later in life, as a result of antidepressant exposure, in a sex dependent manner.

Poster 38

CM304 a sigma1 receptor antagonist enhances the antinociceptive effects of the cannabinoid receptor agonist CP55,940 but not that of morphine in mice

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There is currently an opioid overdose epidemic and sigma1 receptor (σ_1R) antagonists in combination with other drugs may provide a viable, safe pharmacological option for treating pain. This study compared pharmacological effects of the σ_1R antagonist CM304 alone and in combination with morphine or the cannabinoid agonist CP55,940 in C57BL/6J mice. Rectal temperature, tail withdrawal latency from warm water of various temperatures (45°C, 50°C and 55°C) and counts of unhabituated locomotor activity were measured in this order. Basal latency for tail withdrawal systematically decreased from 10 seconds at 45°C to 1.3 seconds at 55°C. Morphine dose-dependently increased maximum possible effects (MPE) up to 100% at 55°C (ED_{50} value: 11.4 mg/kg). CP55,940 was less active at 55°C (E_{max} value: 49.5%). However, CM304 (56 mg/kg) dose-dependently produced an upward shift in the CP55,940 dose-effect function such that 100% MPE was achieved at 3.2 mg/kg CP55,940 but was inactive against the antinociceptive effects of morphine. While CM304 alone did not alter tail withdrawal latency at 55°C, it did decrease activity and rectal temperature. However, CM304 produced an upward shift in the dose-effect function of morphine-induced hyperactivity and a rightward shift in the dose-effect curve of CP55,940-induced hypothermia.

The present results may not support the development of a σ_1R antagonist as an adjunct to opioids for analgesia. However, the results indicate that a σ_1R antagonist could be used to increase the analgesic efficacy of cannabinoid agonists.

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Poster 39

Mixing alcohol and painkillers: the effect of ethanol and non-steroidal anti-inflammatory drugs on serotonergic neurons

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Labels warn consumers not to take over-the-counter (OTC) analgesics if they have been drinking alcohol. Yet warning labels are disregarded all the time: For example, misuse of acetaminophen is the leading cause of acute liver failure in the United States each year. When it comes to the effects of mixing alcohol with non-steroidal anti-inflammatories (NSAIDs), some of the most widely used OTC painkillers in the country, research has largely been performed on the deleterious effects of ethanol and NSAIDS on the liver and kidney. Little research, however, has been done on how this combination affects the brain. This study examined the impact of mixing ethanol with NSAIDs in serotonergic neurons. We hypothesized that cells treated with both ethanol and an NSAID would experience increased rates of cell death. After treating human neuroblastoma SHSY-5Y cells were cultured, they were treated with one of the following: ibuprofen, aspirin, sodium naproxen, or acetaminophen, a non-NSAID that was used as a positive control. They were then treated with a physiologically relevant dose of ethanol for 24 hours or left untreated. To measure cell viability, oxidative stress, and protein expression of apoptosis markers (PARP fragmentation and Caspase-3 activation), end-point assays and western blotting were performed. We found that markers of oxidative stress were increased and cell viability was reduced in cells treated with both an NSAID (or acetaminophen) and ethanol. The results indicate that using NSAIDs in conjunction with ethanol may increase apoptosis in serotonergic neurons.

Poster 40

The effects of eating a high fat diet on sensitivity of female rats to dopamine D_1 receptor agonist SKF 82958-induced eye blinking

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Eating a high fat diet can lead to several negative health consequences such as obesity, type 2 diabetes, and dopamine system dysfunction. Eating high fat chow enhances sensitivity of rats to the behavioral effects of drugs that act on dopamine systems. For example, rats eating high fat chow are more sensitive than rats eating standard chow to the unconditioned behavioral effects (i.e., yawning and penile erections) induced by the dopamine D_2/D_3 receptor agonist quinpirole. Drugs that act on dopamine D_1 receptors also produce unconditioned behavioral effects in rats (i.e., eye blinking and locomotion); however, it is not known if eating high fat chow also enhances sensitivity of rats to these effects. In order to test the hypothesis that eating high fat chow will enhance the sensitivity of rats to the behavioral effects of dopamine D_1 receptor agonist SKF 82958, rats were tested weekly using cumulative doses (0.01. 0.032, 0.1, 0.32, 1.0, 3.2 mg/kg) and eye blinking was measured in male and female rats eating either standard chow (17% kcal from fat) or high fat chow (60% kcal from fat). SKF 82958 significantly induced eye-blinking in male and female rats. In females, eating high fat chow for three weeks modestly, though not significantly, increased SKF 82958-induced eye-blinking as compared to standard chow fed controls. Based on these results, ongoing experiments are examining the impact of a history of eating high fat chow (e.g., pre-feeding for several weeks prior to SKF 82958 testing) on sensitivity of rats to dopamine D_1 agonist-elicited eye-blinking. Further, additional experiments are examining other unconditioned behavioral effects of SKF 82958 (i.e., locomotion and sensitization) in rats eating different diets. These results add to the growing literature demonstrating sex differences regarding psychostimulants, as well as the relationship between diet and drug sensitivity.

Poster 41

The intriguing effects of substituents in the n-phenethyl moiety of norhydromorphone

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Opioid overdoses have resulted in 122,000 deaths globally in 2015, up from 18000 deaths in 1990. In the United States in 2017, over 49,000 deaths involved opioids. Death from opioid overdose occurs due to respiratory depression; thus, the need to develop opioid analgesics that do not cause respiratory depression while retaining analgesic properties is immense. There is evidence that a mixed μ/d agonist may exhibit potent analgesic activity and reduced respiratory depression. It is well-known that the N-substituent in the classical opioid type structure can alter the agonist activity of prototypical opioids to antagonists; however, exactly how the N-substituent interacts with amino acids in the receptor to enable that change remains uncertain. We decided to use *N*-phenethylnorhydromorphone, a recently synthesized opioid agonist that displayed extremely high μ-receptor affinity (Ki = 0.04 nM) and relatively modest delta receptor affinity (Ki = 1.7 nM; d/m ratio = 43) as our template, and see if we could modulate its interaction with opioid receptors by adding substituents in various positions on the aromatic ring in the *N*-phenethyl moiety. We discovered that we could induce the change from agonist to antagonist with certain novel substitution patterns and one derivative did interact with both the MOR and DOR and was a potent agonist for both. The synthesis of *N*-phenethylnorhydromorphone derivatives and *in vitro* and *in vivo* data are presented in the poster.

Poster 42

Effects of methocinnamox (MCAM) on the antinociceptive effects of morphine in rats with hindpaw inflammation

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Opioid abuse in the United States remains a serious public health problem, with millions of Americans meeting DSM-V criteria for substance use disorder. Methocinnamox (MCAM) is a long lasting *mu* opioid receptor selective antagonist that potentially could be effective for treating opioid abuse. However, if a patient treated with MCAM is injured and needs pain relief (e.g., during and after surgery), opioids likely would not be effective due to MCAM occupying the *mu* receptors. The current study tested the effectiveness and duration of action of MCAM in rats with hindpaw inflammation in advance of studying non-opioid drugs with antinociceptive properties that would be expected to remain effective in MCAM-treated rats. All rats (n=16) received an injection of Complete Freund's Adjuvant (CFA) in one hindpaw and saline in the other hindpaw. The day after CFA administration, one group of rats (n=8) received 10 mg/kg MCAM subcutaneously, whereas the second group (n=8) received vehicle subcutaneously. Two and four days after CFA administration, the effects of morphine (1.78 – 17.8 mg/kg) were determined on paw thickness, paw withdrawal force, and body temperature. CFA increased paw thickness from 3 mm to 8 mm; there was not a significant difference in paw thickness before and after morphine. Morphine dose-dependently increased paw withdrawal force from <20 g to >50 g in vehicle-treated rats but did not increase paw withdrawal force in MCAM-treated rats. Morphine increased body temperature by ~2°C in both groups. Overall, MCAM blocked antinociceptive but not hyperthermic effects of morphine. The antinociceptive effects of other drugs (non-*mu* opioid agonists, drug mixtures) should be determined during the period when MCAM is active.

Poster 43

Assessing the stability of two novel CB1 receptor negative allosteric modulators

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The endocannabinoid signaling system (ECSS) regulates stress and anxiety and contributes to the rewarding effects of drugs of abuse. The cannabinoid receptor 1 (CB1R) is critically involved in drug seeking and relapse behaviors; agents that inhibit CB1R signaling are therefore potential pharmacologic tools for managing abuse of psychostimulants, opioids, nicotine, and ethanol. Mood-depressant side effects of CB1R inverse agonists like rimonabant limit their clinical use and signify the need to develop alternate agents that dampen ECSS activity. CB1R-negative allosteric modulators (CB1R-NAMs) are a potentially safer alternative to inhibition of CB1R signaling that are expected to produce less anhedonia than orthosteric CB1R inverse agonists. We have discovered two CB1R-NAM lead compounds (CWC-1-001, **1**; CWC-1-002, **2**) that have improved "drug-like" properties compared to the current art. To determine the structural stability of **1** and **2**, we conducted a Q1A accelerated stability study using a Caron 7000-10 stability chamber. Samples were analyzed over 6 months at 40° C and a 75% relative humidity. Samples were analyzed at 8 time points using NIR, IR, Raman, HPLC, gCOSY NMR, gHSQC NMR, and ^{1}H NMR. This study found evidence of significant degradation of **1** and little degradation of **2**. One of the degradant products of **1** was determined to be 4-bromophenylisocyanate by HPLC, a likely result of urea decomposition. The superior chemical stability of **2** makes this an ideal lead for development of CB1R-NAMs as anti-addiction agents.

Poster 44

Tolerance to in vivo effects of synthetic cannabinoid MAM-2201 in male and female mice

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MAM-2201 is a novel synthetic cannabinoid (SC) agonist with a limited in vivo profile in the scientific literature. Unlike other drugs from this class, MAM-2201 appears to have been specifically designed by clandestine chemists as a drug of abuse. MAM-2201 is the result of modifying the structure of the 1st generation SC, JWH-018, with two substitutions, each previously shown to increase potency. Previously, we demonstrated that MAM-2201 elicits cannabinoid-like effects in the cannabinoid tetrad, and THC-like discriminative stimulus effects, but no data regarding repeated administration of MAM-2201 are available. Consistent with our previous work with THC and other SCs, we hypothesized that repeated administration of MAM-2201 would be more potent in female mice than in males, and would result in rapid and complete tolerance to hypothermic effects but not to locomotor effects. Adult male and female CD1 mice (n=6 per group) were implanted with radiotelemetry probes that recorded core temperature and locomotor activity. After 7 days of recovery, mice received discrete injections of vehicle, or increasing doses of MAM-2201 (0.3, 1.0, and 3.0 mg/kg; IP). Drug abstinence days were interposed between MAM-2201 doses, and doses were increased until core temperatures below 30°C were observed. Once this "maximal hypothermic dose" was determined, mice received daily injections at this dose for the next 10 days to determine the rate and extent of tolerance development as a function of sex. MAM-2201 dose-dependently decreased core temperatures and inhibited exploratory activity in both male and female mice. No differences in drug sensitivity were observed between male and female mice on either measure. Daily administration of the maximal hypothermic dose of MAM-2201 (3 mg/kg) produced incomplete tolerance to both hypothermic and locomotor effects over the 10 day treatment period, and no differences were observed between males and females. These studies were supported by DA039143 and by ASPET.

Poster 45

The maternal opioid morbidity study

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From 2012 to 2015, drug overdose was the leading cause of maternal death; defined as the death of a woman while pregnant or within 1 year postpartum. Of the overall maternal deaths due to drug overdoses, 58% of those cases involved the use of opioids.[1] Given the alarming proportion of maternal death related to opioid use, it is imperative to understand contextual factors that may contribute to maternal morbidity. Preliminary findings from a small subset of pregnant women using opioids (N = 23) suggested that they experienced high rates of stressful and/or traumatic life events. Therefore, the purpose of this qualitative exploratory study was to further investigate contextual factors surrounding opioid use relapse and overdose. The study sample included 99 women who either directly or indirectly experienced relapse and/or overdose from opioids during pregnancy or within a year after delivery. Through semi-structured interviews and focus groups, participants were asked to describe and elaborate upon their lived experiences with opioids. Using a thematic analysis, six themes emerged including, loss, isolation, unaddressed trauma, stress, jail release, and mental illness. These themes will be used in future research to develop an instrument that will identify opioid-related risks associated with maternal death. The results of this study demonstrate the importance of having trauma-informed harm reduction services integrated within community-based settings. Further, the insight gained from this investigation can help to develop and optimize services and resources, tailoring them to meet the specific needs of this vulnerable population.

1. Maternal Mortality and Morbidity Task Force and Department of State Health Services (2018). Joint biennial report. Retrieved January 23, 2019 from: https://www.dshs.texas.gov/mch/maternal_mortality_and_morbidity.shtm

Poster 46

Trace amine-associated receptor 1 and its thyroid hormone-derivative ligand T1AM may act as modulators of the immune response and cancer progression in vitro

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Since its discovery in 2001, the major focus of Trace Amine-Associated Receptor 1 (TAAR1) research has been on its role in monoaminergic regulation, drug-induced reward and psychiatric conditions. More recently, TAAR1 expression and functionality in immune system regulation and immune cell activation has become a topic of emerging interest. Here, we incorporate open-source expression and cancer survival data meta-analyses to provide strong evidence for TAAR1 expression in the immune system and cancers revealed through NCBI GEO datamining. These findings establish connections and logical directions for further study of TAAR1 in immunological function, and its potential role as a mediator or modulator of immune dysregulation, immunological effects of psychostimulant drugs of abuse, and cancer progression. Further, we investigate TAAR1 as a novel modulator of cancer cell functionality induced by the potent TAAR1 agonist T1AM in vitro to further elucidate a possible role in cancer progression.

Poster 47

The effects of eating a high fat diet on methamphetamine-induced conditioned place preference

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Eating a high fat diet can cause several negative health consequences, including dysfunction to dopamine systems. For example, eating a high fat laboratory chow enhances sensitivity of rats to methamphetamine-induced locomotion. However, it is not known if sensitivity to the rewarding effects of methamphetamine are similarly enhanced in rats eating high fat chow. Females are more sensitive than males to the behavioral effects of psychomotor stimulants in general, and therefore might also be particularly vulnerable to high fat diet-induced enhanced sensitivity to these drugs. To test the hypothesis that eating high fat chow enhances sensitivity of rats to the rewarding effects of methamphetamine, female Sprague-Dawley rats were fed standard laboratory chow (17% kcal from fat) or high fat chow (60% kcal from fat) for 4 weeks prior to conditioned place preference (CPP) training, using a biased design. Rats were trained on alternating days rats with saline or methamphetamine (0.32 or 1.0 mg/kg, i.p.) and were restricted to one of two sides (wire mesh vs rod flooring) of a CPP apparatus. After 8 alternating training days, rats had free access to the entire apparatus, and time spent in the drug-paired side versus the saline-paired side was examined. Methamphetamine induced a significant CPP in all rats, regardless of diet or dose of methamphetamine; however, there were no differences in magnitude of CPP between rats eating high fat chow and rats eating standard chow. Previous literature suggests that females might be more sensitive to the rewarding effects of methamphetamine, necessitating the use of smaller doses. As such, future studies will examine a wider range of doses of methamphetamine, as well as other conditioned behavior (i.e., self-administration) and will include male subjects to study potential sex differences.

Poster 48

Eating a high fat diet enhances sensitivity of male and female rats to methamphetamine-induced locomotion and sensitization

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Eating a diet high in fat can lead to obesity and insulin resistance, but it can also enhance sensitivity of rats to the behavioral effects of drugs acting on dopamine systems. For example, male rats eating a high fat laboratory chow are more sensitive to the locomotor stimulating effects of methamphetamine. In general, females are more sensitive than males to psychomotor stimulants; however, it is not known if eating high fat chow similarly enhances sensitivity of females to methamphetamine. To test the hypothesis that there might be sex differences regarding the impact of eating a high fat diet on sensitivity of rats to locomotion and sensitization induced by methamphetamine, male and female Sprague-Dawley rats (n= 11-12/group) ate either standard (17% kcal from fat) or high fat chow (60% kcal from fat) and were tested once per week with methamphetamine (0.1-3.2 mg/kg) using a cumulative dosing procedure for 6 weeks. Male and female rats eating high fat chow were more sensitive to the locomotor-stimulating effects methamphetamine than control rats eating standard chow. Further, after repeated testing with methamphetamine, both female and male rats eating high fat chow also developed locomotor sensitization more quickly than rats eating standard chow. These results are consistent with previous studies examining methamphetamine in males; but contrast previous work examining both the impact of eating high fat chow on sensitivity of male and female rats to cocaine-induced locomotion and sensitization. Taken together with previous research, these results highlight the importance of studying both males and females in parallel. Future experiments will examine the impact of eating high fat chow on sensitivity of rats to dopamine receptor agonists and dopamine receptor expression.

Poster 49

Sex comparisons of binge alcohol-induced neurodegeneration

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It is estimated that over 90% of heavy alcohol consumption is in the form of binge drinking. There is also evidence indicating that females may be more vulnerable to the neurotoxic effects of alcohol. We have recently shown that weekly binge ethanol (5 g/kg) administration for 11 weeks increases partial activation (priming) of microglia in the hippocampus and causes significant dentate gyrus (DG) cell loss despite an increase in neurogenesis in female rats. However, it is not known whether significant damage occurs with fewer weeks of exposure, nor is it known whether the emergence or magnitude of cell loss is sex-dependent. We hypothesized that cellular damage would be greater in female rats and also that cellular damage would be detectable with fewer than 11 weekly doses. Animals (64 male and female adult Long-Evans rats) were administered 5g/kg ethanol (or an iso-caloric control dose) via intra-gastric gavage once-weekly for 3 or 8 weeks. Neither BEC or behavioral intoxication measures differed over time or between the sexes. Brains were collected 4 days following the final ethanol dose, and immunohistochemically processed for neurons (NeuN) and microglia (IBA1). Stereology was used to quantify target cell populations in the hippocampus and medial prefrontal cortex (mPFC). After 3 weeks, binge ethanol significantly decreased the number of NeuN+ cells in the DG of both sexes in comparison to controls. After 8 weeks, DG cell loss was comparable to what we previously observed after 11 weeks. Both 3 and 8 weeks of binge ethanol significantly increased the total number of microglia (IBA1+) in the hippocampus in males and females. After 8 weeks, the number of primed microglia increased in both sexes. In the mPFC, 8 weeks of binge ethanol increased both microglial priming and total microglial number in both sexes. Our results show hippocampal cell loss and an increased inflammatory response in ethanol-vulnerable regions following repeated binge episodes and demonstrate no sex-differences in alcohol-induced neurodegeneration from a weekly binge model. Future work will examine behavioral changes and additional cellular outcomes. (R01AA025380)

Poster 50

Female rats eating high fat chow acquire methamphetamine self-administration faster than rats eating standard chow

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Eating a diet that is high in fat contributes to increased risk of chronic diseases and mortality, even in the absence of obesity. Eating a high fat diet can also impact the same brain reward pathways (i.e., dopamine systems) that are targeted by drugs of abuse. Preclinical studies have demonstrated that rats eating high fat chow are more sensitive to the unconditioned behavioral effects of drugs that act on these dopamine systems (e.g., cocaine). Further, the majority of evidence demonstrating that diet impacts drug sensitivity has investigated only male subjects, despite probable sex differences. In order test the hypothesis that eating high fat chow increases sensitivity of female rats to the positive reinforcing effects of methamphetamine (0.01-1.78 mg/kg/infusion), female Sprague-Dawley rats (n = 30) were fed either standard (17% kcal from fat) or high fat chow (60% kcal from fat) for 6 weeks prior to self-administration procedures. Following i.v. catheter implantation, rats were trained to respond for 0.1 mg/kg/infusion methamphetamine under a fixed ratio (FR) 1 schedule of reinforcement. Rats eating high fat chow met acquisition criteria faster (14 +/-2 days) than rats eating standard chow (25 +/- 4 days). Preliminary (n = 5-8/group) dose-response curve assessments under a FR 5 schedule of reinforcement demonstrate that rats eating high fat chow respond less for methamphetamine than rats eating standard chow, at least at the training dose (0.1mg/kg/infusion). These preliminary results suggest that female rats eating high fat chow might be more sensitive to the reinforcing effects of methamphetamine than control rats eating standard chow. Future work will examine the relative reinforcing effectiveness of methamphetamine in female rats eating different diets using a progressive ratio schedule of reinforcement. These data expand previous research and add to the growing literature on the effects of diet on drug sensitivity.

Poster 51

Does plasma membrane monoamine transporter function undermine antidepressant effectiveness?

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The poor effectiveness of antidepressants is hypothesized to be attributable, in part, to high volume transporters with low selectivity (i.e., "uptake-2" mechanisms; e.g., plasma membrane monoamine transporter, PMAT) that undermine antidepressant blockade of highly selective, low volume transporters (i.e., "uptake-1" transporters) such as the serotonin transporter. We hypothesized that genetically reduced function of PMAT would enhance the ability of antidepressants to elicit antidepressant-like behaviors in a forced swim test, and to impair clearance of extracellular serotonin. We compared male and female wildtype (+/+) controls against mice with reduced (+/-) or completely ablated (-/-) PMAT function. Preliminary findings indicate that male -/- mice may selectively exhibit antidepressant-like responses to bupropion and fluvoxamine through an increase in swimming behavior. In contrast, female -/- mice appear to exhibit a depressive-like response specifically to bupropion. Ongoing experiments are also evaluating fluvoxamine- and/or bupropion-elicited changes in serotonin clearance in male +/+ and -/- mice. These initial results support our hypothesis and suggest an unexpected sex-specific contribution of PMAT function in the poor effectiveness of uptake-1 targeting antidepressant drugs. Thus, greater focus on drug discovery for PMAT-selective inhibitors could reveal compounds that are useful as antidepressant adjuvants. Future work will focus on identifying potential mechanisms through which these sex- and genotype-dependent antidepressant responses are mediated.

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Poster 52

Interaction of the cannabinoid agonist (-)-CP 55,940 with the discriminative stimulus, antinociceptive, and diuretic effects of (±)-trans-U50488.

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Kappa (κ) opioid receptor agonists produce both analgesic and diuretic effects. However, these agonists can also produce dysphoria, which markedly reduces their clinical utility. The present experiment was conducted to determine if the optical isomers of the geometric trans isomer of U50488 differentially produced these kappa-mediated effects, and determine if the non-selective cannabinoid receptor agonist (-)-CP 55,940 could modify these effects. These possibilities were assessed with two groups of male rats. The first group (n=12) was used to assess the discriminative stimulus and antinociceptive effects. This was done by training subjects to discriminate 5.6 mg/kg of (±)-trans-U50488 from saline under a fixed-ratio 20 (FR-20) schedule of food reinforcement, and then following sessions used to test cumulative doses of the stereoisomers or (-)-CP 55,940 alone, assessing antinociception with warm-water tail-withdrawal and paw-withdrawal (Von-Frey) procedures. For examining the interaction of these two drugs, a single dose of (-)-CP 55,940 (0.032 or 0.056 mg/kg) was administered prior to cumulative doses of (±)-trans-U50488. The second group (n=6/group) was used to determine the capacity of (±)-trans-U50488 and its isomers for producing an aquaresis. In the rats trained to discriminate (±)-trans-U50488, the (-)-trans-U50488 isomer dose-dependently substituted for the racemate and produced antinociception with comparable potency. In the rats used to assess κ-mediated aquaresis, the (-)-trans-U50488 isomer was again comparably potent to the racemate in producing this effect. The (+)-trans-U50488 isomer did not substitute for the racemate in the discrimination procedure and produced little or no antinociceptive effects at the doses tested. In addition, (-)-CP 55,940 potentiated the discriminative stimulus and antinociceptive effects of the racemate by shifting the dose-effect curves to the left more than 2-fold. Further studies are needed in order to reevaluate the clinical potential of κ opioid receptor agonists as either analgesics or diuretics and determine if cannabinoids in combination with κ opioids can produce any "opioid-sparing" effects.

Poster 53

Corticosterone administration after early adolescent stress selectively blocks stress-induced potentiation of morphine place preference in adulthood

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Opioid use disorder (OUD) is a large public health concern within the United States. A significant predictor of the development of OUD is a pre-existing anxiety disorder, which may contribute to the high comorbidity between anxiety disorders and OUD. Another significant predictor of anxiety and substance abuse disorders in adulthood is childhood or adolescent trauma – psychological or physical. Here we explore the longitudinal effects of early adolescent stress, and the treatment thereof, on the rewarding properties of opioids in adulthood. Using various stressors on mice during early adolescence (PND 30-31), we test the effects of the stress on the rewarding properties of morphine in adulthood (PND 72). To assess morphine reward, we use morphine-induced conditioned place preference (CPP) paradigm in which the motivational properties of morphine are repeatedly paired with a neutral context, that can later elicit an approach behavior toward the morphine-paired context. The effects of stress during adolescence have a long-term effect on potentiating CPP into adulthood. However, no study, to our knowledge, has investigated the effects of treatment interventions post-adolescent stress to alleviate the detrimental effects of stress on both the memory of the stressor and the increased rewarding properties of drugs. A current treatment intervention after trauma in clinical populations is hydrocortisone, a steroid hormone which has shown to be successful at reducing PTSD symptoms three-months after the trauma exposure. We found that the rodent equivalent of hydrocortisone, corticosterone, administration after stress in adolescence selectively ameliorates the impact of the stressor and normalized morphine preference to levels comparable to non-stressed controls. These findings help to uncover potential treatments to aid in the prevention of addictive behaviors.

Poster 54

Differential microRNA expression in nucleus accumbens shell after prolonged cocaine abstinence in environmentally-enriched rats

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MicroRNAs (miRNAs) have emerged as "master regulators" that influence expression of hundreds or even thousands of genes, and recent research has linked several miRNAs to substance abuse and addiction. Here, we investigated the expression of miRNAs in the nucleus accumbens shell (NAcSh) in a model of cue-induced relapse. Twelve male, isolate-housed Sprague-Dawley rats were implanted with jugular vein catheters and trained to self-administer cocaine (0.75 mg/kg/infusion) on a variable ratio 5 (VR5) schedule of reinforcement. After animals achieved stable cocaine intake, they were placed into 21 days of forced abstinence and either maintained in isolation or placed into environmental enrichment (EE). After abstinence, animals underwent a cue reactivity test in which the cue light and tone that was previously paired contingently with cocaine was available to animals on a fixed ratio (FR) 1 schedule in the absence of drug. Active lever presses were used to measure cocaine-seeking behavior. Immediately following the cue reactivity test, animals were sacrificed and brains were flash-frozen. RNA was isolated from NAcSh tissue and processed in a miRNA microarray (nanoString nCounter Rat v1.5). Differential expression analysis was performed using nSolver™ Analysis Software. EE animals showed significantly less cocaine-seeking behavior in the cue reactivity test (independent samples t-test). We identified 16 miRNAs as significantly upregulated in EE animals compared to isolate animals. Some of these miRNAs, including several from the let-7 family, have been implicated in addiction previously, while many are novel findings. Ingenuity Pathway Analysis was used to examine relationships between miRNAs and their gene targets. These findings enhance our understanding of the neurobiological benefits of EE and reveal several therapeutic targets for attenuating drug craving.

Poster 55

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

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The naltrexone derivative 3-iodobenzoyl naltrexamine (IBNtxA) is a novel μ opioid receptor (MOR) agonist. Previous studies reported IBNtxA preferentially signals through truncated MOR splice variants, producing a unique pharmacological profile resulting in potent analgesia with reduced side effects, including no conditioned place preference (CPP) when tested at a single dose. The purpose of this study is to 1) independently verify IBNtxA-mediated analgesia; 2) evaluate a broader range of IBNtxA doses in CPP to more fully assess its abuse liability; 3) determine whether IBNtxA alters morphine CPP expression; and 4) evaluate the discriminative stimulus properties of IBNtxA. We determined that 3 mg/kg IBNtxA was equipotent to 10 mg/kg morphine in the hot plate assay, but showed no place preference. 3 mg/kg IBNtxA also attenuated morphine CPP. Drug discrimination studies are ongoing, but indicate that IBNtxA only partially substitutes for morphine. IBNtxA represents an intriguing lead compound for preclinical drug development, particularly for its potentially unique effects targeting truncated MOR splice variants.

Poster 56

Methamphetamine self-administration increases neurotensin-dependent long-term depression of dopamine D2 autoreceptor signaling in dopamine neurons

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Midbrain dopamine neurons play physiological roles in many processes including reward and motivated behavior. Neurotensin (NT) is a neuropeptide implicated in substance use disorders which modulates dopamine neuron excitability in part by decreasing dopamine D_2 autoreceptor-mediated inhibition. However, the mechanisms involved in release and signaling of endogenous NT are poorly understood. Here we combined patch clamp electrophysiology of dopamine neurons in midbrain slices from transgenic mice with blue light stimulation to specifically activate either NT-expressing inputs to the midbrain or dopamine neurons. We found that low frequency stimulation of dopamine neurons alone was sufficient to induce long-term depression of D2 autoreceptor inhibitory postsynaptic currents (D2-LTD) in the substantia nigra pars compacta (SNc) but not the ventral tegmental area (VTA). D2-LTD was blocked by either calcium chelation or inhibition of vacuolar type H^+-ATPase in the patched cell, or by preincubation of the slice with a non-selective NT type 1/2 receptor antagonist. Next, we investigated NT-expressing inputs to the midbrain from either the nucleus accumbens or lateral hypothalamus, both brain regions implicated in the etiology of substance use disorders, and found that low frequency stimulation of these inputs failed to induce D2-LTD. Finally, we found that methamphetamine self-administration increased the magnitude of D2-LTD. Thus, NT could be released by SNc dopamine neurons and act as a feed-forward mechanism in which increased NT signaling increases excitability of dopamine neurons which in turn drives methamphetamine-motivated behavior. These findings improve our understanding of how endogenous NT induces synaptic plasticity that may play a role in methamphetamine use disorder.

Poster 57

Combination therapy of Opioid, $GABA_B$, and 5-HT1A towards improved analgesics

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Prescription opioids, such as morphine, are the gold standard for managing pain, but suffer from the potential for abuse and overdose. This had led to the current opioid epidemic, and new approaches to treating pain are urgently required. In parallel to our approach of developing new opioids such as UMB425, we are also considering repurposing drugs that are currently FDA-approved for new and innovative uses and through combination with other drugs that enhance the analgesic effects of opioids. In this study, morphine, the $GABA_B$ receptor agonist baclofen and the $5\text{-}HT1_A$ receptor agonist buspirone were studied alone and in combination in rats to produce acute antinociception, as assayed in the hot plate test. Additionally, we tested these drugs to identify drug-induced disruptions behavior in rats through measurement of schedule-controlled operant responding for food, which is sensitive to drug-induced disruptions in behavior from numerous drug classes that act in the CNS. Morphine, baclofen, and buspirone each independently produce antinociception, as indicated from an increased thermal response latency and decrease operant responding for food. When we combine morphine with either baclofen or buspirone, the result is a significant leftward-shift of the plotted dose response curve of each drug to increase thermal response latency, and a decrease in operant responding for food. Similar effects are seen when we combine baclofen and buspirone. Naltrexone antagonizes the effects of the combinations of baclofen and morphine, and separately, buspirone and morphine, which demonstrates that opioid receptors, at least in part, mediate some of our observed effects. Similarly, CGP35348 also antagonizes the effects of the combinations of baclofen and morphine, and separately, baclofen and buspirone. We suggest that a combination therapy involving $GABA_B$ and $5\text{-}HT1_A$ agonists may be useful when combined with opioid agonists for the treatment of pain.

Poster 58

The effects of docosahexaenoic acid on high fat chow-induced enhanced sensitivity to the behavioral effects of psychomotor stimulant drugs

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There are many negative health consequences of eating a high fat diet, including obesity, diabetes and heart disease. For example, eating high fat laboratory chow enhances sensitivity of rats to the behavioral effects of drugs of abuse (i.e., methamphetamine). Our laboratory has recently demonstrated that dietary supplements that are rich in omega-3 fatty acids (i.e., fish oil) can prevent and reverse this high fat diet-induced enhanced sensitivity to dopaminergic drugs. However, fish oil contains two major omega-3 fatty acids, and it is not known which fatty acid is driving the beneficial effects of fish oil. Docosahexaenoic acid (DHA), one of the fatty acids found in fish oil, is also widely expressed in the brain. In humans, doctors recommend DHA supplementation to aid in neuronal development among infants, and for the prevention of high cholesterol and heart diseases in adults. To test the hypothesis that daily dietary supplementation with DHA will prevent high fight diet-induced enhanced locomotor sensitization to methamphetamine, rats eating standard chow (17% kcal from fat), high fat chow (60% kcal from fat), or eating standard or high fat chow with 19% DHA oil (w/w) oral supplementation or nightly injection (300 mg/kg; i.p.) were tested once weekly with methamphetamine (0.1-3.2 mg/kg; i.p.) or cocaine (0.1-17.8 mg/kg; i.p. using a cumulative dosing procedure. Preliminary data suggest that i.p. administration of DHA does not impact cocaine-induced locomotion; however, it is anticipated that oral dietary supplementation of DHA will prevent high fat diet-induced enhanced sensitivity to methamphetamine-induced locomotion. The results of this experiment contribute to a growing body of literature examining the impact of diet on drug sensitivity, as well as the literature supporting beneficial health effects of omega-3 fatty acids.

Poster 59

Conformationally restrained Phenyldecahydroisoquinolines as opioid receptor ligands

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Conformationally restrained opioid ligands have been an important tool for understanding the structure activity relationship of opioids with the opioid receptors. A notable example of these ligands, the phenylmorphans, were first synthesized in 1955 and have been a rich source of pharmacologically interesting compounds. In an effort to advance our understanding of the opioid receptors, we sought to study a novel set of conformationally restrained ligands analogous to the phenylmorphans and the oxide-bridged phenymorphans. In morphine and morphine-like structures the phenyl ring is locked in position by both the benzylic carbon at C-10 and by the C-5 oxide bridge. By removing the C-10 benzylic carbon, the phenyl ring can be rotated in approximately 45° increments by opening and reclosing the oxide bridge on various positions of the isoquinoline scaffold. We report the synthesis toward this novel scaffold, as well as functional activity at the opioid receptors and structural analysis of some of these rotational isomers.

Poster 60

Methcathinone decreases dopamine transporter function after self-administration and *in vitro* exposure

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Synthetic cathinones, including methcathinone (MCAT), are psychoactive substances with high abuse potential. MCAT administration in rats causes rapid and persistent striatal dopaminergic deficits. Multiple high-dose injections persistently (at least 30 d), and a single high-dose administration rapidly (within 1 h), decreases striatal [^{3}H]dopamine (DA) uptake, as assessed in synaptosomes prepared from treated rats. The present study aims to extend these studies by assessing the effects of both MCAT self-administration and *in vitro* exposure on the DA transporter. We hypothesized that both MCAT self-administration and *in vitro* exposure will rapidly decrease [^{3}H]DA uptake in striatal synaptosomes. For self-administration experiments, adult male Sprague-Dawley rats were trained to self-administer MCAT and [^{3}H]DA uptake was assessed *ex vivo*. For *in vitro* studies, synaptosomes from naïve male rats were incubated with MCAT, washed by repeated centrifugation, and then [^{3}H]DA uptake was assessed. Differences between two groups were determined by a Student's t-test and differences between $\geq$ 3 groups were assessed by analysis of variance. Results revealed that MCAT is readily self-administered by rats (n = 10). Further, 7 d of MCAT self-administration decreased striatal [^{3}H]DA uptake, as assessed 1 h after the final self-administration session. Incubation of striatal synaptosomes from naïve rats with MCAT at 37˚C likewise decreased [^{3}H]DA uptake; an effect that was prevented when incubation was conducted at 4˚C (n = 5 - 6), suggesting that second messengers and/or post-translational modifications contributed to this deficit. This hypothesis was confirmed by findings that co-incubation with the non-specific PKC inhibitor, bisindolylmaleimide I, prevented the MCAT-induced decrease in synaptosomal [^{3}H]DA uptake (n = 5 – 6). Ongoing studies are investigating the specific PKC subtype underlying the MCAT-induced deficit in transport, and whether the in vitro phenomenon models the impact of MCAT self-administration. (Supported by DA R01-DA039145).

Poster 61

Morphine discrimination: effects of mixed efficacy opioid ligands

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Mu opioid receptor (MOR) agonists have antinociceptive properties but also have abuse liability impacting their safety in the clinical setting. Some studies have suggested that delta opioid receptor (DOR) antagonists may limit adverse effects associated with MOR agonists, such as rewarding properties. Therefore, the purpose of this study was to investigate the effects of mixed efficacy MOR agonist/DOR antagonist ligands, all of which produce antinociceptive effects, in male Sprague-Dawley rats (N=5-6) trained to discriminate morphine (3mg/kg) from saline on a fixed ratio (FR) 10 schedule of food reinforcement. We hypothesized that the mixed efficacy MOR agonist/DOR antagonist ligands would fully generalize to morphine and be equipotent to morphine. We evaluated 3 novel mixed efficacy MOR agonist/DOR antagonist compounds, AMB67, AAH8 and UMB425 as well as known MOR agonists morphine, fentanyl, and partial agonists buprenorphine and nalbuphine. Similar to the known MOR agonists, the mixed efficacy ligands AMB67 and UMB425 fully generalized to the discriminative stimulus effects of morphine in a dose-dependent manner; however, AAH8 failed to generalize to morphine. All ligands decreased rates of responding. Interestingly, the rate decreasing effects of AAH8 were blocked by naloxone, suggesting these effects were opioid receptor mediated. Overall, these data suggest that DOR activity may be able to alter the discriminative stimulus properties of MOR agonists and potentially the reinforcing properties of MOR agonists. Future studies will further explore MOR/DOR mixed efficacy ligands with different affinities for and activities at MORs and DORs.

Poster 62

Methocinnamox (MCAM) prevents heroin-induced respiratory depression.

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Opioid use disorder (OUD) affects over 2 million Americans, and there is an ever-growing number of deaths due to overdose. Mu opioid receptor agonists are widely abused and include prescription opioids like oxycodone and illicit opioids like heroin. The primary effect of opioids contributing to overdose death is respiratory depression. Currently, the opioid receptor antagonist naltrexone (e.g. ReVia, Vivitrol) is used for prevention of both relapse and overdose in those with OUD and the antagonist naloxone (Narcan) is used to reverse overdose. However, naltrexone and naloxone are reversible and relatively short-lived, making it possible to surmount their protection by taking a larger dose of opioid, possibly resulting in overdose and death. Methocinnamox (MCAM) is a potent, long-lasting, selective, and pseudoirreversible mu opioid receptor antagonist that might be useful for preventing relapse, as well as protecting against and reversing the fatal respiratory-depressant effects of opioids. The current study aims to test the hypothesis that MCAM will attenuate respiratory depression due to heroin administration. Male Sprague-Dawley rats (N = 8) were given 0.32, 0.56, or 1.78 mg/kg of heroin and ventilatory parameters were recorded using a whole-body plethysmography system. When compared to baseline, heroin dose-dependently decreased the frequency of breathing by 10%, 40%, and 51% (respectively). On a separate day, rats were given a 30-minute pretreatment with either vehicle or MCAM (10 mg/kg), followed by an i.p. injection of 3.2 mg/kg heroin. Breathing frequency was decreased by 45% in rats that received vehicle; however, in rats that received MCAM before heroin, frequency was decreased only 4% from control. This study demonstrates that pretreatment with MCAM provides protection against heroin-induced respiratory depression. Future studies will explore the duration of effect for MCAM as well as determining full dose-response curves for all drugs being evaluated.

Poster 63

Assessment of the rate-decreasing effects of fentanyl and furanyl fentanyl and the sensitization of naloxone to opioid pretreatment in CD1 mice

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Fentanyl analogues are emerging drugs of abuse partially fueling the current “opioid crisis” in the US. The pharmacological properties of many of these novel fentanyl analogues are largely unknown. These studies assessed the rate altering effects of fentanyl and furanyl fentanyl following acute administration, alone and in the presence of naltrexone. Subsequent studies utilized precipitated withdrawal to assess the sensitization to the rate-decreasing effects of naloxone induced by acute opioid pretreatment. Male CD1 mice were trained on a FR10 schedule to press levers for milk reinforcement. Acute administration (SC) of both opioids dose-dependently suppressed response rates (fentanyl ED_{50}=0.07 mg/kg, furanyl fentanyl ED_{50}=0.16 mg/kg), and administration of naltrexone produced rightward shifts in the dose-effect curves for both opioids. Following repeated treatment with fentanyl (0.3, 0.56. 0.78. and 1 mg/kg) or furanyl fentanyl (0.3, 1, 3 mg/kg), administration of naloxone (1, 3, 10 mg/kg) (IP) elicited dose-dependent disruption of operant responding, and was more potent in this regard in fentanyl-treated mice than in furanyl fentanyl-treated mice. These results suggest that like fentanyl, the widely abused analogue furanyl fentanyl similarly disrupts the performance of behavioral tasks following acute administration via agonist interaction with opioid receptors. Following repeated administration of furanyl fentanyl, administration of naloxone disrupts operant responding, suggesting opioid dependence and a nalolxone-precipitated withdrawal state. The decreased potency of naloxone to disrupt operant responding in furanyl fentanyl dependent mice may have implications for reversing furanyl fentanyl overdose, although studies to confirm this are needed. These studies supported by DEA contract HHSF223201610079C.

Poster 64

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

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Mu opioid receptor agonists (e.g., oxycodone) are the “gold standard” for treating moderate to severe pain despite the adverse effects (abuse, respiratory depression, and physical dependence) 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. *Kappa* opioid receptor agonists have antinociceptive effects and might be useful for treating pain in mixtures because they are devoid of reinforcing effects and are not abused. By combining *mu* agonists with drugs that are not reinforcing (and perhaps punishing), adverse effects might be avoided while maintaining adequate pain relief. This study compared the effects of remifentanil (*mu* opioid receptor agonist; 0.001-0.01 mg/kg/infusion) and a drug with well-established punishing effects, histamine (H_{1-4} receptor agonist; 0.32-3.2 mg/kg/infusion), alone and in mixtures to test the hypothesis that remifentanil/histamine mixtures are less reinforcing compared with remifentanil alone. Male Sprague Dawley rats (n=11) could choose (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 + histamine, rats responded predominantly for the pellet alone; conversely, when choosing between a pellet and a pellet + remifentanil, rats responded predominantly for the pellet + remifentanil. The effects of remifentanil/histamine mixtures generally were not different from the effects of the constituent doses of remifentanil alone but were different from the constituent doses of histamine alone. The effects of a mixture containing 0.001 mg/kg/infusion remifentanil and 3.2 mg/kg/infusion histamine were different from the effects of the constituent doses but not saline. Reinforcing doses of remifentanil combined with punishing doses of histamine can yield mixtures that are neither reinforcing nor punishing, offering “proof-of-principle” for using drug mixtures to avoid adverse effects of opioid receptor agonists. It remains to be determined whether *mu*/*kappa* mixtures avoid reinforcing or punishing effects as well as other adverse effects.

Poster 65

Adolescent ketamine pre-exposure does not alter cocaine preference in adult female C57BL/6 mice

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Major Depressive Disorder (MDD) is a prevalent illness that affects females at a higher rate than their male counterparts. Unfortunately, close to 60% of MDD patients do not receive treatment, and when they do, nearly half of them are unresponsive to traditional antidepressants, like fluoxetine. As such, alternative pharmaceutical treatments for MDD are being explored, particularly for juvenile patients – given that the first incidence of MDD is usually reported during this period of development. Recently, ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has shown promising antidepressant efficacy in adolescent treatment-resistant MDD patients. Nevertheless, the possible long-term effects of ketamine exposure during early development have not been assessed. Although there has been some progress in breaching our understanding of how ketamine works by using preclinical models, a limitation of this approach is that most of this work has been done using males as subjects. Thus, we examined whether exposure to ketamine during adolescence results in long-lasting changes in sensitivity to the rewarding properties of cocaine in adulthood using female C57BL/6 mice. Specifically, mice received either ketamine (20 mg/kg) or saline (VEH) for 15 consecutive days during adolescence (Postnatal Day [PD] 35-49). Twenty-one days after ketamine exposure, once mice reached adulthood (PD70), we assessed their behavioral responsivity to cocaine (0, 2.5, 5, 7.5 mg/kg) using the conditioned place preference (CPP) test. Our results show that adult female mice spent significantly higher time in the cocaine-paired side, as a function of cocaine dose ($p<0.05$). However, juvenile ketamine pre-exposure during adolescence did not influence the magnitude of preference for environments previously paired with the stimulant, when compared to VEH pre-treated controls, at the same doses of cocaine ($p>0.05$, respectively). Together, our findings suggest that exposure to ketamine during adolescence does not alter sensitivity to the rewarding properties of cocaine in adulthood, in female C57BL/6 mice

Poster 66

Novel selective D3R antagonists with a 6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol "head" group

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The dopamine D3 receptor (D3R) is involved in the craving response in drug addictions. Molecules which block D3R (D3R antagonists) are very valuable as potential therapeutics to treat substance abuse disorders. Poor pharmacokinetic properties and sub-optimal selectivity especially versus the closely related D2 receptor (D2R), have limited the clinical availability and utility of D3 antagonists. We hypothesize that a progressive combination of in silico docking, synthesis and bioassays will lead to the discovery of novel, selective and potent D3R antagonists. The ligand design was based on a classical D3R pharmacophore comprising an amine-containing “head” moiety, a hydrocarbon linker “body” and an arylamide “tail” region. A tetrahydroisoquinoline motif representing the “head” portion was retained in all the analogues, with variations in the aryl linker moiety and the arylamide “tail” region. After docking at the D3R crystal structure, the top ranked analogues (based on Glide scores) were synthesized. Thereafter, the synthesized molecules were subjected to binding and functional activity assays at dopamine receptors (D1R-D5R) in vitro. Data from this structure-activity relationship (SAR) study indicate that the introduction of an aryl moiety in the linker portion is unfavorable for D3R affinity. D3R affinity was found to be sensitive to substitutions in the tail region. A number of ligands with strong D3R affinity (Ki = 20-60 nM) and selectivity (>30-fold) versus other dopamine receptors from modifications at the tail site were identified. We conclude that further SAR optimization by tuning aryl substituents at the tail region is warranted in subsequent analog generations.

Poster 67

Predicting motivation to change alcohol use among drunk driving recidivist: The roles of locus of control and negative alcohol expectancies

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The investigation examines how locus of control and perceived negative alcohol expectancies are related to motivation to reduce alcohol use among a high-risk population of drinkers, especially those with more than one drunk driving arrest. A total of 57 participants with at least two previous DWI arrests were recruited from either correctional treatment facility or the community. Participants completed a battery of questionnaires assessing demographics, physical/psychiatric conditions, legal history, and psychosocial factors including motivation to change alcohol use (MOC), locus of control (LOC) and negative alcohol expectancies (NAE). The result from a hierarchical regression analysis showed that external LOC was negatively associated with MOC among recidivists ($\beta = -.38$, S.E. = .07, $p < .05$). Neither proximal nor distal NAE has significant associations with MOC (proximal NAE: $\beta = .33$, S.E. = .50, $p = .11$; distal NAE: $\beta = -.01$, S.E. = .41, $p = .99$), but acted as moderators of the relationship between LOC and motivation to change alcohol use. Those with greater external LOC showed stronger MOC when they have greater proximal NAE ($\beta = 1.01$, S.E. = .13, $p < .01$), but weaker MOC with distal NAE ($\beta = -.89$, S.E. = .08, $p < .01$). The result of this investigation suggests that motivation to reduce alcohol use of drunk driving recidivists is dependent on the belief about their control over life events (i.e., locus of control) and the perception of negative consequences of their drinking (i.e., negative alcohol expectancies). LOC has been considered to be a stable and difficult to change personality trait. But the impact of NAE on the relationship between LOC and motivation to change suggest it as malleable target of intervention. Treatment for recidivists with greater external LOC can be effective in motivating them to reduce alcohol consumption when it focuses on enhancing the awareness of the proximal negative outcomes of alcohol consumption.

Poster 68

Characterization of the discriminative stimulus effects of 3,4-methylenedioxypyrovalerone (MDPV) in female Sprague-Dawley rats

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3,4-Methylenedioxypyrovalerone (MDPV), one of several synthetic cathinones, is a popular constituent of illicit “bath salts.” In preclinical studies utilizing drug discrimination methods with male rodents, MDPV has been characterized as similar to both cocaine and MDMA, although some discrepancies have been noted in study outcomes, perhaps due to methodological differences. The aim of the current study was to evaluate the discriminative stimulus effects of MDPV in female rats. Twelve adult female Sprague-Dawley rats were trained to discriminate 0.5mg/kg MDPV from saline using a resetting fixed ratio 20 schedule of food reinforcement. Substitution tests were given with MDPV (0.05-0.5 mg/kg), cocaine (2.5-10 mg/kg) and MDMA (0.75-3 mg/kg). After completing substitution tests with MDPV in all animals, half the rats were assessed with cocaine and then MDMA and the other half were assessed with these substances in the opposite order. A visual analysis of dose response curves suggests the test order influenced the level of substitution by MDMA and cocaine, with higher mean levels of substitution observed with the second drug compared to the first drug. Preliminary statistical analyses indicate test order is not statistically significant. However, all animals have not yet completed these tests. The current findings with female rats are consistent with previous published studies using male rats that MDPV shares similar discriminative stimulus effects with cocaine. MDMA substitution for the MDPV cue is more variable among previous study reports and the current preliminary results indicate test order may influence these outcomes. Substitution tests with other monoaminergic agents are still in progress, with plans to systematically evaluate sex differences in the neurochemical mechanisms underlying the discriminative stimulus effects of MDPV.

Poster 69

Assessment of sex differences in α-pyrrolidinopentiophenone (α-PVP)-induced taste avoidance, place preference, thermoregulation, motor activity and stereotypies in Sprague-Dawley rats

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Although the synthetic cathinones are becoming well characterized in relation to their use and abuse potential, male subjects have primarily been investigated in such assessments (though see King et al., 2015; Daniel & Hughes, 2016; McClenahan et al., 2018). In relation to the specific bath salt α-PVP, no papers have reported data comparing potential sex differences. To address this, the present work examined the ability of racemic α-PVP (0, 1.5, 3 and 6 mg/kg, i.p.) to induce conditioned taste avoidance, conditioned place preference, thermoregulatory changes, general motor activity and stereotypies in adult male and female Sprague-Dawley rats (n = 24/sex). All animals underwent a combined taste avoidance/place preference conditioning procedure during which they were given access to a novel saccharin solution, injected with drug or vehicle and then placed on their non-preferred side of a place conditioning apparatus. They were subsequently tested for changes in temperature and motor activity/stereotypies following vehicle or α-PVP. Dose-dependent taste avoidance (Trial x Dose interaction, $p < 0.05$) and place preferences (Test x Dose interaction, $p < 0.05$) were evident, although there was no significant effect of Sex or an interaction with Sex; all ps > 0.05). α-PVP also produced dose-dependent hyperthermia, although again there were no interactions involving Sex and Dose. Finally, α-PVP increased motor activity and stereotypies in a sex-dependent manner (Time-point x Dose x Sex; all ps < 0.05) with females displaying greater effects at several, but limited, sampling periods (for related sex comparisons with MDPV, see Hambuchen et al., 2017; for sex comparisons with pentedrone, pentylone, and methylone, see Javadi-Paydar et al., 2017). The present data suggest that for a number of behavioral and physiological indices, the effects of α-PVP were not sex dependent (with limited sex differences in activity and stereotypies). Further work should examine use and abuse potential and if sex is a biological variable for these behavioral endpoints.

Poster 70

Design and synthesis of novel antagonist ligands for dopamine D4 receptor as molecular tools to study cocaine use disorders

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The Dopamine 4 receptor (D4R) is a part of the D2-like class of dopamine receptors, and it is enriched in the prefrontal cortex where it plays an important role such as cognition, attention and decision making. Previous studies have found D4R antagonist ligands to be implicated that cocaine use disorders (CUD), attention-deficit hyperactivity disorders, and Parkinson's disease. Currently, there are no FDA approved drugs for D4R to treat CUD. Hence, developing novel antagonist ligands with higher affinity and selectivity with reduced or no off target receptor binding can be used as molecular tools to study CUD, leading to discovery of new medicines. By using computational modeling with the recently crystallized D4 receptor, we have designed a library of compounds by starting with the D4R antagonist 2-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)propyl)benzo[*d*]thiazole as our parent compound. We hypothesized that structural modifications of the parent compound template would produce novel ligands with high affinity and receptor selectivity. These novel ligands were synthesized, characterized, and their in vitro binding affinities were determined using [3H]N-methylspiperone radioligand binding in HEK293 cells expressing dopamine D2-like receptors. By modifying the pyrimidinylpiperidinyl moiety, we have identified several high-affinity compounds ($K_i \leq 5$ nM) with >100-fold selectivity at the D4R versus D2 and D3 receptors. Our new lead compound was selected based on in vitro binding profiles and evaluated in functional assays measuring β-arrestin recruitment and cAMP production. The results from these in vitro studies will be shown during this presentation.

Poster 71

Preparing first responders to reduce opioid overdose deaths in Texas

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Texas has experienced a significant increase in opioid-related deaths in recent years. In 2016 the state reported 1,375 overdose deaths, almost doubling the number reported in 2010. While opioid-use disorder is a multifaceted public health crisis that must be addressed systematically (behavior, education, and social change), fatal overdoses continue to increase. Texas is among several states that has chosen to adopt a harm reduction approach for addressing this crisis. Over the past year, the UT Health San Antonio, School of Nursing has taken a leading role in this effort. We are partnering with the Texas Overdose Naloxone Initiative (T.O.N.I) to distribute Narcan and train both traditional and non-traditional first responders (community members) in the reversal of opioid overdose using this life saving medication. Following a brief (5-10 minute) educational intervention, almost anyone can recognize and respond to an opioid overdose. While difficult to capture the immediate benefits of drug monitoring programs, drug take back days, and opioid-use education, the distribution of Narcan and training to use it offers a direct benefit to our community through the saving of lives. To date, our team has distributed more than forty-thousand doses of Narcan across Texas and trained close to six hundred new responders. The evaluation of program outcomes and impact are on-going.

Poster 72

Dopamine D4 receptor-selective compounds reveal structure-activity relationships that engender agonist efficacy

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The dopamine D4 receptor (D4R) plays important roles in cognition, attention, and decision making. Novel D4R-selective ligands have promise in medication development for neuropsychiatric conditions, including Alzheimer's disease and substance use disorders (SUD). To identify new D4R-selective ligands, and to understand the molecular determinants of agonist efficacy at D4R, we report a series of eighteen novel ligands based on the classical D4R agonist A-412997 (2-(4-(pyridin-2-yl)piperidin-1-yl)-N-(m-tolyl)acetamide). Compounds were profiled using radioligand binding displacement assays, β-arrestin recruitment assays, cAMP inhibition assays, and molecular dynamic computational modeling. We identified several novel D4R-selective ($K_i \leq 4.3$ nM and >100-fold vs. other D2-like receptors) compounds with diverse partial agonist and antagonist profiles, falling into three structural groups. These compounds highlight receptor-ligand interactions that control efficacy at D2-like receptors and may provide insights to targeted drug discovery leading to a better understanding of the role of D4Rs in neuropsychiatric disorders.

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Maharaj ("Raj") Ticku, PhD

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

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

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

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