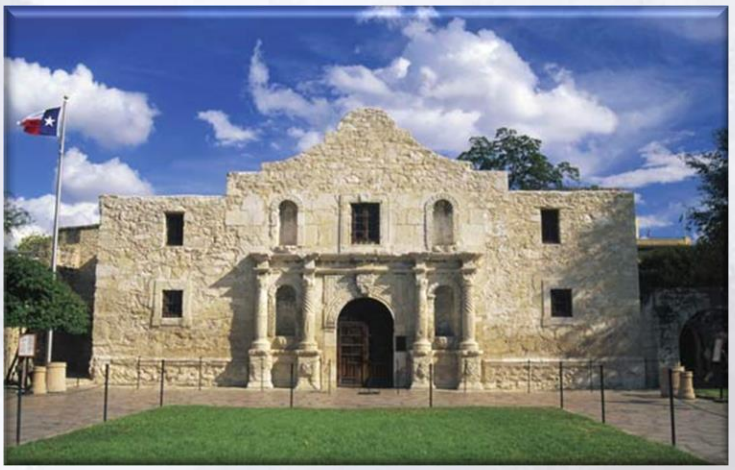
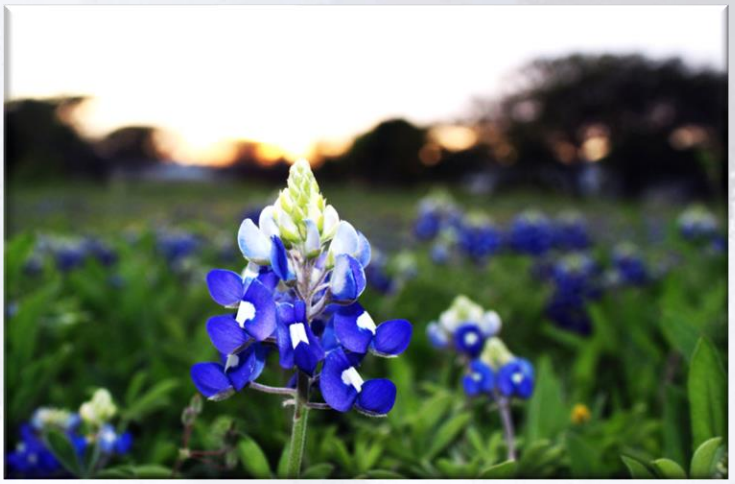
14TH ANNUAL BEHAVIOR, BIOLOGY, and CHEMISTRY:

Translational Research in Addiction

San Antonio, Texas | Embassy Landmark | 26-27 February 2022





ARTT Addiction Research, Treatment & Training CENTER OF EXCELLENCE

NIH National Institute on Drug Abuse

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BBC Publications

BBC 2011

Stockton Jr SD and Devi LA (2012) **Functional relevance of μ–δ opioid receptor heteromerization: A Role in novel signaling and implications for the treatment of addiction disorders: From a symposium on new concepts in mu-opioid pharmacology.** *Drug and Alcohol Dependence* 121, 167-72. PMC3288266

Traynor J (2012) **μ-Opioid receptors and regulators of G protein signaling (RGS) proteins: From a symposium on new concepts in mu-opioid pharmacology.** *Drug and Alcohol Dependence* 121, 173-80. PMC3288798

Lamb K, Tidgewell K, Simpson DS, Bohn LM and Prisinzano TE (2012) **Antinociceptive effects of herkinorin, a MOP receptor agonist derived from salvinorin A in the formalin test in rats: New concepts in mu opioid receptor pharmacology: From a symposium on new concepts in mu-opioid pharmacology.** *Drug and Alcohol Dependence* 121, 181-88. PMC3288203

Whistler JL (2012) **Examining the role of mu opioid receptor endocytosis in the beneficial and side-effects of prolonged opioid use: From a symposium on new concepts in mu-opioid pharmacology.** *Drug and Alcohol Dependence* 121, 189-204. PMC4224378

BBC 2012

Zorrilla EP, Heilig M, de Wit H and Shaham Y (2013) **Behavioral, biological, and chemical perspectives on targeting CRF1 receptor antagonists to treat alcoholism.** *Drug and Alcohol Dependence* 128, 175-86. PMC3596012

BBC 2013

De Biasi M, McLaughlin I, Perez EE, Crooks PA, Dwoskin LP, Bardo MT, Pentel PR and Hatsukami D (2014) **Scientific overview: 2013 BBC plenary symposium on tobacco addiction.** *Drug and Alcohol Dependence* 141, 107-17. PMC4227301

BBC 2014

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

BBC 2015

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

BBC 2016

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

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Felicity Say

Samantha Scott

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Sarah Uribe

Kimberly Whiting

Kristen Woodhouse

Tyler Zarin

Abby Loudermilk Travel Award

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

Pre-doctoral

2022 – Kimberly M Holter

Post-doctoral

2022 – Renata Christina Nunes Marchette

Program Overview

FRIDAY 25 FEBRUARY 2022

3:00 PM – 5:00 PM	**Pathways to Careers in Science Workshop**
4:00 PM – 7:00 PM	**Registration – Embassy Landmark**
7:00 PM – 9:00 PM	**BBC Opening Reception, Embassy Landmark**

SATURDAY 26 FEBRUARY 2022

8:00 AM – 8:10 AM	Welcome and Opening Remarks	
8:10 AM – 10:10 AM	Plenary Symposium:	Chair: Gregory T Collins and Berra Yazar-Klosinski
	Development of Psychedelics for the Treatment of Mental Health and Substance Use Disorders **Matt Johnson, PhD** | Johns Hopkins University *Human behavioral pharmacology and therapeutics of psilocybin* **Berra Yazar-Klosinski, PhD** | Multidisciplinary Association for Psychedelic Studies (MAPS) *Risk/benefit profile of MDMA-assisted therapy for treatment of PTSD* **Javier Gonzalez-Maeso, PhD** | Virginia Commonwealth University *Molecular target and mechanisms of psychedelic-induced plasticity* **David Olson, PhD** | University of California Davis *Psychedelics and related plasticity-promoting neurotherapeutics*	
10:10 AM – 10:20 AM	Coffee Break	
10:20 AM – 11:45 AM	Poster Session I	
11:45 AM – 12:45 PM	Lunch	
12:45 PM – 2:00 PM	Open Oral Communications I	Chairs: Renata Marchette and Erik Garcia
2:00 PM – 2:10 PM	Coffee Break	
2:10 PM – 3:35 PM	Poster Session II	
3:35 PM – 3:45 PM	Coffee Break	
3:45 PM – 5:00 PM	Open Oral Communications II	Chairs: Corinde Wiers and Emily Jutkiewicz
5:00 PM – 5:20 PM	Coffee Break	
5:20 PM – 6:20 PM	Special Lecture	Chair: Thomas Keck
	Jean Lud Cadet, MD | National Institutes of Health, National Institute on Drug Abuse *Modeling methamphetamine addiction in rodents: epigenetic consequences*	
6:20 PM – 7:30 PM	Cocktail Hour and Poster Viewing	
7:30 PM – 9:30 PM	Dinner Science Trivia and Entertainment	

SUNDAY 27 FEBRUARY 2022

7:45 AM	Travel Awardee Group Photo	
8:00 AM – 9:30 AM	Open Oral Communications III	Chairs: Austin Zamarripa and Sally Huskinson
9:30 AM – 9:40 AM	Coffee Break	
9:40 AM – 11:10 AM	Open Oral Communications IV	Chairs: Kimberly Holter and Briana Mason
11:10 AM – 11:20 AM	Coffee Break	
11:20 AM – 12:20 PM	Special Lecture	Chair: Lynette C Daws
	Laura M Bohn, PhD | The Scripps Research Institute *Imparting diversity into opioid receptor signaling*	
12:20 PM – 12:30 PM	Travel and Presentation Awards	
12:30 PM – 1:30 PM	Adjournment and Lunch	

Program Details

Friday 25 February 2022

Pathways to Careers in Science Workshop	3:00 PM – 5:00 PM	*UT Health Campus*
Registration	4:00 PM – 7:00 PM	*Bluebonnet Foyer*
Opening Reception	7:00 PM - 9:00 PM	*Lantana Ballroom*

A badge is required for the opening reception. Additional tickets can be purchased in advance or at the registration desk for $75.00.

Saturday 26 February 2022

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

Development of Psychedelics for the Treatment of Mental Health and Substance Use Disorders

(Chair: Gregory T Collins and Berra Yazar-Klosinski)

Psychedelics, such as psilocybin, have a long history of ritual and medicinal use. Although early evidence suggested that synthetic psychedelics, such as LSD, could aid in the treatment of various mood, and alcohol use disorders, there has been a de facto ban on federally funded psychedelic research since the mid-1960s. Driven in large part by non-profits, private companies, and philanthropic efforts, research into the therapeutic potential of psychedelics has seen a resurgence of over the past 20 years. This symposium brings together leading experts in the field to ongoing research, with topics ranging from medical chemistry efforts to develop novel, non-hallucinogenic, psychedelics, to recently completed Phase III clinical trials on MDMA-assisted therapy for post-traumatic stress disorder. Ultimately, this symposium will highlight the promise and pitfalls of developing psychedelics as treatments for mental health and substance use disorders.

8:10 AM – 8:40 AM	**Matt Johnson** | Johns Hopkins University *Human behavioral pharmacology and therapeutics of psilocybin*
8:40 AM – 9:10 AM	**Berra Yazar-Klosinski** | Multidisciplinary Association for Psychedelic Studies (MAPS) *Risk/benefit profile of MDMA-assisted therapy for treatment of PTSD*
9:10 AM – 9:40 AM	**Javier Gonzalez-Maeso** | Virginia Commonwealth University *Molecular target and mechanisms of psychedelic-induced plasticity*
9:40 AM – 11:10 AM	**David Olson** | University of California Davis *Psychedelics and related plasticity-promoting neurotherapeutics*

Coffee Break	10:10 AM – 10:20 AM	
Poster Session I (odd posters judged)	10:20 AM – 11:45 AM	*Bluebonnet C/Foyer*
Lunch	11:45 AM – 12:45 PM	*Lantana Ballroom*
Oral Communications I	12:45 PM – 2:00 PM	*Bluebonnet AB*

(Chairs: Renata Marchette and Erik Garcia)

12:45 PM – 1:00 PM	**Renata Marchette** | National Institutes of Health, NIDA *Hyperalgesia and peripheral cytokines as biomarkers of compulsive-like opioid intake*
1:00 PM – 1:15 PM	**Harrison Elder** | Virginia Commonwealth University *Respiratory stimulation by methylxanthines and their interactions with fentanyl and oxycodone*
1:15 PM – 1:30 PM	**Siavash Shahbazi Nia** | Texas Tech University Health Sciences Center *Selective kappa opioid receptor antagonists as potential candidates for treatment of neuropathic pain, eliminating opioid-induced addiction*
1:30 PM – 1:45 PM	**Michael Wedemeyer** | University of Texas Health Science Center at San Antonio *Hemi-equilibrium action of buprenorphine*
1:45 PM – 2:00 PM	**Kristen Woodhouse** | University at Buffalo *Antinociceptive interactions between alpha2/alpha3-selective GABAA receptor modulator KRM-II-81 and opioids in female rats*

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

Coffee Break 2:00 PM – 2:10 PM

Poster Session II (even posters judged) 2:10 PM – 3:35 PM *Bluebonnet C/Foyer*

Coffee Break 3:35 PM – 3:45 PM

Oral Communications II 3:45 PM – 5:00 PM *Bluebonnet AB*

(Chairs: Corinde Wiers and Emily Jutkiewicz)

3:45 PM – 4:00 PM **Corinde Wiers** | University of Pennsylvania
Elevated transferrin saturation in individuals with alcohol use disorder: association with HFE polymorphism and alcohol withdrawal severity

4:00 PM – 4:15 PM **Brent Kisby** | Texas Tech University Health Sciences Center
Cell-type specific gene expression changes in the mouse prefrontal cortex after chronic ethanol drinking

4:15 PM – 4:30 PM **Lindsey Galbo** | Wake Forest University
Effects of long-term ethanol drinking on cognition in cynomolgus monkeys

4:30 PM – 4:45 PM **Thang Le** | Yale University
The neural processes underlying avoidance learning dysfunction in problem drinking

4:45 PM – 5:00 PM **Marissa Jones** | East Tennessee State University
Effects of alcohol withdrawal on sleep macroarchitecture and microarchitecture in female and male rats

Coffee Break 5:00 PM – 5:20 PM

Special Lecture: Jean Lud Cadet 5:20 PM – 6:20 PM *Bluebonnet AB*

Modeling methamphetamine addiction in rodents: epigenetic consequences

(Chair: Thomas Keck)

Cocktail Hour and Poster Viewing 6:20 PM – 7:20 PM *Bluebonnet C/Foyer*

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

Additional tickets can be purchased in advance or at the registration desk for $75.00

Science Trivia and Entertainment *Bluebonnet AB*

Join us for an hour of fun, science, trivia, and prizes!

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

Sunday 27 February 2022

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

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

(Chairs: Austin Zamarripa and Sally Huskinson)

8:00 AM – 8:15 AM — **Justin Strickland** | Johns Hopkins University
Real-world assessment of the therapeutic and impairing effects of cannabis using remote data collection approaches

8:15 AM – 8:30 AM — **Austin Zamarripa** | Johns Hopkins University
Individual and interactive effects of vaporized delta-9-tetrahydrocannabinol (THC) and limonene

8:30 AM – 8:45 AM — **Miguel Urbina** | University of Texas at El Paso
Effects of nicotine vapor exposure on motivation for rewards in adolescent male rats

8:45 AM – 9:00 AM — **Emma Bondy** | University of Kentucky
Chemogenetic inhibition of accumbens microglia reduces cue-induced nicotine seeking behavior

9:00 AM – 9:15 AM — **Erin Wood** | University of Texas Health Science Center at San Antonio
Paternal substance use disorder and adolescent substance use initiation: role of protective and risk factors

9:15 AM – 9:30 AM — **Samantha Scott** | Arizona State University
5-HT1B receptor agonist produces a similar abstinence-dependent modulation of motivation for cocaine in male and female rats

Coffee Break — 9:30 AM – 9:40 AM

Oral Communications IV — 9:40 AM – 11:10 AM — *Bluebonnet AB*

(Chairs: Kimberly Holter and Briana Mason)

9:40 AM – 9:55 AM — **Kimberly Holter** | Wake Forest University
Combination of submaximal doses of an mGlu5 negative allosteric modulator and an adenosine A2A agonist reduces reinforcing strength of cocaine

9:55 AM – 10:10 AM — **Gisela Camacho Hernandez** | National Institutes of Health, NIDA
Illuminating the monoamine transporters: high affinity fluorescent probes for visualization of DAT and NET

10:10 AM – 10:25 AM — **Peter Manza** | National Institutes of Health, NIAAA
Speed of methylphenidate's uptake influences brain activation patterns: a simultaneous PET-fMRI study

10:25 AM – 10:40 AM — **Tyler Zarin** | East Tennessee State University
Effects of single- and dual-hypocretin receptor antagonists on compulsive methamphetamine self-administration in male rats

10:40 AM – 10:55 AM — **Katharine Nelson** | Medical University of South Carolina
The importance of the perirhinal cortex to the nucleus accumbens neural pathway for novelty recognition and salience in methamphetamine self-administering rats

10:55 AM – 11:10 AM — **Shailesh Khatri** | University of Kentucky
Cocaine use during oxycodone withdrawal reduces somatic signs of withdrawal and is associated with aberrant accumbens glutamatergic plasticity

Coffee Break — 11:10 AM – 11:20 AM

Special Lecture: Laura M Bohn — 11:20 AM – 12:20 PM — *Bluebonnet AB*

Imparting diversity into opioid receptor signaling

(Chair: Lynette C Daws)

Travel and Presentation Awards — 12:25 PM – 12:30 PM

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

See you at BBC 2023!

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

Oral Communications

Oral Communication 1-1

Hyperalgesia and peripheral cytokines as biomarkers of compulsive-like opioid intake

Marchette, Renata C.N.[1]; Carlson, Erika R.[1,2]; Vendruscolo, Leandro F.[1]; Koob, George F.[1]

[1]Neurobiology of Addiction Section, INRB, NIDA IRP, Baltimore, MD, USA; [2]Department of Pharmacology, University of Texas at Austin, Austin, TX, USA.

Rodent models are useful for understanding the mechanisms that underlie opioid addiction, but most preclinical studies have focused on the rewarding and consummatory aspects of opioids without components of compulsive-like drug taking or seeking. We aimed to characterize several opioid-related behavioral measures in mice of both sexes using a model of vaporized fentanyl self-administration. Female and male C57BL/6J mice were assigned to short access (1 h; ShA) or long access (6 h; LgA) to fentanyl vapor self-administration and subsequently tested in a battery of behavioral tests. Compared to mice in the ShA condition, mice in the LgA condition escalated fentanyl intake, were more motivated to work to obtain the drug, and exhibited increased sensitivity when fentanyl was adulterated with the respiratory irritant capsaicin (i.e., to model punished drug taking). Moreover, mice allowed LgA to fentanyl exhibited greater hyperalgesia during spontaneous withdrawal and greater naloxone-precipitated somatic signs of withdrawal. Mice tested on LgA conditions showed reduced levels of the cytokine IL-17 in the plasma compared to mice on the ShA condition. Because we did not identify significant sex differences, we combined data from males and females and performed a principal component analysis to reduce data dimensionality. This analysis indicated qualitative differences in the distribution of behavioral measures and cytokines between ShA and LgA groups. Overall, the results support the hypothesis that compulsive-like opioid taking may be driven by motivational withdrawal, but not somatic withdrawal, and that motivational withdrawal may be associated with elevated levels of IL-17 and corticosterone. Furthermore, only in the LgA group, punished drug taking was positively correlated with motivation, hyperalgesia, and IL-17 plasma levels. We conclude that hyperalgesia and IL-17 might be biomarkers of compulsive-like opioid intake.

Oral Communication 1-2

Respiratory stimulation by methylxanthines and their interactions with fentanyl and oxycodone

Elder, Harrison J[1]; Walentiny, David M[1]; Beardsley, Patrick M[1,2]

[1]Department of Pharmacology & Toxicology, Virginia Commonwealth University School of Medicine, Richmond, VA. [2]Center for Biomarker Research and Precision Medicine, Virginia Commonwealth University, Richmond, VA.

Rationale: Non-opioid respiratory stimulants could potentially rectify naloxone's inadequate reversal of opioid-induced respiratory depression by extending the duration of recovery without precipitating withdrawal or preventing opioid analgesia. The methylxanthines, caffeine and theophylline, are adenosine receptor antagonists that stimulate respiration via nuclei located in the pons and medulla, and their effects on opioid-induced respiratory depression warrant exploration. **Methods:** The effects of caffeine (3, 10, 30, 100 mg/kg) and theophylline (3, 10, 30 mg/kg) on breath frequency (freq), tidal volume (TVb) and minute volume (MVb) were recorded in adult male Swiss Webster mice (n=8 per condition) using whole-body plethysmography. MVb was chosen as the primary dependent measure as it is equal to TVb x freq. Doses of caffeine (10 mg/kg) and theophylline (30 mg/kg) that produced the greatest increase in basal MVb were then tested following pretreatment with ED50 doses of fentanyl (0.3 mg/kg) or oxycodone (10 mg/kg) which have been shown to depress MVb by 50% from baseline. All drugs were administered s.c. Data were statistically analyzed in 5-min bins using 2-Way ANOVAs followed by Holm-Šídák post-hoc tests to compare treatment conditions at individual timepoints. **Results**: Under basal conditions, caffeine and theophylline significantly ($p<0.05$) increased MVb at 3, 10, and 30 mg/kg. Caffeine significantly depressed MVb at the highest dose tested (100 mg/kg). Theophylline (30 mg/kg), but not caffeine (10 mg/kg), completely reversed oxycodone-induced depression of MVb. Neither drug reversed fentanyl-induced decreases in MVb. **Conclusions:** Theophylline and caffeine increase MVb under basal conditions, and theophylline reversed MVb deficits following oxycodone, but neither it nor caffeine had a beneficial effect on fentanyl-induced respiratory depression.

Oral Communication 1-3

Selective kappa opioid receptor antagonists as potential candidates for treatment of neuropathic pain, eliminating opioid-induced addiction

Shahbazi Nia, Siavash[1]; Hossain, Mohammad A[1]; Ji, Guangchen[5, 6]; Obeng, Samuel[2, 3]; Nozohouri, Saeideh[1]; Patel, Dhavalkumar[1]; Kalem, Raja R[4]; Jonnalagadda, Sravan[7]; Sifat, Ali E[1]; Hiranita, Takato[3]; Abbruscato, Thomas J[1]; Trippier, Paul C[7, 8, 9]; Putnam, William[4]; Neugebauer, Volker[5, 6, 10] and German, Nadezhda A[1, 6]

[1]Department of Pharmaceutical Sciences, Jerry H. Hodge School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, TX, USA; [2]Department of Medicinal Chemistry, College of Pharmacy, College of Pharmacy, University of Florida, Gainesville, Florida 32610, United States; [3]Department of Pharmacodynamics, College of Pharmacy, University of Florida, Gainesville, Florida 32610, United States; [4]Clinical Pharmacology & Experimental Therapeutics Center, Texas Tech University Health Sciences Center, Dallas, TX, USA; [5]Department of Pharmacology and Neuroscience, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA; [6]Center of Excellence for Translational Neuroscience and Therapeutics, Texas Tech University Health Sciences Center, Lubbock, TX, USA; [7]Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska Medical Center, Omaha, NE, USA; [8]Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE, USA; [9]UNMC Center for Drug Discovery, University of Nebraska Medical Center, Omaha, NE, USA; [10]Garrison Institute on Aging, Texas Tech University Health Sciences Center, Lubbock, TX, USA.

Neuropathic pain (NP) is a chronic condition caused by a lesion or disease of the somatosensory system, including peripheral fibers and central neurons, affecting 7–10% of the general population. The patients with NP generally have low response to analgesics such as NSAIDs or weak opioids such as codeine while more potent opioids such as morphine and methadone are proven efficacious. The use of opioids for the treatment of NP is a double-edged sword. It can result in numerous side effects, particularly opioid dependence. The challenges involved with the use of opioids highlight the need for novel non-opioid therapeutic options for the treatment of NP. Recently, inhibition of Kappa Opioid Receptors (KOR) has been determined as a potential non-opioid therapeutic option for the treatment of NP, lacking the side effects of opioids.
Our lab has designed and synthesized a set of monocyclic, bicyclic, and tricyclic diketopiperazine-based ligands with a varying degree of selectivity between opioid receptor subtypes. Selective kappa opioid receptor (KOR) ligands with the optimal pharmacokinetic

Oral Communication 1-4

Hemi-equilibrium action of buprenorphine

Wedemeyer, Michael, J; Berg, Kelly, A; Clarke, William, P
Department of Pharmacology, UT Health San Antonio, TX USA

Despite the US government declaring the opioid crisis a public health emergency in 2017, opioid overdose deaths have increased by 50%. Individuals with opioid use disorder have increased risk of opioid related death, and medication such as buprenorphine can facilitate recovery by reducing opioid cravings and withdrawal effects. While buprenorphine is clinically described as a partial agonist of the mu opioid receptor (MOR), the literature demonstrates that its pharmacological characteristics are complex. In ongoing studies we are rigorously characterizing the pharmacological actions of buprenorphine at the human MOR. A genetically encoded biosensor was used to monitor cAMP levels in real time in HEK293 cells expressing a low density of the human MOR. In these cells, buprenorphine acted as an antagonist, reducing the potency of the MOR agonist, DAMGO, in a concentration-dependent manner, similar to the action of the MOR antagonist naloxone. Unlike the effect of naloxone, buprenorphine also decreased the maximal response of DAMGO, an effect that saturated with increasing concentrations of buprenorphine. Both effects of buprenorphine were prevented by pre-treatment with naloxone followed by rigorous washout, suggesting these effects were mediated by the orthosteric site. Given the slow rate of dissociation of buprenorphine from MOR and the rapid time-course involved in the cAMP response, we considered that the observed effects of buprenorphine were due to hemi-equilibrium conditions. Computations conducted using hemi-equilibrium equations support the hypothesis that the antagonist effects of buprenorphine in this system are due to hemi-equilibrium. As a frontline treatment for opioid use disorder, an understanding of buprenorphine's pseudo-irreversible binding may elucidate buprenorphine's unique properties and facilitate future drug discovery. This work is supported by the Institutional NRSA (T32, DA031115) Postdoctoral Training in Drug Abuse Research at UT Health San Antonio and a grant from NIH/NIDA (RO1 DA038645).

Oral Communication 1-5

Antinociceptive interactions between α2/α3-selective GABAA receptor modulator KRM-II-81 and opioids in female rats

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Chronic pain affects approximately 20% of adults worldwide. Opioids have been increasingly prescribed to treat chronic pain, despite evidence that chronic opioid treatment leads to tolerance and pain sensitization, or opioid-induced hyperalgesia (OIH). Thus, analgesics that can be effectively combined with opioid therapies to increase their efficacy and mitigate their side effects are sorely needed. This study examined the antinociceptive effects of α2/α3-selective GABAA receptor modulator, KRM-II-81, alone and in combination with fentanyl in a model of chronic inflammatory pain (complete Freund's adjuvant or CFA), investigated whether KRM-II-81 could reduce the extent to which antinociceptive tolerance develops to morphine in CFA-treated rats, and determined whether KRM-II-81 could reverse the OIH alone and in combination with other analgesics. Antinociceptive effects were studied at fixed ratios (1:1, 1:3, 3:1) using von Frey filaments to measure mechanical nociception. Area under the curve (AUC) and dose-addition analysis were used to assess drug interactions. Combining KRM-II-81 and fentanyl increased AUC relative to KRM-II-81 and fentanyl alone at all fixed ratios. Twice-daily treatment with morphine for 11 days led to significant antinociceptive tolerance to morphine in CFA-treated rats, while twice-daily treatment with KRM-II-81 and morphine combined did not lead to significant antinociceptive tolerance after 11 days at all fixed ratios. Furthermore, KRM-II-81 fully reversed mechanical sensitivity caused by OIH, and produced additive to supra-additive interactions when combined with gabapentin or ketamine. These findings support the idea that α2/α3-selective GABAA receptor modulators could serve as novel analgesics for treating chronic pain and for mitigating side effects of opioid analgesics.

Oral Communication 2-1

Elevated transferrin saturation in individuals with alcohol use disorder: Association with HFE polymorphism and alcohol withdrawal severity

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Iron loading has been consistently reported in those with alcohol use disorder (AUD), but its effect on the clinical course of the disease is not yet fully understood. We conducted a cohort study to examine whether peripheral iron measures, genetic variation in *HFE* rs1799945, and their interaction differed between 594 inpatient participants with alcohol use disorder (AUD) undergoing detoxification and 472 healthy controls (HC). We also assessed whether *HFE* rs1799945 was associated with elevated peripheral iron and can serve as a predictor of withdrawal severity. AUD patients showed significantly higher serum transferrin saturation than HC. Within the AUD group, transferrin saturation significantly predicted withdrawal symptoms (CIWA-Ar) and cumulative dose of benzodiazepine treatment during the first week of detoxification, which is an indicator of withdrawal severity. *HFE* rs1799945 minor allele carriers showed elevated transferrin saturation compared to non-carriers, both in AUD and healthy controls. Exploratory analyses indicated that, within the AUD cohort, *HFE* rs1799945 predicted CIWA withdrawal scores and this relationship was significantly mediated by transferrin saturation. We provide evidence that serum transferrin saturation predicts alcohol withdrawal severity in AUD. Moreover, our findings replicated previous studies on elevated serum transferrin saturation in AUD and an involvement of *HFE* rs1799945 in serum transferrin saturation levels in both AUD and healthy controls. Future studies may use transferrin saturation measures as predictors for treatment; or potentially treat iron overload to ameliorate withdrawal symptoms.
Dr. Wiers' lab is currently following up on these findings by investigating associations between serum transferrin saturation and brain iron stores in AUD using quantitative susceptibility mapping magnetic resonance imaging (QSM-MRI).

Oral Communication 2-2

Cell-type specific gene expression changes in the mouse prefrontal cortex after chronic ethanol drinking

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Excessive alcohol (ethanol) consumption is one of the criteria for alcohol use disorder (AUD). Every-other-day (EOD) alcohol drinking in mice increases ethanol consumption over weeks, however, it is unclear which brain cell-types are key for regulating this drinking behavior. One of the primary brain regions affected by ethanol and involved in regulation of ethanol consumption is the Prefrontal Cortex (PFC). The goal of this study was to identify cell-type-specific gene expression changes within the PFC after alcohol drinking in mice. Male C57BL/6J male mice (n=4/ group) were randomly assigned to either the ethanol drinking group or water drinking group. We used the (EOD) drinking paradigm for a total of 17 alcohol sessions, which resulted in higher levels of ethanol drinking at the end of the procedure, compared with baseline. Twenty four hours after the last drinking session, brains were harvested and cell nuclei from the PFC were isolated for single nucleus RNA Sequencing (snRNA-Seq). We identified 27,207 nuclei which were organized into 30 discrete clusters. To identify cell-type clusters, we used known molecular markers of various cell types, such as astrocytes (*Slc1a3*), microglia (*C1qa*), endothelial cells (*Flt1*), and inhibitory and excitatory neurons. In addition, we identified rare cell types such as pericytes (*Rgs5*). We used DESeq2 to identify differentially expressed genes (DEGs) in different cell types between the two drinking groups. With respect to global DEGs, we identified 1,337 genes at nominal p value of less than 0.05 with 731 genes down-regulated and 606 genes up-regulated in the ethanol drinking group compared with the water drinking group. We further identified DEGs in specific cell types. Cell types most responsive to ethanol exposure were certain inhibitory neurons (i.g., DEGs: *Vip*, *Gad2*), some excitatory neurons (i.g., DEGs: *Kcnq5*, *Kcnh7*), endothelial cells (i.g., DEGs: *Ptprm*, *Pltp*), and microglia (i.g., DEGs: *Hexb*, *Cst3*). The data taken together suggest a large heterogeneity of responses in PFC cell types to prolonged drinking in mice.

Oral Communication 2-3

Effects of long-term ethanol drinking on cognition in Cynomolgus Monkeys

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Previous studies have shown that long-term alcohol drinking negatively impacts prefrontal-mediated executive function behaviors such as cognitive flexibility and impulsive choice. A better understanding of the timing and extent of cognitive deficits that result from specific drinking patterns is essential as these deficits can encourage escalation of drinking. In the present study, adult male cynomolgus monkeys lived in social groups with stable social dominance hierarchies. Position in the hierarchy reflects a continuum from environmental enrichment in high-ranking (dominant; DOM; n=6) monkeys to chronic social stress in low-ranking (subordinate; SUB; n=6) monkeys. Monkeys self-administered EtOH 22 hours/day, 4 days/week in the home cage and performed cognitive assessments on non-drinking days using a touchscreen monitor that delivered food rewards. Monkeys performed a stimulus discrimination and reversal task (SD/SDR) to assess effects of EtOH on cognitive flexibility and a delay discounting task to assess impulsive choice at the start of 22 hrs/day access and again after 4 or 6 months of drinking. We hypothesized that SUBs would have greater EtOH intakes compared to DOMs and, as a result, would show greater impairment in cognitive flexibility and more impulsive choice. As hypothesized, SUB monkeys maintained greater (1.77 ± 0.95 g/kg) mean daily EtOH intakes than DOM monkeys (0.85 ± 0.91 g/kg) during 6 months of 22 hrs/day access. However, with the SD/SDR task, there were no rank-related differences in trials to criterion or number of errors at baseline or after 6 months of drinking. On the delay discounting task both groups showed decreased impulsive choice from baseline to 4 months of free access, with a greater effect in DOM monkeys. Although there are rank-related differences in mean EtOH intake, monkeys did not show significant EtOH-induced deficits in these cognitive behaviors. This study is ongoing and cognitive function will continue to be assessed until monkeys reach one year of EtOH access.

Oral Communication 2-4

The neural processes underlying avoidance learning dysfunction in problem drinking

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Drinking as an avoidance coping behavior is increasingly considered to play a central role in the maintenance of problem drinking and escalation to alcohol use disorders. As drinking escalates, consumption is progressively driven by individuals' heightened sensitivity to the painful consequences of alcohol intake cessation. Paradoxically, chronic alcohol use heightens pain reactivity which further motivates drinking as an avoidance coping strategy. Over time, this maladaptive behavior becomes increasingly less amenable to cognitive control, trapping drinkers in a spiraling cycle of drinking and distress. Yet, the underlying circuits of avoidance learning in problem drinking are poorly understood. Here, we examined avoidance learning in 18 problem drinkers and 31 social drinkers who performed a probabilistic learning go/no-go task to associate visual cues with outcomes to avoid painful electric shocks and optimize monetary reward. We hypothesized that relative to social drinkers, problem drinkers would exhibit (1) poorer avoidance learning, (2) weakened prefrontal cortical activation to avoidance learning; and (3) greater pain circuit activity in responses to pain. Our findings confirmed the hypotheses. Specifically, problem drinkers showed lower learning rate during pain avoidance conditions, coupled with reduced dorsolateral prefrontal cortical activity. Brain regions implicated pain reactivity including the insula, dorsal anterior cingulate cortex, amygdala, and periaqueductal gray showed hyperactivation during shock feedback and this activity was positively correlated with the drinking-to-cope measure. The current work sheds light on the involvement of avoidance learning dysfunction in problem drinking.

Oral Communication 2-5

Effects of alcohol withdrawal on sleep macroarchitecture and microarchitecture in female and male rats

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Prevalence of sleep disruptions are higher among people with alcohol use disorders (AUD) compared to non-AUD individuals, particularly in alcohol withdrawal. Although women generally have a higher risk of developing sleep disorders, few studies have investigated sex differences in sleep disruptions following chronic alcohol exposure. The present study examined sex differences on sleep macroarchitecture (time spent in sleep and sleep onset latency) and microarchitecture (sleep bout rate and sleep spindles) prior to chronic, intermittent ethanol vapor exposure (baseline), during acute alcohol withdrawal and through protracted abstinence in female and male rats. Females and males showed reduced time spent in rapid eye-movement (REM) sleep during acute withdrawal, which returned to baseline levels in protracted abstinence. Females had decreased REM sleep onset latency during protracted abstinence more fragmentation of REM sleep than males. Although there were no overall changes to total time spent in non-REM (NREM) sleep during acute withdrawal, NREM intra-spindle frequency increased and returned to baseline levels following protracted abstinence, in both females and males. Results demonstrate macroarchitectural and microarchitectural changes in sleep following chronic alcohol exposure, suggesting need for therapeutic interventions for sleep disturbances during withdrawal in individuals with AUD. Sex differences were observed in REM sleep, highlighting the importance of including both sexes in alcohol-related sleep studies. Future studies aim to discover potential sleep biomarkers and how underlying neuronal mechanisms of chronic disrupted sleep perpetuate alcohol misuse.

Oral Communication 3-1

Real-world assessment of the therapeutic and impairing effects of cannabis using remote data collection approaches

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Access to medicinal cannabis is expanding rapidly; yet little controlled data exist on therapeutic efficacy and how variations in cannabinoid composition alter the balance between medicinal benefit and performance impairment. Participants in this study (N=25; 64% female) prospectively completed assessments of mood, sleep, cannabis use, and subjective feelings of impairment using a phone application immediately before and for 8 weeks after newly initiating medicinal cannabis use. All participants met criteria for clinically relevant anxiety and/or depression and were recently registered with the Maryland medicinal cannabis program. Mood and impairment were assessed at wake up, bedtime, two random midday timepoints, and immediately before and the expected time of peak post-dose effects based on route of administration for each episode of cannabis use. Results here focus on cannabis data collected in 632 independent use events and analyzed using generalized linear mixed effect models. Reductions in anxiety and depressive symptoms were observed post-administration that were similar across routes of administration. Impairment (e.g., subjective high, perceived driving impairment) was detected and differed by route of administration and gender, with less impairment reported with oral administration and among women. Evaluation of dose effects showed greater decreases in perceived driving ability and increases in subjective high when higher THC doses were administered, but no differences by CBD dose. In addition to implications for studying medicinal cannabis, these data replicate canonical cannabinoid effects, thus demonstrating the feasibility of using this remote data collection method to evaluate drug effects over extended periods to balance the rigor of real-time pharmacodynamic measurement with the generalizability of real-world environments.

Oral Communication 3-2

Individual and interactive effects of vaporized Delta-9-Tetrahydrocannabinol (THC) and limonene

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This controlled human laboratory study is evaluating whether the terpenoid limonene mitigates acute the anxiogenic effects commonly associated with administration of high doses of delta-9-tetrahydrocannabinol (THC). Healthy adults (n=16) completed nine, double-blind outpatient sessions in which they inhaled vaporized THC alone (15 or 30mg THC), limonene alone (1 or 5mg), THC and limonene together (15mg THC/1mg limonene; 15mg THC/5mg limonene; 30mg THC/1mg limonene; 30mg THC/5mg limonene), or placebo. Outcomes assessed before and for 6 hours after drug administration included: working memory performance, psychomotor performance, and subjective drug effects. Both THC doses reliably induced anxiety, as evidenced by significantly increased ratings of "anxious/nervous" and "paranoid" compared with placebo (*ps*<0.05). When 1mg limonene was paired with THC, anxiety ratings were comparable to those observed when THC was administered alone. However, 5mg limonene paired with THC trended towards significance with lower ratings of "anxious/nervous" (p=0.08; cohen's d = 0.48) and "paranoid" (p=0.10; d = 0.42) compared with THC alone. Other subjective drug effects (e.g., "Like Drug Effect") increased after THC exposure, but ratings for these items did not differ in the presence of limonene (*ps*>0.05), suggesting limonene selectively attenuated anxiogenic effects of THC. Limonene, when combined with THC, did not alter cognitive/psychomotor function (*ps*>0.05). Interestingly, limonene reduced THC-associated "heart racing" ratings (p=0.08; d = 0.65) despite having no effect on vitals (*ps*>0.05). In sum, THC-induced anxiety symptoms were moderately reduced by higher doses of limonene, but limonene did not alter other pharmacodynamic effects of THC (i.e., subjective and cognitive effects, heart rate increases). Future research should continue to examine the anxiogenic effects of limonene, which could inform the development of novel cannabinoid-based medicines that reduce side effects associated with cannabis use

Oral Communication 3-3

Effects of nicotine vapor exposure on motivation for rewards in adolescent male rats

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In recent years, there has been a dramatic increase of nicotine vapor consumption via electronic nicotine delivery systems, such as e-cigarettes, particularly in adolescents. Pre-clinical studies have investigated the rewarding and withdrawal effects of nicotine through traditional routes of administration, such as intravenous self-administration. While there is an increase of investigation on the effects of nicotine vapor exposure on global health, its effects on the brain and behavior remain unclear. The goal of this project is to assess changes in behavioral measures of motivation for rewards following repeated nicotine vapor exposure and withdrawal during adolescence in rats. Male adolescent Sprague-Dawley rats (N = 24) were pair-housed, food restricted to 90% of their feeding weight, and tested in the progressive ratio (PR) task as a measure of reward seeking motivation. All rats were trained, then introduced to daily exposures of 0 mg/mL nicotine vapor vehicle (50/50 propylene glycol/vegetable glycerin, 30 vapor puffs per day), immediately followed by training in the PR task. The subjects were then divided into two groups, one continued to be exposed to 0 mg/mL vehicle and the other began to receive 24 mg/mL nicotine vapor, followed by testing in the PR task for a total of 10 days. Nicotine treatment was then ceased, and subjects underwent PR testing during withdrawal from nicotine vapor. The results revealed that during nicotine vapor exposure, slight increases in lever presses were seen in the 24 mg/mL nicotine group relative to vehicle controls. When vapor exposure was ceased, the vehicle controls showed an increase in total lever presses relative to controls while the 24 mg/mL nicotine vapor group remained unchanged. Our findings suggest a need to investigate the neurobiological mechanisms that contribute to nicotine vapor induced changes in adolescent motivation for rewards.

Oral Communication 3-4

Chemogenetic inhibition of accumbens microglia reduces cue-induced nicotine seeking behavior

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Microglia are activated following nicotine self-administration (SA) and this may be a critical neuroimmune response in the nucleus accumbens core (NAc). While changes in microglia and immune function have been shown following nicotine use, the role of microglia in nicotine seeking behavior has not. Further, it has been a challenge in the field to virally transduce microglia *in vivo*. The goals of the current study were to (1) validate a recombinase-driver transgenic methodology to chemogenetically control NAc microglial activation prior to nicotine-cue reinstatement (RST), and (2) determine the role of NAc microglia in nicotine-seeking behavior. The current experiments utilized a cre-recombinase-expressing rat line, the LE-Tg(Cx3cr1-cre)3Ottc strain, verified via co-localization of Iba1 immunohistochemistry and fluorescence from intra-NAc cre-dependent Designer Receptor Exclusively Activated by Designer Drugs (DREADD) constructs in microglia. This approach was utilized to inhibit or stimulate NAc microglia of male and female rats prior to nicotine cue-induced RST. Following nicotine SA (0.06 mg/kg/infusion, FR1, paired with light+tone compound stimulus) and extinction training, intra-NAc clozapine-N-oxide was administered prior to RST. Rats were sacrificed for microglial morphology analysis and electrophysiological recording of glutamate plasticity. Preliminary findings show chemogenetic inhibition of microglia reduces cue-induced nicotine seeking within 15 minutes (trend: ANOVA; p=0.056). Ongoing analyses will determine if inhibition of microglia results in morphological changes and reductions in RST-induced increases in NAc glutamate plasticity. While our prior research shows a nicotine-induced neuroimmune response in the NAc, our current findings suggest a critical role of microglia in driving nicotine seeking behavior using a novel chemogenetic approach. Funding**:** NIDA grant R01DA046526, R21 DA049130, R21DA044479, DA045881 (to CDG)

Oral Communication 3-5

Paternal substance use disorder and adolescent substance use initiation: Role of protective and risk factors

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Father substance use disorder (FH+) increases risk for early adolescent substance use initiation (SUI). Certain social and environmental factors can influence risk for early SUI. The present study was to understand how FH+ predicts alcohol and marijuana SUI (AUI and MUI, respectively) and how this link is moderated by social and environmental factors. For the present study, 387 adolescents (307 FH+) were recruited between 2010-2012 when the adolescent was 10-12.5 years old. At baseline, adolescents and parents completed assessments to measure the social, environmental, and transmissible risk factors for early SUI. Follow-ups occurred every 6 months thereafter in which participants reported if they had engaged in SUI. Using survival analyses, 266 participants reported AUI (214 FH+) and 219 participants reported MUI (192 FH+). FH+ participants engaged in MUI significantly earlier than FH- participants (FH+ IR=0.13/person year, p<0.001). FH+ engaged in AUI earlier but not at a statistically significant level (FH+ IR=0.14/person year, p=0.092). Risky peers were found to exacerbate the effect of FH+ on both AUI (HR=4.88, p=0.002) and MUI (HR=4.16, p=0.015). Positive father-youth relationships marginally delayed AUI (HR=0.11, p=0.053) while positive mother-youth relationships marginally delayed MUI (HR=0.69, p=0.077) for FH+ youth. The present study finds that while FH+ increases risk for SUI, the link is moderated by social relationships and might be substance dependent. Future research and interventions should focus on improving adolescent social relationships to reduce adolescent SUI.

Oral Communication 3-6

5-HT_{1B} receptor agonist produces a similar abstinence-dependent modulation of motivation for cocaine in male and female rats

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Previous findings indicate that serotonin 1B receptors (5-HT_{1B}Rs) modulate cocaine self-administration (SA) in opposite directions depending on the phase of the addiction cycle in male rats. In this study, we compared the effects of the selective 5-HT_{1B}R agonist, CP94253 (CP), on cocaine self-administration under a progressive ratio (PR) schedule of reinforcement and on cue-induced cocaine-seeking behavior after protracted abstinence in male and female rats. Male and female Sprague-Dawley rats were trained to self-administer 0.75 mg/kg, IV cocaine on an FR1 schedule of reinforcement for 3 hours/day. Once reinforcement rates stabilized, rats transitioned to self-administering 0.375 mg/kg, IV cocaine on a PR schedule. After reaching stability once again, rats were repeatedly tested for the effects of CP (0, 3.2, 5.6 and 10 mg/kg, SC) given 15 minutes prior to the start of a session of cocaine SA on the PR schedule. To examine the effects of CP on cue reactivity, male and female rats with a history of SA were placed into abstinence for 21 or 60 days then tested twice after pretreatment with vehicle or CP (5.6 mg/kg, SC) 15 minutes prior to the SA session, with order of vehicle and CP tests counterbalanced. Test sessions lasted 2 h during which the cocaine-conditioned light and tone cues previously paired with cocaine infusions were delivered on an FR1 schedule without cocaine. Results indicate that CP (5.6 mg/kg) increases cocaine intake on the PR schedule regardless of sex in rats that have not experience prolong abstinence, but attenuates active and inactive lever responses in rats after 21 or 60 days abstinence. These findings suggest that regardless of sex, CP has opposing effects on motivation for cocaine depending on whether or not rats experience abstinence from cocaine. Thus, the 5-HT_{1B}R agonist may be a useful treatment for cocaine use disorder after a period of abstinence.

Oral Communication 4-1

Combination of submaximal doses of an $mGlu_5$ negative allosteric modulator and an adenosine A_{2A} agonist reduces reinforcing strength of cocaine

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There are currently no FDA-approved medications for Cocaine Use Disorder (CUD). Negative allosteric modulators (NAMs) targeting the metabotropic glutamate receptor 5 ($mGlu_5$) may be a promising pharmacotherapy for CUD. In rats, $mGlu_5$ NAMs can attenuate self-administration (SA) and reinforcing strength of cocaine. However, at doses aligning with maximum therapeutic effects, concerns regarding adverse effect liability of these compounds linger including risk of cognitive impairments and sedation. One potential avenue to mitigate adverse effect risk and maximize therapeutic potential is through the use of combination therapies. Activation of the adenosine A_{2A} receptor also reduces cocaine SA and reinforcing strength. However, at these necessary doses, food-maintained responding was also decreased. Importantly, $mGlu_5$ and adenosine A_{2A} receptors have been found to heterodimerize in key regions implicated in CUD including the striatum. The goal of these studies was to determine if a combination of $mGlu_5$ NAM VU0424238 with adenosine A_{2A} agonist CGS-21680, at doses that have no effects alone, would reduce the reinforcing strength of cocaine without altering food-maintained responding. Male (n=20) and female (n=6) Sprague-Dawley rats were trained on a progressive ratio (PR) schedule for cocaine (0.5 mg/kg/infusion; i.v.) or food (sucrose pellet). A dose response curve for both VU0424238 (0.56-30 mg/kg; i.p.) and CGS-21680 (0.056 mg/kg-0.3 mg/kg; i.p) were generated. Then, doses of VU0424238 (0.56 and 1.0 mg/kg; i.p.) and CGS-21680 (0.056 mg/kg; i.p.) that did not significantly decrease cocaine or food breakpoint were selected for combination studies. Ongoing results support the hypothesis that combinations of submaximal doses of VU0424238 and CGS-21680 will reduce the reinforcing strength of cocaine without impacting the reinforcing strength of food.

Oral Communication 4-2

Illuminating the monoamine transporters: High affinity fluorescent probes for visualization of DAT and NET

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Dopamine (DA), serotonin (5-HT) and norepinephrine (NE) transporters (DAT, SERT and NET respectively) control monoamine homeostasis by mediating re-uptake of these neurotransmitters from the extracellular space into the cell. Dysregulation of monoamine transporters (MATs) is linked to neuropsychiatric disorders, including substance use disorder. Fluorescent ligands have emerged as useful pharmacological tools to visualize protein expression and distribution in distinct cell systems. The previously reported fluorescent cocaine-based analogue JHC1-064, has been extensively used as a tool to study MATs due to its high affinity for all three membrane proteins. Nevertheless, lack of selectivity of this fluorescent probe across MATs contributes to certain staining limitations. This has been overcome in SERT with an *S*-citalopram-based probe, VK2-83, but remains a challenge for DAT and NET. In this study, utilizing the NET selective inhibitor nisoxetine and the atypical DAT inhibitor JJC8-087 as parent compounds, rhodamine-labeled fluorescent probes, with high affinity and preferential binding for the NET and DAT have been designed and synthesized, with the goal of obtaining preferential fluorescent tools to study expression and distribution of DAT and NET in distinct cell systems, including tissue.

Oral Communication 4-3

Speed of methylphenidate's uptake influences brain activation patterns: a simultaneous PET-fMRI study

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The faster an addictive drug enters the brain, the greater its rewarding effects. Yet it is unclear how human brain function changes as a function of the speed of a drug's brain delivery, which is relevant to the mechanisms underlying their rewarding effects. Here we used simultaneous 11C-raclopride PET-fMRI to examine brain activity, dopamine signaling, and euphoria (feeling of 'high') to fast (IV; 0.25 mg/kg) versus slow (oral; 60 mg) methylphenidate (MP) in a double-blind, counterbalanced, placebo-controlled study in healthy adults (n = 20, 10 male/10 female; three sessions per individual). We hypothesized that oral and IV MP would evoke decreases and increases in striatal activation, respectively, because slow dopamine release would be likely to stimulate high-affinity inhibitory D2 receptors, whereas fast dopamine release would be sufficient to temporarily stimulate the lower-affinity excitatory D1 receptors. We found that IV MP elicited a stronger 'high' than oral MP with a faster rise and fall, replicating prior work (p < .05). As hypothesized, IV MP elicited a pattern of relatively fast (~5 min duration) increased activation in bilateral head of caudate and dorsal anterior cingulate cortex, whereas oral MP elicited a pattern of slow, plateauing reduction in activation in ventral striatum, with additional clusters in ventromedial/ventrolateral prefrontal cortex and amygdala/hippocampus (FDR corrected p < .05). However, the overall levels of 'dopamine increases' to MP did not significantly differ between oral and IV sessions, as predicted (we chose the IV and oral doses because they were previously shown to achieve comparable dopamine transporter blockade in the brain). Thus, the speed rather than the overall magnitude of dopamine increases may be driving different patterns of brain activation that contribute to a drug's rewarding effects. We speculate the divergent patterns of striatal signaling may reflect predominantly excitatory D1 signaling to IV MP versus inhibitory D2 signaling to oral MP.

Oral Communication 4-4

Effects of single- and dual-hypocretin receptor antagonists on compulsive methamphetamine self-administration in male rats

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The hypocretin/orexin (HCRT) system modulates compulsive-like stimulant taking in rats, involving both HCRT-receptor 1 (-R1) and -receptor 2 (-R2). Few studies, however, have examined the role of HCRT-R2 or HCRT-R1/2 on methamphetamine (METH) taking behavior, in particular. In this study, we examine the effects of HCRT-R1, -R2, and dual -R1/2 antagonists on METH self-administration in rats. Three cohorts of male rats were allowed either short (1 h; ShA; n=7-10/cohort) or long (6 h; LgA; n=7-9/cohort) access to METH intravenous self-administration for 14 sessions (FR1). Each cohort of rats was systemically administered a single- or dual- HCRT-receptor antagonist 30 min prior to behavioral testing in a latin-square design: cohort 1, selective HCRT-R1 antagonist (RTIOX-276; RTI; 0, 10, and 20 mg/kg); cohort 2, selective HCRT-R2 antagonist (JNJ-10397049; JNJ; 0, 10, and 20 mg/kg); and cohort 3, dual HCRT-R1/2 antagonist (Suvorexant; SUV; 0, 30, and 60 mg/kg). A separate cohort of METH-naïve rats (n=6 per group) was given vehicle and the highest dose of each antagonist before testing in a beam break apparatus for generalized effects on locomotor. Administration of RTI and SUV at the highest doses significantly reduced METH intake in LgA ($p<0.01$, $p<0.05$), but not ShA ($p=0.14$, $p=0.06$), rats in the first hour. Administration of JNJ, however, had no effect on METH intake in the first hour in either ShA ($p=0.58$) or LgA ($p=0.58$) rats, but had deferred effects in LgA rats reducing overall METH intake over the full 6 h session ($p<0.05$). Beam breaks were significantly reduced following RTI ($p<0.05$) and SUV ($p<0.05$) in ShA, but not LgA, rats, although both JNJ ($p<0.05$) and SUV ($p<0.05$) reduced beam breaks in METH naïve rats. These results suggest HCRT-R antagonism as a potential pharmacological target for treatment of stimulant use disorder, for which there is currently no approved pharmacotherapy in humans. Future studies will consider targeted brain regions of interest for the modulation of METH-taking modulated by HCRT neurotransmission.

Oral Communication 4-5

The importance of the perirhinal cortex to the nucleus accumbens neural pathway for novelty recognition and salience in methamphetamine self-administering rats

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Methamphetamine (meth) impairs executive function and relapse but the relationship between these meth effects are not well understood. We hypothesize that the perihinal cortex (PRH) to nucleus accumbens (NA) pathway is a link between meth induced cognitive impairment in terms of memory deficits and relapse. The goal of this work is to determine the behavioral relevance of this unexplored circuit. To this end, we used a novel cue relapse paradigm where meth-conditioned cues compete with novelty for control over behavior. First, we show that long access (LgA,6 hr, daily) meth self-administration (SA) produces focused responding on the meth associated lever but that short access (ShA, 1 hr, daily) meth SA results in equal response patterns on both novel and meth associated levers in adult male Sprague Dawley rats (n=32). Consistently, neural activation of the PRH is greatest in the PRH of ShA rats indicating this brain area is engaged during encounters with the novel cue. To determine the circuit involved, we used a dual virus circuit inhibition strategy to test the role of the PRH-NA circuit in ShA rats (n=16). Specifically, AAVrg-hSyn-eGFP-Cre was microinjected into the NA and AAV2-hSyn-DIO-hM4D(Gi)-mCherry was injected into the PRH. Rats underwent ShA Meth SA for 21 days followed by 7 days of forced abstinence. Then rats were injected with Clozapine-N-oxide (CNO; 10 mg/kg, ip) or vehicle (Veh, saline, ip) prior to chamber placement with both novel and meth associated levers. Using two-way ANOVAs, Veh rats responded similarly on both the active and novel levers ($p=0.1608$). CNO rats responded more on the active lever relative to both the inactive ($p<0.0002$) and novel ($p<0.0029$) levers. These findings indicate that the PRH-NA pathway may be an important neural circuit in both the recognition of novelty and novelty salience.

Oral Communication 4-6

Cocaine use during oxycodone withdrawal reduces somatic signs of withdrawal and is associated with aberrant accumbens glutamatergic plasticity

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Opioid use disorder (OUD) is a leading public health crisis in the US. Individuals with OUD frequently use other substances, including cocaine. Self-administration (SA) of these substances alters synaptic-plasticity within the medium spiny neurons (MSNs) of nucleus accumbens core (NAcore), whereby cocaine potentiates AMPA-to-NMDA current ratios (A/N), and opioids induce long-term depression (LTD) of NAcore-MSNs. The current study determined whether cocaine use during oxycodone withdrawal reduces somatic withdrawal signs, and reverses oxycodone-induced LTD as measured by A/N. Male/Female long evans rats (N=34) underwent oxycodone (0.03 mg/kg/infusion,) or food and cocaine (0.25 mg/kg/infusion) FR-1 SA in an A-B-A-B design. Rats underwent oxycodone-SA ("A") then cocaine-SA ("B") phase, and following the second phase of oxycodone-SA, rats underwent one cocaine-SA session at the 24-hr oxycodone/food withdrawal timepoint, then NAcore-A/N were measured via slice-electrophysiology. Somatic-signs of withdrawal were measured at 0, 22, and 24-hr post-oxycodone or food-SA. Cocaine consumption significantly increased following oxycodone withdrawal, but not following food-SA. Further, cocaine-SA reduces somatic signs of oxycodone withdrawal, but did not significantly alter somatic signs in the food control group. Finally, NAcore A/N was decreased in the oxycodone/cocaine SA group as compared to the food/cocaine SA group, demonstrating LTD induced by oxycodone SA that is not reversed by cocaine. Cocaine use during oxycodone-SA reverses oxycodone withdrawal, but does not reverse oxycodone-induced LTD in NAcore MSNs. Together, these data suggest that oxycodone use induces persistent changes in glutamatergic signaling, which may exacerbate motivation for cocaine co-use due to alleviation of withdrawal symptomatology.

Poster Presentations

Poster 1

Effects of cannabinoid antagonists in rats discriminating fentanyl

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Extensive evidence suggests the existence of a functional interaction between endogenous cannabinoids and opioid systems. Targeting cannabinoid CB_1 receptors might be a promising approach for developing new medications for opioid addiction. The present studies were undertaken to evaluate the effects of CB_1 antagonists in rats (n=8) trained to discriminate, i.p., injections of 0.032 mg/kg fentanyl from saline on a 10-response fixed-ratio (FR-10) schedule of food reinforcement. Results show that the μ-opioid agonists (fentanyl, morphine, and oxycodone) substituted fully for fentanyl, whereas the response rates, whereas the neutral CB_1 antagonist AM4113 blocked fentanyl discrimination at doses that did muscarinic antagonist atropine did not substitute for fentanyl. Pretreatment studies with a μ-opioid receptor antagonist show that naltrexone antagonized fentanyl's effects. Interestingly, pretreatment studies with CB_1 antagonists show that rimonabant (inverse agonist) produced attenuation of fentanyl's discriminative-stimulus effects at doses that significantly decreased not modify rates of responding. Our findings are consistent with our recent work showing that AM4113 attenuates heroin self-administration in rats, without producing depressive-like effects. Collectively, these data suggests that CB_1 neutral antagonists that block CB_1 receptors with rimonabant-like potency, devoid of unwanted side-effects, may be therapeutically advantageous for countering the abuse-related behavioral effects of opioids.

Poster 2

Effect of sex and position in the social hierarchy on cognition training and cognitive flexibility in cynomolgus macaques

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Nonhuman primates have proven to be useful subjects for addiction research, including the understanding of cognitive predictors of vulnerability to developing substance use disorders. This study aimed to determine how sex and position in the social hierarchy influence monkey's speed of training to use a touch-screen apparatus as well as performance on a standard test of cognitive flexibility: a stimulus discrimination/reversal (SD/SDR) task. Subjects were 12 adult cynomolgus monkeys (6 per sex). A custom-designed touchscreen with an integrated pellet dispenser was mounted to each monkey's home cage; they were required to touch a target stimulus to receive a food reward. Each training session lasted 80 trials and the difficulty of the task was progressively increased by shrinking the stimulus every 20 trials. For each monkey, the number of training sessions required to reach 80% accuracy without omitting more than 15% of trials was determined. A two-way ANCOVA controlling for age revealed that male macaques reached the criterion in significantly fewer training days than females, [$F(1,7)=12.50$, $p=0.010$]. Also, subordinate monkeys had a significantly faster rate of acquisition than dominant monkeys [$F(1,7)=6.31$, $p=0.040$]. Moreover, preliminary data on the SD/SDR task suggests that male macaques may have lower levels of cognitive flexibility when compared to females. In summary, these results suggest that male and subordinate macaques engage in more exploratory behaviors and thus more readily learn how to perform a training task when compared to female and dominant macaques. However, male macaques may also exhibit lower rates of cognitive flexibility on the SD/SDR task when compared to females. Given that deficits in cognitive flexibility may increase vulnerability to substance use disorders, it is important to further investigate sex differences in baseline cognitive abilities.

Poster 3

Neuronal correlates of motivational and somatic signs of heroin withdrawal

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A hypothesized driver of opioid addiction is drug-taking to avoid somatic and motivational withdrawal symptoms. The current literature shows that the presentation of cues conditioned to opioid withdrawal is sufficient to elicit somatic and motivational signs. We hypothesized that brain structures associated with the manifestation of motivational and somatic signs of opioid withdrawal partially overlap. Here, we used a schedule of repeated injections of escalating heroin doses to cause opioid dependence in C57BL/6J mice of both sexes. This schedule reliably caused opioid withdrawal-induced hyperalgesia during spontaneous withdrawal (N=23/group) and somatic signs of withdrawal precipitated by the μ-opioid receptor antagonist naloxone (N=22/group). We measured brain regional neuronal activity changes following behavior assessment by counting neurons expressing c-Fos through the brain (N=6/group). A two-way analysis of variance (ANOVA) with sex and treatment as between-subjects factors revealed no significant sex differences in the behavioral results and c-Fos expression. While heroin exposure resulted in activation of autonomic and limbic structures, by a principal component analysis, we found hyperalgesia and somatic withdrawal associated with c-Fos expression in the dorsal raphe (DR) and locus coeruleus (LC). In conclusion, opioid withdrawal-induced hyperalgesia and somatic withdrawal recruit independent but also common brain regions. Understanding common neurobiological mechanisms could help identify new targets for treating both motivational and somatic symptoms of opioid withdrawal.

Poster 4

Evaluating microtubules as potential PET imaging biomarker for substance use disorder

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While novel strategies are being explored to understand the mechanisms underlying SUDs, there is an unmet need to develop more sensitive and quantifiable imaging biomarkers. Recent studies are beginning to focus on new SUD biomarkers and microtubules (MTs) are emerging as one of the promising candidates. MTs are structural cytoskeleton hetero-dimer units formed from α- and β-tubulin monomers. Their structural integrity is critical for key biophysical functions essential for the neural circuitry that is dysregulated in SUDs including alcohol and cocaine. Our new approach will be using our first brain-penetrating PET radiotracer, [^{11}C]MPC-6827 for *in vivo* MT imaging. We recently reported its synthesis and *in vivo* PET imaging in rodents and nonhuman primates and demonstrated high brain uptake, ideal test-retest characteristics, and excellent pharmacokinetics and specificity. As the first step of validating the MTs as a potential imaging biomarker in a SUD model, here we report the cellular uptake of [^{11}C]MPC-6827 in a patient-derived neuronal cell line (SH-SY5Y) i. with and without EtOH, and ii. treatment with naltrexone (NTX) or acamprosate (ACP), FDA-approved drugs to treat alcohol use disorder (AUD). SH-SY5Y cells were treated with 100mM EtOH for 3 days, and radiotracer binding was determined. [^{11}C]MPC-6827 was added, and incubated for 30, 60, and 90 min (n=6). To demonstrate the effect of EtOH concentrations, cells were treated with different (10-100mM) concentrations of EtOH for 3 days and incubated with [^{11}C]MPC-6827 for 30 min. To demonstrate tracer specificity, cells were pretreated with the nonradioactive MPC-6827 (1.0 μM), and 60 min later, radiotracer was added. EtOH- and saline (controls)-treated cells were added with NTX or ACP (100 μM or 400 μM, 24 h) and incubated with [^{11}C]MPC-6827 for 30 min. Counts-per-minute values (using γ counts) were then matched with the protein concentration per well and the data was expressed as % injected dose/mg of protein present in each well. Radioactive uptake decreased with increasing concentration of EtOH i.e., 33(±2)% with 100mM vs. 7(±1)% with 10mM EtOH compared to the baseline. EtOH-treated cells demonstrated ~31(±2)% decrease in radioactive uptake compared to untreated controls at all three incubation time points. In the self-blocking assays, uptake was 73(±1)% lower after MPC-6827 was added, demonstrating specificity. Uptake in EtOH-treated cells

Poster 5

Eating a high fat diet enhances sensitivity of rats to the unconditioned effects of serotonergic drugs

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Drugs that act on serotonin (5-HT) systems can induce unconditioned effects in rats, including lower lip retraction (LLR), flat body posture (FBP), penile erections (PE), and forepaw treading (FT). To test the hypothesis that eating a high fat diet enhances the sensitivity of rats to these effects, male (n= 16) and female (n=16) rats eating high fat (60% kcal from fat) or standard (17% kcal from fat) laboratory chow were tested once weekly with cumulative doses of 5-HT receptor agonists (8-OH-DPAT [0.01-1.0 mg/kg, s.c.], lorcaserin [1.0-32.0 mg/kg, i.p.], and WAY 163909 [1.0-32.0 mg/kg, i.p.] alone and in combination with antagonists selective for 5-HT_{1A} (WAY 100635; 0.178 mg/kg, s.c.), or 5-HT_{2C} (SB 242084; 1.0 mg/kg; i.p.) receptors. Scores for each unconditioned effect were analyzed using 3-way ANOVAs with diet, sex, and drug as factors, while food consumption and body weight were analyzed using 2-way ANOVAs with diet and day as factors, and Bonferroni post hoc comparisons where appropriate. 8-OH-DPAT induced LLR, FBP, and FT, while WAY 163909 and lorcaserin only induced FT. Rats eating high fat chow were more sensitive to 8-OH-DPAT-induced LLR and FT (induced by all three drugs), as compared to rats eating standard chow. Lorcaserin and WAY 163909-induced PE were not different between rats eating high fat or standard chow. FT, LLR and FBP were attenuated by WAY 100635. In contrast, PE were attenuated by SB 242084. These results suggest that diet (e.g., type and amount of food consumed) might impact sensitivity of individuals to some of the adverse effects of serotonergic drugs.

Poster 6

Discovery of novel fatty acid amides as serotonin 5-HT2C and dual 5-HT2C/5-HT2A receptor positive allosteric modulators

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The serotonin (5-HT) 5-HT2C receptor (5-HT2CR) and 5-HT2AR are recognized as promising therapeutic targets for several central nervous system (CNS) psychoneurological disorders. Allosteric modulation of these priority targets represents a novel strategy to facilitate ongoing pharmacological development. The endogenous fatty acid amide oleamide has been described as an allosteric modulator at 5-HT receptors. Herein, a novel series of oleamide analogues were designed, synthesized, and evaluated as 5-HT2CR and dual 5-HT2A/2CR positive allosteric modulators (PAMs). Molecular docking experiments defined a similar, spatially distinct allosteric site for both the 5-HT2Rs, differentiated by more compact and narrower ligand occupation in the 5-HT2AR relative to the 5-HT2CR. Compound JPC0323 exhibited good on-target properties and an acceptable in vitro drug-like profile. We present a novel series of in vitro chemical probes for exploring the pharmacological mechanisms that underlie disorders implicating the 5-HT2CR and 5-HT2AR.

Poster 7

Development of N-(*m*-tolyl)acetamide analogue as D_4R ligand to treat substance abuse disorder

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The dopamine D_4 receptor (D_4R) regulates neural signals to modify behavior. It plays an important role in cognition, attention, and decision making. The D_4R represents a selective approach to treatment neuropsychiatric disorders such as substance abuse disorders. Previous studies have shown D_4R-ligand agonists improve cognitive performance and motor activity. We hypothesized that increasing the alkyl chain at the meta position on the aromatic ring in the extended binding pocket will increase binding affinity and selectivity for the D_4R over D_2R and D_3R subtypes. Hence, we designed, synthesized a series of novel ligands based on the parent compound A-412997 (2-(4-(pyridin-2-yl)piperidin-1-yl)-N-(*m*-tolyl)acetamide). Followed by an *in vitro* radioligand and functional studies analysis using β-arrestin recruitment and cAMP inhibition assays of synthesized compounds. We have identified several novel D_4R-selective (Ki ≤ 2.2 nM and >100-fold vs. other D_2-like receptors) compounds with diverse partial agonist profiles. Followed by an *in vitro* metabolic analysis of selected compounds. The ligands display high binding affinity and selectivity for D_4R with high stability in human liver microsome. These developed compounds may lead to medication discovery to treat neuropsychiatric disorders.

Poster 8

Effects of opioids on antinociception, operant performance, and respiratory depression

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The present experiments were conducted to examine the effects of opioids on operant performance, antinociception, and respiration. Eight squirrel monkeys were trained to press a lever for delivery of milk under a fixed ratio 10 schedule of reinforcement. After each delivery of milk, a 30 second time-out period occurred in which the subject's tail was immersed in either 35° or 52° C water, and the latency to remove the tail was recorded. The response rate of lever presses during the operant task was also recorded. Additionally, respiratory depression was examined using a ventilation chamber in which subjects were exposed to air and air with 5% CO2 in 10-minute alternating increments. Minute volume, frequency of breaths, tidal volume, and ratio of minute volume in 5% CO2 versus air were measured. Dose-response functions using tail withdrawal latency, response rate, and ventilation were determined for fentanyl, alfentanil, oxycodone, morphine, and heroin. All opioids tested showed a dose-dependent increase in antinociception and a decrease in response rate in the operant task, showing behavioral disruption. Dose dependent decreases in minute volume, frequency of breaths, tidal volume, and ratio of minute volume in CO2 versus air were displayed in all tested opioids. The potency ratios of the ED_{50} values across the procedures were calculated to determine a preclinical estimate of the therapeutic index of each drug. These initial studies provide a strong foundation for future work that will examine the ability of monoclonal antibodies to block fentanyl's antinociceptive, behaviorally-disruptive, and respiratory depressant effects. This study will be informative on whether monoclonal antibodies could be a useful treatment in preventing fentanyl overdose. (NIH/NIDA: 1U01DA051071-01A1)

Poster 9

The phytocannabinoids Δ⁹-tetrahydrocannabinol and cannabidiol do not affect choice for fentanyl in a food drug choice procedure in rhesus monkeys

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A growing number of reports indicate phytocannabinoids like Δ⁹-tetrahydrocannabinol (THC) or cannabidiol (CBD) may decrease some problematic effects of opioid receptor agonists (physical dependence, reward), or enhance their therapeutic effects (pain relief). In rhesus monkeys, THC enhances the acute antinociceptive effects of opioids. However, THC does not enhance other effects of opioids including physical dependence, ventilatory depression, reinforcing effects, or their discriminative stimulus effects. The present studies sought to determine the effects of THC, CBD and THC/CBD mixtures on i.v. fentanyl self-administration in rhesus monkeys (n=4) in a food drug choice procedure. Fentanyl dose was adjusted for each animal to find the largest dose that occasioned <20% drug choice (0.0001 mg/kg/infusion), and the smallest dose that elicited >80% drug choice (0.001 or 0.0032 mg/kg/infusion). CBD (10-17.8 mg/kg), THC (0.032-1 mg/kg), and THC/CBD mixtures (dose ratios of 1:10 and 1:32) were delivered i.v. 15 minutes prior to testing sessions. CBD, THC and mixtures of CBD/THC did not affect choice for either dose of fentanyl. The results of the present study suggest that the phytocannabinoids CBD or THC, alone and in mixtures, do not enhance the rewarding effects of opioids and add to the growing body of evidence that phytocannabinoids may be a safe adjuvant to enhance the antinociceptive effects of opioids.

Poster 10

Social defeat stress induces depression-related behavior in male prairie voles

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Major depressive disorder (MDD) is a mental illness that affects millions of people worldwide, making it the leading cause of disability. Chronic stress exposure is a well-recognized risk factor for the development of MDD, in which social stress, in particular, plays a role in the etiology of mood-related disorders. The chronic social defeat stress (CSDS) paradigm has been useful in investigating the development of mood disorders; however, the current murine models lack key social structures that relate to human behavior, which are necessary to fully explore the mechanisms leading to these ailments. Thus, the purpose of this study was to examine if CSDS in male prairie voles induces depression-related outcomes. To achieve this, adult (postnatal day [PD] 60+) male prairie voles were exposed repeatedly (7 days) to a more aggressive partnered male prairie vole, resulting in the physical defeat of the experimental animal (5 minutes per day). Controls (same-sex siblings) were handled daily and housed in pairs. Twenty-four hours after the last CSDS exposure, separate cohorts of voles were tested on the social interaction, forced swim test, and sucrose preference tests - behavioral endpoints that are commonly used to evaluate depression-related behavior. When compared to controls, CSDS-exposed animals displayed decreases in sociability and increased immobility on the forced swim test. However, no differences in sucrose preference or general locomotor activity, were observed as a function of CSDS. Collectively, these findings indicate that CSDS exposure induces depression-related, but not anhedonia-like, behavior in adult male prairie voles.

Poster 11

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

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Eating a high fat diet enhances sensitivity of rats to methamphetamine-induced locomotor sensitization. However, it is not known if sensitivity to other (i.e., the rewarding) effects of methamphetamine are similarly enhanced among rats eating a high fat diet. To test the hypothesis that eating a high fat diet enhances sensitivity of rats to the rewarding effects of methamphetamine, female and male Sprague-Dawley rats (n = 8/group) were fed either a standard (17% kcal from fat) or a high fat (60% kcal from fat) laboratory chow for 4 weeks prior to conditioned place preference (CPP) training, using a biased design. Before training, rats were given 30-min access to both sides of the chamber to determine side preference. Thereafter, during training rats had 30-min access to one of two distinct sides of the CPP chamber following injections of either saline or methamphetamine (0.1, 0.32, 1.0 mg/kg, i.p.) for 8 days, (alternating between drug and saline daily). Following training, rats had access to the full chamber for 30 minutes, following a saline injection and time spent in the drug and saline paired sides was assessed. Differences in preference score were analyzed using a two-way ANOVA with diet and dose as factors. Similar ANOVAs were used to analyze body weight and food consumption. Rats eating high fat chow weighed more than rats eating standard chow; however, there were no significant differences in average daily caloric intake. Methamphetamine induced a significant CPP among male and female rats at the two largest doses tested (0.32 and 1.0 mg/kg; as compared to saline and 0.1 mg/kg); however, the magnitude of this effect was not different between rats eating high fat chow and rats eating standard chow. These data suggest that while diet might impact sensitivity to some drug effects, other effects might remain unchanged. Future studies will explore other animal models of drug abuse (e.g., intravenous self-administration).

Poster 12

Exploring a role for organic cation transporter 3 in ethanol and cocaine co-abuse

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Concurrent use of cocaine and alcohol is a major cause for emergency hospitalization, underscoring a vital need to understand the mechanistic basis of this highly addictive, and dangerous drug combination. Both cocaine and ethanol (EtOH) increase extracellular dopamine (DA), norepinephrine and serotonin. However, there's no evidence for EtOH interacting with DAT, NET or SERT. Thus, EtOH may be acting elsewhere to inhibit uptake of these monoamines. Organic cation transporter 3 (OCT3) is emerging as an important player in regulation of monoamine signaling, yet its contribution to actions of abused drugs that act primarily by increasing extracellular levels of monoamines, remains unclear. To address this, we used high-speed chronoamperometry to interrogate the effects of local application of EtOH, cocaine, and their combination on clearance of exogenously applied DA from extracellular fluid in striatum of male and female constitutive OCT3+/+ and OCT3-/- mice *in vivo.* EtOH inhibited DA clearance and enhanced the ability of cocaine to inhibit DA clearance in male (n = 11-12/dose) and female (n = 11-12/dose) OCT3+/+ mice, effects that were lost in OCT3-/- (n = 8-10M & 8-10F/dose) mice. Next, using conditioned place preference (CPP) to assess the rewarding properties of the administration of EtOH, cocaine, or both, we found that the combination of EtOH (1000 mg/kg) and cocaine (3.2 mg/kg) produced robust CPP in male (n = 16/dose) and female (n = 16/dose) OCT3+/+ mice, an effect lost in OCT3-/- mice (n = 7M & 7F/dose). Taken together, results suggest that potentiation of the neurochemical and behavioral effects of cocaine by EtOH are OCT3 dependent. OCT3 may be a putative target for therapeutic intervention in the treatment of EtOH and cocaine co-abuse.

Poster 13

The reinforcement enhancing effects of nicotine increase demand for self-administered nicotine in a microeconomic model

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Nicotine (NIC) increases responding for non-drug reinforcers in humans and non-humans. Using microeconomic models, recent studies have shown that NIC increases demand for visual stimuli (VS) and alcohol. We sought to investigate whether these effects of NIC would increase demand (maximum price paid) for self-administered NIC. In Experiment 1, female rats (n=7) were shaped to respond for a saccharin reinforcer (SACC, 0.2 % w/v). After shaping, rats were instrumented for intravenous NIC self-administration (IVNSA). During IVNSA, rats received one of three reinforcers for meeting the schedule of reinforcement: NIC infusion (0.2 ug/inf), SACC (0.12 ml), or both (NIC+SACC). The price of each reinforcer was manipulated by systematically increasing the ratio schedule of reinforcement (FR1, FR3, FR12, etc.). After rats were tested with each reinforcer at each price, curve-fits were performed to estimate economic parameters (Hursh, 2008). The principal measure of demand was P_{max}, which estimates the point at which consumption declines at a greater rate than the increase in price. The combination of NIC and SACC robustly increased P_{max} relative to NIC or SACC alone. However, it is possible that the reinforcing effects of NIC and SACC were additive – combining any two reinforcers could be expected to increase P_{max}, relative to either one alone. Experiment 2 investigated whether two non-drug reinforcers (SACC and VS) increased P_{max} in an additive manner. Female rats (n=6) were shaped to respond for SACC+VS, SACC, and VS; consumption was measured across price. The combination of SACC+VS did not increase P_{max} relative to SACC alone, disconfirming that any two reinforcer combinations can increase demand. These studies show that the reinforcement enhancing effects of self-administered NIC can be measured in a microeconomic model. Further studies should explore the impact of making multiple reinforcers contingent on a single response, as it is a common approach to measuring consumption of drug commodities (i.e., drug+cue).

Poster 14

Nicotine does not speed the development of recovery-like behavior in a rat model of alcohol use and recovery following chronic ethanol exposure

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Chronic ethanol exposure decreases cognitive flexibility which may impede recovery from alcoholism. A possible mechanism responsible for this decrease may be ethanol-induced hypofunction of the nicotinic acetylcholine system. Our focus for this study was to see if stimulation of the nicotinic acetylcholine system would improve cognitive flexibility and facilitate recovery. We used our previously established operant rat model of recovery, in which stimuli that occasioned drinking become increasingly ineffective over sessions in which the rat engages in alternate behavior (food-maintained responding) instead of working for ethanol. We explored whether nicotine exposure (0.1mg/kg) would positively shift the rat's response towards food and away from ethanol. Rats were exposed to 10 or 20 days of extra-session ethanol exposure using a post-prandial drinking (PPD) procedure. During this time, rats also responded during daily operant sessions where contingencies were arranged such that rats were exposed to a stimulus (ETH) signaling ethanol was available and food was not. After completing the PPD sessions, rats were either injected (s.c.) with nicotine or vehicle solution 15 minutes prior to each daily recovery-like session in which a distinct stimulus signaled both food and ethanol were available. On select days (0,1,2,4,8) after the recovery-like phase was initiated rats were exposed to ETH and food and ethanol responses were compared. Contrary to our hypothesis, nicotine-exposed rats persisted in responding for ethanol longer both within and between test sessions than controls, suggesting nicotine further slowed shifts in discriminative control over drinking. Enhancing nicotine signaling did not speed the shift in discriminative control over drinking under these experimental conditions. Experiments using additional nicotine and ethanol doses are planned.

Poster 15

Spironolactone decreases alcohol drinking in alcohol dependence

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Alcohol use disorder (AUD) is characterized by heavy alcohol consumption and the emergence of a negative emotional state when alcohol is unavailable. One specific criterion for a diagnosis of AUD is the development of tolerance to alcohol, when higher amounts of alcohol are needed to produce the same effect. In the U.S., an estimated 14.4 million adults suffer from AUD and alcohol misuse is the third leading preventable cause of death. Thus, there is an urgent need to identify new targets for the treatment of AUD. Prior research has identified several neuroendocrine systems that are dysregulated in AUD, including the mineralocorticoid system. In the brain, mineralocorticoid receptors (MR) are predominantly expressed in limbic regions, where they are primarily activated by glucocorticoids and regulate stress reactivity. In the present study, we sought to investigate the effects of MR antagonism on alcohol tolerance and alcohol drinking in a preclinical model of dependence. We hypothesized that blockade of MR would block both alcohol tolerance and drinking. Adult male Wistar rats were exposed to chronic, intermittent alcohol vapor exposure to induce alcohol dependence. We then evaluated the effects of spironolactone, a MR antagonist, on alcohol drinking during operant alcohol self-administration sessions. We found that systemic administration of spironolactone dose-dependently decreased alcohol drinking in dependent rats. We then evaluated the effect of spironolactone on alcohol-induced motor incoordination using an accelerating rotarod test. We found that dependent rats exhibited less motor incoordination following a systemic administration of alcohol (1.5 g/kg) compared with nondependent rats, indicating alcohol tolerance. However, spironolactone did not reverse tolerance to the motor incoordination effects in dependent rats. These results suggest that MR is not involved in the mechanisms of alcohol tolerance, but is involved in alcohol consumption.

Poster 16

Similar sex differences in withdrawal from nicotine that was delivered via osmotic pump versus vapor inhalation

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Our prior work has revealed that sex differences in anxiety-like behavior elicited by nicotine withdrawal are modulated in the interpeduncular nucleus (IPN). This work induced dependence via continuous delivery of nicotine in a surgically implanted osmotic pump. The pump method is limited because it does not incorporate repeated withdrawal from inhaled nicotine. Thus, the goal of this study was to compare sex differences in anxiety-like behavior and activation of the IPN (via Fos expression) during withdrawal from nicotine delivered via pumps versus inhalation methods. Briefly, female and male rats were exposed to nicotine continuously via osmotic pumps (3.2 mg/kg/base) or intermittently via vapor procedures (90-min daily of 24 mg/mL). After 14 days of exposure, nicotine withdrawal was induced following administration of the nicotinic receptor antagonist mecamylamine (3.0 mg/kg/sc). The rats were assessed for physical signs of withdrawal and anxiety-like behavior on an elevated plus maze (EPM). Ninety min later, the rats were perfused and Fos expression was assessed using immunohistochemical procedures. The results revealed that under both routes of administration, females displayed similar withdrawal-induced increases in physical signs as males but greater anxiety-like behavior. Also, females displayed greater activation of the IPN than males, with the largest Fos expression in the ventral portions of the IPN under both routes of nicotine administration. Interestingly, we did note that there were larger sex differences in the anterior sections of the IPN following pump versus vapor exposure. Together, these data suggest that nicotine dependence under both regimens elicits similar behavioral effects of withdrawal, but perhaps distinct region-specific activation patterns in the IPN.
Our previous work revealed that female rats display greater anxiety-like behavior during withdrawal as compared to males. Research in our laboratory has recently examined sex differences in withdrawal-induced activation patterns in the IPN in adult female and male rats, however data was collected using nicotine osmotic pump exposure.

Poster 17

The effects of gabapentinoids on heroin-induced ventilatory depression and reversal with naloxone

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A growing body of epidemiological evidence suggests increasing misuse of gabapentinoids (gabapentin and pregabalin, calcium channel inhibitors used to treat some neuropathic pain conditions) in people with opioid use disorder. Over the past decade, gabapentinoids have become increasingly prevalent in opioid overdose deaths. Despite these trends little research has evaluated potentially harmful interactions between gabapentinoids and opioids. This study evaluated the effects of gabapentin and pregabalin on the ventilatory depressant effects of heroin, and the reversal of heroin-induced ventilatory depression by naloxone. Rats were given pregabalin (1-32 mg/kg), gabapentin (10-100 mg/kg), or saline i.v. 30 minutes prior to receiving increasing doses of heroin (0.1-1 mg/kg) while ventilation was monitored using whole-body plethysmography. Naloxone (0.0056-0.01 mg/kg) or saline was administered i.v. 5 minutes following the final infusion of heroin. Minute volume was the primary outcome of this study. Heroin dose-dependently reduced minute volume and naloxone dose-dependently reversed this effect. Neither pregabalin nor gabapentin altered the ventilatory depressant effects of heroin. However, pretreatment with gabapentin or pregabalin dose-dependently attenuated the ability of naloxone to reverse heroin-suppressed minute volume. These findings suggest that gabapentinoids might diminish the effectiveness of naloxone to reverse opioid overdose in humans, a possible explanation for the prevalence of these drugs in opioid overdose deaths. It is important to determine whether similar interactions occur between gabapentinoids and naloxone for reversing the effects of other *mu* opioid receptor agonists such as fentanyl.
Funding: Welch Foundation AQ-0039

Poster 18

Effects of naloxone and almitrine on opioid-induced respiratory depression

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As the fatal opioid epidemic persists, drug overdoses involving an opioid continue to increase. Opioid overdose deaths primarily occur by respiratory depression where opioids inhibit both peripheral and central areas responsible for maintaining respiratory rhythm and flow. Respiratory stimulants can reverse opioid overdoses, and the only currently available options are opioid receptor antagonists, such as naloxone. Almitrine is a respiratory stimulant that acts on carotid bodies and does not affect the analgesic component of opioid use nor precipitates withdrawal in chronic users. We tested the hypothesis that naloxone and almitrine would reverse heroin-induced respiratory depression. Male and female Long-Evans rats underwent intravenous (i.v.) catheter surgery. After habituation to plethysmography chambers, the rats were randomly assigned to either naloxone or almitrine and were tested in a within-subjects, Latin-square, design with 4 tests one week apart. In each session, all rats received heroin (600 µg/kg, i.v.) followed 5 min later by either naloxone (0, 100, 300, 1000 µg/kg; i.v.) or almitrine (0, 500, 1000, 2000 µg/kg; i.v.) over 1 min. All doses of naloxone improved breathing rhythm and flow control parameters, with 100 µg/kg having the longest effects. The highest dose of almitrine, 2000 µg/kg, improved flow control parameters, but not breathing rhythm parameters, suggesting a peripheral effect. These findings indicate that respiratory stimulants, acting on targets other than the opioid system, might be an effective alternative or complimentary approach to reverse opioid-induced respiratory depression and represent potential new treatments to reverse opioid overdoses. This work was supported by NIDA IRP, NIH.

Poster 19

Long-term effects of juvenile ketamine and/or social stress on spatial memory performance in adult male mice

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The novel and fast-acting antidepressant, ketamine, is currently being used for the management of treatment resistant depression in adolescent patients. However, the possible long-term effects of ketamine exposure during adolescence have not been assessed. Thus, we examined whether repeated exposure to concomitant ketamine and social stress, during the adolescent stage of development, results in long-lasting spatial memory alterations in male C57BL/6 mice (N=54; 9 per group). Specifically, mice were exposed to social stress (vicarious defeat stress paradigm) along with ketamine treatment (0 or 20 mg/kg) from postnatal day (PD) 35-44. Once mice reached adulthood (PD70), we assessed spatial memory performance using the Morris water maze test. Our results suggest that adult mice pre-exposed to ketamine during adolescence displayed impaired spatial memory performance, in the absence of social stress history. Furthermore, we uncovered that adolescent ketamine exposure, in combination with social stress, prevented stress-induced spatial memory impairments in adulthood. Together, our findings suggest that ketamine as a treatment for stress-induced illnesses (i.e., depression) does not lead to changes in spatial memory performance whereas recreational ketamine use may result in spatial memory impairment.

Poster 20

Discriminative stimulus properties of *Cannabis Sativa* terpenes

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Terpenes are a large, diverse class of compounds produced by *Cannabis Sativa* and traditionally thought to impart flavor and aroma to cannabis. While decades of research have been devoted to the study of the actions of phytocannabinoids like Δ^9-tetrahydrocannabinol (THC) or cannabidiol, very little is known about the pharmacological activity of terpenes and whether they may have interactions with compounds like THC. Several recent reports have indicated that terpenes exert therapeutic effects (e.g. antinociception), and these effects may be mediated via cannabinoid CB1 receptors. The present studies sought to determine whether the terpenes linalool, α-humulene, Y-terpinene, and limonene produce discriminative stimulus effects similar to THC in rats discriminating 3.2 mg/kg of THC from vehicle (n=7). While the synthetic cannabinoid receptor agonist JWH-018 produced responding on the THC-paired lever, none of the terpenes occasioned responding predominantly on the THC lever. The results of these studies indicate that terpenes do not produce discriminative stimulus effects similar to THC and may not possess central nervous system CB1 receptor agonist activity. Ongoing studies aim to assess whether linalool, α-humulene, Y-terpinene, and limonene alter the potency of THC in the same drug discrimination assay.

Poster 21

Examination of pharmacotherapies for nicotine use in a rodent model of diabetes

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There is a lack of information on the effectiveness of pharmacotherapies used to treat diabetes on nicotine use. As a first step in addressing this issue, we examined the effects of insulin and bromocriptine (Cycloset) on nicotine intravenous self-administration (IVSA) and glucose levels in a rodent model of diabetes. Insulin is a commonly prescribed hormone treatment that normalizes glucose levels in patients with diabetes. Bromocriptine is a dopamine agonist that that normalizes post-meal increases in blood glucose levels. Briefly, female and male rats received a chronic high-fat diet (HFD) plus a low dose of streptozotocin (STZ; 25 mg/kg) that induces insulin resistance. Control rats received a regular diet (RD) plus a low dose of STZ. STZ is toxic to insulin-producing beta cells and produces an increase in glucose levels. The rats were then given extended access to IVSA of nicotine (0.03 mg/kg for 6 weeks) in an operant box where they continued to consume their respective diet and performed nose poke responses for water deliveries. Each nicotine dose was delivered for 4 days with 3 intermittent days of abstinence in their home cage. Plasma glucose levels were assessed every day of the IVSA regimen. The rats received systemic administration of bromocriptine (3.0, 3.0, 10 mg/kg) and then insulin (0.75 U/kg) each day for one week at 6 pm at the onset of their night cycle. The results revealed that bromocriptine dose-dependently increased nicotine intake and peripheral glucose levels, and these effects were greater in HFD+STZ rats relative to RD+STZ controls. In contrast, insulin administration reduced nicotine IVSA and glucose levels in HFD+STZ rats versus controls. Our findings suggest that pharmacotherapies that reduce glucose levels may be more effective at reducing nicotine use in patients with diabetes.

Poster 22

Zolmitriptan attenuates the acquisition of methamphetamine conditioned place preference in adolescent male and female rats

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Activation of serotonin (5-HT)1B receptors disrupts the expression, but not the acquisition, of methamphetamine (METH) preference in adult male mice. In the present study, we examined whether administration of Zolmitriptan, a 5-HT1B receptor agonist, affects the development of METH preference in adolescent rats using a 10-day Conditioned Place Preference (CPP) procedure. On postnatal day (PD) 28, baseline preference for a two-sided apparatus was assessed. In two day cycles, rats received an injection of Zolmitriptan (0 or 10 mg/kg) 15 min before the administration of METH (0, 0.125, 0.25, 0.5, 1.0 mg/kg) on one day and saline administration on the other day before being confined to one side of the two-chamber apparatus for 30 min. This two day cycle was repeated over the next 6 days. On day 10, preference for the METH-paired side was assessed. Male rats exhibited METH-induced CPP at either the 0.25 or 0.5 mg/kg dose of METH, but this preference was attenuated in the lowest dose of METH when administered Zolmitriptan. In females METH-induced CPP was evident for all METH doses, and again Zolmitriptan pretreatment attenuated the preference for METH, except when female rats were pretreated with the 0.5 mg/kg METH dose. The present findings demonstrate that activation 5-HT1B receptors with Zolmitriptan reduces the acquisition of METH-induced CPP in male and female adolescent rats. These findings constrast prior work in adult male mice, and suggests that age, sex, and species may be important factors in demonstrating a role of 5-HT1B receptors in reducing the acquisition of METH reward. Overall, these findings further add to a growing body of literature that points to the 5-HT1B receptor as a pharmacological target for the treatment of psychostimulant addiction.

Poster 23

Childhood trauma drives alcohol consumption behavior via executive function domain factors in the Addictions Neuroclinical Assessment

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Background: The Addictions Neuroclinical Assessment (ANA) is a clinical framework composed of three neurofunctional domains thought to underlie substance use disorders (SUDs): Executive Function (EF), Negative Emotionality (NE), and Incentive Salience (IS). Previous analyses showed that childhood trauma drove alcohol consumption via NE and IS domain factors. The present study extends this work by examining how childhood trauma drives alcohol consumption via EF-related processes. **Method:** N=300 individuals (41% female; 68% with current AUD diagnosis) completed the ANA battery, which consisted of behavioral and self-report assessments. EF measures were response inhibition, short-term memory, inferential reasoning, task switching, mental rotation, attention, metacognition, interoception, and impulsivity. Childhood trauma was assessed with the Childhood Trauma Questionnaire (CTQ), Quantity and frequency of drinking and heavy drinking was assessed using the 90-day Timeline Follow-back. EF domain factors were derived using factor analysis. Associations between domain factors, childhood trauma, and alcohol consumption was modeled using Structural Equation Modeling, covarying for age and sex. **Results:** Five EF factors were derived: Response Inhibition (Inh), Working Memory (WM), Rumination (Rum), Interoception (Int), and Impulsivity (Imp) (CFI=0.92, TLI=0.91, RMSEA=0.05). Childhood trauma drove drinking and heavy drinking frequency via WM impairments and Imp (p's<.001). Association between childhood trauma and average drinks per day was driven only by Imp (p<.001). **Conclusions:** Childhood trauma drives alcohol consumption behavior via EF-related processes, which were captured within the ANA framework. Future work will use this framework to examine other risk factors to improve our understanding and prognosis of SUDs.

Poster 24

Evidence for neuroinflammation in the prefrontal cortex and striatum induced by binge-like intake of methamphetamine and the synthetic cathinone methyldioxypyrovalerone (MDPV)

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Classic amphetamines such as d-amphetamine and methamphetamine (METH) have been studied with regards to their ability to produce neuroinflammation. However, the potential neuroinflammatory effects of designer psychostimulants, such as the synthetic cathinone methylenedioxypyrovalerone (MDPV) are far less understood. The purpose of this study was to measure potential differences in neuroinflammatory markers associated with the use of MDPV or methamphetamine in the prefrontal cortex (PFC) and striatum. Both male and female rats performed intravenous self-administration of either MDPV (0.05 mg/kg/infusion), meth (0.05 mg/kg/infusion) as a reference drug, or saline. Animals were given three separate 96-hour drug access periods to emulate binge-like drug intake. Three weeks after the final access period, brain regions were analyzed for astrocyte and microglia density and leukocyte infiltration using ELISA and IHC techniques. Analysis of brains from animals with a history of METH intake showed an increase in MCP-1, CX3CL1, IL-6, IL-18 and IFN-gamma levels in both the PFC and striatum as compared to saline controls. Males with a history of MDPV intake showed increased IL-6 levels in both the PFC and striatum, whereas females with a history of MDPV intake showed decreased IL-6 levels in the PFC only. There were no differences in astrocyte or microglia density in either region between any experimental groups. We observed slight evidence of leukocyte infiltration into the PFC in both MDPV and METH groups. This study provides evidence that both MDPV and METH use are associated with increases in neuroinflammatory markers three weeks after binge-like access, with degree and direction of some markers being dependent on sex and type of psychostimulant.

Poster 25

The role of κ-opioid receptor antagonism in opioid self-administration and opioid withdrawal-induced hyperalgesia

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Chronic opioid intake leads to hyperalgesia during withdrawal, which is thought to contribute to compulsive drug taking through negative reinforcement. Our group has shown that dynorphin and κ-opioid receptors (KORs) are involved in heroin withdrawal-induced hyperalgesia. However, the role of the dynorphin-KOR system in compulsive drug taking, and the relationship between drug taking and hyperalgesia, is not fully understood. Here, we hypothesized that KOR antagonism would decrease fentanyl (FTN) self-administration and withdrawal-induced hyperalgesia in heroin-dependent mice. To test this hypothesis, we trained male and female C57BL/6J mice to self-administer vaporized FTN and split them between short-access (ShA; 1 h sessions) and long-access (LgA; 6 h sessions) groups. Mice tested in LgA sessions escalated their FTN intake, whereas those tested in ShA sessions did not. We tested the short-acting KOR antagonist aticaprant (0, 0.3, 1, 3, 10, 30 mg/kg, oral), which failed to reduce FTN self-administration in both groups. Following three weeks of abstinence, a single treatment with the long-acting KOR antagonist norBNI (10 mg/kg, intraperitoneal) significantly reduced the re-escalation of FTN in mice in LgA but not in ShA conditions. In a second experiment, we induced dependence in prodynorphin knockout and wildtype mice by treating them with escalating doses of heroin. The same dose of norBNI (10 mg/kg, intraperitoneal) failed to reduce opioid withdrawal-induced hyperalgesia. These data suggest that extended blockade of KORs is necessary to decrease opioid self-administration in dependent mice and the dose of norBNI that is sufficient to prevent re-escalation of FTN intake does not reverse opioid-induced hyperalgesia.

Poster 26

Deletion of microglial CB_1Rs impairs cocaine reinforcement

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Cannabinoid 1 receptors (CB_1Rs) are critically involved in the rewarding effects of cocaine and relapse to drug seeking. However, the cell type specific mechanism mediating this effect is unknown. Chronic cocaine exposure activates microglia and alters cytokine signaling, which has been linked to cocaine locomotor sensitization, suggesting the possible involvement of a microglial CB_1R mechanism in cocaine action. To test this hypothesis, we used conditional $CB_1^{-/-}$ mice with CB_1Rs selectively deleted from microglia (CX3CR1-$CB_1^{-/-}$) and measured changes in cocaine self-administration (experiment 1) and cocaine place preferences (experiment 2). Briefly, CX3CR1-$CB_1^{-/-}$ mice (n=11) demonstrated attenuated responding for 0.5 mg/kg/infusion cocaine under both fixed ratio 2 and progressive ratio schedules as well as greater drug-seeking under extinction conditions relative to CB_1 flox controls (n=11). However, no differences between the two mice strains were observed during a cocaine reinstatement test or in the development of cocaine place preferences at 10 mg/kg (n=8/group). In experiment 3, CB_1 flox mice (n=3/group) were injected with 0 or 20 mg/kg cocaine i.p. for 7 days and brains were extracted following the 8th and final injection for RNAscope in situ hybridization. CB_1R RNA expression in microglia was upregulated in the NAc, but not the VTA following chronic cocaine exposure. These findings suggest that microglia CB_1Rs play a role in cocaine addictive behavior potentially via changes in endocannabinoid signaling in the NAc.

Poster 27

Drugs as discriminative stimuli in conditioned taste aversion learning: Signaling danger vs. safety

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If an animal is injected with a drug prior to receiving a pairing of saccharin with the emetic LiCl and on alternate days an injection of the drug vehicle prior to a pairing of saccharin with the LiCl vehicle, they rapidly learn the discrimination, avoiding saccharin when preceded by the drug and consuming the same saccharin solution when preceded by the vehicle. While drug discriminations can be readily acquired under such conditions, less is known about whether such learning occurs when the drug vehicle signals the pairing of saccharin and LiCl, while the drug signals safety, i.e., a pairing of saccharin with vehicle. To address this, in the present experiment (under otherwise identical parametric conditions), different groups of animals were trained with the abovementioned contingencies with morphine (10 mg/kg, i.p.) as the stimulus drug. As expected, when morphine served as the cue predicting a pairing of saccharin with LiCl (and the morphine vehicle signalling safe access to saccharin), the discrimination was acquired in roughly six trials. On the other hand, when the morphine vehicle signalled the saccharin-LiCl pairing (and morphine itself signalled safe access to saccharin), no discrimination was acquired with subjected avoiding saccharin following either the morphine vehicle or morphine. These data suggest that when morphine signals the saccharin-LiCl pairing, it is the salient cue (as an occasion setter) and controls subsequent consumption of the LiCl-associated saccharin. On the other hand, when vehicle is given prior to the saccharin-LiCl pairing, no drug-induced stimuli compete with the taste cue in the control of consumption and consumption is controlled completely by saccharin. Under these conditions, such control is unaffected by the subsequent signalling of safety by the morphine stimulus. Such findings suggest that discriminative control with morphine as a safety cue may require additional safe trials to overcome stimulus control by taste alone.

Poster 28

Benzofuran derivatives substitute for the discriminative stimulus effects of MDMA in male Sprague-Dawley rats

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3,4-Methylenedioxymethamphetamine (MDMA) is currently under evaluation in phase III clinical trials for the treatment of post-traumatic stress disorder (PTSD). MDMA is also a popular abused substance with risks for cardiovascular toxicity and neurotoxicity. Characterization of the behavioral and neurochemical effects of novel psychoactive substances (NPS) can aid in the development safer alternative therapeutic agents. Preclinical drug discrimination is a behavioral assay with pharmacological specificity for characterizing *in vivo* drug activities in the central nervous system. This study assessed the discriminative stimulus effects of the enantiomers of 5-(2-methylaminopropyl) benzofuran, 5-(2-methylaminobutyl)benzofuran, and 6-(2-methylaminobutyl) benzofuran. Eight adult male Sprague-Dawley rats were trained in a two-lever operant drug discrimination procedure to discriminate MDMA (1.5 mg/kg) from saline. Stimulus substitution tests were conducted with (RS) 5-MAPB, (R)-5-MAPB, (S)-5-MAPB, (R)-5-MBPB, (S)-5-MBPB, (R)-6-MBPB, and (S)-6-MBPB. All substances produced full substitution for MDMA. In separate experiments, serotonin release and reuptake assays with rat synaptosomes indicated these substances are substrate releasers of serotonin with nanomolar potency; slightly higher potency was observed with the S-enantiomers. The benzofuran scaffold may allow development of substances that retain MDMA-like therapeutic effects while reducing toxicities associated with MDMA. Future studies are planned to characterize the relative contribution of 5-HT and dopamine to the behavioral effects of selected benzofuran derivatives.

Poster 29

PET imaging studies of Kappa opioid receptors in socially housed female and male monkey models of cocaine use disorder

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Cocaine use disorder (CUD) persists as a worldwide public health problem for which there is no FDA-approved pharmacotherapy. Using socially housed monkeys, we showed that there was an inverse relationship between dopamine (DA) D2/D3 receptors (D2/D3R) and vulnerability to cocaine abuse in males (subordinates more vulnerable than dominants), but the opposite in females (dominants more vulnerable than subordinates). The present study extended this characterization to include positron emission tomography (PET) imaging of the kappa opioid receptor (KOR) system; KOR and its endogenous ligand, dynorphin, are implicated in the neurobiological regulation of aversive states, stress and substance abuse. The first aim was to investigate KOR system, combining PET imaging with [^{11}C]EKAP and primate social behavior in cocaine-naïve male and female monkeys (N=8/sex) living in same-sex social groups of 4/pen. The second aim of this ongoing study is to investigate how those baseline KOR measures change following chronic cocaine self-administration and to assess the neural plasticity of KOR system following protracted abstinence. The primary dependent variable was binding potential (BP), which is an in vivo measure of the ratio of receptor density to receptor affinity. In cocaine-naïve animals, the lowest BPs across all regions of interest were observed in dominant females and subordinate males; these are the two most vulnerable phenotypes to cocaine reinforcement. Preliminary data in males indicates that after 100 mg/kg cocaine intake the baseline differences between dominant and subordinate monkeys are exacerbated. Supported by R01 DA017763-15 and T31 DA041349-05

Poster 30

RDS04-010, a novel atypical dopamine transporter inhibitor promising for the treatment of cocaine use disorder: Evidence from computational modeling and experimental animals

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Compared to cocaine, atypical dopamine transporter (DAT) inhibitors have been found to bias the conformation equilibrium of DAT differently and display distinct behavioral profiles. Specifically, cocaine traps DAT in an outward-facing conformation and results in a typical rewarding behavioral profile, while stabilizing DAT in inward-facing conformations by atypical inhibitors is less rewarding and may have therapeutic potential for treatment of psychostimulant use disorders. Here we report two novel and structurally similar DAT inhibitors that are predicted to display distinct DAT binding modes – RDS04-010, similar to previously reported JJC8-091, prefers an inward-facing conformation of DAT, while RDS03-094 prefers a more outward-facing conformation. Systemic administration of RDS04-010 dose-dependently inhibited cocaine self-administration (SA), shifted cocaine SA dose-response curve downward, decreased motivation for cocaine seeking under progressive ratio reinforcement conditions, and inhibited cocaine-primed reinstatement of drug-seeking behavior. In contrast, RDS03-094 displayed more cocaine-like behaviors. Pretreatment of RDS03-094 produced biphasic effects on cocaine SA with a low dose causing a downward shift, while higher doses resulting in an upward shift. RDS03-094 also evoked reinstatement of cocaine-seeking behavior. Notably, in a drug substitution test, RDS03-094 was able to maintain SA in rats trained to SA cocaine, whereas RDS04-010 failed to maintain SA when it replaced cocaine and indeed, blocked cocaine SA. Collectively, these findings suggest that RDS04-010 is a promising atypical DAT inhibitor with favorable therapeutic potential in reducing cocaine use and relapse. In contrast, RDS03-094 is more cocaine-like, supporting self-administration and inducing reinstatement to cocaine seeking, similar to other typical DAT inhibitors (e.g., JJC8-088, GBR12909).

Poster 31

An anti-fentanyl vaccine blocks fentanyl-induced disruption of schedule-controlled responding in male and female Sprague Dawley rats

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An effective anti-fentanyl vaccine may be a viable treatment strategy for Opioid Use Disorder and overdose. Here, we assessed a CRM-FEN + dmLT conjugate vaccine on fentanyl and morphine-induced effects on schedule controlled responding in male and female Sprague Dawley rats. Rats were food restricted and allowed to lever press for sucrose pellets in daily 30-minute sessions under an FR15 schedule of reinforcement. Once maintenance criteria was met, rats were randomly administered doses of fentanyl (FEN, 0.01, 0.03, 0.05 and 0.1 mg/kg, SC) then morphine (MOR, 0.3, 1.0, 3.0, 10 mg/kg, SC). Following initial testing, rats received FEN-CRM (5ug) conjugate with the adjuvant dmLT (1ug) at 0, 3 and 6 weeks. Serum samples were obtained at 6, 8 and 10 weeks and amounts of anti-FEN antibodies determined with ELISA. At 8 weeks post-initial vaccination, rats were again allowed to lever press for sucrose pellets. Once rats met testing criteria, they were administered additional random doses of FEN and MOR. FEN dose-dependently decreased lever pressing in both male and female rats, whereas MOR increased lever pressing 150% across all doses tested. Vaccination with CRM-FEN produced appreciable amounts of anti-FEN antibodies that completely blocked FEN-induced decreases in response rate in both male and female rats. Vaccination had no effect of MOR on response rate in either sex. Overall, FEN profoundly decreased whereas MOR increased schedule-controlled response rate. Vaccination with CRM-FEN + dmLT produced anti-FEN antibodies that completely blocked the rate-decreasing effects of FEN. The effect of the vaccine was specific to FEN. Further development of this anti-fentanyl vaccine is warranted.

Poster 32

To the rescue: Bootstrap estimation to enhance preclinical discovery

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Substance use disorders (SUDs) remain a significant public health concern as evidenced by over 92,000 overdose deaths in 2020. Despite this public health emergency there are still no FDA-approved medications for stimulant use disorder and medication assisted therapeutics for opioid use disorder do not prevent all instances of overdose and relapse. Translating preclinical discoveries to meaningful clinical outcomes remains a problem. The causes of these shortcomings are vast, but a lack of reproducibility and/or overestimating preclinical effects are major contributors. To address these concerns, we reanalyzed self-administration data from rats (n=18) to demonstrate the effects of sample size on variability and mean estimation. The Central Limit Theorem suggests that variability of resampled mean estimates should decrease as sample size is increased. To meet these objectives and test our hypothesis, we resampled various sample sizes and used estimation statistical methods (i.e., bootstrap resampling) to locate the best estimate (mean) and the precision surrounding it. Next, to better illustrate the effect of sample size on mean estimates we simulated a single experiment by resampling once for each sample size. We found that the precision of the estimate was positively correlated with sample size, such that precision is better when sample size is greater. These findings indicate that reproducibility is strongly tied to the precision of the estimate and that adequate sample size is critical for obtaining an accurate estimate. Determining the precision of the estimate is important because it will inform researchers about the reliability and reproducibility of the observed effects. Together these contribute to more confidence in preclinical discoveries which will translate to meaningful clinical outcomes.

Poster 33

Characterization of nonhuman primate sleep using electroencephalogram telemetry and implications for the treatment of substance use disorder

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Sleep disruption is a common aspect of many psychiatric illnesses and has been implicated as a target in finding new pharmacotherapies for substance use disorders. Nonhuman primates are the ideal animal subject for studying sleep due to their similarity to humans regarding duration and stages of sleep including N1, N2, and N3 stages of non-REM sleep and REM sleep, sleep spindles and K-complexes. This allows for the utilization of nonhuman primates for longitudinal, within-subject design studies evaluating the relationship between quality of sleep and vulnerability, maintenance, and potential pharmacotherapies for substance use disorder. The goal of the present research is to examine sleep quality and architecture in cocaine-naive freely moving young (5-12 year old) male and female cynomolgus macaques and then again after acquisition of cocaine self-administration, throughout maintenance and following potential treatments. For this study, we evaluated baseline sleep architecture, defined as the amount of time spent in various stages of sleep, as well as sleep quality, meaning the amount of delta power present during NREM sleep. We recorded from monkeys for 16 hours at a time, 12 of which the lights in the room were off. We specifically examined the influence of single- vs. pair-housing and the impact of wearing a primate collar in male (N=4) and female (N=4) monkeys. Female animals were evaluated in both the follicular and luteal phases in order to better evaluate changes in sleep throughout the menstrual cycle. While the data are still being analyzed, this characterization is necessary for informing us on how future studies will be conducted in order to evaluate sleep using EEG telemetry and how sensitive sleep architecture is in freely moving male and female cynomolgus macaques. Supported by DA017763

Poster 34

Is the dopamine D4 receptor a pharmacotherapeutic target for alcohol use disorder?

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Alcohol use disorder (AUD) affects more than 15 million people in the United States. Current pharmacotherapeutic treatments for AUD are only modestly effective, necessitating the identification of new targets for medications development. The dopamine D4 receptor (D4R) is a target of interest in the development of medications for psychostimulant addiction, but has been largely unexplored for AUDs. In this study, we investigated the effects of the classic D4R antagonist L-745,870 and the novel, high-affinity D4R-selective antagonist CAB01-019 in rodent models of alcohol use disorder using adult male CD-1 mice. L-745,870 was tested for effects in operant food and ethanol self-administration tasks. Food-restricted mice were trained to nose poke for delivery of palatable food (vanilla Ensure) or alcohol rewards (8% w/v in water). L-745,870 (1.5 and 3.0 mg/kg, i.p.) did not significantly attenuate ethanol or food self-administration compared to vehicle. Additional testing with L-745,870 pretreatment during conditioned place preference (CPP) training did not significantly affect the rewarding value of 2.0 g/kg ethanol using a three-compartment CPP apparatus. Similar tests with CAB01-019 are ongoing. These results, and future studies exploring whether D4R antagonism affects relapse-like responding in reinstatement models, will provide a comprehensive analysis of whether D4R antagonism affects alcohol-taking and -seeking behaviors.
Research support: NIH (DA041560, DA050896), Rowan University

Poster 35

Sex differences in approach behavior toward a port that delivers nicotine plumes in an electronic vapor delivery system

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The goal of our laboratory is to utilize rodent models to study the underlying mechanisms of nicotine use in humans, particularly in vulnerable populations. To more closely mimic human use patterns, the present study employed passive exposure to nicotine vapor for 14 days in adolescent and adult female and male rats. We examined age and sex differences in approach behavior toward a port that delivered nicotine plumes on Day 1 and 14 of our vapor exposure regiment. Group differences in physical signs of withdrawal and plasma levels of the nicotine metabolite cotinine were assessed on Day 14. The results revealed that over time, female rats displayed a larger increase in approach behavior than males, an effect that was significantly larger in adolescent rats. The female adolescent rats displayed higher cotinine levels than all other groups, an effect that was likely related to higher nosepoke responses in the port that delivered nicotine vapor. These findings suggest that nicotine vapor produces greater motivational effects in adolescent female rats versus males. This work provides a foundation for future studies examining the mechanisms that modulate age and sex differences produced by chronic nicotine vapor exposure, particularly under conditions that involve voluntary self-administration of nicotine vapor.

Poster 36

A pilot study evaluating the reinforcing effects of pregabalin in rats trained to self-administer heroin

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Pregabalin (Lyrica®) is an inhibitor of α2δ subunit-containing calcium channels, and a widely prescribed prescription drug approved for the treatment of partial-onset seizures and some neuropathic pain disorders. Pregabalin misuse is significantly more prevalent in people with opioid use disorder than the general population, 20% compared with 1%, respectively, suggesting pregabalin may have abuse potential in subjects with a history of opioid misuse. Despite mounting epidemiological evidence, the reinforcing effects of pregabalin have not been evaluated experimentally. This experiment sought to determine whether pregabalin (i.v.) maintains responding in rats trained to self-administer heroin. Male Sprague-Dawley rats were trained to self-administer heroin (0.0178 mg/kg/inf) in a 2-hour session under a fixed ratio 1, 30-second timeout schedule of reinforcement. Saline and pregabalin (17.8 mg/kg/inf) were then substituted for heroin for at least 7 days, until responding was stable. Out of 7 rats trained to self-administer heroin, 4 responded for a significantly greater number of infusions of pregabalin compared with saline. These findings suggest that pregabalin serves as a reinforcer in rats trained to self-administer heroin, though a larger study evaluating multiple doses of pregabalin is needed to confirm these findings. Future studies will also determine whether the reinforcing effects of pregabalin are specific to subjects with a history of opioid agonist self-administration, and whether interactions exist between the reinforcing effects of gabapentinoids and opioids, as some individuals report using pregabalin to enhance the euphoric effects of opioids.
Funding: Welch Foundation AQ-0039

Poster 37

Methylone pre-exposure differentially impacts the aversive effects of MDMA, MDPV and fluoxetine in male and female Sprague-Dawley rats

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The abuse potential of a drug is thought to be a balance of its rewarding/aversive effects, and several subject (e.g., sex) and experiential (e.g., drug history) factors impact this affective balance. The synthetic cathinones have recently begun to be examined to characterize their effects and how they are affected by drug history. Pre-exposure to a drug generally attenuates its own (and others') aversive effects, shifting the affective balance to reward. The present study assessed the effects of pre-exposure to methylone, a first-generation synthetic cathinone that serves as a substrate releaser for DA and 5-HT, on taste avoidance induced by the synthetic cathinone MDPV (highly selective DA reuptake inhibitor), MDMA (5-HT substrate releaser) and the antidepressant fluoxetine (selective 5-HT reuptake inhibitor). Male and female Sprague-Dawley rats (n = 127) were exposed to vehicle or methylone (10 mg/kg) every 4th day for a total of five injections prior to taste avoidance conditioning in which a novel saccharin solution (1 g/L) was paired (five times) with MDPV (1.8 mg/kg), MDMA (1.0 mg/kg), or fluoxetine (10 mg/kg). Under these conditions, methylone pre-exposure attenuated the aversive effects of MDPV (males and females) and MDMA (only in males) [$p < 0.05$] while having no impact on the aversive effects of fluoxetine for either sex ($p > 0.05$). That the strongest attenuation occurred with MDPV with only moderate effects with MDMA and no effect with fluoxetine suggests that the aversive effects of methylone may be mediated by DA. Together, these results suggest that drugs with common neurochemical substrates likely interact to impact abuse potential and these interactions may be sex dependent.

Poster 38

Delta opioid receptor activation potentiates the reinforcing properties of cocaine paired cues

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Presentation of external cues that have been associated with previous cocaine taking behavior can induce craving and subsequent drug use, known as relapse. I hypothesized that drugs previously shown to induce reinstatement of cocaine seeking behavior in animal models, such as cocaine and the delta opioid receptor agonist SNC80, would also increase responding for cocaine-paired cues in the New Response Acquisition Procedure. The first phase of this procedure is Pavlovian Conditioning in which 5 light-tone stimuli per day are presented either concurrently (Paired) or separately (Unpaired) with intravenous injection of cocaine (320 ug/kg/infusion) for 10 days. Following Pavlovian Conditioning, animals undergo the second phase, called Acquisition (ACQ), in which novel operant manipulanda (one active, one inactive nose poke) are introduced into the chamber (no cocaine is available), and responding on a random ratio 2 (RR2) schedule of reinforcement results in presentation of the light-tone stimulus only. On the fourth day of ACQ, a drug challenge (3.2 mg/kg SNC80 s.c., 10 mg/kg cocaine i.p., or vehicle) was administered acutely before the start of the session, and responding was evaluated. SNC80 produced a robust increase in responding for the cocaine paired cue in the Paired Pavlovian group but not in the Unpaired group. Conversely, cocaine did not alter responding for cocaine paired cues in either Paired or Unpaired groups. These data suggest that conditions previously shown to induce reinstatement may not necessarily specifically increase the conditioned reinforcing properties of cocaine. These studies may provide insight into the underlying neurobiology mediating the conditioned reinforcing effects of drug-paired

Poster 39

Cocaine-vs-social choice in rats is sensitive to reinforcer magnitude and price manipulations

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AIM: Cocaine use disorder occurs in an environmental context that includes both the abused drug and non-drug reinforcers, such as social interaction and relationships with family and friends. Accordingly, preclinical research has begun to incorporate social interaction into animal models of drug abuse. The goal of the present study was to determine the sensitivity of a cocaine-vs-social interaction choice self-administration procedure in male and female rats to reinforcer magnitude and response requirement (i.e., cost) manipulations.
METHODS: Operant responding for social interaction with a conspecific rat and intravenous cocaine self-administration were initially trained separately in rats (n=8, 4 per sex). Subsequently, cocaine-vs-social interaction choice was determined at different cocaine doses (0–1.8 mg/kg/inf) in a discrete-trial choice procedure with equal fixed-ratio (FR3) requirements for both cocaine and social interaction. Next, rats were switched to a discrete-trial choice procedure where social interaction was held constant at FR3 and response requirement on the cocaine lever was a progressive-ratio (PR) schedule.
RESULTS: Rats allocated behavior between cocaine and social interaction depending upon the unit cocaine dose. Rats chose social interaction over no or small cocaine doses (0-0.1 mg/kg/inf) under both the equal FR and PR discrete-trial choice procedures. Rats showed a decrease in cocaine choice between 0.32 mg/kg/inf cocaine and social interaction under the cocaine PR discrete-trial procedure compared to the equal FR procedure. However, rats chose larger cocaine doses (1–1.8 mg/kg/inf) over social interaction under both procedures.
CONCLUSIONS: The results demonstrate that cocaine-vs-social choice under a discrete-trial choice procedure is sensitive to reinforcer magnitude manipulations such as drug dose. Furthermore, these results provide an empirical foundation to test candidate medications for cocaine use disorder and investigate the neurobiology of drug-vs-social choice.

Poster 40

Behavioral characterization of dopamine D3 and serotonin 2C receptor ligands for the treatment of substance use disorders

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Medications that target the dopamine (DA) D_3 and serotonin ($5HT_{2C}$) receptors can reduce the reinforcing effects of stimulant and opioid drugs of abuse. However, clinically available drugs that act at DA D_3 (i.e., buspirone) and $5HT_{2C}$ receptors (i.e., lorcaserin) have limited effectiveness at reducing drug-taking at doses approved for use in humans. Strategies to improve the therapeutic potential of these drugs include increasing selectivity for DA D_3 and $5HT_{2C}$ receptors, and/or administering DA D_3 and $5HT_{2C}$ ligands in combination. Accordingly, adult Sprague Dawley rats (n=8 males, 8 females) were first trained to self-administer cocaine (0.32 mg/kg/inf), fentanyl (0.0032 mg/kg/inf), or mixtures of 0.32 mg/kg/inf cocaine and 0.0032 mg/kg/inf fentanyl under a fixed ratio schedule prior to transitioning them to a progressive ratio schedule of reinforcement. Once responding stabilized (difference of ≤2 reinforcers over 2 days), rats were treated with the selective $5HT_{2C}$ agonist, CP-809101 (0.32-10 mg/kg; IP), the DA D_3 partial agonist, VK-4-40, and a DA D_3 antagonist, VK-4-116 (1-32 mg/kg, IP) in order to determine their potency and effectiveness to reduce stimulant and opioid self-administration. CP809101 was equipotent and effective at reducing responding for cocaine, fentanyl, and their combination. Responding for fentanyl was more readily suppressed by VK-4-40 and VK-4-116 than responding for cocaine, regardless of sex. These data suggest that they may be useful treatments for substance use disorder across drug classes and provide the foundation for experiments that will use these novel drugs in mixtures.

Poster 41

Dietary and substance use habits of college students during the COVID-19 pandemic

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The COVID-19 pandemic has been a time of unprecedented stress, but it is not known if this stressor might have led to changes in psychological wellbeing, dietary intake, and substance use among college students. Previous studies demonstrate that eating a diet high in fat or sugar can increase the sensitivity of rats to the effects of drugs of abuse, suggesting that the relationship between diet and substance use might be complex, and could provide insight into factors that contribute to vulnerability for substance use disorder. To test the hypothesis that the stress of the COVID-19 pandemic is associated with an increase in caloric intake (specifically fat and carbohydrates), 23 students from The University of Texas at El Paso were surveyed to assess psychological wellbeing, dietary intake, and substance use. It was hypothesized that students who used substances would consume a greater amount of carbohydrates and fat than students who did not use substances. Group differences in caloric intake were analyzed using the Mann-Whitney U Ranking Comparisons test and regression analyses. Participants who used substances during the pandemic ate fewer grams of protein on average as compared to participants who did not use substances (which corresponded to a slight, though non-significant increase in carbohydrate intake). Further, participants who reported being more worried about COVID-19 ate fewer calories on average, regardless of substance use. Although these findings deviate from expected outcomes, they add to a growing literature exploring the impact of increased stress from a global event on food intake and substance use. These results also converge with previous research findings that alcohol use affects macronutrient intake, which is significant in the context of public health and addiction research.

Poster 42

The emergence of insulin resistance following a chronic high-fat diet regimen coincides with an increase in the reinforcing effects of nicotine in a sex-dependent manner

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The present study assessed the sex-dependent effects of insulin resistance on the reinforcing effects of nicotine. Female and male rats received a chronic high-fat diet (HFD) or regular diet (RD) for 8 weeks. A subset of rats then received vehicle or a dose of streptozotocin (STZ; 25 mg/kg) that induces insulin resistance. To assess insulin resistance, glucose levels were measured 15, 30, 60, 120, and 180 min after an insulin injection (0.75 U/kg). Nine days later, the rats were given extended access to intravenous self-administration (IVSA) of nicotine (0.015, 0.03, 0.06 mg/kg) in an operant box where they consumed their respective diet ad libitum and performed responses for water deliveries. Each nicotine dose was delivered for 4 days with 3 intermittent days of abstinence in their home cage. The day after the last IVSA session, physical signs were compared following administration of mecamylamine (3.0 mg/kg) to precipitate nicotine withdrawal. The results revealed that there were no changes in insulin resistance or nicotine intake in HFD alone rats regardless of sex. Insulin resistance was observed in HFD-fed rats that received STZ, and the magnitude of this effect was greater in males versus females. Our major finding was that nicotine intake was greater among HFD + STZ female rats as compared to males. Lastly, the physical signs of withdrawal were similar across all groups. Our results suggest that females diagnosed with disorders that disrupt insulin signaling, such as diabetes may be at risk of greater vulnerability to nicotine use due to enhanced reinforcing effects of this drug.

Poster 43

Involvement of endogenous ghrelin system in the maintenance and reinstatement of cocaine motivated behaviors: a role of adrenergic action at peripheral β1 receptors

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Cocaine addiction is a significant medical and public concern. Despite decades of research effort, development of pharmacotherapy for cocaine use disorder remains largely unsuccessful. This may be partially due to insufficient understanding of the complex biological mechanisms involved in the pathophysiology of this disorder. In the present study, we show that: (1) elevation of ghrelin by cocaine plays a critical role in maintenance of cocaine self-administration and cocaine-seeking motivated by cocaine conditioned stimuli; (2) acquisition of cocaine-taking behavior is associated with the acquisition of stimulatory effects of cocaine by cocaine-conditioned stimuli on ghrelin secretion, and with an upregulation of ghrelin receptor mRNA levels in the ventral tegmental area (VTA); (3) Blockade of ghrelin signaling by pretreatment with JMV2959, a selective ghrelin receptor antagonist, dose dependently inhibits reinstatement of cocaine-seeking triggered by either cocaine or yohimbine in behaviorally extinguished animals with a history of cocaine self-administration; (4) JMV2959 pretreatment also inhibits brain stimulation reward (BSR) and cocaine-potentiated BSR maintained by optogenetic stimulation of VTA dopamine neurons in DAT-Cre mice; (5) Blockade of peripheral adrenergic β1 receptors by atenolol potently attenuates the elevation in circulating ghrelin induced by cocaine, inhibits cocaine self-administration and cocaine reinstatement triggered by cocaine. These findings demonstrate that the endogenous ghrelin system plays an important role in cocaine-related addictive behaviors and suggest that manipulating and targeting this system may be viable for mitigating cocaine use disorder.

Poster 44

Effects of prenatal opioid exposure and early life adversity on opioid-induced antinociception

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Diagnoses of maternal opioid use disorder at delivery increased more than 500% between 1999 and 2017 in the United States. Altered sensitivity to opioid analgesia later in life is one potential outcome shared by prenatal opioid exposure (POE) and early life adversity (ELA) that may contribute to poorly controlled pain and increased risk of opioid addiction. The contributions of POE and ELA, alone and in combination, to opioid analgesic response in humans remains unknown. In this study, we used a rat model of combined POE and ELA to disambiguate their long-term effects more quickly and with greater experimental control than human studies. We hypothesized that combined POE and ELA will decrease morphine-induced antinociception in adolescence relative to POE or ELA alone. Cumulative dose-response of morphine-induced antinociception was determined on test day 0 (1.0-30 mg/kg morphine, s.c.). On test days 1-12, rats were dosed with 18 mg/kg, s.c., every 12 hours, and WWTW was conducted on odd test days. Preliminary results of this ongoing study indicate that morphine-induced antinociception was *enhanced* on test day 0 in POE males (n = 2). These rats exhibited 100% maximum possible effect (MPE) and significantly higher potency (mean ED50=5.96 mg/kg; 95% CI = -12.12, 24.05), while mean MPE for ELA, POE+ELA, and control males (n=2-3) was less than 70% and mean ED50>17 mg/kg for each group. All males exhibited partial tolerance throughout the 12-day chronic morphine treatment period. In the POE males, MPE decreased from 100% on test day 1 to 58% on test day 11. For the remaining male groups, MPE decreased from 44-57% on test day 1 to 12-23% on test day 11. There were no apparent group differences in the females. These results suggest a complex sex-dependent interaction between POE and ELA on opioid antinociception.

Poster 45

The effects of delta-9 tetrahydrocannabinol (THC) on responding for non-drug reinforcers in rats

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Although cannabis is widely consumed by humans for the intoxicating effects that are mediated by THC, pre-clinical models of THC self-administration have been difficult to establish. We hypothesized that THC may have reinforcement enhancing effects comparable to other drugs (e.g., nicotine and caffeine) which are also widely consumed by humans but difficult to establish as primary reinforcers in non-human animals. To investigate whether THC is a reinforcement enhancer, male (M, n=8) and female (F, n=8) rats were shaped to self-administer a reinforcing saccharin solution (0.2% w/v) in standard operant chambers equipped with infrared beams to monitor locomotor activity. At baseline, we found a significant sex difference for active lever responses and reinforcers earned (F<M, $p<0.05$) but not activity. In subsequent tests rats were pretreated with intraperitoneal injections of THC (0, 0.75, 1.5, and 3 mg/kg). Each dose was tested for a minimum of 6 days. Pretreatment with 1.5 and 3 mg/kg THC significantly reduced active responses, reinforcers earned, and activity in both M and F rats ($p<0.05$). There were no sex differences after THC treatment, M and F rats were equally suppressed. The 0.75 mg/kg dose initially suppressed active responses, reinforcers earned, and activity ($p<0.05$), however these effects dissipated across repeated tests (Drug x Session interaction, $p<0.05$). Additional tests with a visual stimulus (VS) reinforcer are currently being conducted. These findings suggest that rats are very sensitive to the motor suppressant effects of THC in the context of ongoing operant behavior. Additional doses and reinforcers need to be tested to disconfirm the hypothesis that THC has a reinforcement enhancing effect.

Poster 46

Behavioral economic demand analysis of drug self-administration

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The relative value of drugs of abuse is known to be influenced by a variety of factors, including genetics, behavioral and pharmacologic histories, the availability of alternative reinforcers, and the sex of the subject. Within-session demand curve analyses provide an efficient and highly translational approach for determining how environmental, behavioral, or pharmacologic manipulations impact the relative value (i.e., economic demand) of drug reinforcers. The current study used a preclinical multiple component schedule of drug self-administration to rapidly assess economic demand for cocaine (0.032-1.0 mg/kg/inf), 3,4-methylenedioxypyrovalerone (MDPV) (0.0032-0.1 mg/kg/inf), and alpha-Pyrrolidinovalerophenone (α-PVP). Available unit-doses of drug increased across each of 4, 20-min components, with the response requirement increasing from a fixed ratio (FR) 1 to FR3, FR10, FR18, and FR32 occurring across sessions. Demand for cocaine, MDPV, and α-PVP from the current study replicated previous elasticity coefficients, curves, and rank orders from studies which employed previously validated drug demand procedures. This alternative demand procedure allows for more rapid testing of a range of doses across different prices while still preserving the integrity of behavioral economic demand theory and results from demand-curve analyses. Validation of this multiple component schedule of self-administration allows for efficient within-subject testing to characterize the reinforcing effectiveness of drugs and investigate pharmacotherapeutic agents more readily.

Poster 47

In vivo pharmacology of different DREADD ligands on locomotor activity in rats

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Aim: Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) are engineered receptors that can be encoded in viral vectors, expressed in specific cell targets, and activated by selective agonists such as clozapine *N*-oxide (CNO). Despite the increasingly pervasive use of chemogenetic tools in preclinical neuroscience research, there remain gaps in our fundamental knowledge regarding in vivo pharmacology of different DREADD agonists. The goal of the current study was to characterize the potency and time course of CNO, Compound 21 (C21), and deschloroclozapine (DCZ) in transgenic Tyrosine Hydroxylase (TH):Cre rats before and after intra-VTA hM3Dq excitatory DREADD injection.
Methods: Ten adult TH:Cre Sprague-Dawley rats (5 female, 5 male) served as subjects. Locomotor activity was monitored for two hours following d-amphetamine (vehicle, 0.1-3.2 mg/kg, IP; positive control), DCZ (vehicle, 0.32-320 µg/kg, IP), CNO (vehicle, 0.32-10 mg/kg, IP), and C21 (vehicle, 0.1-3.2 mg/kg, IP) administration. Behavioral sessions were conducted twice a week prior to and starting three weeks after bilateral intra-VTA hM3Dq DREADD virus injection. Brain tissue was collected after experiment completion for immunohistochemical verification of DREADD expression in TH-positive cells.
Results: d-amphetamine (0.32-3.2 mg/kg, IP) significantly increased locomotor activity both before and after stimulatory DREADD virus injection. DCZ, CNO, and C21 did not significantly alter locomotor activity pre-DREADD virus injection. DCZ significantly increased activity following DREADD virus injection. CNO and C21 activity studies are ongoing.
Conclusions: Results support the utility of locomotor activity for determining the in vivo potency and time course of different DREADD ligands. Preliminary results suggest that DCZ was less effective than d-amphetamine.

Poster 48

Long-term effects of fluoxetine exposure on autophagy and tau phosphorylation in the prefrontal cortex and hippocampus of male mice

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The selective serotonin reuptake inhibitor (SSRI) fluoxetine (FLX) represents the current drug of choice for the management of pediatric mood-related illnesses. Of concern, accumulating preclinical evidence suggests that ontogenic SSRI exposure leads to depression-related phenotypes in adulthood. Depressive symptomatology constitutes a risk factor for other neurological disorders, such as Alzheimer's disease (AD), and thus it is possible that juvenile FLX history may exacerbate the development of neurodegenerative diseases. AD is characterized by the pathological accumulation of hyperphosphorylated Tau – which can be the result of impaired function of protein degradation pathways, such as autophagy and ubiquitin-proteasome system (UPS). However, the possibility that adolescent FLX negatively impacts these pathways to cause abnormal protein accumulation in adulthood, has not been previously explored. Thus, we subjected C57BL/6 adolescent male mice to FLX (20 mg/kg) during adolescence (PD35-49). After a 21-day resting period without FLX, animals were euthanized as adults (PD70) and, using immunoblotting analysis, we evaluated levels of protein markers of the autophagy and the UPS, as well as AD-associated forms of phosphorylated Tau, in the hippocampus and prefrontal cortex. We show, for the first time, that juvenile FLX alters the expression of autophagy protein markers (LC3-II and p62), particularly in the prefrontal cortex. Furthermore, we demonstrate that adolescent FLX exposure can induce accumulation of AD-associated variants of Tau, in both the hippocampus and prefrontal cortex. Our results indicate that adolescent history of FLX may have enduring effects in neuronal protein degradation, adversely influence clearance of abnormal proteins, potentially predisposing individuals to development of neurodegenerative conditions later in life.

Poster 49

The role of dopamine in the conditioned reinforcing effects of cocaine

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One major contributor to relapse is the ability of environmental cues that have been associated with drug-taking behavior to evoke drug-craving and -seeking behaviors. Dopamine is thought to play an important role in the primary and conditioned reinforcing properties of drugs; however, it has not been evaluated under stringent conditions of conditioned reinforcement. Therefore, the current study evaluated dopamine levels in the nucleus accumbens (NAc) during the New Response Acquisition procedure. This procedure begins with Pavlovian Conditioning in which subjects receive five infusions of cocaine (320 ug/kg/inf) and either simultaneous (Paired) or separate (Unpaired) presentations of a light+tone stimulus per day for 10 days. Then, novel operant manipulanda are introduced into the chamber, and responses produce presentations of cues formerly associated with cocaine (Acquisition). Dopamine levels in the NAc shell and core during the third day of Acquisition were collected via microdialysis in 10-minute bins throughout the Acquisition session and analyzed by high performance liquid chromatography coupled with mass spectrometry. Consistent with our previous findings, subjects in the Paired Pavlovian Conditioning group make more active responses than inactive responses for cue presentations than Unpaired subjects. Our results show that there are no significant group differences in the levels of dopamine between Paired and Unpaired subjects in the NAc shell nor core. We manipulated dopamine levels by local infusion of cocaine (7 or 46 ug), which failed to alter responding in either Paired and Unpaired groups. These data suggest that increasing dopamine levels does not drive responding for cocaine paired cues. Future studies will probe other neurotransmitter systems and circuits in mediating the conditioned reinforcing properties of cocaine paired cues and could identify potential targets for treating relapse.

Poster 50

Quantification of polyunsaturated fatty acid content of inflamed and non-inflamed dental pulp tissue following surgery using targeted mass spectrometry

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There is a need to explore non-opioid based interventions to minimize risk of opioid dependence following surgery. Previous research has shown a relationship between certain polyunsaturated fatty acids and intensified nociceptive-like responses in chronic pain conditions, but this remains unprobed in a post-surgical model. Omega-3 and omega-6 polyunsaturated fatty acids are major constituents of cellular membranes as well as precursors for many metabolic pathways in humans. Despite sharing metabolic pathways, omega-3 and omega-6 fatty acid metabolites exhibit opposing biological activity (anti-inflammatory vs pro-inflammatory, respectively) which necessitates balance, especially considering the precursors are only acquired through diet. Disproportionately elevated levels of omega-6 fatty acids therefore represent a reliable predictor for inflammation and post-surgical pain. The focus of this study is surgically extracted dental pulp samples from humans. Included are 24 non-inflamed dental pulp samples and 30 inflamed dental pulp samples. Dental pulp is removed from the extracted tooth and pre- and post-surgical pain levels are noted. The lipids are extracted through a modified Bligh and Dyer method, and then they undergo base-catalyzed saponification. The resulting free fatty acids are quantified using targeted lipidomics via UPLC-LC/MS/MS in negative ionization mode. The results are analyzed for statistical relevance. The results indicate there is a clear correlation between patients who report higher pain scores and the unequal distribution of omega-6 and omega-3 fatty acids. This work can lead to identification of new oxylipin metabolite-based drug targets resulting from elevated omega-6 levels that avoid the use of opioids.

Poster 51

Effects of chronic cocaine and binge-like ethanol self-administration on dopamine D2-like and D3 receptor function in in rhesus monkeys

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Most individuals with cocaine use disorder also co-abuse alcohol; however, little is known about the behavioral and pharmacological mechanisms that promote the co-abuse. For example, although studies in humans and laboratory animals have documented that chronic use of alcohol or cocaine can decrease dopamine D2-like receptor (D2R) availability and increase dopamine D3 receptor (D3R) function, effects of co-abuse of these substances have not been studied. The present study examined long-term cocaine self-administration in rhesus monkeys with or without concurrent daily ethanol consumption. Twelve adult male monkeys self-administered cocaine (0.1 mg/k per injection) on a fixed ratio 30 schedule five days per week. Six of them consumed 2.0 g/kg ethanol over one hour, five days per week, to model binge drinking and six drank a non-alcoholic solution. To measure D2R availability, positron emission tomography (PET) scans were performed using [11C]raclopride when monkeys were drug-naive and again after monkeys had self-administered approximately 400 mg/kg cocaine. To measure the function of D3R, the ability of the D3R agonist quinpirole to elicit yawns was measured at the same time points. As expected, chronic cocaine self-administration decreased D2R availability, particularly in the putamen. However, this effect was not observed in monkeys who consumed ethanol. In contrast, the potency of quinpirole was increased in ethanol-drinking monkeys, whereas no systematic change was observed in the control group. Results suggest that chronic alcohol use can modulate the effects of cocaine on brain dopamine function and that effects on D3R are likely to be involved in promoting co-abuse.

Poster 52

THC exposure during adolescence produces subtle but enduring effects on touchscreen assays of motivation and learning in nonhuman primates

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The extent to which cannabis use during adolescence affects behavioral processes in adulthood is a source of great speculation but is currently not well understood. This is problematic given rising rates of marijuana consumption in youth, along with increases in potency of its primary psychoactive constituent, Δ9-tetrahydrocannabinol (THC). To address this knowledge gap, longitudinal studies were conducted to examine behavioral effects of THC exposure during adolescence in male and female squirrel monkeys. Motivation was first assessed in an economic demand task in which subjects completed increasing response requirements for a palatable food reward varying in magnitude. Orderly demand curves described consumption decreases as a function of both increases in response requirements and decreases in reward magnitude. However, adolescent THC exposure produced dosage-related impairments in motivation generally and sensitivity to reinforcer magnitude specifically. In the repeated acquisition task, subjects learned the reinforcement contingency associated with a stimulus given simultaneous presentation of two novel pictures onscreen. Following accurate responding, another novel stimulus set is presented until mastery was again achieved in this learning-to-learn paradigm. Dosage-related deficits were observed on rate of acquisition across successive discriminations, compared to drug-free control subjects. Finally, the inhibition of previously learned responses after contingency reversals of a mastered stimulus discrimination was assessed. This task also revealed dosage-related impairments related to THC history. Taken together, subtle but persistent deleterious effects of adolescent THC exposure were found in these paradigms and provide much-needed translational information.

Poster 53

Economic demand for fentanyl, methamphetamine, and cocaine in morphine dependent and withdrawn rats

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The co-injection of cocaine and heroin (i.e., speedballs) has been common for decades, however, recent estimates suggest the popularity of stimulant-opioid mixtures is increasing, with over 50% of treatment-seeking opioid users reporting regular stimulant use. The goal of the current study was to determine how opioid dependence and withdrawal affect economic demand for fentanyl, cocaine, and methamphetamine. Male Sprague Dawley rats (n=21) were trained to self-administer fentanyl (3.2 mg/kg/infusion) under a fixed ratio schedule of reinforcement. Opioid dependence was established by administering escalating doses of morphine (10-40 mg/kg) twice-daily for four days, and subsequently maintained by once-daily injections of 40 mg/kg morphine. To evaluate the impact of opioid dependence and withdrawal on economic demand for drugs, rats were allowed to self-administer fentanyl (10 mg/kg/inf), cocaine (1 mg/kg/inf), and methamphetamine (0.32 mg/kg/inf), with sessions occurring either 12- or 20-hrs after morphine injections, respectively. Response requirements incremented across sessions until no infusions were earned. Demand for fentanyl was greater (significantly smaller □ value) in rats deprived of morphine for 20-hrs relative to rats deprived of morphine for 12-hrs and rats that are non-dependent. Economic demand for cocaine or methamphetamine were unchanged by states of opioid dependence or withdrawal. The current studies provide direct evidence that economic demand for fentanyl was increased in opioid-withdrawn rats relative to opioid dependent (but not undergoing opioid withdrawal) and non-dependent rats. These findings suggest that motivations to use opioids can be influenced by the state of the individual whereas motivations to use stimulants are largely unchanged regardless of whether individuals are in a state of opioid dependence or withdrawal.

Poster 54

Treatment of addiction with a novel class of DAT inhibitor

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Dopamine Active Transporters (DAT) is an important recognition site for cocaine and mediates its acute behavioral and reinforcing effects that contribute to abuse liability. *In vitro* studies have shown that cocaine blocks the uptake of the monoamines like dopamine, serotonin, and norepinephrine, with behavioral effects being attributed mostly to inhibition of dopamine uptake. Thus, compounds that target DAT are viewed as a potential pharmacological treatment of cocaine abuse, addiction, and dependence. Several preclinical studies demonstrate that DAT inhibitors can effectively attenuate cocaine self-administration, whereas drug effectiveness is correlated with DAT occupancy. In addition, recent reports showed selected DAT inhibitors, like modafinil, to reduce the rewarding effects of selected drugs and decrease abuse and addiction liability.
Recently, our lab has reported a novel class of achiral urea analogs capable of inhibiting DAT with a high degree of selectivity and potency. Favorable pharmacokinetic profile, the ability to cross the BBB *in vivo,* and metabolic stability prompt us to evaluate the lead compound in the experimental autoimmune encephalomyelitis (EAE) mouse model. We have observed that this compound has lowered neuroinflammation, a pathological marker associated with chronic drug abuse. Here we present the project's status, providing more information on our

Poster 55

Predicting choice from response latencies: A potential treatment target for behavioral allocation disorders

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Understanding how choices are made is necessary to prevent harmful choices and encourage healthy choices. Rational Choice Theory is the dominant model of choice behavior; however, the Sequential Choice Model (SCM) may better predict choice behavior through a framework of adaptive choice. In this experiment, the SCM is used to predict choice between two simultaneously available options based on the response latency for each option presented independently. Food-reinforced behavior in 16 female Lewis rats was observed under three high-cost conditions (FR10, FR20, FR40) with the low-cost condition always being FR5. Two levers with varying high or low cost were presented either simultaneously or independently. The latency to the first response on each lever in each trial, as well as the number of fixed-ratios completed on each lever were recorded. The relationship between latency to choose the right versus left lever during simultaneous or independent lever presentations was determined for each contingency condition by linear regression. Subjects were then administered separate pretreatments of amphetamine and pentobarbital to assess the pharmacological effects on this relationship. The probability of shorter response latency for independently presented options significantly predicts the pattern of responding when both options are simultaneously available. The relationship was strongest when the high-cost condition was FR10 or FR20; and was not greatly affected by amphetamine or pentobarbital pretreatments. The latency to respond for reinforcement in isolation may predict choice when two options are simultaneously available, *i.e.,* choice was predicted by the SCM. One implication of this is increasing the latency to respond for a problematic outcome or decreasing the latency to respond for more healthful outcome may make healthy choices more frequent.

Poster 56

Development of a nonhuman primate model of punishment of alcohol drinking

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Continued alcohol drinking despite negative consequences is a defining characteristic of alcohol use disorder (AUD). In rodents, persistent drinking in the presence of the bitter tastant quinine may represent an AUD-vulnerable phenotype. In this study, we extended rodent studies by developing a nonhuman primate model of quinine-induced punishment of ethanol drinking. Five female rhesus monkeys with more than 5 years experience drinking ethanol were studied using a two-bottle choice paradigm. Monkeys were given access to two visually distinct bottles, one containing a 4% ethanol solution and the other containing water, for 3 hours per day. Percent choice was measured as ml of ethanol consumed over the total amount of liquid consumed. Ethanol intake (g/kg) was also calculated. Once choice was stable (±10% of the 3-day mean), one concentration of quinine (0.01-5.6 g/L) was added to the ethanol solution for one day. In a second study designed to validate the choice procedure, quinine (0.1, 1.0 g/L) or sucrose (1%, 2.5%) was added to the water of "low" or "high" ethanol choosing monkeys, respectively. Finally, monkeys were given different ethanol concentrations (0%-8%) as the alternative to water to determine how choice and intake depend on the available ethanol concentration. Adding quinine to the ethanol solution resulted in a quinine concentration-dependent decrease in ethanol choice and intake. Adding quinine or sucrose to the water alternative resulted in predictable changes in ethanol choice (increases and decreases, respectively). Finally, ethanol choice and intake were changed across available ethanol concentrations. The concentration that resulted in the highest choice was not always the concentration at which the highest intake was observed. These results establish a novel, translational nonhuman primate model of punishment of ethanol drinking that will be used to investigate the effects of anxiolytics on ethanol drinking and quinine-induced punishment thereof.

Poster 57

Adolescent fluoxetine exposure induces persistent gene expression changes in the hippocampus of adult male C57BL/6 mice

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Fluoxetine (FLX), a selective serotonin reuptake inhibitor, is the first line of pharmacological intervention in pediatric patients suffering from affect-related illnesses, such as anxiety and depression. Although the use of this antidepressant treatment has been deemed efficacious in the juvenile population, the enduring neurobiological consequences of adolescent FLX exposure are not well understood. Thus, we explored for persistent molecular adaptations in the adult hippocampus, as a function of adolescent FLX pretreatment. To do this, we administered daily peritoneal injections of FLX (20 mg/kg/day) to male C57BL/6 mice during adolescence (postnatal day [PD] 35-49). After a 21-day washout period (PD70), whole hippocampal tissue was dissected, and subsequent qPCR analysis was ran to assess changes in the expression of genes associated with neuronal survival. Specifically, we evaluated major intracellular signal transduction pathways, including the Ras-mitogen-activated protein kinase (MAPK), phosphatidylinositide-3-kinase (PI3K)/AKT pathway, as well as several transcription factors. Our results indicate that adolescent FLX treatment results in a long-term upregulation of mRNA levels across numerous genes from the ERK, and PI3K/AKT pathways, along with increases of the transcription factors CREB, ΔFosB, and zif268. Additionally, adolescent FLX treatment resulted in persistent increases of transcripts associated with cytoskeletal integrity (-actin) and caspase activation (DIABLO), while decreasing genes associated with metabolism (fucose kinase) and overall neuronal activation (c-Fos). Collectively, these data indicate that adolescent FLX exposure mediates persistent alterations in hippocampal gene expression in adulthood, thus, questioning the safety of early-life exposure to this antidepressant medication.

Poster 58

Binge-like alcohol exposure during adolescence increases relapse-like alcohol consumption in a sex-specific manner in male and female C57BL/6J mice

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Adolescence is a critical time regarding brain development. Chronic alcohol consumption during adolescence can contribute to alcoholism, anxiety, and stress. The study aimed to establish a relationship between sex differences and effects of adolescence binge-like alcohol exposure on relapse-like alcohol consumption. Male and female C57BL/6J mice were initially tested for anxiety-like behavior using the light/dark test on postnatal day (PND) 24, early adolescence. Mice were then exposed to intermittent ethanol vapor or air (as a control) exposure between PND 28-44. Mice were then repeatedly tested for escalations in relapse-like alcohol consumption during emerging adulthood using a limited access (2 hr/day) two-bottle choice (2BC) drinking paradigm. Mice were tested for 2BC for 5 consecutive days, followed by 2 days without access to ethanol. Mice were then re-exposed to the inhalation chambers. These procedures were repeated two more times. Preliminary results show female mice had a higher anxiety-like phenotype on PND 24. Adolescent ethanol-exposed male and female mice showed increased ethanol consumption from PND 45-49. In males, this difference was maintained across testing periods, PND 57-61 and PND 69-73; however, escalations in ethanol consumption were not observed in the male mice. In female mice, this difference was no longer present after the first testing period, but the air-exposed female mice did show escalations in 2BC ethanol drinking. These data highlight that 1) male mice exposed to ethanol during adolescence show sustained increases in ethanol consumption compared to controls; and 2) air-exposed female mice showed escalated ethanol drinking; an effect not observed in ethanol-exposed female mice. We will explore the relationship between anxiety-like phenotypes as a predictor for developmental trajectories in ethanol consumption.

Poster 59

Assessing the synergistic effects of morphine and MP-III-024 co-administration: Enhanced antinociception with reduced side effects

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Opioid analgesics are critical for acute and chronic pain management, but important side effects—including tolerance, constipation, respiratory depression, and abuse liability—limit their safety and utility. To provide patients with safer analgesic options, it is critically important to identify of new pharmacotherapeutic strategies to treat pain. Activation of μ-opioid receptors (MORs) in central and peripheral nociceptive pathways mediates opioid analgesia and their critical side effects. Antinociception can also be achieved via selective enhancement of GABAergic signaling at ionotropic $GABA_A$ receptors. α2/α3 $GABA_A$ receptors can be selectively targeted with the novel imidazodiazepine positive allosteric modulator (PAM) MP-III-024, which produces antinociceptive effects with limited behavioral disruption. We recently reported that MP-III-024/morphine co-administration produces synergistic antinociceptive effects. Herein, we evaluated whether MP-III-024/morphine co-administration produces sub-additive or synergistic effects in behavioral tests sensitive to morphine side effects. Co-administration of MP-III-024/morphine at a 0.94/1 ratio (synergistic in models of antinociception) produced sub-additive effects in morphine-induced hyperlocomotion and in measures of behavioral disruption in food-maintained operant responding. Ongoing studies are evaluating the effects of MP-III-024/morphine co-administration on tolerance in the hot plate test and in conditioned place preference.

Poster 60

Activation of the preoptic area correlates with psychostimulant effects of cocaine

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Males and females respond differently to drugs of abuse. Prevailing evidence indicates that gonadal hormones play a role in this sex difference. The medial preoptic area (mPOA), located in the anterior hypothalamus, is a key integrator of hormonal signaling, it holds one of the highest concentrations of gonadal hormone receptors, and is anatomically connected to the mesolimbic reward system. While evidence supports a modulatory role for the mPOA in cocaine-induced neural and behavioral activity, whether cocaine induces cellular activity in this region is still unknown. To answer this question, we examined cocaine-induced neural activation, using Fos-immunoreactivity (Fos-ir) as a marker of cellular activation, in the mPOA of cocaine-naïve males (n=10) and naturally cycling female rats (n=19) that received an i.p. injection of cocaine hydrochloride (10mg/kg) or vehicle control. Additionally, cocaine-induced changes in locomotion were measured. Both male and female rats displayed significantly greater cocaine-induced locomotion. Differences in locomotion emerged when females were divided by estrous cycle stage. Females that received cocaine during proestrus or estrus, when estradiol is highest, displayed significantly greater cocaine-induced locomotion compared to females in diestrus and metestrus, when estradiol is lower. Interestingly, Fos-ir in the mPOA was not significantly higher in either males or females receiving cocaine, but Fos-ir was higher in females that were in proestrus/estrus when compared to males, regardless of drug group. Furthermore, Fos-ir in the rostrocentral portion of the mPOA positively correlated with locomotion in both male and females that received cocaine, suggesting a role for the mPOA in modulating cocaine response. Implications of these findings for sex differences in cocaine response are discussed.

Poster 61

Spironolactone affects heroin-induced antinociception in male and female mice differently

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Current pharmacological treatments for opioid use disorder (OUD) directly target the opioid system to reduce withdrawal and cravings. Increasing evidence supports targeting systems that become dysregulated during chronic opioid administration such as the hypothalamic-pituitary-adrenal (HPA) axis may prove efficacious in treating opioid-related behaviors. The HPA axis dysregulation can cause an increase in mineralocorticoid and glucocorticoid release and receptor signaling during drug abstinence. Mineralocorticoid receptors (MRs) are found within the central amygdala and hippocampus, brain regions associated with reward and reinforcement. The present study used models of thermal nociception in male and female C57BL/6J mice. The hot-plate test was used to measure opioid-induced antinociception (a sign of opioid intoxication) and the cold-plate test was used to measure opioid withdrawal-induced hyperalgesia (a sign of opioid withdrawal). We determined the effects of the MR antagonist spironolactone (0, 25, and 50 mg/kg, intraperitoneal) on these opioid-related behaviors. We hypothesized that spironolactone would attenuate both the antinociceptive effects of heroin and the withdrawal effects of opioid exposure. Contrary to our hypothesis, spironolactone increased heroin-induced antinociception in male but not female mice and did not affect the magnitude of heroin withdrawal-induced hyperalgesia in either male or female mice. These results suggest that MR antagonism, at the doses we used, does not contribute to the withdrawal effects of heroin, but additional studies are necessary to confirm these findings.

Poster 62

Oxytocin attenuates reinstatement of alcohol-seeking in male and female rats via the central amygdala

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Alcohol Use Disorder (AUD) can lead to serious health issues and affects about 5.6% American adults with many recovering alcoholics attributing stress as a primary cause of relapse. Biological sex is an important variable in addiction and should be considered when examining the effects of stress-induced relapse behavior and when investigating potential therapeutic options. Oxytocin has been shown to produce anxiolytic effects and studies have found that it attenuates stress-induced reinstatement of drug-seeking behaviors. The central amygdala (CeA) expresses oxytocin receptors and mediates oxytocin's anxiolytic effect. We hypothesized that systemic and intra-CeA administration of oxytocin would attenuate yohimbine-induced ethanol-seeking behavior in an ethanol reinstatement paradigm in both male and female rats. We trained female (n = 21) and male (n = 21) Sprague-Dawley rats in an ethanol self-administration and reinstatement paradigm. Animals were trained to self-administer ethanol followed by an extinction period. Ethanol-seeking behavior was then reinstated through yohimbine administration. Rats received systemic (1 mg/kg; i.p.) or intra-CeA (0.5 µg) oxytocin prior to yohimbine administration. A one-way ANOVA was used to analyze differences in lever pressing behavior between groups during reinstatement. We found that yohimbine administration reinstated ethanol-seeking behavior in both female and male rats. Systemic administration of oxytocin successfully attenuated yohimbine-induced ethanol-seeking behavior in both female and male rats. Direct infusions of oxytocin into the CeA similarly attenuated yohimbine-induced ethanol-seeking behavior, suggesting that the CeA is a major structure driving this effect. These findings suggest that commercially available neuropeptide oxytocin may act as a viable pharmacotherapeutic target to attenuate the effect of stress on alcohol-seeking behavior in both males and females.

Poster 63

Methionine synthase: A target for novel small molecules to inhibit cocaine and methamphetamine induced neuronal death

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Background: Oxidative-stress induced cell death is involved in the pathology of psychostimulant (cocaine and methamphetamine) addiction neuropathies. These conditions potentially cause neuronal and functional changes via multiple mechanisms - epigenetic alterations (DNA hypomethylation) and reactive-oxygen species (ROS) accumulation. Our laboratory has synthesized a novel antioxidant small molecule: SA-31, with predictive neuroprotective and broad-spectrum reactive oxygen species (ROS) scavenging abilities and increase methionine synthase (MS) enzyme, a key enzyme largely responsible for DNA methylation, neuronal growth and survival. **Methods:** Compound SA-31 was synthesized and characterized in our lab. Human neuroblastoma cells SH-SY5Y were cultured and subjected to either t-butyl hydrogen peroxide (TBHP, 65 µM), or cocaine hydrochloride (1.5mM) or Methamphetamine (METH, 3.5 mM) followed by co-treatment with SA-31 for 24 hours. Cell viability was assessed using MTT assay. Level of intracellular MS and SOD enzymes were assessed using ELISA. **Results:** Compound SA-31 was not cytotoxic at varying concentrations and rescued the cells from TBHP, cocaine and METH-induced cell death at100uM and 1000µM. MS and SOD activity levels were significantly reduced following TBHP and METH exposure; however, treatment of the cells with SA-31 increased the activity of the aforementioned enzymes. **Conclusion**: SA-31 is a neuroprotective compound, as it prevents TBHP and psychostimulant induced cell death in SH-SY5Y cells. Increasing MS and SOD enzyme activities is one of the mechanisms by which neuroprotection was attained. Future studies will address the potential of SA-31 to progress further in pre-clinical drug development, with a future application for the treatment of substance abuse disorder.

Poster 64

Behavioral assessment of the anxiolytic and antidepressant-like effects of chronic, intermittent low-dose Psilocybin in male Sprague-Dawley rats

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Anecdotal reports suggest that microdosing with psychedelics such as psilocybin, may reduce anxiety and promote positive mood and cognitive flexibility. Despite the increasing popularity of microdosing, few studies have systematically evaluated the effects of chronic, intermittent sub-perceptual doses of psilocybin that approximate dosing patterns similar to those reported by users who have microdosed. The current study evaluated the effects of chronic, intermittent low-dose (CILD) psilocybin treatment using three rodent models predictive of anxiolytic or antidepressant effects: the Light/Dark conflict test (L/D), an open field test (OFT), and the forced swim test (FST). Rats were treated with vehicle or psilocybin (0.025, 0.05, 0.1 mg/kg) every 72 hours over a 48-day period. Tests were conducted 48 hours after the eight injection (day 24) (L/D, OFT), 48 hours after the 16th injection (day 48) (L/D, OFT, FST), and 12 days after the last injection (day 58) (OFT, FST). Results from the current study failed to indicate significant between group differences in exploratory, locomotor, or swimming behavior of rats in the L/D, OFT, or FST paradigms. However, significant differences were observed between test days. Rats administered 0.1 mg/kg psilocybin entered the light compartment significantly sooner in the L/D test on day 48 than was observed on day 24. Additionally, rats administered 0.05 or 0.1 mg/kg spent significantly more time in the center of the open field apparatus on day 48 and/or 58 compared to time spent in center on day 24. Overall, the lack of anxiolytic and antidepressant-like effects of CILD psilocybin between groups in the current study suggest that there may be distinct differences between sub-threshold, "microdosing" of psychedelics and hallucinogenic high doses. Future research involving additional behavioral tests is warranted to elucidate the behavioral effects of CILD psilocybin, absent of the subjective human experience.

Poster 65

Pharmacokinetic evaluation of high affinity D_4R-selective ligands to treat substance use disorder

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The dopamine D_4 receptor (D_4R), a G protein-coupled receptor, is predominantly expressed in the prefrontal cortex in which it plays an important role in cognition, attention, and decision making. Studies have indicated D_4R-selective ligands as a promising medication development to treat neuropsychiatric conditions such as substance use disorders (SUD). D_4R ligands have been shown to alter cognition and behavior in animal models of drug addiction. A better understanding of D_4R-mediated signaling is essential to treating D4R-associated disorders, including SUD. Despite its clinical importance, there are currently no FDA approved medications that target the D_4R and for example cocaine abuse disorder treatment. The present study focuses on the design of D_4R ligands based on the parental phenylpiperazine scaffold and pharmacokinetic analysis in rat and human liver microsomes, followed by preliminary *in vivo* analysis. We identified several compounds with high binding affinity and D_4R selectivity (Ki ≤ 6.87 nM and >91-fold vs. other D_2-like receptors (D_2R, D_3R)) with diverse partial agonist and antagonist profiles. Based on the analysis profiles, a few were selected for *in vitro* metabolic stability in rats and human liver microsomes of which some displayed acceptable stability profile. Of these CAB-01-019 (with good stability profile) was selected for *in vivo* pharmacokinetics in rats where it displayed excellent brain penetration with AUCbrain/plasma>3. These ligands display high binding affinity and subtype selectivity for D_4R with high stability in rat and human liver microsome. Development of these compounds may provide insights to targeted drug discovery leading to a better understanding of the role of D_4Rs in neuropsychiatric disorders such as SUD.

Poster 66

The role of muscarinic and NMDA receptors of the substantia nigra in reward-related learning

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Reward-related learning has an essential adaptive function necessary for survival during which animals learn about rewards. This type of learning has been implicated in pathologies of motivational processes including drug addiction. A big part of reward-related learning is the acquisition of associations between rewards and stimuli (i.e., conditioned stimuli, CS) that predict or accompany those rewards. In this study, we investigated the mechanisms underlying conditioned approach learning with the focus on the role of muscarinic acetylcholine (mACh) and NMDA glutamate receptors in the substantia nigra (SN), the brain region implicated in reward. Rats were exposed to 3 (in Exp. 1) or 7 (in Exp 2) conditioning sessions during which 30, random light/tone (CS) presentations were paired with delivery of food pellets (US), followed by a test session with CS only presentations. Bilateral microinjections of scopolamine (a mACh receptor antagonist) or AP-5 (a NMDA antagonist) into the SN were made either prior to each conditioning session (Experiment 1; to test effects on acquisition) or prior to the CS-only test (Experiment 2; to test effects on performance of the learned response). Scopolamine and AP-5 produced dose-related significant reductions in the acquisition of conditioned approach but had no effect on its performance. These results suggest that mACh and NMDA receptors in the SN are key players in the acquisition of reward-related learning. Importantly, these findings redefine the role of the SN, which has traditionally been known for its involvement in motor processes and suggest that the SN possesses the attributes to function as a hub of integration of primary reward and conditioned stimulus signals.

Poster 67

Pharmacological evaluation of the Kratom Alkaloid Mitragynine at adrenergic α_2 receptors

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Adrenergic α_2 receptors ($A\alpha_2$Rs) are hypothesized to be an active site of action of mitragynine (MG), an abundant kratom alkaloid, in addition to actions at μ-opioid receptors (MORs). Here we assessed the functional specificity of MG activity at the $A\alpha_2$R. An *in vitro* study using a GTPγS binding assay demonstrated that MG is not an agonist at the human $A\alpha_{2A}$R. In rats discriminating 32 mg/kg MG (i.p.) from vehicle, no dose of the $A\alpha_2$R agonists (lofexidine and clonidine) and antagonists (yohimbine and atipamezole) fully substituted for MG. However, the antagonists shifted to the right and down the dose-effect function of MG discrimination. In rats discriminating 0.032 mg/kg lofexidine (i.p.) from vehicle, MG fully substituted for lofexidine. In rats self-administering the MOR agonist remifentanil, no dose of MG or lofexidine substituted for remifentanil. When administered as a pretreatment, MG and lofexidine dose-dependently shifted the dose-effect functions of remifentanil self-administration downward; yohimbine reversed the effects of lofexidine but not of MG. These results suggest that MG can function as an agonist at $A\alpha_2$R as one of multiple receptor targets *in vivo*.

Virtual Presentations

Virtual Presentation 1

The role of CRFR1 in rat heroin intravenous self-administration

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Maladaptive behaviors associated with heroin addiction are thought to result from a dysregulation of the interaction between reward and stress circuits. Interactions between extrahypothalamic corticotropin releasing factor (CRF) and the mesolimbic dopamine (DA) system play a critical role in relapse and drug-seeking. However, alterations at intersecting regions during heroin use and their contribution to the escalation of heroin use is not fully understood.
Here, we examined the effects of repeated heroin (N = 4) or saline (N = 4) intravenous self-administration (IVSA) on CRFR1 mRNA expression on DA neurons in the ventral tegmental area (VTA) of rats using RNAscope *in-situ* hybridization and confocal microscopy; mRNA transcripts were quantified using open-source software Cell Profiler. We also are currently examining the role of CRFR1 in the VTA during heroin IVSA using bilateral intracranial injections of antalarmin, a selective CRFR1 antagonist, in 8 rats trained to intravenously self-administer heroin for 18, 3-hour daily sessions under an FR1 schedule of reinforcement.
We found that rats exposed to heroin IVSA expressed significantly more CRFR1 mRNA transcripts on VTA dopamine neurons than their saline counterparts.
These results suggest that repeated heroin exposure may lead to mesolimbic dopamine aberrations via CRFR1 upregulation, further investigations are being done to determine the involvement of CRFR1 in the rewarding effects of heroin.

Virtual Presentation 2

Investigating the effects of PMAT deficiency on cocaine- and amphetamine-induced locomotor sensitization

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The plasma membrane monoamine transporter (PMAT) is a polyspecific cation transporter that, in the brain, predominantly takes up monoamines such as dopamine and serotonin. We hypothesize the functional contribution of PMAT emerges when impairment of higher affinity transporters, including dopamine or serotonin transporters, occurs - such as after psychostimulant exposure. No studies have evaluated the contribution of PMAT to behavioral responses to cumulative doses of psychostimulants. Mice of both sexes constitutively deficient in PMAT were utilized for the present experiments. We hypothesized that relative to wildtype controls, mice with reduced or ablated PMAT function would exhibit augmented cocaine and D-amphetamine sensitization, because compensatory monoamine uptake by PMAT would be impaired in these mice when higher affinity transporters are pharmacologically inhibited. Male and female mice went through a cocaine- or D-amphetamine-induced locomotor sensitization paradigm for 5 total days. Each day, after a baseline test (30 min) of locomotor activity in an open field arena, injections of saline (vehicle) then cocaine or D-amphetamine were administered. Subsequent locomotor responses to each injection were recorded in 10-minute intervals using ANY-maze software. The total (cumulative) doses used for cocaine were 5-40 mg/kg every day for 5 consecutive days. For D-amphetamine, cumulative doses of 0.1-9.98 mg/kg were administered every 3 days for a total of 5 days of injections. Our results indicate that PMAT is not inhibited by cocaine, but suggest PMAT may contribute to D-amphetamine-induced dopamine efflux and sex-specifically influence psychostimulant sensitization processes. Future examinations will determine how PMAT function is mediated by sex hormones.

Virtual Presentation 3

Synthesis and pharmacological evaluation of N-substituted 6,7-benzomorphans

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Ever since its discovery, morphine has been widely used for acute and chronic pain. However, its harmful side-effects and highly addictive nature have led scientists to look for other morphine-like compounds with similar potency but fewer of these side-effects. One such possible class of morphine-like compounds is the 6,7-benzomorphans which have antinociceptive activity similar to that of morphine. In this work, a series of (-)-*N*-phenethyl-6,7-benzomorphans have been synthesized with electron withdrawing or donating substituents on the aromatic ring of the *N*-phenethyl moiety. The compounds were examined for agonist activity in a cAMP assay and were found to be potent, fully efficacious *m* opioid receptor (MOR) agonists. The *para*-substituted *N*-phenethyl-6,7-benzomorphans were found to be highly potent with the *p*-bromo-substituted compound having EC_{50} value in the subnanomolar range (~7 times more potent than morphine), as measured in the forskolin-induced cAMP accumulation assay.

Virtual Presentation 4

Locomotor and discriminative stimulus effects of six synthetic cathinones

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Aims: Synthetic cathinones are derived from the natural occurring cathinone which is the main psychoactive component in the khat plant. They stimulate the release of dopamine while inhibiting the reuptake or epinephrine, norepinephrine, and serotonin. They are used recreationally due to their psychostimulant effects, low cost and their high potency. Six cathinones were tested in vivo to determine the motor stimulant and discriminative efficacy and potency in comparison with methamphetamine.
Methods: Locomotor activity was tested in 288 male Swiss-Webster mice to screen for locomotor stimulant or depressant effects and to identify behaviorally active dose ranges along with times of peak effect. Discriminative stimulus effects of six synthetic cathinones were tested in 32 male Sprague-Dawley rats trained to discriminate methamphetamine (1 mg/kg, 10-minute pretreatment) from saline.
Results: In the locomotor activity tests, BMDP produced a 30 minute stimulant phase. MMMP and 3-MMC stimulated locomotor activity for 2 hours; while 4F-3Me-α-PVP stimulated locomotor activity for 3 hours. 4-CDMC stimulated locomotor activity between 3 and 4 hours; while 3,4-MD-PV8 stimulated locomotor activity the longest for 4 hours. 3-MMC and 4-CDMC fully substituted for the discriminative stimulus of methamphetamine. BMDP and MMMP failed to fully substitute. methamphetamine. Each compound suppressed response rate for at least one dose.
Conclusions: The synthetic cathinone compounds had locomotor effects similar to methamphetamine; however they were less potent. Two of the compounds 4-CDMC and 3-MMC fully substituted for methamphetamine suggesting a similar subjective effect. These results suggest that these compounds could be used recreationally as substitutes for methamphetamine, whereas BMDP and MMMP may be of less interest on the illicit market
Support: Supported by DEA contracts 15DDHQ20F00000952 and 15DDHQ21F00000340.

Virtual Presentation 5

A rapid procedure to assess shifts in discriminative control over drinking during recovery-like behavior

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Previously, we developed an operant procedure using rats to assess shifts in discriminative control over alcohol us. A drinking phase (ETH, a stimulus signals that ethanol alone is available), is followed by varying numbers of recovery-like sessions (RCV, a distinct stimulus signals that both food and alcohol are available). In subsequent test sessions, rats were exposed to the ETH stimulus under extinction, and responses were recorded. Food responses during test sessions increased as a function of the number of RCV sessions completed. However, this procedure required repeated training and testing per time point. Thus, we developed a more efficient procedure, allowing for continuous assessment of stimulus control over drinking across varying recovery time points. We extended the model by evaluating the impact of an extended period of drinking (ETH) and sex effects. Male and female rats (n=55) responded under ETH conditions for either 10 or 20 consecutive sessions, then moved into the recovery-like phase where they responded under RCV conditions for 16 consecutive sessions. Prior to RCV sessions 0, 1, 2, 4, 8, and 16, rats were exposed to the ETH stimulus under extinction conditions and responses on food and ethanol levers were recorded. The total number of food responses during test sessions prior 5 responses for ethanol was the primary measure. Each measure was analyzed using repeated measures ANOVA with day of recovery and drinking status as factors. Consistent with the earlier procedure, the number of food responses during ETH tests increased as a function of the number of RCV sessions completed. There was a significant effect of recovery day $F[5, 198]=3.2$, $p<0.01$. Consistent with the earlier procedure and clinical evidence, stimulus control over drinking decreases following longer periods of recovery. Under conditions tested, longer drinking history did not affect this relationship and sex differences were not apparent.

Virtual Presentation 6

Abuse liability and behavior pharmacology profiles of six cannabinoid compounds

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Background: Despite the efforts of the Drug Enforcement Agency (DEA) to safeguard the public from these hazardous compounds, analogs of synthetic cannabinoids have increasingly been observed in the illicit drug market (EMCDDA 2017). Unfortunately, the pharmacological activity of these drugs is either unknown or understudied. Therefore, in a collaborative effort with the DEA, the authors aimed to evaluate 6 synthetic cannabinoids for their ability to depress spontaneous locomotor activity (LMA) in mice and to test for substitution for Δ^9-tetrahydrocannabinol (Δ^9-THC) in a drug discrimination (DD) assay in rats. These assays enable us to determine the potency and efficacy of these compounds relative to the commonly abused Δ^9-THC. **Methods:** ADB-BUTINACA, FUB-AKB-48, 4F-MDMB-BICA, 5F-EMB-PICA (2201), FUB-144, and 5Cl-AKB-48 were tested for their ability to depress LMA in male Swiss-Webster mice. The discriminative stimulus effects of these cannabinoids were assessed in male Sprague-Dawley rats that were trained to discriminate Δ^9-THC (3 mg/kg) from saline. **Results:** Data indicated that locomotor depressant effects of ADB-BUTINCA (ED50 = 0.12 mg/kg), 4F-MDMB-BICA (ED50 = 0.2 mg/kg), and 5F-EMB-PICA (2201) (ED50 = 0.69 mg/kg) occurred within 10 min following injection and lasted between 30-90 minutes. The depressant effects of FUB-AKB-48 (ED50 = 0.12 mg/kg), FUB-144 (ED50 = 6.1 mg/kg), and 5Cl-AKB-48 (ED50 = 7.3 mg/kg) were delayed and not evident until 20-40 min following injection. All 6 cannabinoids fully substituted for the discriminative stimulus effect of 3 mg/kg of Δ^9-THC. **Conclusions:** A range of potencies in both behavioral assays were observed, with ADB-BUTINACA being the most potent and 5Cl-AKB-48 the least potent. Therefore, the behavioral pharmacology profiles of the 6 compounds provided confirmation of their potential abuse as substitutes for Δ^9-THC.
Supported by NIH N01DA-18-8936

Virtual Presentation 7

Developmental toxicity of maternal, paternal, and dual parental alcohol consumption and the long-term effects on offspring growth, craniofacial, and neurological development

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In order to redress the stigma that Fetal Alcohol Spectrum Disorders (FASDs) are exclusively the mother's fault, we sought to investigate the contributions of both parents. We hypothesized that FASD-associated developmental defects would become exacerbated in a dual parental model of alcohol consumption. Using a 2 x 2 factorial design, we generated offspring from: control, maternal, paternal, and dual parental alcohol-exposed groups. Pregnancies were either terminated to evaluate fetal measures or allowed to continue to birth in order to generate offspring for behavioral studies. We found evidence of fetal growth restriction in both male and female fetuses in all alcohol exposed groups. Using craniofacial morphometrics we identified FASD associated facial dysmorphology in both sexes of all treatment groups, while fetal brain weight was only increased in the maternal ethanol group. Finally, we sought to understand whether these FASD phenotypes persisted into later adult life. Using the open field maze, nestlet shredding, marble burying, and novel object recognition tests beginning in early adolescence and continuing through mature adulthood, we found altered behavioral phenotypes in all alcohol exposed groups throughout development. These findings highlight the importance of environmental exposure of both parents.

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2022 Behavior, Biology, and Chemistry: Translational Research in Addiction Attendees

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Notes

Notes

Notes

Poster Index

Maharaj ("Raj") Ticku, PhD

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

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

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

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

Maharaj Ticku Memorial Travel Fellowship for New Investigators

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

2022 – Corinde E Weirs

See you at BBC 2023!

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