BBC Publications

BBC 2011

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

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

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

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

BBC 2012

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

BBC 2013

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

BBC 2014

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

BBC 2015

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

BBC 2016

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

Acknowledgements

Special thanks to Allentown, Brian Kangas, Erik Garcia

FUNDING FOR THIS CONFERENCE WAS MADE POSSIBLE (IN PART) BY R13DA029347 FROM THE NATIONAL INSTITUTE ON DRUG ABUSE. THE VIEWS EXPRESSED IN WRITTEN CONFERENCE MATERIALS OR PUBLICATIONS AND BY SPEAKERS AND MODERATORS DO NOT NECESSARILY REFLECT THE OFFICIAL POLICIES OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES; NOR DOES MENTION BY TRADE NAMES, COMMERCIAL PRACTICES, OR ORGANIZATIONS IMPLY ENDORSEMENT BY THE U.S. GOVERNMENT.

Session Chairs

Cristal Ahmed
Hina Andleeb
Gregory Collins
Christopher Cunningham
Rajeev Desai
Lindsey Galbo-Thomma
Erik Garcia
David Kearns
Travis Moschak
Siara Rouzer
Justin Strickland

Presentation Judges

Jeremy Bailoo
Kelly Berg
Bruce Blough
Nora Charles
Gregory Collins
Christopher Cunningham
Lynette Daws
Rajeev Desai
Andrew Eagle
Bill Fantegrossi
Michael Forster
Erik Garcia
Takato Hiranita
Sally Huskinson
Brian Kangas
David Kearns
Thomas Keck
Oleg Klykov
Mei-Chuan Ko
Travis Moschak
Jacques Nguyen
Samuel Obeng
Justin Strickland
Keith Warren
Michael Wedemeyer
Susan Wood

Organizing Committee

Charles P France (Chair)
Gregory T Collins
Lindsey K Galbo-Thomma
David R Maguire
Analisa Tapia
Julia R Taylor

Program Committee

Gregory T Collins (Chair)
Alessandro Bonifazi
Rajeev I Desai
Lee Gilman
KC Leong
Justin C Strickland

Travel Awards Committee

David R Maguire (Chair)
Cassandra D Gipson-Reichardt
Sally L Huskinson
Brian D Kangas
David N Kearns
Vanessa Minervini
Jacques D Nguyen

Maharaj ("Raj") Ticku, PhD

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

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

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

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

Maharaj Ticku Memorial Travel Fellowship for New Investigators

2012 – Jun-Xu Li	2013 – Kevin B Freeman	2014 – Christopher W Cunningham
2015 – Brian D Kangas	2016 – Clinton E Canal	2017 – Thomas M Keck
2018 – Comfort A Boateng	2019 – Stephen J Kohut	2020 – Lee Gilman
2022 – Corinde E Weirs	2023 – Justin C Strickland	2024 – Zijun Wang
2025 – Jacques D Nguyen	2026 – Hina Andleeb	

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 who are researching substance use disorders using female subjects, at the annual meeting of Behavior, Biology, and Chemistry: Translational Research in Substance Use Disorders.

Predoctoral	Postdoctoral
2022 – Kimberly M Holter	2022 – Renata Christina Nunes Marchette
2023 – Gwendolyn Burgess	
2024 – Cristina Rivera Quiles	2024 – Laia Castell Almuni
2025 – Alexa-Rae Wheeler	
2026 – Cristal Ahmed	2026 – Siara Rouzer

Travel Awardees

George Adamson	Ana Sofia Chavarria	Maia Maras	Mahfuz Sakib
Tiffany Aguirre	Teresa Cho	Vena Martinez	Neha Sawant
Philip Antwi-Adjei	Emily Cronin	Justin Mastio	Thomas Shellenberg
Devon Applegate	Soren Emerson	Jessica McInerney	Neha Skandan
Ayesha Baig	Cristiane Favoretto	Jocelyn Morales	Spencer Snow
Harrison Benson	Althea Floge	Seyedeh Leila Mousavi	Amelie Soyer
Nicholas Bloom	Shawn Flynn	Renee Nosko	Theophilus Torgbenu
Daniel Borgatti	Jenna Kramer	Zachary Pierce-Messick	Afroza Tumpa
Felise Bressler	Nana Kofi Kusi-Boadum	Gorana Puzovic	Sarvesh Kumar Verma
Eliza Brooks	Melissa Lewis	Nokomis Ramos-Gonzalez	Fernanda Villa-Ortiz
Diego Cecena	Tian Li	Kaitlyn Rojas	John Westphal
Padam Chaudhary			You Zhang

Program Overview

FRIDAY 20 MARCH 2026

3:00 PM – 6:00 PM	Registration – Embassy Landmark, Bluebonnet Foyer	
4:00 PM – 6:00 PM	Pathways to Careers in Science Workshop – Embassy Landmark, Bluebonnet AB	
6:00 PM – 8:00 PM	BBC Opening Reception and Networking – Embassy Landmark, Bluebonnet Foyer	

SATURDAY 21 MARCH 2026

8:00 AM – 8:05 AM	Welcome and Opening Remarks	
8:05 AM – 10:05 AM	Plenary Symposium: *Kratom: From Plant to Policy* **Abhisheak Sharma** | University of Florida *Kratom: History and medicinal chemistry* **Jenny Wilkerson** | Rutgers University *The kratom alkaloid mitragynine as a novel therapeutic for cancer-related pain relief and substance use disorders* **Oliver Grundmann** | University of Florida *The kratom pharmacology puzzle pieces: How user surveys inform a complex pharmacological interplay* **Jack Henningfield** | Pinney Associates *Kratom, mitragynine and 7-hydroxymitraginine: Abuse potential and implications for DEA scheduling and policy to mitigate unintended consequences*	Chair: Gregory Collins
10:05 AM – 11:35 AM	Poster Session I and Refreshments	
11:35 AM – 12:50 PM	Lunch	
12:50 PM – 2:20 PM	Open Oral Communications I	Chairs: Cristal Ahmed and Erik Garcia
2:20 PM – 3:50 PM	Poster Session II and Refreshments	
3:50 PM – 5:20 PM	Open Oral Communications II	Chairs: Hina Andleeb and Rajeev Desai
5:20 PM – 5:30 PM	Refreshment Break	
5:30 PM – 6:30 PM	Special Lecture **Meg Haney** | Columbia University *Human behavioral pharmacology of cannabis*	Chair: Justin Strickland
6:30 PM – 7:30 PM	Cocktail Hour and Poster Viewing	
7:30 PM – 9:30 PM	Dinner and Science Trivia	

SUNDAY 22 MARCH 2026

8:15 AM	Travel Awardee Group Photo	
8:30 AM – 10:00 AM	Open Oral Communications III	Chairs: Lindsey Galbo-Thomma and Siara Rouzer
10:00 AM – 10:10 AM	Refreshment Break	
10:10 AM – 11:40 AM	Open Oral Communications IV	Chairs: David Kearns and Travis Moschak
11:40 AM – 11:50 AM	Refreshment Break	
11:50 AM – 12:50 PM	Special Lecture **Susruta Majumdar** | Washington University in St. Louis *Allosteric control of opioid receptor function using structure based design*	Chair: Christopher Cunningham
12:50 PM – 1:05 PM	Travel and Presentation Awards	
1:05 PM	Adjournment	

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

Program Details

Friday 20 March 2026

Registration	3:00 PM – 6:00 PM	*Bluebonnet Foyer*
Pathways to Careers in Science Workshop	4:00 PM – 6:00 PM	*Bluebonnet AB*
Opening Reception	6:00 PM – 8:00 PM	*Bluebonnet Foyer*

Saturday 21 March 2026

Complimentary Breakfast	7:30 AM	*Breakfast Café*
Welcome and Opening Remarks	8:00 AM – 8:05 AM	*Bluebonnet AB*
Plenary Symposium	8:05 AM – 10:05 AM	*Bluebonnet AB*

Kratom: From Plant to Policy
(Chair: Gregory Collins)

8:05 AM – 8:35 AM **Abhisheak Sharma** | University of Florida
Kratom: History and medicinal chemistry

8:35 AM – 9:05 AM **Jenny Wilkerson** | Rutgers University
The kratom alkaloid mitragynine as a novel therapeutic for cancer-related pain relief and substance use disorders

9:05 AM – 9:35 AM **Oliver Grundmann** | University of Florida
The Kratom pharmacology puzzle pieces: How user surveys inform a complex pharmacological interplay

9:35 AM – 10:05 AM **Jack Henningfield** | Pinney Associates
Kratom, mitragynine and 7-hydroxymitraginine: Abuse potential and implications for DEA scheduling and policy to mitigate unintended consequences

Poster Session I and Refreshments (odd posters judged)	10:05 AM – 11:35 AM	*Bluebonnet C/Lantana*
Lunch	11:35 AM – 12:50 PM	*Bluebonnet AB*
Oral Communications I	12:50 PM – 2:20 PM	*Bluebonnet AB*

(Chairs: Cristal Ahmed and Erik Garcia)

12:50 PM – 1:05 PM **Maia Maras** | National Institute on Drug Abuse
MRI-1867, a Novel Peripherally Acting CB1 Receptor Antagonist, Shows Promise in Treating Opioid Use Disorders in Rodents

1:05 PM – 1:20 PM **Nokomis Ramos-Gonzalez** | Washington University in St. Louis
Fine tuning of kappa opioid receptor signaling by targeting orthosteric subpockets

1:20 PM – 1:35 PM **Kaitlyn Rojas** | Baylor University
Semaglutide, a glucagon-like peptide-1 receptor agonist, attenuates motivation to self-administer intravenous fentanyl

1:35 PM – 1:50 PM **Althea Floge** | Wake Forest University School of Medicine
Effects of social manipulations on alcohol drinking in male socially housed nonhuman primates

1:50 PM – 2:05 PM **Cristal Ahmed** | East Tennessee State University
Examining the role of adolescent nicotine use on alcohol consumption in a rodent model of dopaminergic dysregulation

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

Oral Communications II 3:50 PM – 5:20 PM *Bluebonnet AB*
(Chairs: Hina Andleeb and Rajeev Desai)

3:50 PM – 4:08 PM **Padam Chaudhary** | Rowan University
Evaluating Buprenorphine as an Opioid Overdose Reversal Agent

4:08 PM – 4:26 PM **Emily Cronin** | Wake Forest University School of Medicine
Lack of reinstatement of extinguished cocaine self-administration by bifunctional nociceptin/orphanin FQ peptide (NOP)/mu opioid peptide (MOP) receptor agonists in rhesus monkeys

4:26 PM – 4:44 PM **Soren Emerson** | Vanderbilt University
Selective Exclusion of Inactive Neurons Regulates Ensemble Plasticity

4:44 PM – 5:02 PM **Aditi Rudrashetty** | University of Mississippi Medical Center
Effects of Alcohol Drinking on Novelty-Directed Behavior and Sleep in Rhesus Macaques

5:02 PM –5:20 PM **Thomas Shellenberg** | University of Kentucky
Effects of simulated and real opioid withdrawal on opioid and money delay discounting in people who use fentanyl daily

Refreshment Break 5:20 PM – 5:30 PM

Special Lecture 5:30 PM – 6:30 PM *Bluebonnet AB*
Meg Haney | Columbia University
Human behavioral pharmacology of cannabis
(Chair: Justin Strickland)

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

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

Science Trivia *Bluebonnet AB*
Sponsored by CPDD - 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 22 March 2026

Complimentary Breakfast — 7:30 AM — *Breakfast Café*

Travel Awardee Group Photo — 8:15 AM — *Hotel Lobby*

Oral Communications III — 8:30 AM – 10:00 AM — *Bluebonnet AB*

(Chairs: Lindsey Galbo-Thomma and Siara Rouzer)

8:30 AM – 8:48 AM — **Payton Kahanek** | University of Texas at Austin
Mapping Phenotypic Predictions of Delay Discounting onto Fentanyl Self-Administration in Heterogenous Stock Rats

8:48 AM – 9:06 AM — **Mohammad Alkhatib** | Rowan University
Design and Optimization of Sigma Receptor Ligands for Opioid-Free Pain Therapy

9:06 AM – 9:24 AM — **Lindsey Galbo-Thomma** | University of Texas Health Science Center at San Antonio
Effects of bifunctional mu-opioid and nociceptin/orphanin FQ receptor agonists on fentanyl and methamphetamine self-administration in monkeys

9:24 AM – 9:42 AM — **Siara Rouzer** | Texas A&M University College of Medicine
Sex-Dependent Corticostriatal Gene Network Disruption Accompanies Elevated Alcohol Consumption in Prenatal Drug-Exposed Offspring

9:42 AM – 10:00 AM — **Vena Martinez** | University of Texas Medical Branch at Galveston
Preclinical analyses of NMUR2 small compound agonist NY0128 as a potential therapeutic for cocaine use disorder

Refreshment Break — 10:00 AM – 10:10 AM

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

(Chairs: David Kearns and Travis Moschak)

10:10 AM – 10:28 AM — **Amelie Soyer** | Rowan University
Evaluating synergistic analgesia and improved safety profile of fentanyl combined with MP-III-024, a selective α2/α3GABAA receptor positive allosteric modulator

10:28 AM – 10:46 AM — **Cristiane Favoretto** | University of Mississippi Medical Center
Oxycodone dose-dependently alters sleep-wake and respiratory function in rats

10:46 AM – 11:04 AM — **Shawn Flynn** | University of Michigan
Differential antagonism of mu opioid receptor agonists

11:04 AM – 11:22 AM — **Zachary Pierce-Messick** | Johns Hopkins University School of Medicine
Value-Based Decision-Making in People Recovering from Opioid Use Disorder

11:22 AM – 11:40 AM — **Hina Andleeb** | Concordia University Wisconsin
Structure-guided discovery of thiazole-based inhibitors of sterol carrier protein-2 for endocannabinoid transport modulation

Refreshment Break — 11:40 AM – 11:50 AM

Special Lecture — 11:50 AM – 12:50 PM — *Bluebonnet AB*

Susruta Majumdar | Washington University in St. Louis
Allosteric control of opioid receptor function using structure based design
(Chair: Christopher Cunningham)

Travel and Presentation Awards — 12:50 PM – 1:05 PM — *Bluebonnet AB*

Adjournment — 1:05 PM

See you at BBC 2027!

Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee

Abby Loudermilk Travel Awardee

BBC Travel Awardee

Menu Overview

Complimentary breakfast served by the Embassy Suites weekdays 6:30 – 9:30 AM and weekends 7:30 – 10:30 AM.

Friday Dinner Reception – **Italian Buffet**

Caesar Salad

Parmesan Chicken

Shrimp Scampi

Vegetable Lasagna

Penne Aglio e Olio, Oven Roasted Vegetables

Tiramisu

Saturday Lunch – **Mediterranean Buffet**

Greek Salad

Grilled Chicken with Lemon Cream Sauce

London Broil with Mushroom Onion Glaze

Rice Pilaf, Roasted Potatoes with Onions

Raspberry Lemon Crème Cake

Saturday Dinner – **Mexican Dinner Reception***

Mexican Fiesta Salad

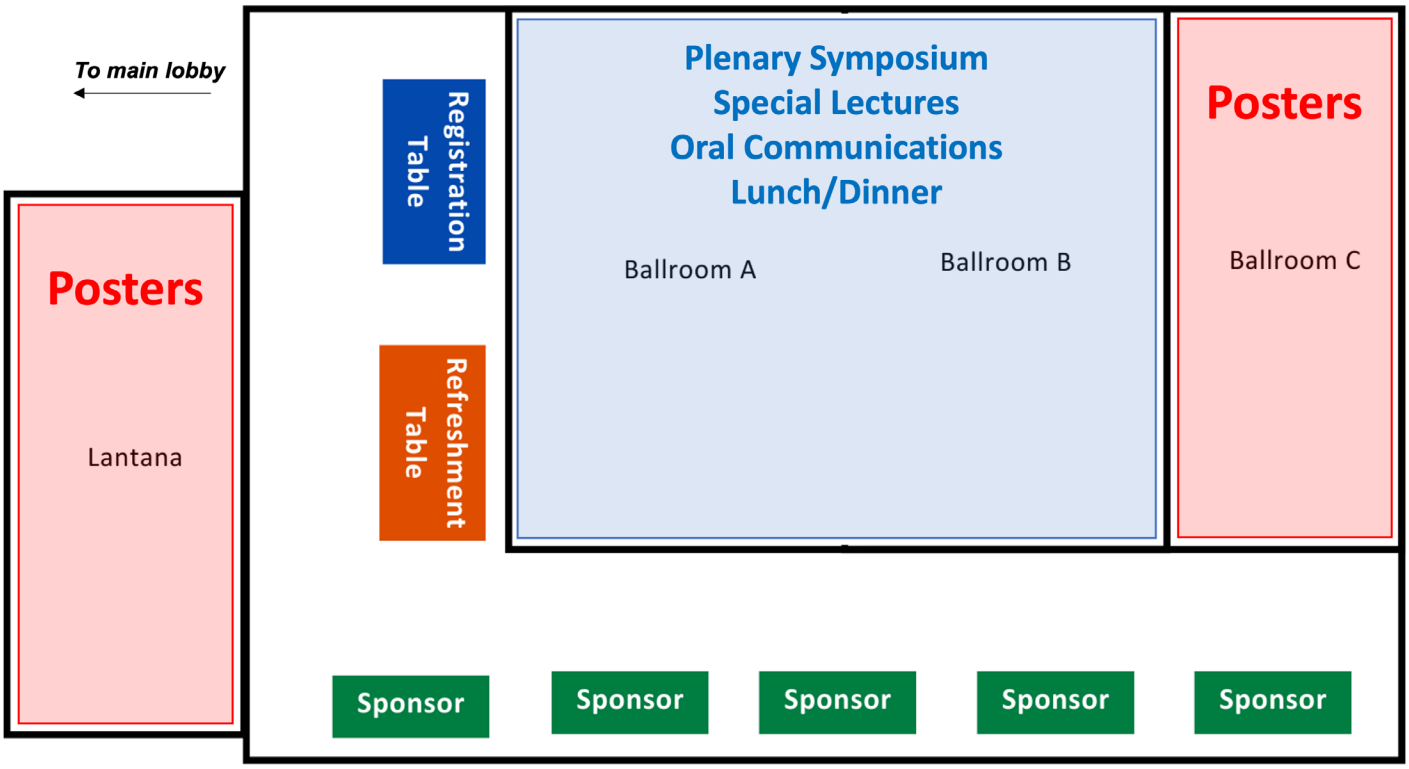
Grilled Marinated Chicken Breast with Cilantro Poblano Cream Sauce

Cilantro Lime Rice, Corn and Black Bean Salsa

Dulce de Leche Cheesecake

Tres Leches cake

For those with dietary restrictions, please utilize the colored table tent provided



SCAN

To view the whole program

Oral Communications

Oral Communication 1-1

MRI-1867, a Novel Peripherally Acting CB1 Receptor Antagonist, Shows Promise in Treating Opioid Use Disorders in Rodents

Maia Maras[1], Emily Linz[1], Guo-Hua Bi[1], Pinaki Bhattacharjee[2], Malliga R. Iyer[2], Zheng-Xiong Xi[1]

[1]Addiction Biology Unit, NIDA-IRP, Baltimore, MD, USA
[2] Section on Medicinal Chemistry, NIAAA-NIH, Rockville, MD, USA

The cannabinoid CB1 receptor (CB1R) is a major regulator of addiction-related behaviors and a target for developing treatments for substance use disorders. Although the first CB1R antagonist, rimonabant, effectively reduced drug-taking in preclinical studies, its severe CNS-mediated psychiatric side effects halted clinical use. Safer CB1R antagonists that avoid these central effects are urgently needed. This study evaluated MRI-1867, a peripherally restricted CB1R inverse agonist/antagonist that does not cross the blood–brain barrier, as a potential treatment for opioid use disorder. Adult male rodents were tested using heroin and cocaine self-administration, dopamine-dependent optical intracranial self-stimulation (oICSS), hot plate analgesia, and open-field locomotion. MRI-1867 produced three major outcomes: (1) robust reductions in heroin self-administration (and moderate reductions in cocaine) without affecting locomotion; (2) inhibition of dopamine-dependent oICSS maintained by optically stimulated midbrain dopamine neurons; and (3) enhancement of oxycodone-induced analgesia. These findings suggest that peripheral CB1R antagonism can decrease opioid-taking behavior while improving analgesic responses, supporting MRI-1867 as a promising therapeutic candidate. Ongoing work aims to identify peripheral CB1R sites and assess whether CB1R deletion in primary sensory neurons alters MRI-1867's effects on opioid reward and analgesia. Acknowledgements: Supported by NIDA IRP (ZX Xi) and NIAAA IRP (M. Iyer).

Oral Communication 1-2

Fine tuning of kappa opioid receptor signalling by targeting orthosteric subpockets

Ramos-Gonzalez, Nokomis[a] ; Varga, Balazs R.[a] ; Thotamune Kankanamalage[b] , Waruna; Keith, Michael[a] ; Barnali Paul[a] , Alexis Knoll[a] , Qianru Jiang[a] ; Karunarathne, Ajith[b] ; McLaughlin, Jay P.[c] ; Che, Tao[a] ; Majumdar, Susruta[a]

[a]Center for Clinical Pharmacology, Washington University School of Medicine, St. Louis, MO. [b] Department of Chemistry, Saint Louis University, Saint Louis, MO. [c] Department of Cellular and Systems Pharmacology, University of Florida, Gainesville, FL.

The Kappa opioid receptor (KOR) represents a viable alternative to the mu opioid receptor for developing analgesics. Prior literature evidence suggests that the βarrestin-2 pathway may mediate some of the KOR adverse effects in mice. To design functionally selective ligands, we targeted a subpocket made up of transmembrane domain 5 (TM5) and extracellular loop 2 (ECL2) on the MP1104 template, confirmed by solving a cryo-EM structure of a lead compound; balanced ligand MP1104 targets TM2/3. Molecular dynamics simulations confirm key interacting residues in the subpocket. Lead compounds display high G protein efficacy, minimal GRK3 recruitment, decreased C-terminal tail phosphorylation, minimal β-arrestin1/2 recruitment and low receptor internalisation, whilst MP1104 displays high potency and efficacy in all assays.
In mice, a lead compound displays KOR mediated analgesia, and decreased motor impairment compared to a standard agonist. With extensive pharmacological, structural and computational studies, we develop a platform for ligands that maintain G protein efficacy with minimal β-arrestin recruitment. Findings could lead to next generation of KOR therapeutics as well as enable us to explore the role of the β-arrestin pathway in KOR pharmacology. N.R-G thanks the PhRMA Foundation Postdoctoral Fellowship (ISNI ID: 0000 0000 9959 8153, Crossref Funder ID: 100001797).

Oral Communication 1-3

Semaglutide, a glucagon-like peptide-1 receptor agonist, attenuates motivation to self-administer intravenous fentanyl

Rojas, Kaitlyn E. [1] ; Gee, Sarah[1] ; Wernette, Chris[1] ; Wang, Eric[1] ; Nguyen, Emily[1] ; Nguyen, Jacques D. [1]

[1]Department of Psychology and Neuroscience, Baylor University, Waco, TX USA

Previous research has shown that glucagon-like peptide-1 receptor (GLP-1R) agonists may serve as therapeutic agents for substance use disorder. Addressing existing gaps in the literature, our study investigated the ability of semaglutide, a specific GLP-1R agonist, to decrease intravenous self-administration of fentanyl. Female Wistar rats (N=32) were trained to self-administer intravenous fentanyl at fixed-ratio 1 (FR1) for 21 sessions under short- (ShA; 1 hour; n=16) or long-access (LgA; 8 hours; n=16) conditions. The animals then received injections of semaglutide (0.1 mg/kg, s.c.; n=8) or saline (0.9%, s.c.; n=8) prior to an additional FR1 session. The animals began a progressive ratio (PR), testing motivation to self-administer fentanyl (0-10 µg/kg/inf, i.v.) at a constant dose of semaglutide (0.1 mg/kg, s.c.) or saline. Next, the animals underwent a semaglutide (0-0.1 mg/kg, s.c.) dose response procedure where they returned to the original FR1 and self-administered fentanyl (2.5 µg/kg/inf, i.v.). 18-24 hours following drug discontinuation, the animals were monitored for spontaneous motor activity and symptoms of opioid withdrawal. Semaglutide dose-dependently decreased rewards earned ($p<0.05$) without altering lever discrimination. Under PR, semaglutide decreased motivation to self-administer intravenous fentanyl assessed by breakpoint. Interestingly, semaglutide decreased spontaneous locomotor activity for animals trained under ShA ($p<0.05$) but not LgA conditions. Semaglutide also decreased opioid withdrawal scores for ShA animals ($p<0.05$) but not LgA. Our findings show that semaglutide may serve as a therapeutic agent for opioid use disorder and encourage further work to evaluate GLP-1R agonists as treatments for substance use disorder more broadly.
Support for this study was provided by NIH DA047413

Oral Communication 1-4

Effects of social manipulations on alcohol drinking in male socially housed nonhuman primates

Floge, Althea P; Cronin, Emily A; Epperly, Phillip M, Czoty, Paul W

Department of Translational Neuroscience, Wake Forest University School of Medicine, Winston-Salem NC, USA.

The social environment can influence alcohol use, but the behavioral mechanisms underlying this effect are not fully understood. The present study examined the effects of two social manipulations on ethanol intake in a nonhuman primate (NHP) model of alcohol use disorder. Eight adult male cynomolgus monkeys lived in two social groups of four in established linear dominance hierarchies. Monkeys had access to a 4% ethanol solution 22 hours/day, 5 days/week via an operant "drinking" panel in the home cage. During ethanol access, monkeys were individually housed but had visual access to one social partner. In the first study, one day each week, access to ethanol was restricted for one partner (his panel was not turned on) and the test subject's ethanol intake was measured. We hypothesized that removing the social partner's access would decrease ethanol drinking. We found that the extent of decrease was not related to social rank but was negatively related to baseline ethanol intake. That is, monkeys with higher ethanol intakes were less sensitive to the manipulation expected to decrease drinking. In the second study, a resident/intruder paradigm was used to examine the effects of acute social stress on ethanol drinking. A dominant- or subordinate-ranked monkey was removed from his home cage and placed into one quadrant of the other social pen. Fifteen minutes later, the monkey was returned to his home cage and provided access to ethanol and water for 22 hours. We hypothesized that this intruder experience would serve as a form of enrichment for dominants, decreasing ethanol consumption, and as a stressor for subordinates, increasing ethanol consumption. Although this hypothesis was supported for the most dominant monkeys, others were unaffected. Taken together, these results suggest that ethanol drinking in NHP models is sensitive to social manipulations. Support: P50 AA027556, URECA fellowship from WFU.

Oral Communication 1-5

Examining the role of adolescent nicotine use on alcohol consumption in a rodent model of dopaminergic dysregulation

Ahmed, Cristal D.; Cuozzo, Anthony M.; Willis, Liza J.; Sigunov, Andrei; Brown, Russell W.; Deehan, Gerald A.; Gass, Justin T.

Department of Biomedical Sciences, Quillen College of Medicine, East Tennessee State University, Johnson City, TN

Elevated sensitivity of dopamine D2 receptors is a feature of schizophrenic psychosis and is frequently associated with high co-occurrence of nicotine and alcohol use disorders. To examine the neurobiological mechanisms driving this comorbidity, we utilized the neonatal quinpirole (NQ) model, wherein agonist treatment induces lifelong, heritable D2 receptor supersensitivity in F1 offspring (QQ). This study evaluated whether adolescent nicotine exposure alters the reinforcing efficacy of ethanol in this vulnerable phenotype. Male and female rats began operant self-administration during adolescence (P30), self-administering 10% ethanol via lickometers on a fixed-ratio schedule for 12 intermittent sessions. To model co-use, systemic nicotine (0.6 mg/kg) was administered prior to self-administration sessions. Following operant self-administration, extinction was measured over a period of up to 15 sessions in a different context, and reinstatement was measured a week following extinction criteria being met. Subsequently, motivation was quantified using a progressive ratio schedule. QQ rats exposed to the nicotine-ethanol combination displayed significantly higher rates of alcohol drinking compared to all other groups, indicating a robust increase in the motivation to consume alcohol. Crucially, tissue analysis of the nucleus accumbens and amygdala revealed that this heightened behavioral drive was accompanied by significant lipid peroxidation. Glutathione levels were also measured in the reward pathway to analyze antioxidant depletion because of alcohol metabolism. These data indicate that D2 supersensitivity interacts with adolescent nicotine to potentiate ethanol reinforcement, a process potentially mediated by accumulated oxidative stress within the mesolimbic reward circuitry.

Oral Communication 2-1

Evaluating Buprenorphine as an Opioid Overdose Reversal Agent

Chaudhary, Padam R[1] ; Afrin, Nadia[1] ; Carroll, Gerard[2] ; Salzman, Matthew[2] ; Keck, Thomas M.[1]

[1]Rowan University, Glassboro, NJ 08028; [2] Cooper Medical School of Rowan University, Camden, NJ 08103

The widespread use of potent synthetic opioids such as fentanyl (FENT) has made it increasingly difficult to manage opioid-induced respiratory depression, the primary cause of fatal overdose. Naloxone (NLX), the standard rescue medication, is often less effective against FENT-induced respiratory depression and can trigger severe withdrawal symptoms. Buprenorphine (BUP), a μ-opioid receptor (MOR) partial agonist and κ-opioid receptor (KOR) antagonist, offers a promising alternative. Because of its mixed receptor activity, BUP can partially activate MOR while displacing high-efficacy opioids like FENT, potentially restoring breathing without inducing extreme withdrawal. This project investigates the potential of BUP, alone or in combination with NLX, to reverse FENT-induced respiratory depression in FENT-dependent mice. Single-dose time-course experiments showed that FENT caused rapid and profound respiratory suppression, while buprenorphine produced a slower onset and less pronounced depression of breathing that resolved relatively quickly. Cumulative dosing procedures revealed that FENT caused a strong, dose-dependent decrease in respiratory rate and increase in tidal volume, whereas BUP displayed a plateau effect consistent with its partial-agonist nature. Following one week of twice-daily FENT administration to induce dependence, mice showed marked rightward shifts in analgesic responses to FENT and BUP, while respiratory responses to subsequent FENT challenges indicate a lower degree of opioid tolerance. Ongoing studies are evaluating the capacity of BUP, alone and in combination with NLX, to reverse FENT-induced respiratory depression in dependent mice and to compare withdrawal symptoms induced by these reversal treatment regimens. If BUP reduces both respiratory suppression and withdrawal severity, these findings may support BUP's potential as an effective rescue treatment for synthetic opioid overdoses.

Oral Communication 2-2

Lack of reinstatement of extinguished cocaine self-administration by bifunctional nocicpetin/orphanin FQ peptide (NOP)/mu opioid peptide (MOP) receptor agonists in rhesus monkeys

Cronin, Emily A; Costa, Marissa B; Collier, Miracle A; Epperly, Phillip M; Czoty, Paul W

Department of Translational Neuroscience, Wake Forest University School of Medicine, Winston-Salem, NC USA

Although cocaine use disorder (CUD) remains a major public health concern affecting ~1.2 million Americans over the age of 12, there are no FDA-approved pharmacotherapies for CUD. Recent evidence supports "bifunctional agonists," which stimulate nociceptin/orphanin FQ peptide (NOP) and mu opioid peptide (MOP) receptors, as CUD medications. For example, we showed that chronic treatment with BU08028 can decrease cocaine reinforcement in monkeys. Drug prime-induced reinstatement of extinguished cocaine self-administration has been used as a model of relapse to cocaine use. The present study examined whether bifunctional agonists can reinstate extinguished cocaine self-administration. Four male rhesus monkeys with long cocaine self-administration histories responded under a multiple schedule consisting of an initial fixed-ratio 5 (FR5) schedule of food pellet delivery followed by an FR30 schedule of cocaine delivery (0.1 mg/kg, i.v.). Following extinction, during which saline was substituted for cocaine (number of injections decreased by 80%), cocaine, buprenorphine or the bifunctional agonists BU08028 or BU12005 (0.01-0.3 mg/kg 0.001-0.1 mg/kg, 0.01-0.17 mg/kg, 0.0001-0.003 mg/kg, respectively) was given pre-session. No more than two tests occurred before cocaine self-administration was re-established then re-extinguished. Cocaine reinstated responding in all four animals. Buprenorphine, the parent compound of BU08028 and BU12005, produced reinstatement in two of four monkeys. However, neither of the bifunctional agonists produced reinstatement up to doses that decreased food-maintained responding. These data suggest that treatment with bifunctional agonists would not lead to relapse to cocaine use and support the continued development of bifunctional agonists as potential treatments for CUD. Support: R01 DA039953, T32 DA041349

Oral Communication 2-3

Selective Exclusion of Inactive Neurons Regulates Ensemble Plasticity

Emerson, Soren D[1] ; Lopez, Alberto J[1] ; Bethi, Rishik[1] ; Konomi-Pilkati, Ainoa[1] ; Clarity, Thomas T[1] ; Leonard, Michael Z[1] ; Thibeault, Kim C[1] ; Rose, Kristie[1] and Calipari, Erin S[1]

1Department of Pharmacology, Vanderbilt University, Nashville, TN USA.

Cocaine use disorder imposes a large burden on public health, particularly because there are no FDA-approved pharmacotherapies. Cocaine produces enduring behavioral changes by engaging small, transcriptionally active neuronal ensembles in the nucleus accumbens (NAc). Although transcriptional plasticity within these ensembles has been well studied, how they are refined and maintained remains unclear. Here we show that lysine acetyltransferase 2a (KAT2A) provides a cocaine-recruited negative feedback mechanism that acts outside active ensemble neurons. Cocaine increased KAT2A activity at chromatin and KAT2A loss of function in D1 medium spiny neurons reduced cocaine sensitization and selfadministration. Single-nucleus RNA sequencing revealed that KAT2A expression was enriched in non-ensemble neurons and inversely correlated with immediate early gene induction. With repeated cocaine exposure, KAT2A activity rose as the number of active neurons declined. Longitudinal tracking with single-cell calcium imaging and a novel activitydependent single-nucleus RNA sequencing approach showed that repeated exposure rerecruited a stable subset of highly responsive cells defined by low KAT2A expression. These results identify a mechanism by which transcriptional regulators in surrounding, non-active populations shape and stabilize neuronal ensembles, revealing a previously unrecognized principle of circuit plasticity in addiction.

Oral Communication 2-4

Effects of Alcohol Drinking on Novelty-Directed Behavior and Sleep in Rhesus Macaques

Rudrashetty, Aditi S[1,2], Borgatti, Daniel[1,2], Glass, Jordan A[2] , Smith, Ashley[2] , Leach, Ashlee[2] , Berro, Lais[2] , and Platt, Donna[2]

[1]Program in Neuroscience, University of Mississippi Medical Center, Jackson, MS, USA; [2]Division of Neurobiology and Behavior Research, Department of Psychiatry, Jackson, MS, USA

Alcohol use disorder (AUD) is a significant public health concern that has been associated with negative effects on both sleep and cognition. Sleep and cognitive problems have been implicated in relapse risk and poor treatment outcomes, highlighting the need to better understand how alcohol impacts these domains. This study aimed to determine the dose-dependent effects of alcohol on cognition and sleep. Cognition was assessed using a novel object recognition (NOR) task conducted in sequential phases of increasing difficulty, accomplished by increasing object complexity and decreasing time to habituate to objects; sleep was measured using actigraphy. Adult male rhesus monkeys (N=8) underwent NOR task testing prior to (baseline) and following periods of alcohol consumption (target intakes: 1.0 g/kg and 2.0 g/kg). Our findings show that under baseline conditions (no alcohol), monkeys successfully recognized the novel object in all phases, directing significantly more behavior to the novel vs. familiar object on test days. Consumption of alcohol under both target doses disrupted NOR performance specifically during the Hard phase. Alcohol also negatively impacted sleep significantly and in a dose-dependent manner: as alcohol intake increased, sleep efficiency decreased, and fragmentation index increased. These results show that alcohol negatively impacts both cognition and sleep. Future studies will examine whether cognitive disruptions are directly related to alcohol exposure or indirectly related to alcohol-induced sleep disturbances. A better understanding of this relationship may inform treatment strategies that target sleep to reduce relapse risk.

Oral Communication 2-5

Effects of simulated and real opioid withdrawal on opioid and money delay discounting in people who use fentanyl daily

Shellenberg, Thomas P.[a,b], Baidwan, Tavishi[c] , Johansen, Alexandra N.[a,b], Strickland, Justin C.[d] , Martinez, Suky[d] , Regnier, Sean D.[a] , Wesley, Michael J.[a,b,e], Babalonis, Shanna[a] , Stoops, William W.[a,b], and Lile, Joshua A.[a,b]

[a]Department of Behavioral Science, University of Kentucky, Lexington, KY. [b] Department of Psychology, University of Kentucky, Lexington, KY. [c] Department of Psychology and Program in Neuroscience, Davidson College, Davidson, NC. [d] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

Delay discounting (DD) is the devaluation of outcomes as delay to their occurrence increases, which can be exacerbated in opioid withdrawal. Data from two prior studies were combined to compare the effects of real and simulated opioid withdrawal on opioid and money DD. Participants with moderate/severe opioid use disorder completed hypothetical DD tasks for opioid pills and money in opioid withdrawn and non-withdrawn conditions. Study 1 participants (n=12) were admitted on an inpatient basis and experienced real, spontaneous withdrawal elicited via double-blind placebo replacement of oxycodone maintenance doses. For Study 2 participants (n=17), withdrawal was simulated in an outpatient setting by verbally instructing subjects to imagine that they were experiencing typical withdrawal signs and symptoms. Mixed models evaluated condition (withdrawn, non-withdrawn), withdrawal type (real, simulated), and their interaction as predictors of DD rates (i.e., k values). Participants displayed increased discounting rates for opioid pills during the withdrawn condition, regardless of withdrawal type (B=1.54, p=.003). For money, there was a significant condition by withdrawal type interaction (p=.005), such that only participants in the simulated withdrawn condition discounted money more steeply, likely reflective of preexisting group differences (B=2.50, p<.001). Overall, these results support the validity of simulated withdrawal as a proxy when real withdrawal is contraindicated or not feasible. Further development of alternative experimental tools in addiction research is warranted.

Oral Communication 3-1

Mapping Phenotypic Predictions of Delay Discounting onto Fentanyl Self-Administration in Heterogenous Stock Rats

Kahanek, Payton[1] , Mitchell, Suzanne[2] , Palmer, Abraham[3] , and Orsini, Caitlin A[4]

[1]College of Pharmacy, University of Texas, Austin, TX; [2] Dept of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR; [3] Dept of Psychiatry, University of California, San Diego, CA; [4] Dept of Psychology, University of Texas, Austin, TX USA

Substance use is associated with altered delay discounting, or the decline in the subjective value of a reward as a function of the delay(s) to its receipt. Identifying predictive factors, such as impaired decision making, that may confer vulnerability to substance use disorders is crucial to develop targeted interventions. Paralleling clinical studies, preclinical studies have identified that high delay discounting, or a steeper devaluation of reward as delay increases, predicts intake of psychostimulants, alcohol, nicotine, and cannabis. It is unclear whether delay discounting similarly predicts opioid intake. This study aims to determine the predictive relationship between delay discounting and fentanyl self-administration in rats. Previous genome-wide association studies identified single nucleotide polymorphisms linked to delay discounting in heterogenous stock rats, which were used to train a predictive model for estimating phenotypes in subsequent generations. Rats predicted to exhibit high (n=11) and low discounting (n=5) underwent jugular catheter surgery and were trained to self-administer intravenous fentanyl for 21 days. To measure drug-seeking under risk of punishment, rats underwent 7 sessions in which fentanyl delivery was paired with a 50% probability of footshock. Following punishment-induced extinction, rats were tested for cue-induced reinstatement of fentanyl-seeking. Across 21 days of self-administration, high and low-discounting rats escalated their fentanyl intake to a similar extent. Unexpectedly, during punished sessions, low-discounting rats continued to self-administer fentanyl while high-discounting rats reduced fentanyl intake. Finally, low-discounting rats reinstated to a greater degree than high-discounting rats. Collectively, this work highlights the behavioral mechanisms linking delay discounting and opioid use to inform targeted treatment strategies.

Oral Communication 3-2

Design and Optimization of Sigma Receptor Ligands for Opioid-Free Pain Therapy

Alkhatib, Mohammad A.[1] ; Sola, Sergio[1] ; Dhote, Pawan[2] ; Nguyen, Norman[1] ; Jordan, Shannon[1] ; Wang, Feijun[2] ; Webber, Nakoa[1] ; Nucci, Nathaniel V. [1] ; Haider, Shozeb[3] ; Frankowski, Kevin[2] ; Keck, Thomas M.[3]

[1]Department of Biological & Biomedical Sciences, Rowan University, Glassboro, NJ, USA; [2]UNC Eshelman School of Pharmacy, Chapel Hill, NC, USA; [3]University College London, UCL School of Pharmacy, London, United Kingdom

Despite the effectiveness of opioid medications in treating pain, they have serious side effects that include addiction and overdose, highlighting the need for new non-opioid pain therapies. Sigma receptors (σ_1 and σ_2) have emerged as promising non-opioid therapeutic targets due to their expression in key pain-control regions of the CNS. σ_1 and σ_2 receptors lack structural homology but share similar orthosteric binding features; both function as integral membrane-associated chaperones in the endoplasmic reticulum. Preclinical studies demonstrate that σ_1 antagonists can enhance opioid-induced analgesia or act synergistically as dual μ-opioid receptor agonist/σ_1 antagonists, while σ_2 agonists produce effective opioid-independent analgesia. These findings highlight the therapeutic potential of developing ligands that selectively target σ_1 or σ_2 receptors to achieve effective pain relief while minimizing opioid-associated side effects. We have explored potential σ_1- and σ_2-selective scaffolds and leveraged the structure–activity relationship (SAR) study for further optimization of a novel scaffold that lacks the typical aromatic moiety tethered to a basic nitrogen found in most σ_1/σ_2 ligands. In this study, the binding affinities of the resulting compound library were evaluated using radioligand displacement assays, revealing interesting receptor selectivity patterns. Ongoing efforts include refining a QSAR model to design novel next-generation compounds that may lead to safer alternatives for pain management and a deeper understanding of sigma receptor signaling.

Oral Communication 3-3

Effects of bifunctional mu-opioid and nociceptin/orphanin FQ receptor agonists on fentanyl and methamphetamine self-administration in monkeys

Galbo-Thomma, Lindsey K.; France, Charles P.[1,2]

Departments of [1] Pharmacology and [2] Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX

From 2021-2024, 43% of the ~309,000 overdose deaths in the US involved opioid-stimulant co-use, yet no medications are approved for treating that co-use. Because opioids and stimulants have distinct pharmacological actions, an effective medication must have bifunctional properties. This study examined the ability of the bifunctional mu-opioid and nociceptin/orphanin FQ (MOP and NOP, respectively) receptor partial agonist buprenorphine and high efficacy agonist cebranopadol to modify intravenous fentanyl (0.32 µg/kg/inf) and methamphetamine (10 µg/kg/inf) self-administration in male and female nonhuman primates (NHPs; n=3-4/treatment). NHPs earned up to 30 infusions per session, which occurred twice daily. Buprenorphine (0.01-1.0 mg/kg) and cebranopadol (0.32-5.6 µg/kg) were administered 30 min before morning sessions. The potency of buprenorphine varied among NHPs (0.032-1.0 mg/kg); buprenorphine dose-dependently decreased fentanyl self-administration (defined as ≥20% fewer infusions than baseline) in all NHPs. Larger buprenorphine doses were needed to decrease methamphetamine compared to fentanyl self-administration in 3 NHPs, whereas a smaller dose decreased methamphetamine compared to fentanyl self-administration in a fourth NHP. There was less variation in the potency of cebranopadol (1.0-1.78 µg/kg) to dose-dependently decrease fentanyl self-administration. Methamphetamine self-administration was decreased by large doses up to 5.6 µg/kg and only in 2 of 3 NHPs. Buprenorphine decreased self-administration the day after treatment and for 1-5 days, whereas cebranopadol decreased self-administration the day of treatment and typically in the morning but not afternoon session. These findings suggest that bifunctional MOP/NOP agonists could be effective at reducing opioid-stimulant co-use.

Oral Communication 3-4

Sex-Dependent Corticostriatal Gene Network Disruption Accompanies Elevated Alcohol Consumption in Prenatal Drug-Exposed Offspring

Rouzer, Siara K[1] ; Miranda, Rajesh C[1]

[1]Department of Neuroscience & Experimental Therapeutics, Texas A&M University College of Medicine, Bryan, TX USA

Prenatal exposure to alcohol or cannabinoids increases vulnerability for alcohol misuse in adults. However, with increasing rates of polysubstance use among people of child-bearing age, it is yet unknown whether prenatal co-exposure imposes distinct risk for exposed offspring. To address this gap, pregnant C57Bl/6J mice were assigned to one of four groups: drug-free controls, alcohol-exposed, cannabinoid-exposed or alcohol and cannabinoid co-exposed. Drug exposure occurred daily between Gestational Days 12-15, with dams receiving an injection of cannabinoid agonist CP-55940 (750µg/kg) or vehicle prior to placement in vapor chambers for 30 min inhalation of ethanol or room air. Adult offspring underwent operant self-administration tests of alcohol-seeking prior to tissue collection from the medial prefrontal cortex (mPFC) and dorsomedial striatum (DMS), regions that interact to control goal-directed drug-seeking behavior. Tissues were processed for bulk RNA sequencing, and weighted gene co-expression network analysis was performed to identify exposure-sensitive gene modules. Our results revealed that all prenatal drug exposures increased alcohol consumption in female offspring, while only co-exposure produced this increase in males. In the mPFC, prenatal alcohol exposure increased vascular signaling gene expression in females, while in males, this exposure upregulated metabolic–morphogenetic pathway genes and suppressed a synaptic vesicle cycling module. In the DMS, a neuromodulatory signaling module was selectively suppressed, with alcohol reducing expression in males and cannabinoids reducing expression in females. Taken together, prenatal alcohol and cannabinoid exposures reshape corticostriatal gene network architecture in sex-specific ways that correspond with heightened alcohol-seeking behavior. These changes may represent sex-dependent mechanisms through which prenatal drug exposure confers long-term risk for alcohol use disorder.

Oral Communication 3-5

Preclinical analyses of NMUR2 small compound agonist NY0128 as a potential therapeutic for cocaine use disorder

Martinez, Vena, K.[1] , Sun, Hong[1] , Fox, Robert[1] , Zhang, Cun[1] , Borzou, Ardavan[2] , Zhou, Jia[1] , Cunningham, Kathryn[1] and Hommel, Jonathan, D.[1]

[1]Center for Addiction Sciences and Therapeutics, The University of Texas Medical Branch, Galveston, Texas USA; [2] CompuFlair, Houston, Texas USA

Cocaine use disorder (CUD) is a debilitating problem driven in part by relapse cocaine seeking with no FDA-approved medications to maximize treatment success. Neuromedin U (NMU) receptor 2 (NMUR2) is a putative “druggable target”. We identified that NMU regulates the nucleus accumbens shell (NAcSh), a key brain region in reward processing. Knockdown of NMUR2 in projections to the NAcSh increased cocaine intake in male rats. We hypothesize that systemic administration of small molecule NMUR2 agonist NY0128 will modulate the NAcSh neural network to suppress cocaine seeking in male rats.

Male Sprague Dawley rats were trained in a cocaine (0.75 mg/kg) intravenous self-administration assay (IVSA) on a fixed ratio 5 (FR5) schedule (n=8). NY0128 (3-30 mg/kg, sc) was injected 24 hr prior to cocaine cue test; a one-way ANOVA for repeated measures was employed for analyses. Three rats from this cohort also had gradient lens implants in the NAcSh; an ordinary one-way ANOVA was used to assess calcium transients and network dynamics during cocaine seeking.

Our data demonstrate that systemic NY0128 decreases active lever presses ($p<0.05$) during cocaine cue tests, supporting the idea that the NMU system regulates aspects of cocaine seeking. NY0128 also decreases total calcium fluorescent units (CFU) ($p<0.05$), CFU per event ($p<0.05$), and event rate in the NAcSh ($p<0.05$) during cue test, providing a link between cocaine seeking and NAcSh neural network dynamics.

These results strongly support the continued development and optimization of small-molecule NMUR2-targeted strategies as a viable intervention for addressing CUD.

Oral Communication 4-1

Evaluating synergistic analgesia and improved safety profile of fentanyl combined with MP-III-024, a selective α2/α3GABAA receptor positive allosteric modulator

Soyer, Amelie[1] ; Jimenez, Alida[1] ; Tumpa, Afroza[1] ; Basak, Kona[1] ; Chaudhary, Padam R. [1] ; Shakil Ahmed[1] ; Chowdhury, Maria[1] ; Mondal, Prithu[3] ; Martinez, Diana[2] ; Cook, James M. [3] ; Keck, Thomas M.[1]

[1]Rowan University, Glassboro, NJ; [2] Cooper Medical School of Rowan University, Camden, NJ; [3]University of Wisconsin-Milwaukee, Milwaukee, WI

The ongoing opioid epidemic, and the dangerous side-effect profile of opioid analgesics, underscores the urgent need for safer pain management strategies. The potent µ-opioid receptor agonist fentanyl is a critical analgesic, but its clinical utility is severely constrained by dangerous side effects, including respiratory depression, tolerance, and high abuse potential. This study explores a novel dual-pharmacology strategy to improve fentanyl's therapeutic index by combining it with MP-III-024, a positive allosteric modulator of GABAA receptors that selectively targets α2/α3 subunit containing receptors. We hypothesize that fixed-ratio combinations of fentanyl and MP-III-024 will produce synergistic antinociceptive effects without potentiating opioid-related side effects. To test this hypothesis, adult male and female CD-1 mice were tested in a range of behavioral and physiological tests. The antinociceptive effects of fentanyl and MP-III-024 were evaluated using a cumulative-dosing procedures in the hot plate test, revealing that the combination of fentanyl with MP-III-024 increased antinociceptive responses compared to fentanyl alone in both sexes. The fentanyl + MP-III-024 curve is consistently positioned above the fentanyl curve across cumulative doses in both the latency (seconds) and %MPE graphs, with this upward shift indicating enhanced analgesic effects at equivalent fentanyl doses when combined with MP-III-024. The potentiation is visually apparent in both male and female subjects. Ongoing studies are evaluating fentanyl and MP-III-024 in other nociception models as well as assays evaluating respiratory depression and abuse liability. These studies support a dual-target strategy to improve opioid safety

Oral Communication 4-2

Oxycodone dose-dependently alters sleep-wake and respiratory function in rats

Favoretto, Cristiane Aparecida[1] ; Reeves-Darby, Jaren[1] ; Ni, Rachel[1] ; Garlington, Ashlee[1] ; Berro, Lais[1]

[1]Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS, USA

Sleep disorders are both a risk factor for and a symptom associated with opioid use or opioid use disorder. Opioids also can induce respiratory depression/apnea, which heightens the risk of overdose, particularly during sleep. However, the relationship between the sleep-and respiratory-related effects of opioids remains poorly understood. Here, we aimed to evaluate the effects of analgesic doses of oxycodone on sleep parameters and respiratory measures in rats. Wistar male adult rats (n=4-5) were implanted with EEG/EMG telemetry devices and received intraperitoneal injections of either vehicle (0.9% saline) or oxycodone (0.3, 1, or 3 mg/kg) and were placed in whole-body plethysmography chambers. Sleep-wake patterns and respiratory function were assessed, with tests conducted every other day, 3h into the light (inactive) phase, for a total of 6h. Our results indicate that oxycodone reduced total sleep time at all doses. Only the highest dose reduced slow-wave sleep and rapid-eye movement (REM) sleep duration, while both 1 and 3 mg/kg oxycodone increased REM onset latency. Oxycodone also dose-dependently increased respiratory frequency and minute volume and decreased tidal volume. These respiratory effects might be associated with disturbed sleep, as wake vs. sleep respiratory patterns physiologically differ. Finally, the doses of 0.3 and 1 mg/kg increased the number of apnea events. Thus, our study suggests that oxycodone dose-dependently alters sleep and respiratory function, potentially inducing sleep-disordered breathing (e.g., sleep apnea). Our next steps include analyzing sleep and respiratory measures concurrently, enabling evaluation of respiratory patterns during sleep vs. wakefulness.

Oral Communication 4-3

Differential antagonism of mu opioid receptor agonists

Flynn, Shawn[1] ; Jiang, Rachel[1] ; and Traynor, John[1]

[1]Department of Pharmacology and Edward F. Domino Research Center University of Michigan, Ann Arbor, MI USA

Recent preclinical studies suggest that larger doses of antagonists are needed to reverse the effects of some “superpotent” synthetic opioids (e.g., carfentanil) and it has been proposed that this is due to the binding kinetics of the agonist, but this difference in antagonist effect across agonists is not fully understood. This study characterized interactions between opioid receptor agonists and antagonists with varying physiochemical properties in vitro to test the hypothesis that the apparent affinities of antagonists will be lower when determined against highly potent, slowly dissociating agonists. Inhibition of forskolin-stimulated cAMP accumulation and recruitment of β-arrestin were measured in CHO cells expressing the human mu opioid receptor. Concentration response curves for the opioid receptor agonists DAMGO, met-enkephalin, fentanyl, BU72, and etorphine were determined in the presence of increasing concentrations of opioid receptor antagonists (e.g., naloxone, CTOP, and methylnaltrexone). The resulting rightward shifts in agonist concentration response curves were quantified and used to determine a pA2 value, the apparent affinity, for each antagonist in the presence of each agonist. All mu agonists concentration-dependently reduced cAMP accumulation and increased β-arrestin recruitment. Opioid antagonists produced concentration-dependent rightward shifts in agonist concentration response curves; however, the magnitude of these shifts, and therefore the pA2 values, varied across agonists. Apparent potencies of antagonists were lower when determined using carfentanil, BU72, and etorphine than other agonists but the magnitude of this difference varied across antagonists. These findings are consistent with the hypothesis that antagonist pA2s would be lower when determined using highly potent, slowly dissociating agonists and that this effect is independent of structural class, supporting the theory that agonist binding kinetics underly this difference.

Oral Communication 4-4

Value-Based Decision-Making in People Recovering from Opioid Use Disorder

Pierce-Messick, Zachary J.[1] , Strickland, Justin C.[2] , Copeland, Amber[3] , Field, Matt[3] , and Bergeria, Cecilia L.[2]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine; [2]Kahlert Institute for Addiction Medicine, University of Maryland, Baltimore; [3]Department of Psychology, University of Sheffield, UK.

Reinforcer-specific value-based decision-making (VBDM) is an emerging framework in addiction science for quantifying the neurobehavioral mechanisms underlying the development of, and recovery from, substance use disorder. VBDM combines behavioral tasks with drift diffusion modeling (DDM) to estimate drift rate and response boundary, reflecting the expected value of an option and the degree of response caution, respectively. We examined human laboratory data to assess the sensitivity of VBDM measures to different stages of recovery. Seventy-one participants in recovery from opioid use disorder completed one screening session and three experimental sessions involving a two-alternative forced-choice task. The screening session included both opioid and non-drug rewards, while experimental sessions included only non-drug rewards to avoid contamination of the experimental manipulations. Experimental conditions involved neutral, visual opioid, or tactile–visual opioid cues (e.g., handling paraphernalia and preparing a sham drug). Participants also completed the Addiction Severity Index, providing information on treatment history. DDM was applied to estimate drift rates and response boundaries. Longer recovery was associated with lower opioid drift rates ($r = -.43$; $p = .002$), indicating reduced expected value for opioid rewards. Non-drug reward drift rates were highest during experimental sessions, with the greatest increases relative to screening following opioid cue exposure ($p < .05$). Test-retest reliability for non-drug reward drift rates across sessions was moderate-to-good ($r = .56$ to $.72$). These findings demonstrate systematic changes in VBDM parameters with recovery status, highlighting the potential of VBDM approaches to track recovery processes and provide novel objective markers for treatment evaluation.

Oral Communication 4-5

Structure-Guided Discovery of Thiazole-Based Inhibitors of Sterol Carrier Protein-2 for Endocannabinoid Transport Modulation

Andleeb, Hina [1] ; Bauer, Caitlin E.[2] ; Medubi, Kayode M.[2] ; Poruthoor, Ashlin J.[3] ; Allen, Malika[4] ; Saxon, Eron[1] ; Leidhegner Elizabeth S.[2] ; Arnold Leggy, A.[2] ; MacKerell, Jr. Alexander D.[3] ; Hillard, Cecilia J. [4] and Cunningham, Christopher W.[1]

[1]Concordia University Wisconsin, Mequon, WI, USA, [2]University of Wisconsin-Milwaukee, WI, USA, [3]University of Maryland, Baltimore, MD, USA, [4]Medical College of Wisconsin, Wauwatosa, WI, USA.

Recent preclinical and human studies suggest that enhancing endocannabinoid (eCB) signaling through the CB1 receptor (CB1R) reduces anxiety. Direct CB1R agonists like Δ9-tetrahydrocannabinol (Δ9-THC) are effective but cause adverse effects such as postural instability and cognitive impairment. Blocking eCB transport and inactivation elevates eCB levels by an indirect mechanism. We were the first to show that the lipid transport protein, sterol carrier protein 2 (SCP-2), binds eCBs and sequesters these molecules intracellularly. Small molecule SCP-2 inhibitors are needed to interrogate the role of SCP-2 in behavior. In our preliminary studies, we observed that the 2-amino-4-phenyl thiazole, SCPI-1, potently inhibits H. sapiens SCP-2, yet showed poor metabolic stability and selectivity over fatty acid amide hydrolase (FAAH), an enzyme that is known to metabolize AEA. In this work, we designed and synthesized a series of novel thiazoles, tested their activity as inhibitors of SCP-2 and FAAH, and determined their metabolic stability in rat liver microsomes (RLMs). Rational probe design was driven by Site Identification by Ligand Competitive Saturation (SILCS). Though assay screening is ongoing, several promising agents have emerged: HAC1-35 has the highest SCP-2 affinity discovered to date (Ki 170 nM), HAC1-15 and HAC1-34 have > 100-fold selectivity for SCP-2 over FAAH, and compounds ES-1d and ES-5d have Ki < 500 nM and a microsomal stability of more than 80 % for two hours. Collectively, we have established a robust framework for probe discovery aimed at elucidating the role of SCP-2-mediated transport in eCB signaling.

Supported by NIH grant R01 MH133315

Poster Presentations

Poster 1

Dissecting the Roles of μ-Opioid Receptors in Glutamatergic and GABAergic Neurons in Ketamine Reward

Adamson, George M[1] ; Bi, Guo-hua[1] and Xi, Zheng-Xiong[1]
[1]Addiction Biology Unit, Molecular Targets and Medications Development Branch, National Institute on Drug Abuse Intramural Research Program. Baltimore MD, 21224

Ketamine [(R,S)-ketamine] is a dissociative anesthetic in clinical use since the 1970s. In 2019, the FDA approved the (S)-ketamine enantiomer (esketamine) for treatment-resistant major depressive disorder, but the neural mechanisms underlying both the antidepressant and rewarding effects of (S)-ketamine remain unclear. Recent studies suggest that μ-opioid receptor (MOR) activation mediates (S)-ketamine reinforcement in rats; however, it is unknown which populations of MOR-expressing neurons are responsible for this action. To address this question, we used Cre-LoxP strategies to selectively delete MORs from GABAergic neurons in Vgat-MOR-KO mice (Vgat-Cre × MOR-flox) or from subcortical VgluT2-positive glutamatergic neurons in VgluT2-MOR-KO mice (VgluT2-Cre × MOR-flox). Consistent with findings in rats, pretreatment with naloxone significantly reduced intravenous ketamine self-administration in both wild-type and VgluT2-MOR-KO mice. Deletion of MORs from VgluT2-positive glutamatergic neurons attenuated ketamine self-administration and shifted the ketamine dose–response curve downward, indicating a critical role for glutamatergic MOR signaling in ketamine reward. In contrast, ketamine-induced hyperlocomotion did not differ between wild-type and VgluT2-MOR-KO mice. These results reveal an unexpected glutamatergic MOR mechanism underlying ketamine reward and provide new insight into the circuitry that may contribute to ketamine's antidepressant effects. Ongoing studies will examine Vgat-MOR-KO mice in ketamine self-administration and incorporate additional behavioral assays such as CPP and locomotor sensitization. Future work will use optogenetic and chemogenetic approaches to define the specific GABAergic and glutamatergic pathways mediating ketamine reward.

Poster 2

Males and females present distinct withdrawal symptoms and NMDA receptor expression after chronic morphine treatment

Aguirre, Tiffany[1] ; Le, Amy[1] ; Crawford, Korey, E. [1] ; Perrotti, Linda, I.[1]

[1]Department of Psychology, The University of Texas at Arlington, Arlington, TX USA

A key factor contributing to ongoing opioid abuse is the severe withdrawal symptoms experienced by opioid dependent individuals. Clinical studies show that women experience more intense and longer opioid withdrawal symptoms, while preclinical findings have found inconsistencies. The purpose of this study was therefore to identify distinct withdrawal symptoms as well as explore NMDA receptor subunit dynamics in intact male and female rats after chronic morphine treatment. Male(n=14) and female (n=16) Long Evans rats were injected with escalating doses of morphine sulfate (i.p. injections of 2.5, 5, 10, 20, 40 mg/kg twice daily) for 10 days. At 12 and 24 h after the last morphine dose, withdrawal behaviors were recorded for 10 minutes. Animals were sacrificed, brain extracted, and tissue punched for Western Blots in the locus coeruleus (LC) and nucleus accumbens core (NAcC). Our results reveal distinct patterns of withdrawal symptoms in males and females. Specifically, at 12 h, females predominantly exhibited intense sniffing, wall climbing, and paw tremors, whereas immobility, genital sniffing and wet-dog shakes were predominant in males. At 24 h, females predominantly exhibited genital sniffing and intense sniffing, whereas immobility, wet-dog shakes, rearing, face rubbing, and paw tremors were predominant in males. At 12h, females showed lower expression of GluN1 than males in the NAcC, but higher in the LC. At 24 h, GluN1 expression decreased in NAcC for both sexes, but increased in the LC only in males. These results suggest that somatic withdrawal symptoms differentially manifest in male versus female rats at 12 and 24 h morphine withdrawal, as well as produce a temporal sex specific change in NMDA receptor expression during morphine withdrawal. Funding source: NIH/NIDA R15DA055201 awarded to L.I.P.

Poster 3

Comparative Behavioral Pharmacology of Illicit Nitazene Opioids

Anchondo, Olivia[1]; Shetty, Ritu[1]; Gatch, Michael[1]

[1]Department of Pharmacology and Neuroscience, College of Biomedical and Translational Sciences, University of North Texas Health, Fort Worth, TX USA

The present study aimed to characterize the *in vivo* pharmacology and abuse liability of several emerging nitazene analogs: fluetonitazene, N-pyrrolidino fluetonitazene, N-desethyl etonitazene, N-desethyl protonitazene, and methylenedioxynitazene. These synthetic opioid analogs continue to appear in the illicit drug supply with unknown pharmacological liabilities and are increasingly associated with severe intoxication and overdose. Male Sprague-Dawley rats (N=37) were trained to discriminate morphine (3.2 mg/kg, s.c.) from saline under a fixed-ratio 10 schedule of food reinforcement in a two-lever operant box. Compounds were tested across a range of doses to produce full effect, defined as full substitution (≥80% morphine-appropriate lever responding). ED50 values were calculated using log-dose linear regression, and response rates were analyzed using repeated-measures ANOVA. All compounds produced full substitution for the discriminative stimulus effects of morphine, consistent with potent mu-opioid receptor agonism and high abuse liability. Naltrexone (1 mg/kg) antagonized the morphine-like discriminative stimulus effects of all test compounds, significantly reducing morphine-appropriate responding and confirming opioid receptor involvement. Relative potency varied substantially across the compounds: some analogs demonstrated potency comparable to fentanyl; others were more comparable to morphine. Fluetonitazene exhibited markedly greater potency than either fentanyl or morphine. Overall, these data demonstrate significant abuse potential across these related nitazenes while highlighting substantial variability in potency. These findings underscore the overdose risk and unpredictability of the nitazene drug class.

Poster 4

Effects of TLR3 activation on temporal immune profiles of brain and blood in male and female FVB/B6 F1 hybrid mice

Antwi-Adjei, Philip[1] ; Shanmugam, Sambantham[1] ; Kisby, Brent[1] ; Ponomarev, Igor[1]

[1]TTUHSC, Dep't of Pharmacology and Translational Neuroscience, Lubbock, Texas, USA

Background: Alcohol use disorder (AUD) is linked to increased inflammation through the activation of receptors like toll-like receptors (TLRs). This activation can influence alcohol-related behaviors such as excessive drinking. Stimulating TLR3 with Poly(I:C) affects alcohol consumption differently in males and females in FVB/B6 F1 hybrid mice, but the immune mechanisms behind this are still unclear. This study examined how these male and female hybrid mice differ in blood and brain inflammatory responses after TLR3 activation. Methods: Mice were administered Poly(I:C), or saline, and blood, prefrontal cortex, and striatal samples were collected at 6, 24, and 48 hours for gene and protein analyses of key cytokines and chemokines. Summary: Activation of TLR3 by Poly(I:C) triggered sex- and tissue-specific time course responses in immune genes and their proteins. For example, the timing of responses for the Ccl2 and Ccl5 genes in the PFC and striatum differed between males and females, indicating sex-specific effects of these molecules on behavior. Protein levels of proinflammatory cytokines and chemokines such as CCL2, CCL5, and IL-6 increased in the striatum of both sexes, with females showing higher fold changes. MMP-9, a molecule crucial for blood-brain barrier permeability and synaptic plasticity, showed greater increases in blood gene levels and striatum protein levels of males compared to females. Conclusion: Our results revealed distinct TLR3-dependent immune gene and protein expression profiles in blood and brain between males and females and suggested different roles for these molecules in regulating alcohol consumption. We also identified CCL5 and MMP-9 as potential targets that may influence sex-specific behavior in immune modulation of alcohol consumption.

Poster 5

Trpv2 Regulates Cocaine Reinforcement and Psychomotor Activation

Applegate, Devon, T[1] ; Rahr, Thomas[1] ; Jentsch, James, D[1]

[1]Department of Psychology, Binghamton University, Binghamton, NY USA

Individual differences in sensitivity to cocaine reinforcement contribute to addiction vulnerability, yet the molecular mechanisms underlying these differences are not fully understood. Transient receptor potential vanilloid 2 (Tprv2) is a candidate modulator of cocaine-related behaviors via control of calcium-signaling. Using genetically diverse inbred mice, we combined immunofluorescence, qPCR, locomotor assays, and intravenous self-administration (IVSA) to evaluate how Tprv2 influences cocaine-related phenotypes. For IVSA, our hypothesis was that systemic pharmacological activation of Trpv2 would reduce cocaine infusions in C3HeB/FeJ mice, a strain that exhibits relatively high Trpv2 expression. We used male and female mice (n = 24) in a within-subject Latin-square design spanning 0.1, 0.5, and 1.0 mg/kg/infusion to assess Trpv2's impact on cocaine's dose-response curve. Our data reveal that Trpv2 activation selectively increases cocaine intake at the lowest unit dose, while effects at moderate and high doses are absent. Supporting analyses demonstrate parallel increases in active lever responding and stable discrimination indices, indicating reinforcement-specific effects. Moreover, activation of Tprv2 with O-1821 potentiated cocaine-induced hyperlocomotion, whereas antagonism with SET2 attenuated it. Regional mapping revealed robust expression of Trpv2 protein in multiple brain regions (mesolimbic, nigrostriatal, etc.), and we also detected substantial colocalization of Trpv2 with tyrosine hydroxylase neurons in the VTA, but this did not differ by strain. These findings motivated us towards defining cell-type-specific expression within the nucleus accumbens (NAc), a region where Tprv2 expression did vary by strain. Ongoing studies are now assessing whether Tprv2 is preferentially expressed in D1- or D2-medium spiny neurons. Together, these findings position Trpv2 signaling within the midbrain and striatum as a key regulator of stimulant reinforcement via modulation of cocaine potency, complementing its role in psychomotor activation.

Poster 6

The role of monoamines in the positive reinforcing effects of affective touch

[1]Baidwan, Tavishi; [1]Folger, Kirsten J.; [1]Foley, Carmella M.; and [1]Smith, Mark A.

[1]Department of Psychology and Program in Neuroscience, Davidson College, Davidson, NC USA.

Affective touch produces positive emotional states and serves as a critical component of social bonding. Although the circuitry of affective touch has been well characterized, the role of central monoamines in the functional consequences of affective touch has not been systematically examined. The objective of this study was to examine the role of central monoamines in the positive reinforcing effects of affective touch. To this end, male and female rats were treated with selective (GBR-12909, atomoxetine, fluoxetine) and nonselective (*d*-amphetamine, cocaine, MDMA) monoamine releasers and reuptake inhibitors and placed into an apparatus divided into two equally sized areas. When rats were in the "touch" area, they were "petted" by a blinded experimenter; when rats were in the "no touch" area, they were left undisturbed. All drugs were tested across a 10-fold dose range, and saline and oxytocin were tested as negative and positive controls, respectively. Affective touch served as a positive reinforcer as indicated by a preference for the "touch" area. Oxytocin, the nonselective monoamine reuptake inhibitor, cocaine, and the nonselective monoamine releaser, *d*-amphetamine, robustly increased the reinforcing effects of touch. To a lesser degree, the selective dopamine reuptake inhibitor, GBR-12909, increased the reinforcing effects of touch, whereas the nonselective monoamine releaser, MDMA, decreased the reinforcing effects of touch. These data suggest that drugs that increase synaptic concentrations of dopamine, particularly those with high addiction liability, increase the positive reinforcing effects of affective touch. These data also suggest MDMA may lack the entactogenic effects in rodents that are commonly reported in primates.

Poster 7

Impact of Chronic Opioid Use on the Accuracy and Interpretation of Intraoperative Neuromonitoring Signals

Baig, Aamena M.[1,2], Jahangiri, Faisal R.[1,2]

[1]Department of Neuroscience, School of Behavioral and Brain Sciences, The University of Texas at Dallas, Richardson, TX, [2]Global Innervation LLC, Dallas, TX.

Chronic opioid use is highly prevalent among patients undergoing complex spinal and neurosurgical procedures. While the acute effects of bolus opioids on neural signaling are well-recognized, the chronic adaptation of the nervous system to long-term opioid exposure remains poorly quantified in the context of Intraoperative Neurophysiological Monitoring (IONM). This study synthesizes existing clinical data to determine if chronic opioid exposure significantly alters baseline somatosensory (SSEP) and motor evoked potentials (MEP). We conducted a systematic review of peer-reviewed literature utilizing PubMed, Cochrane, and Google Scholar databases. Our analysis focused on studies that compared baseline IONM parameters, specifically amplitude and latency, between opioid-naïve patients and chronic opioid users, defined as those who have used opioids for more than three months. We synthesized data from 12 primary studies to effectively assess the correlation between opioid-induced neural plasticity and signal reliability. The analysis revealed that chronic opioid exposure is associated with a statistically significant suppression of baseline SSEP amplitudes, with mean reductions ranging from 20% to 40% compared to opioid-naïve controls. Furthermore, long-acting opioids were found to prolong N20 and P37 latencies by an average of 0.53ms ($p < 0.05$). Findings indicate that MEP thresholds are notably higher in chronic users, often requiring increased stimulation intensity to achieve reliable baselines. These changes are attributed to opioid-induced functional remodeling of sodium channels and to the collapse of dendritic spines, which together elevate the threshold for neural excitability. Chronic opioid use leads to significant alterations in baseline IONM signals that closely resemble indicators of intraoperative neural compromise. These findings clearly indicate that standard "warning thresholds" must be customized for chronic users to prevent false-positive alerts. It is essential for clinicians to adopt opioid-sparing anesthetic regimens and meticulously document any pre-existing signal attenuation to ensure the reliability of IONM as a crucial surgical safeguard

Poster 8

Investigating the role of sigma-2 receptors in cocaine-induced plasticity in nucleus accumbens

Baig, Ayesha[1] ; Mousavi, Leila[1] ; Jassim, Hebatallah[1] ; Kolber, Benedict[1] ; Eagle, Andrew[1]

[1]School of Behavioral and Brain Sciences, University of Texas at Dallas, Richardson, TX USA

Cocaine addiction is a serious health burden in the US, with no FDA-approved treatments. Cocaine use causes long-lasting changes in the brain's reward system, particularly in the nucleus accumbens (NAc), including alterations in excitatory neurotransmission and AMPA receptor phosphorylation, which contribute to behavioral sensitization and drug craving. Understanding how to reverse or prevent cocaine-induced synaptic changes is essential for developing new therapeutic strategies for addiction. Sigma-2 receptors (σ_2R) are atypical receptors that lack an endogenous ligand, are highly expressed on the ER lumen, modulate dopaminergic and glutamatergic signaling, and are known to mediate cocaine behavior. We hypothesized that the σ_2R ligand siramesine reduces cocaine-induced locomotion and synaptic plasticity. Male and female C57BL/6J mice received daily intravenous pretreatment with siramesine or vehicle control, followed 1 h later by experimenter-administered chronic cocaine or saline (10 mg/kg, IP). Locomotor activity was measured immediately in an open-field chamber for 30 minutes across multiple days. Siramesine dose-dependently inhibits cocaine-induced locomotion. To determine whether behavioral effects correspond to molecular changes, NAc tissue will be analyzed via Western blot to measure AMPA receptor phosphorylation as a molecular marker of synaptic plasticity. We are also currently replicating these studies in σ_2R (TMEM97) knockout mice to test the necessity of σ_2R in mediating cocaine's effects. These findings will clarify how σ_2R activation influences cocaine-induced neural adaptations and will provide a platform to test whether natural product derivatives of σ_2R-selective lipopeptides from marine cyanobacteria similarly affect cocaine behavior and plasticity.

Poster 9

Initial Exposure to Human Immunodeficiency Virus then Nicotine Drives Interferon Signaling in the Blood-Brain Barrier

Baig, Javaria[1] ; Campbell, Preston J[1] ; Piedras-Castro, Isabel[2] ; Zhang, Yong[3] ; Abbruscato Thomas J[3] and Almodovar, Sharilyn[1]

[1]Department of Immunology & Molecular Microbiology, Texas Tech University Health Sciences Center, School of Medicine, Lubbock, TX 79430, USA [2] Center for Biotechnology and Genomics, Texas Tech University, Lubbock, TX 79409 [3] Department of Pharmaceutical Sciences, Texas Tech University Health Sciences Center School of Pharmacy, Amarillo, Texas 79106

Around 50% of people with Human Immunodeficiency Virus (HIV) develop HIVassociated neurocognitive disorder (HAND). Compared to the general population, people with HIV (PWH) are more likely to misuse nicotine. Nicotine addiction and HIV infection damage blood brain barrier (BBB), resulting in inflammation. How HIV and/or nicotine affect BBB remains poorly understood. We hypothesize that HIV combined with nicotine detrimentally affects BBB function and integrity, compared to HIV alone. We used a 4-cell human BBB model including brain microvascular endothelial cells, astrocytes, pericytes, and microglia exposed to HIV and/or nicotine in different sequence in vitro, followed by scRNA-seq analysis using Gene Set Enrichment Analysis. Intriguingly, we found significantly upregulated expression of interferon (IFN)-gamma and -alpha genes in all cell types except for microglia in HIV followed by nicotine and in quiescent vascular in HIV-treated BBB. In nicotine-treated BBB cells, HIV induces IFN signaling when BBB is exposed to HIV before nicotine. Our preliminary work highlights the complex dysregulation of BBB integrity and function in PWH with pre-existing or subsequent nicotine addiction. Therapeutic targets must be identified to help PWH with nicotine addiction and reduce progression of HAND

Poster 10

Sex-dependent effects of drinking alcohol during the withdrawal period on withdrawal symptom severity in rats

Bankston, Kylee[1]; Hill, Regan B[1]; Gonzales, Rueben A[2,3] Monfils, Marie H[1,2]; Lee, Hongjoo J[1]

[1]Department of Psychology, [2]Institute for Neuroscience, [3]Division of Pharmacology and Toxicology, University of Texas, Austin, TX, USA.

Many individuals with Alcohol Use Disorder (AUD) become physically dependent on alcohol, which entails experiencing withdrawal symptoms in its absence. It is thought that physical dependence contributes to the maintenance of AUD, as individuals will drink alcohol to relieve aversive symptoms of withdrawal— a type of learning known as negative reinforcement. A rodent model of AUD induces physical dependence via chronic intermittent ethanol (CIE) vapor exposure but does not account for the negative reinforcement learning that is present in human cases. Thus, the aim of this experiment was to determine if drinking alcohol during the withdrawal period models negative reinforcement learning in rats. To induce physical dependence, Long-Evans rats (n=78; 46 males) were exposed to CIE vapor (14 hrs on:10 hrs off daily) 5 days a week for 4 weeks after being conditioned to drink 15% ethanol in the homecage. To model negative reinforcement, rats were given access to a bottle containing 15% ethanol for 2 hrs during withdrawal (i.e., 6-8 hrs post-vapor cessation) twice a week. As a control, half of the subjects were exposed to air instead of vapor and half of each vapor/air group were not given alcohol during the withdrawal period. Withdrawal symptom severity was measured weekly with behavioral scoring of posture, tail stiffness, irritability, and ventromedial distal (VMD) limb flexion during the withdrawal period. We found that drinking alcohol during the withdrawal period reduced withdrawal symptom severity in males, particularly by the 4th week (Mdiff=1.39±0.41, $t(69)=3.39$, $p=0.02$), but not females. Interestingly, vapor groups drank less during withdrawal than air groups ($F(1,36)=16.22$, $p<0.001$), suggesting alcohol became aversely associated with the withdrawal state. These findings suggest that oral access to alcohol during withdrawal is an insufficient model for negative reinforcement in rats.

Poster 11

The Evidence for a lack of biological sex differences in Isoflurane anesthesia and Methamphetamine Self-Administration after accounting for individual and group-level variability

Basak, Kona[1] and Martin, Job[2]

[1]Department of Chemistry & Biochemistry, Rowan University, Glassboro, NJ USA; [2] Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ USA.

We recently developed a new model termed the MISSING (Mapping Intrinsic Sex Similarities as an Integral quality of Normalized Groups) model, which revealed no biological sex differences in psychostimulant-induced locomotor activity when individuals and their respective behavioral groups were considered. However, that study focused on locomotor activity induced by a psychostimulant. It is unclear if the MISSING model would be applicable to other types of behavioral effects. Our aim for this study was to validate the MISSING model for isoflurane-induced anesthesia and methamphetamine (METH) self-administration. We employed male (n = 20) and female (n = 20) Long Evans rats for the isoflurane study and from these, we used n = 10 males and n = 7 females for the METH self-administration study. We conducted jugular catheterization surgeries under isoflurane anesthesia followed, after recovery, by METH self-administration (0.1 mg/kg/infusion, FR 1). We assessed several variables. We employed gaussian mixtures model clustering analysis of principal components (PCA-GMM clustering) to determine distinct clusters, if any, after which we conducted Two-way ANOVA with factors being sex and cluster to determine if there were sex differences within identified clusters (MISSING model). PCA-GMM revealed two distinct mixed-sex groups for both isoflurane anesthesia and METH self-administration. For all the variables assessed, there were no sex differences within each identified cluster. Our study validates the MISSING model for drug effects that are related and unrelated to behavior.

Poster 12

Identification of EphB1/2 Tyrosine Kinase Inhibitors for Peripheral Neuropathic Pain

Benson, Harrison[1], Oritz, Yuma[1], Ojo, Bisola[1], Frimpong-Manson, Kofi[1], Khodavirdilou, Lida[1], Tareq, Syed[1], Sy, Simon[1], Kaur, Komalpreet[1], Pournaghi, Marjaneh[1], Akter, Ayesha[1], Patel, Dhaval[1], Diab, Hanin[2], Thompson, Jon[2], Abbruscato, Thomas[1], Ewida, Heba[1], Wilkerson, Jenny[1], Ahmed, Mahmoud Salama[1]

[1]Department of Pharmaceutical Sciences, Jerry H. Hodge School of Pharmacy, TTUHSC.
[2] School of Veterinary Medicine, Texas Tech University, Amarillo, TX

Although opioids are commonly used for peripheral neuropathic pain (PNP), including chemotherapy-induced peripheral neuropathy (CIPN) treatment, they are only partially efficacious for short-term pain management, and the response to their long-term use is widely variable. Peripheral neuropathy is associated with multiple pathophysiological iterations leading to pain hypersensitivity. EphB receptor tyrosine kinases had been validated for modulation of neuropathic and chronic inflammatory pain models. Therefore, our hypothesis is to elucidate the molecular mechanisms associated with administration of novel EphB1/2 tyrosine kinase inhibitors to reverse pain signaling associated with CIPN and injury-induced peripheral neuropathy. We recruited high throughput virtual screening against EphB1 and EphB2 tyrosine kinase catalytic binding domains to identify thienopyridine and thienopyrazine based scaffolds. Next, we designed and synthesized 30 novel EphB1/2 tyrosine kinase inhibitors with IC50 values ranging from 250-200 nM via ADP-Glo based screening assay. This was associated with full profiling for CNS-MPO scoring coupled with in vitro blood brain barrier permeability assays to reveal two lead analogs (HBA-020 and HBA-030) that have good BBB permeability profiles. Furthermore, kinome profiling against 140 kinases validated the selectivity of HBA-020 towards EphB1/2 tyrosine kinase, with no inhibition to EphB3 nor EphA1-5. Oral administration of HBA-020managedto reverse paclitaxel-induced mechanical allodynia in a dose dependent manner in vivo. Additionally, HBA-020 was able to reverse Chronic constriction injury (CCI)- induced mechanical allodynia and thermal hyperalgesia in vivo.

Poster 13

Optimizing MDMA: Neurochemical Mechanisms Underlying Prohedonic Efficacy and Abuse Potential

Bloom, Nicholas, B[1] , LaMalfa, Kayleigh, S[1] , Blough, Bruce, E[2] , Kangas, Brian, D[1]

[1]McLean Hospital, Harvard Medical School [2] Center for Drug Discovery, RTI International

Within psychedelic research, there is great interest in 3,4-methylenedioxymethamphetamine (MDMA) for conditions such as PTSD and depression/anhedonia. However, MDMA's abuse potential remains a significant barrier to its clinical viability. Unlike typical psychedelics, MDMA is a nonselective releaser of both serotonin and dopamine and this neurochemical profile is strongly linked to its reinforcing effects. To parse mechanisms underlying these unwanted (abuse-related) effects from those desirable (therapeutic), we compared MDMA with PAL-314 (a relatively more dopamine-selective releaser) and PAL-335 (a relatively more serotoninselective releaser) in female and male Long Evans rats. A touchscreen-based Probabilistic Reward Task (PRT) and high- vs. low-dose MDMA drug discrimination were used to probe anhedonic- and abuse-related effects, respectively. In the PRT, all drugs were similarly prohedonic, but at the highest dose tested (10 mg/kg) MDMA and PAL-335 (but not PAL-314) impaired performance. In drug discrimination, rats trained with a high dose (5 mg/kg) of MDMA required fewer sessions to acquire the discrimination than the low dose (1 mg/kg) group. In both cases, MDMA produced expected dose-dependent interoceptive cues. Ongoing substitution testing with PAL-314, PAL-335, and other dopamine and serotonin releasers that vary in selectivity will aim to identify relative neurochemical contributions to MDMA's abuse potential. Taken together, the present studies highlight the importance of determining the role of neurochemical drivers in both MDMA's desirable prohedonic efficacy and unwanted abuse-related effects. In turn, this approach might lead to a more comprehensive understanding of MDMA's profile and inform ways in which it might be modified to optimize its clinical viability.

Poster 14

Suvorexant reverses the acute effects of methamphetamine on sleep and cognition in rhesus monkeys

Borgatti, Daniel A[1 2]; Rowlett, James K[1 2 3], Berro, Lais F[1 2 3]

[1]Department of Psychiatry and Human Behavior, UMMC, Jackson, MS USA; [2] Graduate Program in Neuroscience, UMMC, Jackson, MS USA; [3] Center for Innovation and Discovery in Addictions, UMMC, Jackson, MS USA

Methamphetamine use has been shown to negatively affect sleep and cognitive function. We hypothesized that methamphetamine-induced sleep disruption (MISD) would cause cognitive deficits via an orexinergic mechanism. Monkeys (n=6) were fitted with actigraphy and actigraphy-based sleep was recorded during baseline and after administration of saline or methamphetamine, i.m., at 15:00h. At 17:00h, monkeys were given the orexin antagonist, suvorexant, p.o. The next day, they completed the intra-dimensional/extra dimensional (ID/ED) set-shifting or delayed non-match to sample (DNMS) task. Methamphetamine disrupted sleep and sleep impairment was associated with next-day performance deficits on the ID/ED task. Suvorexant improved MISD and reversed performance deficits. Acute methamphetamine administration did not affect DNMS performance. Our study showed MISD performance deficits on set-shifting that could be reversed by orexinergic treatment of associated sleep impairments.

Poster 15

Effects of early life stress on adult risk-taking behavior

Bow, Hannah F[1] ; Kelly, Megan A[2] and Orsini, Caitlin A[2]

[1]Interdisciplinary Neuroscience Program, University of Texas at Austin, Austin, TX USA; [2] Department of Psychology, University of Texas at Austin, Austin, TX USA.

Adverse childhood experiences are a risk factor for an estimated 30% of adult-onset psychiatric diseases, including substance use disorders, anxiety, Attention-Deficit/Hyperactivity Disorder (ADHD), and bipolar disorder. Many of these same conditions are characterized by maladaptive risk-based decision making. Thus, studying the ways in which early adversity alters adult risk-taking behavior may reveal novel therapeutic targets. To this end, this study examined the effects of the limited bedding and nesting (LBN) model of early resource scarcity on adult risk-based decision making in male and female Long-Evans rats. Litters were culled to equal numbers of male and female pups, then randomly assigned to control or LBN conditions. Maternal behavior was video monitored continuously from postnatal day zero (P0) through P21. The LBN manipulation was implemented from P2 through P14. There were no group differences in pup weights on P7, but by P14, LBN pups weighed significantly less than control pups. This was only a transient effect, however, as there were no group differences by P21. On P21, rats were weaned and maintained on standard housing conditions until adulthood. As adults, rats were trained and tested on the Risky Decisionmaking Task (RDT) in which rats choose between a "safe" lever that yields a small food reward and a "risky" lever that yields a large food reward paired with an increasing chance of a mild footshock. There were no group differences in task acquisition, suggesting instrumental learning was not affected by the LBN manipulation. Upon reaching behavioral stability, group differences in percent risky lever choice will indicate that early life adversity, in the form of LBN, has long-lasting effects on risk-taking behavior. These findings may highlight neurobehavioral pathways by which early adversity contributes to later life psychiatric disorders.

Poster 16

Sex Differences in the Ventilatory Depressant Effects of Gabapentin Alone and in Combination with Fentanyl in Rats

Bravo, Gilberto[1,3], Mijares, Abram E.[1,3], Grisham, Amanda K.[1,3], Patel, Maya N.[1,3], Shi, Yonggong[1,3], Mazhar, Talha[1,3], Varma, Harsha K.[1,3], France, Charles P.[1,3], and Hiranita, Takato[1,3]

Departments of Pharmacology[1] and Psychiatry[2] , and Addiction Research, Treatment and Training Center of Excellence[3] , University of Texas Health Science Center at San Antonio

While the toxicity of gabapentinoids (gabapentin and pregabalin) alone is limited, they are increasingly detected in opioid overdose victims. However, the ability of gabapentinoids to alter opioid-induced hypoventilation and whether sex differences exist in these interactions have not been rigorously characterized. The objective of this study was to determine whether gabapentinoids alone alter ventilation, whether they modify opioid-induced hypoventilation, and whether these effects differ between males and females. Whole-body plethysmography was used to measure ventilation (minute volume [VE]) under normal air in adult male and female rats (n = 8/sex). After a 30-minute habituation period, saline or drug was administered intravenously and ventilation was recorded for 60 minutes. Baseline VE was higher in females than in males (725 and 414 mL/min/kg, respectively). Fentanyl (0.1 mg/kg) significantly decreased VE to approximately 50% of saline control in male and female rats. The duration of hypoventilation by fentanyl was 8 and 15 minutes in male and female rats, respectively. No dose of gabapentin (100, 178, and 320 mg/kg) significantly decreased VE in males, whereas larger doses (178 and 320 mg/kg) slowly produced a significant and sustained decrease in VE in females to 70% of saline control. Similar results were obtained with pregabalin (32, 100, and 178 mg/kg). In males, gabapentin did not alter the magnitude of fentanyl-induced hypoventilation but prolonged its duration. In females, gabapentin did not alter the magnitude of fentanyl-induced hypoventilation, and the duration of hypoventilation was similar to that produced by gabapentin alone. These results indicate sex differences in the ventilatory depressant effects of gabapentin alone and in combination with fentanyl. This study was supported by USPHS grant R01DA058018 (TH) and Welch Foundation grant AQ-0039 (CPF)

Poster 17

Effects of Acute and Protracted Oxycodone Withdrawal on Perineuronal Nets and Dynorphin-A

Bressler, Felise J.[1] , Jewanee, Sarah S.[1] , Schwartz, Ben[1] , & Nguyen, Jacques D.[1]

[1]Baylor University, Department of Psychology and Neuroscience

Prescription opioid use and misuse has contributed to the ongoing opioid epidemic in the United States, and the negative consequences of oxycodone addiction on public health have been exacerbated. However, the behavioral and neurobiological outcomes of opioid withdrawal are not fully understood. In this study, 48 Adult male Wistar rats were divided into three groups: High-Dose oxycodone (4 mg/kg, s.c.; n=16), Low-Dose oxycodone (2 mg/kg, s.c.; n=16) and a saline control group (0 mg/kg, s.c.; n=16). Subjects were injected twice daily for 6 days and once on day 7 for a total of 13 injections. Following injections, subjects underwent either a 24-hour abstinence period or a 30-day abstinence period. We hypothesized that subjects exposed to repeated oxycodone injections compared to subjects injected with saline vehicle will exhibit withdrawal-like effects. Furthermore, subjects during 24-hour abstinence will exhibit more withdrawal-like effects and have differing results in perineuronal nets and dynorphin-A compared to the 30-day abstinence subjects. Data confirmed that subjects exhibited a dose-dependent tolerance to the antinociceptive effects of oxycodone. During the 24-hour abstinence period, there was a dose-dependent change in weight change scores and significant differences in locomotor activity between groups. Data demonstrates dose-dependent hyperalgesia during the 24-hour abstinence period as shown by significant differences in tail withdrawal latencies. During the 30-day abstinence period, both tail withdrawal latency and locomotor activity were nonsignificant, suggesting a normalization of behavior after 30 days of abstinence. Preliminary results suggest a difference in perineuronal nets and dynorphin-A between saline and drug conditions. Ongoing analyses involve long-access self-administration of oxycodone to further elucidate neurobiological effects of oxycodone withdrawal during a prolonged contingent paradigm. This research was supported by NIH grant DA047413.

Poster 18

A Test of the Substitutability between Cocaine and Social Interaction in Male and Female Rats

Brooks, Eliza M[1;] Bird, Toni[2], Rego, Felipe[1], Olivero-Gomez, Claudia[2], Kearns, David N[2]

[1] Department of Neuroscience, American University, Washington, DC USA; [2] Department of Psychology, American University, Washington, DC USA.

Previous research found that cocaine and social interaction were substitutes in male rats. The goals of the present study were to 1) compare males and females on the substitutability of cocaine and social interaction, and 2) investigate how the relationship between these reinforcers potentially changes after periods of extended, intermittent access to cocaine. We hypothesized that rats would increase their allocation of behavior toward cocaine following intermittent access. Long-Evans rats chose between cocaine and social interaction available at varying prices. In male rats (N=16), the allocation of behavior shifted towards the cheaper option upon price changes (p=.027), indicating that cocaine and social interaction were partial substitutes. In contrast, female rats (N=17) did not systematically alter their allocation of behavior (p=.591), suggesting cocaine and social interaction were independent goods. Female rats, but not male rats (p<.0001), escalated cocaine self-administration over 12 days of 6-hour intermittent access to cocaine. While extended, intermittent access did not change the way reinforcers interacted with either sex, when choice procedures were reintroduced, cocaine and social interaction were again partial substitutes in male rats, but independent goods in female rats (p=.020). This study builds upon previous research on the economic relationship between social reinforcers and drug reinforcers by extending the results to female rats. While prior research indicates that social interaction is protective against cocaine self-administration, the results of this study suggest that this may be modulated by sex. Future research will be needed to determine why cocaine and social reinforcement interact differently in males and females.

Poster 19

Neurocircuitry-based Drug Discovery for Alcohol Use Disorder

Buchanan, Katherine A[1,2]; Borzou, Ardavan; Martinez, Vena K[2] ; Sun, Hong[2] ; Fox, Robert G[2] ; Carr, Crystal C[2] ; Merritt, Christina R[2] ; Miller, Sierra N; Kasper, James M; Cunningham, Kathryn A[2,3]; Hommel, Jonathan D[2,3]

[1]Department of Biochemistry, Cellular, and Molecular Biology; [2] Center for Addiction Sciences and Therapeutics; [3] Department of Pharmacology and Toxicology, The University of Texas Medical Branch, Galveston, TX USA

Alcohol misuse is a prominent public health concern contributing to 3 million deaths globally and over 200 acute and chronic diseases and injury-related conditions. The most common form of alcohol misuse is binge drinking which is defined as a drinking pattern leading to blood alcohol concentrations of at least 0.08% within 2 hours. Binge drinking contributes to an increased risk of developing an alcohol use disorder later in life. Based on the 2023 National Survey on Drug Use and Health, approximately 10% of individuals ages 12 and older had alcohol use disorder. As alcohol misuse is known to disrupt executive function and decision making, studies have shown the medial prefrontal cortex (mPFC) is strongly implicated in alcohol misuse behaviors. Neural activity in the mPFC following ethanol exposure primarily inhibits neural activity, however, we expanded analytical strategies of local mPFC neural populations to better understand these effects on a neural network level. To date, results show calcium intensity clusters and fluctuates across time. As the mPFC is commonly implicated in behaviors related to drugs of abuse, we also hypothesized behavior would correlate to calcium intensity measurements. We observed possible correlations and anti-correlations between behavior and UMAP-based neuronal clustering. We introduce a binge-like dose of ethanol intraperitoneally to visualize changes in the mPFC via in vivo calcium imaging in a male Sprague-Dawley rat model (n=272 neurons across 3 animals). Our research investigating how the mPFC is involved in alcohol use on the neural network level will continue to pave the way for future studies pursuing therapeutic targets for alcohol use disorder.

Poster 20

Occurrence of Toxic Metals in Prenatal, Postnatal, and Infant Supplements

Buice, Taylor[1], Krutsch, Kaytlin[2], Bailoo, Jeremy D.[1], Deonarine, Amrika[3]

[1]Department of Cell Biology & Biochemistry, Texas Tech University Health Sciences Center, Lubbock. Lubbock, TX, USA; [2]InfantRisk Center, Department of Pediatrics, Texas Tech University Health Sciences Center, Amarillo. Amarillo, TX, USA; [3]Department of Civil, Environmental and Construction Engineering, Texas Tech University, Lubbock, TX, USA.

Approximately 70% of pregnant women use prenatal and postnatal supplements; however, under the Dietary Supplement Health and Education Act, these products are not subject to pre-market approval by the U.S. Food and Drug Administration. As a result, supplements may contain toxic metals—including arsenic (As), cadmium (Cd), lead (Pb), chromium (Cr), nickel (Ni), and selenium (Se)— that pose risks during critical windows of fetal and infant development, including neurotoxicity and impaired neurodevelopment. Chronic low-level exposure to these metals produces biological and behavioral effects that parallel those observed with substance use, including altered dopaminergic signaling, deficits in cognition and executive function, low birth weight, and long-term behavioral dysregulation. To assess possible metal exposure, a variety of prenatal, postnatal, and infant supplements were microwave-digested, then analyzed by Inductively Coupled Plasma Mass Spectrometry. The maximum contaminant levels (MCLs) for drinking water established by the U.S. Environmental Protection Agency were used as benchmarks for safe consumption levels. In some prenatal supplements, concentrations of As (0.2±0.1 ppm), Cd (0.05±0.02 ppm), and Pb (1.0±1.3 ppm) exceeded their MCLs (As: 0.01 ppm, Cd: 0.005 ppm, Pb: 0.01 ppm). Postnatal products showed similar elevations, and infant supplements contained elevated Cr (0.2 ppm), Ni (1.1 ppm), and Se (0.08±0.08 ppm) (MCLs, Cr: 0.1 ppm, Ni: 0.07 ppm, Se: 0.05 ppm). These findings indicate that pregnancy-related supplements may represent an underrecognized source of toxic metal exposure with toxicological effects that mirror those of substance use, underscoring the need for stricter oversight during vulnerable developmental periods.

Poster 21

Effects of Rgs7bp knockout on voluntary alcohol intake in male and female mice

Diego E Cecena[1] ; Paige C Bensing[1] Caleb Tang[1] ; Kirill A. Martemyanov[2] and Eric P Zorrilla[1]

[1]Department of Translational Medicine The Scripps Research Institute, La Jolla CA USA; [2] Dept Physiology and Biophysics, U Miami School of Medicine

Alcohol use disorder (AUD) is a prevalent, growing public health issue in need of novel therapeutic targets. Regulator of G-protein Signaling (RGS) proteins are intracellular regulators of G-protein-coupled receptor (GPCR) signaling, and RGS7-binding protein modulates signaling of RGS7 subfamily proteins (RGS6, 7, 9, 11) via subcellular localization of their Gβ5 partner complexes. The presented study test the hypothesis that RGS7BP influences voluntary alcohol consumption using adult male and female Rgs7bp knockout (KO; MGI: 3373065) and wild-type (WT) mice (KO: n = 12; WT: n = 9). Mice received ad libitum chow and water plus intermittent (3x/week, 24-hr/day) access to ethanol (IAE, 20% v/v ethanol) [EtOH] using a two bottle choice (vs. water) paradigm. Genotype effects on EtOH intake and preference, body weight, and EtOH clearance were assessed across 10 weeks. After 10 weeks of exposure, genotypes were compared for negative affective behavior during acute withdrawal in the elevated plus-maze, marble burying, bottle brush, and forced swim tests. Across the 24-hour access period, sRgs7bp KO drank more ethanol (g/kg) than wt (Genotype, p .05).The results support the hypothesis that Rgs7bp modulates daily ethanol intake and negative affective behavior (anxiety tendencies) under intermittent access.

Poster 22

Investigating the impact of astrocytic OCT3 deletion on the locomotor stimulant effects of amphetamine and astrocyte expression in substantia nigra

Gopakumar Changarathil, Lynette C. Daws

Departments of Cellular & Integrative Physiology and Pharmacology

Organic Cation 3 Transporter (*OCT3*) is a low-affinity, high-capacity bidirectional membrane transporter that we, and others, have shown to be important in mediating amphetamine-induced dopamine (DA) efflux as well as sensitization to the locomotor stimulant and reinforcing properties of amphetamine. Our studies, using genetic and pharmacological manipulations, indicate that *OCT3* could be a novel target to treat amphetamine-type stimulant use disorders. *OCT3* is expressed in both neuronal and glial populations, however, the role of these distinct cell types in the actions of amphetamine remains unknown. Here we begin to fill this knowledge gap by investigating the role of *OCT3* expressed on mature astrocytes by generating a transgenic aldehyde dehydrogenase family 1 member L1 (*Aldh1l1)CreER/OCT3-floxed* mouse line to conditionally ablate *OCT3* from *Aldh1l1* expressing mature astrocytes. Preliminary data suggest that male and female *Aldh1l1CreER/OCT3* mice are more sensitive to the locomotor stimulant effect of amphetamine relative to wildtype (no-*CreER*) controls, as evident by an upward shift in the dose-response curve. These results are consistent with a reduced ability *Aldh1l1CreER/OCT3* mice to recapture amphetamine-evoked DA release, allowing DA to remain in the extracellular milieu longer, thereby sustaining DA signaling. These preliminary findings suggest that astrocytic *OCT3* contribute to the locomotor stimulant effects of amphetamine. In a separate cohort of amphetamine naïve mice, histological analysis conducted one month after tamoxifen-induced *Aldh1l1CreER/OCT3* knockdown (a timepoint parallel to behavioral experiments) revealed a marked increase in the number of glial fibrillary acidic protein positive (*GFAP+*) astrocytes in the cerebral peduncle lying directly below the substantia nigra (SN). The cerebral peduncle, of which the SN is considered part, communicate to control motor function. While the mechanistic function of glial OCT3 in this region remains to be determined, it is tempting to speculate that they are important in maintaining DA homeostasis. Taken together, our results suggest that astrocytic *OCT3* may be important for the acute behavioral response to amphetamine-type psychostimulants, but also long-term glial homeostasis in key brain regions controlling motor activity. Our initial exploratory studies encourage further investigation of astrocytic *OCT3* as a novel cellular target for modulation of amphetamine's behavioral effects and potentially mitigating associated neuroinflammatory processes. Grant support: 5 R01 DA055703 to LCD. GC is supported by T32 DA031115

Poster 23

Identifying Orbitofrontal Cortex Neural Activity Patterns Underlying Impulsive Action and Substance Use Disorder Risk

Chavarria, Ana Sofia[1,2], Romero, Angelica[1], Galvan, Karla[1], Batson, Serina[1], Moschak, Travis[1]

[1]Department of Biological Sciences, University of Texas at El Paso; [2] The SMARTMIND Program

Substance use disorders (SUDs) remain a major public health crisis, affecting millions each year and contributing to significant medical, social, and economic burden. One of the strongest behavioral predictors of SUD vulnerability is impulsive action which has been shown to trace back to activity in the orbitofrontal cortex (OFC). Understanding the neural mechanisms underlying impulsivity is therefore critical for identifying early risk factors and informing preventative strategies. To investigate OFC involvement in impulsive behavior, Wistar rats were trained in an operant cue-titration task in which premature lever presses before cue onset served as the primary measure of impulsivity. Across this cohort, no significant sex-related differences in impulsive responding were observed. To characterize the neural correlates of impulsive action, the rats received stereotaxic surgery for viral delivery of GCaMP6s into the OFC followed by GRIN-lens implantation, enabling in vivo calcium imaging during task performance. Preliminary imaging results revealed that OFC neurons showed heterogeneous activity patterns, with inhibited neuronal activity tracking trial initiation on trials that ultimately resulted in late-response errors. In contrast, excited and non-phasic neurons displayed no consistent relationship to behavioral outcomes in the operant chamber. These findings suggest that decreases in OFC activity may precede or contribute to disruptions in appropriate response timing. Together, this work establishes both a behavioral assay of impulsive action, and an OFC calcium-imaging framework for identifying neural signatures associated with error-prone responding. These preliminary findings lay essential groundwork for future studies examining how physiological or pharmacological manipulations alter OFC-dependent impulsivity and SUD-relevant decision-making processes.

Poster 24

Alprazolam exposure during adolescence dysregulates morphine-reward sensitivity and second messenger signaling in the VTA-NAc pathway in female mice

Cho, Teresa A[1] ; Cardona-Acosta, Astrid[2] , Meisser, Noëlle[1] and Bolaños-Guzmán, Carlos[1]

[1]Department of Psychology and Brain Sciences, Texas A&M University, College Station, TX; [2] College of Pharmacy, University of Texas, Austin, TX

Alprazolam (Xanax; ALP) is a potent, short-acting benzodiazepine (BDZ) commonly prescribed to treat anxiety disorders. However, despite concerns regarding the role it plays in fueling the opioid epidemic, clinical and neurobiological research has yet to systematically assess the effects of ALP exposure in females. This study aimed to investigate the influence of repeated ALP exposure during adolescence on drug-reward and stress response in female mice. Female adolescent [PD35] C57BL6/J mice were pretreated with ALP (0, 0.5, 1.0 mg/kg) twice daily for 14 days. Changes in morphine (MOR; 2.5, 5.0 mg/kg) reward sensitivity were then measured using the conditioned place preference paradigm (CPP). 24-h following the CPP assay, mice were sacrificed to assess the effects of ALP on the extracellular signal regulated kinase 1/2 (ERK1/2) pathway. Results indicate that ALP exposure during adolescence potentiates the rewarding properties of MOR in a dose-dependent manner. In addition, molecular assays showed dose-dependent effects in the expression of downstream targets mTOR and AKT. When assessing the effects of ALP exposure on the progression of the estrous cycle, ALP-pretreated adolescent females trended toward a longer follicular phase, but no significant differences were found. Another cohort was used to assess ALP's effects on naloxone-precipitated MOR withdrawal. Withdrawal scores from both ALP-SAL and ALP-MOR groups were not different when compared to their controls, indicating that ALP does not significantly modulate the experience of MOR withdrawal in adolescent female mice. Together, these findings demonstrate that exposure to ALP during adolescence exerts dose-dependent dysregulation of morphine-reward sensitivity and second messenger signaling within the VTA-NAc, a pathway highly implicated in the regulation of drug reward, in female mice.

Poster 25

Stressful Life Events and Parenting Behavior Influence Adolescent Substance Use

Chupp, Kayla C[1] ; Barry, Chris T[2] ; Charles, Nora E[1]

[1]College for Health, Community, and Policy, UT San Antonio, San Antonio, TX USA; [2] Department of Psychology, Washington State University, Pullman, WA USA

Substance misuse costs upwards of $700 billion and contributes to the loss of over 700,000 lives per year according to National Survey on Drug Use and Health estimates (SAMHSA, 2017). Adolescent substance use can affect current health and lead to longer term problems. Susceptibility to risky substance use behavior is associated with childhood traumatic events (Zarchev et al., 2022) and stressful life events (Low et al., 2012), as well as poor parenting behaviors (Pinquart & Lauk, 2024). Objectives: The current study explored the relationship between adolescent substance use (e.g., frequency, consequences of use), stressful life events, and parenting styles. Methods: The sample (n = 316) are adolescents in a boot camp program for at-risk youth who completed the Youth Risk Behavior Surveillance Survey (YRBSS; CDC, 2016) about their substance use, the Alabama Parenting Questionnaire (APQ; Frick, 1991) for participant-reported parenting behaviors, and the Stressful Life Events Schedule (SLES; Williamson, 2003) about their exposure to stressful events. Results: Heavier alcohol use ($r(314) = .16$, $p = .008$) and marijuana use ($r(314) = .30$, $p < .001$) were positively related to past stressful experiences. Adolescents who reported use of other substances also reported more past stressful experiences (Mdn = 24) than those who did not (Mdn = 18), $U = 8799.0$, $p < .001$. More frequent alcohol ($r(314) = .19$, $p = .001$) and marijuana ($r(314) = .27$, $p = < .001$) use were also positively related to poor parental monitoring, and more frequent marijuana use ($r(314) = -.22$, $p < .001$) was negatively related to parent involvement. Adolescents who used other substances reported poorer parental monitoring (Mdn = 29) and less parental involvement (Mdn = 48) than those who did not use other substances (Mdn = 26; Mdn = 54), $U = 9292.0$, $p < .001$; $U = 10773.5$, $p = .03$. Conclusions: Mitigating the effects of past stressful events and focusing on the improvement of parenting behaviors may reduce at-risk youth substance use and associated problems.

Poster 26

Cocaine-Seeking Behavior After Abstinence: Differential Roles of the Prelimbic Cortex and Anterior Insular Cortex in Punishment Resistance and Relapse

Delgado, Emma N[1], Smoak, Marina[1], Romero, Angelica[1], and Moschak, Travis[1]

[1]Department of Biology, The University of Texas at El Paso, TX, USA

Substance Use Disorders (SUD) are characterized by compulsive drug seeking despite punishment or adverse experiences, driven in part by disruptions in internal homeostasis and decision-making circuitry. The prelimbic cortex (PrL) and anterior insular cortex (INS) are key Salience Network (SN) cortical hubs involved in decision-making, interoception, and action selection, making them strong candidates for understanding punishment-resistant cocaine (C) seeking. This study was conducted to assess the neural activity and determine the role of insula-prelimbic projections (the SN) in drug craving and relapse, using progressive ratio (PR) and self-administration (SA) of cocaine infused with histamine (C-H). We hypothesize that SN engagement in C rats will be heightened during tasks involving greater aversive effects (such as extinction and C-H) compared to tasks involving effort or reward alone, reflected by increased phasic activity. After abstinence, 33 Long Evans rats (n=17F and 16M) underwent extinction, SA, and PR tasks, recorded in operant chambers via nose pokes, and data was processed by CalmAn and NeuroExplorer. Calcium imaging was captured via miniscope camera, observed through a GRIN lens. Stereotaxic surgery was performed to infuse Credependent GCaMP6s and retrograde adeno-associated virus encoding Crerecombinase. In addition, catheter surgery was completed to allow for SA of C and C-H. Preliminary data from suggests that extinction and SA with C-H conditions result in the greatest differences in neural firing between water-saline and C groups. It was also found that in the extinction and PR tasks, C rats exhibited more excitatory and inhibitory phasic neurons, while control rats had a higher proportion of nonphasic neurons. In contrast, the SA with C and SA with C-H sessions showed an inversion of this pattern. The continued collection of data may clarify SN dynamics driving punishment-resistant drug seeking and relapse vulnerability.

Poster 27

Acute Effects of Prenatal Alcohol and Cannabinoid Exposure on Fetal Development

Domen, McKay M.[1]*, Rouzer, Siara K.[1], Miranda, Rajesh C.[1]

[1]Department of Neuroscience & Experimental Therapeutics, Texas A&M Naresh K. Vashisht College of Medicine, Bryan, Texas, USA

Alcohol and cannabinoids are two of the most consumed psychoactive substances today, which subsequently increases risk for prenatal exposure of developing fetuses to these substances. One common symptom shared by prenatal exposure to either alcohol or cannabinoids is intrauterine growth restriction. To investigate acute gestational outcomes, Pregnant C57Bl/6J mice were assigned to one of four groups: drug-free control, alcohol-exposed, cannabinoid-exposed, or alcohol+cannabinoid exposed. Drug exposure occurred daily between Gestational Days 12-14. On each day of exposure, dams first received an intraperitoneal injection of cannabinoid agonist CP-55940 (750ug/kg) or volume-equivalent saline. Then, dams were placed in vapor chambers for 30 minutes to inhale either ethanol or room air. On Gestational Day 18, dams were euthanized for cesarean section and extraction of fetal sacs. Viable fetuses were evaluated on body weight, placental weight, liver weight, and appearance. All forms of prenatal drug exposure reduced weight gain in dams following exposure windows. Fetal reabsorptions occurred more often in dams who experienced alcohol and/or cannabinoid exposures. Exposure to either alcohol or cannabinoids increased viable pup weights on Gestational Day 18, while co-exposure did not change average pup weight from controls. Exposure to alcohol or cannabinoids reduced fetal liver efficiency in viable pups compared to co-exposed and control offspring. Finally, alcohol exposure alone significantly reduced placental efficiency from control and co-exposed litters, while cannabinoid exposure alone produced no differences from other exposures. Our preliminary investigation indicates that both single-drug exposures and co-exposure reduce viable offspring per litter.

Poster 28

Blocking Freezing Behavior in Male and Female C57BL/6J Mice

Folger, Kirsten J.; [1] Romack, Caroline; [1] Cooper, Katelyn; [1] Key, Emma; and [1] Rice, Onarae

[1] Department of Psychology and Neuroscience, Furman University, Greenville, SC USA

Stress and stress-related behaviors are risk factors for substance use disorder and are distinguishing features of post-traumatic stress disorder. The hippocampus, prefrontal cortex, and amygdala are brain regions associated with both stress behaviors and addiction. Interactions between these brain regions are facilitated via dopaminergic projections from the ventral tegmental area. The dopamine D3 receptor has been implicated in the hyperexcitation that occurs in the amygdala leading to the expression of hypervigilant behaviors. This study explored the efficacy of a dopamine D3 receptor antagonist, SB-277011A, in blocking freezing behavior in male and female C57BL/6J mice. Forty mice (20 male and 20 female) were exposed to a modified version of the Single Prolonged Stress (mSPS) procedure to induce freezing behavior. Following a seven-day incubation period, one group of males and females were administered a 6 mg/kg intraperitoneal injection of the dopamine D3 receptor antagonist prior to behavioral testing in an open field arena, while the other group received no treatment and acted as a control for the stress procedure. Time spent freezing prior to stress exposure was compared to time spent freezing following stress exposure and treatment with the antagonist. The female mice showed no significant difference in freeze times following treatment, whereas an increase in freezing behavior was observed in the males (Paired T-test $t(9)= -5.58$, $p=<0.001$). These results suggest that SB-277011A is effective at blocking freezing behavior in female C57BL/6J mice but not in males. This supports further investigation into sex differences that may impact our understanding and treatment of conditions involving stress such as PTSD and substance use disorders.

Poster 29

Locomotor effects of N-ethylmethamphetamine in mice: role of Phase I metabolism

Fomin, Andriy[1] ; Rowe, Sierra[1] ; Gunnell, Melinda[1] ; Avram, Marina[1,3] ; Moran, Jeffery[1,3] and Fantegrossi, William[1]

[1]Department of Pharmacology & Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR; 3 PinPoint Testing, LLC, Little Rock, AR

N-ethylmethamphetamine (N-ethyl-METH) has been identified as an impurity in seized methamphetamine (METH) and is thought to be a byproduct of illicit METH production. Here we assessed the relative potency and effectiveness of N-ethyl-METH to stimulate locomotor activity in mice, in comparison to METH. METH and N-ethyl-METH dose-dependently increased ambulatory distance in adult male NIH Swiss mice. Although N-ethyl-METH (ED50 =5.85 mg/kg) was less potent than METH (ED50=0.983 mg/kg), it was equally effective as a locomotor stimulant (Emax=709.94 m/6hr for N-ethyl-METH vs 715.34 m/6hr for METH). Interestingly, the locomotor stimulant effects of N-ethyl-METH were slower in onset than those of METH, with peak motor effects occurring between ~60 min and ~120 min after injection. In comparison, peak locomotor effects of METH were observed within 10 min of injection. To test the hypothesis that the delayed onset of N-ethyl-METH is due to metabolic conversion, mice were administered the non-specific Phase I metabolism inhibitor 1-aminobenzotriazole (1- ABT, 100.0 mg/kg) or the selective CYP2D6 inhibitor (CYP2d22 in the mouse) quinidine (56.0 mg/kg) prior to injection of N-ethyl-METH or METH. Treatment with 1-ABT or quinidine did not affect spontaneous locomotor activity or alter the locomotor stimulant effects of METH, but both inhibitors completely abolished the locomotor stimulant effects of N-ethyl-METH. These results indicate that Phase I metabolism is required for biological activity of N-ethyl-METH, and suggest that CYP2D6 catalyzes demethylation reactions to convert N-ethyl-METH to METH and/or amphetamine (AMPH). To test this, blood was drawn from mice treated with 1-ABT or saline, then administered N-ethyl-METH. Samples were assayed for N-ethyl-METH, METH, and AMPH using LC-MS/MS. Both METH and AMPH were detected in a time- and treatment-dependent manner, confirming metabolic conversion of N-ethyl-M

Poster 30

Natural and drug reward-induced plasticity in the entorhinal cortex

Fu, Leonard[1]; Eagle, Andrew PHD[1]

[1]Department of Neuroscience, University of Texas at Dallas, Richardson

Motivated behavior—the pursuit of rewards such as food, water, sex, and social interaction—is critical for the survival of species. Successful acquisition of these rewards depends on memory, specifically on learning to associate cues—such as contexts, places, and things—with them, thereby imbuing those cues with motivational value. Cue-reward associative learning can produce changes in synaptic plasticity in the brain. Drugs of abuse, like cocaine, can hijack these same neural systems, producing indelible changes in synaptic plasticity that underlie aberrant drug seeking. The lateral entorhinal cortex (LEC) plays a key role in associative memory. Recent evidence shows the LEC is activated by rewards, and cues associated with rewards; and silencing the LEC disrupts cue-reward learning. However, it remains unclear whether natural reward learning and drug reward learning differentially alter synaptic plasticity in the LEC. To address this question, we analyzed molecular markers of synaptic plasticity in brain tissue from mice that underwent food and cocaine operant self-administration. Self-administration consisted of 10-14 days of testing in an operant chamber, where nose pokes into an aperture produced either dispensation of a sucrose pellet into a magazine or intravenous infusion of cocaine through an indwelling jugular catheter. Visual cues were paired with reward delivery. Fresh biopsy punches were taken from the LEC as well as the nucleus accumbens (NAc), a region important for drug seeking and cocaine-induced plasticity changes. We conducted western blotting to specifically quantify the expression of phosphorylated changes to AMPA receptors (which are important for excitatory transmission) and CaMKII (a kinase important for mediating AMPA receptor function). We found that cocaine altered the expression of these molecular markers of plasticity. Studies examining changes in response to food self-administration are ongoing. These findings reveal that cue-reward associative learning through synaptic changes that may underlie motivated behavior.

Poster 31

Methamphetamine-like locomotor and interoceptive effects of 4F-α-PiHP, a novel substituted cathinone, in mice and rats

Honeywell, Kevin M[1] ; Gunnell, Melinda G[1] ; Gannon, Brenda M[1] ; Fantegrossi, William E[1]

[1]Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR USA

The addition, removal, or substitution of moieties to alter the structure of known drugs is a common strategy in the illicit synthesis of novel drugs of abuse. Here we compared the novel substituted cathinone 4-fluoro-α-pyrroldinoisehexanophenone (4F-α-PiHP) with its structural analog α-pyrrolidinovalerophenone (α-PVP) and the standard psychostimulant methamphetamine (METH) in two rodent assays relevant to abuse potential. In the first experiment, dose-response curves for locomotor effects of each drug were determined in adult male NIH Swiss mice. We found that 4F-α-PiHP had a significantly greater maximum effect (Emax) and half maximum effective dose (ED50) than observed for either α-PVP or METH. Indeed, at the smallest effective dose of each drug, we found that both 4F-α-PiHP and α-PVP induced significantly more locomotor activity than METH. These results indicate that 4F-α-PiHP has a greater stimulant-like effect than the other drugs tested but requires a higher dose to reach such effect. In the second experiment, adult male Sprague-Dawley rats were trained to discriminate 1.0 mg/kg METH from saline in a 2-lever, food-reinforced drug discrimination paradigm. Full dose-effect curves were determined for METH-like effects of METH, 4F-α-PiHP and α-PVP. We found METH, 4F-α-PiHP and α-PVP all fully substituted for the METH training dose with no significant differences in Emax values among drugs. However, the average ED50 value for 4F-α-PiHP was significantly greater than that of α-PVP or METH, recapitulating the larger dose required to elicit stimulant-like effects previously observed in the mouse locomotor studies. These findings indicate 4F-α-PiHP has METH-like abuse potential in two relevant rodent assays and that the transition from inactive to active doses may be more abrupt with 4F-α-PiHP and α-PVP than with amphetamine-type drugs.

Poster 32

Advancing Recovery Science: Establishing a Community-Informed Research Agenda for Peer Recovery Support Services

Jean-Berluche, Ducel[1,2]; Olmos, Daniela I[1,2]; Gallegos, Kierstyn[1,2]; Lindsey, Adrienne[1,2]; Hamner, Richard[1,2]; Potter, Jennifer S[1,2] and Ashford, Robert[1,2]

[1]Department of Psychiatry and Behavioral Sciences, University of Texas at San Antonio, San Antonio, TX USA

[2]Be Well Institute for Substance Use and Related Disorders, San Antonio, TX USA

Peer Recovery Support Services (PRSS) are non-clinical supports delivered by individuals with lived experience to help others initiate, sustain, and maintain recovery from substance use disorder (SUD) and related mental health conditions. Although evidence shows PRSS improves recovery outcomes, key knowledge gaps remain. The Peer Recovery Innovation Network (PRIN), funded by the National Institute on Drug Abuse, was established to advance recovery science with a focus on PRSS and used a two-phase, community-engaged process to develop a field-informed research agenda. In Phase 1, a multidisciplinary External Advisory Board—including recovery scientists, peer specialists, SUD researchers, and individuals with lived experience—generated over 250 research topics. Using a modified Delphi process and the Nominal Group Technique, these were synthesized into 10 priority research areas. Phase 2 used the MetroQuest stakeholder engagement platform to collect broader community input through surveys and ranked prioritization. The resulting agenda identifies key priorities, including peer workforce development, evaluation of PRSS effectiveness, and the role of social determinants of health in recovery, guiding future research and innovation in peer recovery support.

Poster 33

Behavioral Pharmacology of Cafestol in CD-1 Mice

Jimenez AM[1], Soyer A[1], Sorum B[2], Keck TM[1*]

[1]Department of Chemistry and Biochemistry, Rowan University, Glassboro, NJ USA; [2]Department of Biomedical Sciences, Copper Medical School of Rowan University, Camden, NJ USA

Recent work by a collaborator has determined that cafestol, a diterpene extracted from Coffea arabica beans commonly present in unfiltered coffee, is a potent modulator of myelinated neuron activity. Since these neurons are found throughout the brain and body, this compound could have broad impacts on a variety of processes, including touch sensation, mood regulation, memory, and cognition. Since the behavioral pharmacology of cafestol is largely unknown, this study aims to characterize its behavioral and physiological effects in male and female CD-1 mice. Cafestol, administered via intraperitoneal (IP) injection and oral administration (p.o.) for comparison of delivery routes, is being tested in a range behavioral assays, including von Frey (mechanical sensation and inflammatory nociception), hot plate (thermal nociception), novel object recognition (memory), elevated plus-maze (anxiety-like behavior), and upper gastrointestinal (GI) transit (GI motility) assays. By systemically assessing cafestol-induced behavioral effects, this study aims to clarify how cafestol might modulate activity in a variety of physiological systems and processes that depend on proper firing of myelinated neurons.

Poster 34

Cocaine's Modulation of Resting-State Networks

Keitzer, Jeri[1] and Colon-Perez, Luis[1]

[1]Department of Pharmacology and Neuroscience, UNT Health, Fort Worth, TX USA

Rationale: The acute reinforcing effects of cocaine (COC), emanating from dopamine dysregulation and alterations in the mesocorticolimbic system, are well understood. However, this view neglects broader effects: importantly, the brain's distributed networks estimated by BOLD fMRI, or resting-state networks (RSNs). This study, therefore, uses pharmacological fMRI (phfMRI) to identify system-level biomarkers underlying the behavioral effects of acute cocaine administration.
Hypothesis: Acute cocaine administration will significantly alter functional connectivity (FC) across the cortical and subcortical regions encompassing RSNs compared to saline.
Methods: Adult male Sprague-Dawley rats were used (n=5) in a within-subjects design where each rat underwent two fMRIs: a control (saline IP) and experimental scan (10mg/kg COC IP) both lasted 30 minutes with injections done 5 minutes in. Data were preprocessed using RABIES, and FC was assessed via group-level Independent Component Analysis (ICA) with fixed dimensionalities of 12, 15, and 18 components, and visually categorized.
Results: Our ICA identified 3 distinct networks: the DMN, a dorsal/posterior associative network (dpAN), and a cerebellar/brainstem network (CBN), and revealed significant FC changes across them following cocaine administration. *In the DMN*, cocaine induced increased FC in the lateral prelimbic and primary cingulate regions and decreased FC in the medial prelimbic cortex. *In the dpAN*, cocaine increased FC in retrosplenial and hippocampal regions and decreased FC in somatosensory and parietal associative cortices. *In both the DMN and CBN*, cocaine induced anticorrelation in the striatum and primary motor cortex.
Conclusions: Our results demonstrate the acute FC alterations induced by cocaine administration and may represent translatable biomarkers depicting early neurobiological mechanisms modulating behavior in cocaine use disorder.

Poster 35

Effects of Testosterone Treatment on Risk-based Decision Making in Female Rats

Kelly, Megan A[1]; Riley, Erin E[2]; Govind, Trisha[1]; Orsini, Caitlin A[1]

[1]Department of Psychology, The University of Texas, Austin, TX, USA; [2]Department of Psychology, Rhodes College, Memphis, TN, USA.

Decision making requires a complex assessment of rewards and potential risks. There are well-documented sex differences in this process, particularly when choices involve a risk of punishment. These sex differences are largely driven by gonadal hormones, which modulate the neural substrates underlying cost-benefit evaluations. In rodent models, intact females with circulating ovarian hormones are more risk averse relative to ovariectomized females. Conversely, intact males display increased risk taking compared with orchiectomized males. This latter finding suggests androgens promote greater risk taking. While these androgenic effects are well-characterized in males, the influence of testosterone on female decision making remains largely unexplored. To address this gap, we conducted two experiments using female Long-Evans rats trained in the Risky Decision-making Task (RDT), a task in which rats choose between a small, "safe" food reward and a large food reward associated with an increasing probability of footshock. In Experiment 1, we examined the effects of subchronic testosterone (T) treatment on risk taking. Rats (n=10) received daily injections of T (125ug/kg, 500ug/kg) or vehicle for 7 days during RDT testing. Treatment occurred according to a within-subjects design with a minimum of 10 days between successive treatments. In Experiment 2, we examined the effects of chronic, sustained T on risk taking. Rats (n=19) were implanted with testosterone-filled silastic capsules (n=10) or empty controls (n=9) and tested in the RDT. In both experiments, T treatment significantly increased choice of the large, risky reward compared with controls, suggesting that T influences risk-based decision making in females. Regardless of administration route, elevated androgenic signaling shifted the female risk profile toward a more "masculinized," risk-tolerant phenotype. Understanding these hormonal influences is critical for identifying sex-specific biological mechanisms underlying pathological risk taking, such as that observed in substance use disorders and gambling addiction.

Poster 36

Effects of Amphetamine Dose on Acoustic Structure and Temporal Dynamics of Ultrasonic Vocalizations in Female Rats

Kim, Gahyun[1]; Vasquez, Adriana[1,2]; Mendoza, Paola[3]; Monfils, Marie-H[1,3], and Lee, Hongjoo J[1,3]

[1]Department of Psychology; [2]Waggoner Center for Alcohol & Addiction; [3]Department of Neuroscience, The University of Texas at Austin, Austin, TX USA.

Psychostimulant-induced ultrasonic vocalizations (USVs) index hedonic and motivational activation in rodents. However, how repeated amphetamine (AMPH) exposure shapes the temporal dynamics and acoustic structure of USVs remains unclear. We explored AMPH dose-related, either 1 or 2 mg/kg, USV differences in female rats across AMPH sessions, saline sessions, conditioned-place preference tests, and a reinstatement test. Analyses targeted (1) principal frequency structure, assessed via distributional and modal estimates, and (2) within-session temporal dynamics, quantified as call (Flat and Frequency Modulated) counts in 5-minute bins. Kolmogorov–Smirnov tests revealed significant frequency distribution shifts between early and later AMPH sessions in both groups (1 mg/kg: $D = 0.06$, $p = 0.03$; 2 mg/kg: $D = 0.18$, $p < 0.001$). Bootstrap estimation showed a progressive increase in modal principal frequency across repeated AMPH exposure in the 2 mg/kg group (slope = 2.06 kHz/session, 95% CI [1.86, 2.33]), but not in the 1 mg/kg group (slope = 0.06, 95% CI [−0.23, 0.29]). In contrast, saline sessions and drug-free preference tests showed modest, inconsistent slopes (≈ 0.3 kHz/session), indicating that frequency shifts were specific to repeated high-dose exposure. Within-session analyses revealed significant Group × Time interactions during the second AMPH session ($\chi^2(5) = 1036.67$, $p < 0.001$) and reinstatement ($\chi^2(2) = 417.42$, $p < 0.001$), with higher counts in the first bin of the 2 mg/kg group, followed by convergence with and decrease from the 1 mg/kg group across later bins. Similar effects were observed for both call types. Together, these findings indicate that repeated AMPH exposure reorganizes the temporal and acoustic structure of USVs in a dose-dependent way.

Poster 37

Mu-Opioid and 5-HT2A Receptor Heterodimer Formation in the Medial Prefrontal Cortex After a Single Dose of 2,5-Dimethoxy-4-iodoamphetamine

Kramer, Jenna M.[1] ; Brabec, Gavin[1] ; Escarsega, Jade[1] ; Estrella, L. Daniel[2] ; Stauch, Kelly L.[3] ; Garcia, Erik J. [1]

[1]Department of Psychology, Neuroscience and Behavior, University of Nebraska Omaha, Omaha, NE, USA; [2] Department of Neurology, Harvard Medical School & Massachusetts General Hospital, Boston, MA, USA; [3] Department of Neurological Sciences, Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA

The downregulation or desensitization of the mu-opioid receptor (MOR), a G protein-coupled receptor (GPCR), drives oxycodone misuse. The hallucinogenic effects of classic psychedelics are mediated by another GPCR, serotonin 5-HT2A receptor (5-HT2AR). Recent data indicates that the psychedelic compound 2,5-dimethoxy-4-iodoamphetamine (DOI) reduces fentanyl and oxycodone self-administration, but the mechanism by which this occurs is undefined. The purpose of this study was to develop a tolerance model and determine if the therapeutic effect is driven by a physical interaction between MOR and 5-HT2AR in the medial prefrontal cortex (mPFC). Male and female Sprague-Dawley rats were treated with escalating chronic oxycodone doses (1-7.5 mg/kg, 2x/day, s.c.) or saline for ten days. On the eleventh day, the rats were injected with DOI (0.3 or 1 mg/kg, s.c.)or saline, and their head twitch responses were measured. After the assay, whole brains were extracted and prepared for immunohistochemistry to label the MOR and 5-HT2AR. MPFC tissue was imaged on a confocal microscope and analyzed using ImageJ. MOR and 5-HT2AR signals were quantified as the mean gray values of the associated tag's fluorescence. Analysis indicated oxycodone tolerance had no effect on MOR or 5-HT 2AR expression. However, colocalization of the receptors was enhanced after the administration of DOI (1 mg/kg). This suggests that psychedelic treatment induces MOR and 5-HT2AR heterodimer formation only after opioid exposure and thereby provides a novel target for OUD treatment.

Poster 38

Differential Discriminative Stimulus Profiles of α3β4 and α4β2 Nicotinic Receptor Partial Agonists

Kusi-Boadum, Nana Kofi[1] ; Gatch, Michael B. PhD[1] , Shetty, Ritu A. PhD[1] ; Sumien, Nathalie PhD[1] ; and Forster, Michael J. PhD[1]

[1]Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, TX USA.

Purpose: The α3β4 nicotinic acetylcholine receptor (nAChR) remains underexplored as a target for smoking cessation compared to the α4β2 receptor. Although prior work shows that the α3β4 partial agonist AT-1001 produces nicotine-like locomotor effects and attenuates nicotine-induced stimulation, it is unclear whether α3β4 activation reproduces or modulates nicotine's subjective effects. This study used drug discrimination to compare the discriminative stimulus profiles of AT-1001 and varenicline.
Methods: Male Sprague–Dawley rats were trained to discriminate nicotine tartrate (0.1 mg/kg, 5-minute pretreatment) from saline. Substitution and antagonism tests were conducted with AT-1001 and varenicline. Percentage of nicotine-lever responding and response rate were analyzed using repeated-measures ANOVA.
Results: AT-1001 did not substitute for nicotine's discriminative stimulus but partially antagonized nicotine at doses of 5 and 10 mg/kg, reducing nicotine-lever responding to 66.7% and 64.7%, respectively. In contrast, varenicline partially substituted for nicotine over a broad dose range and failed to antagonize nicotine when it was co-administered.
Conclusion: α3β4 receptor activation does not reproduce nicotine's discriminative stimulus but instead modulates it, as reflected by partial antagonism without substitution. The contrasting profiles of AT-1001 and varenicline underscore receptor subtype–specific control of nicotine's subjective effects and support α3β4 modulation as a possible complementary strategy for smoking cessation.

Poster 39

Selective knockdown of oxytocin receptors on dopamine neurons or CB1 receptors on glutamatergic neurons in the ventral tegmental area disrupts the attenuating effect of oxytocin on cocaine conditioned place preference

Le, Grace T.; Moosa, Imaan; Stall, Julia T.; Griffin, Jace A. and Leong, Kah-Chung Ph.D

Department of Psychology, Trinity University, San Antonio, TX USA.

Cocaine use disorder (CUD) is a chronic, relapsing condition with limited treatment options. We have demonstrated that oxytocin (OXT) can attenuate cocaine conditioned place preference (CPP) behavior, but the neural mechanisms underlying this effect remain unclear. Prior evidence suggests that OXT receptor (OXTR) activation on dopamine (DA) neurons in the ventral tegmental area (VTA) modulates excitatory glutamatergic input onto DA neurons via retrograde endocannabinoid signaling and presynaptic type 1 cannabinoid receptor (CB1R) activation. In this study, we explore two complementary aims: (1) selective OXTR knockdown on DA neurons in the VTA, or (2) selective CB1R knockdown on glutamatergic synapses in the VTA is sufficient to diminish OXT's attenuative effect on cocaine reward in male Long-Evans rats (n = 62). To examine this two-fold mechanism, we employed a novel approach combining transgenic Cre animal models and viral-mediated short hairpin RNA (shRNA) to selectively knockdown OXTRs on DA neurons or CB1Rs on glutamatergic terminals in the VTA. Rats were conditioned with cocaine (10 mg/kg) and received either vehicle (VEH) or OXT (3 mg/kg) prior to behavioral testing. Cocaine CPP was assessed by the percent of time spent in the drug-paired chamber between baseline and test and analyzed using a two-way ANOVA. While we consistently show that OXT attenuates cocaine CPP at test, this effect was no longer present in animals with selective knockdown of OXTRs on VTA DA neurons or selective knockdown of CB1Rs on VTA glutamatergic neurons. Together, our findings provide mechanistic insight into how OXT may attenuate cocaine CPP through DA OXTR activation and endocannabinoid-mediated CB1R activation on glutamatergic inputs in the VTA.

Poster 40

Hypoxic and Bradycardic Effects of Fentanyl-Xylazine Co-Exposure and Reversal by Naloxone and Yohimbine in Mice

Lewis, Melissa R.[1] ; Walentiny, D. Matthew[1]

[1]Department of Pharmacology & Toxicology, Virginia Commonwealth University School of Medicine, Richmond, VA

Background: Potent synthetic opioids such as fentanyl dominate the illicit drug supply and depress respiration through μ-opioid receptor (MOR) activation, a crisis exacerbated by increasing adulteration with other CNS-active drugs. Xylazine, a veterinary sedative and α2-adrenergic receptor (α2AR) agonist, is now frequently detected in fentanyl and contributes to respiratory depression by suppressing central noradrenergic signaling, prompting concerns about heightened overdose risks and decreased responsiveness to the MOR antagonist naloxone (Narcan ®). We previously demonstrated that fentanyl and xylazine co-administration (0.3 mg/kg each) produced naloxone-reversible respiratory depression in male mice but co-administration of the α2AR antagonist yohimbine accelerated respiratory recovery. **Methods**: Dose-response curves for fentanyl and xylazine alone were generated in male Swiss-Webster mice to assess changes in blood oxygen saturation and heart rate. Next, mice were administered a fixed dose of fentanyl (3 mg/kg) with varying proportions of xylazine (1:1, 1:3, 1:5.6) and reversibility by naloxone and/or yohimbine was assessed. **Results**: Fentanyl alone caused dose-dependent hypoxia, but not bradycardia whereas xylazine dose-dependently induced bradycardia, but not hypoxia. We hypothesize the combination will reduce oxygen saturation and heart rate with the magnitude of impairment worsening as the proportion of xylazine in the mixture is increased. Naloxone is predicted to partially reverse hypoxia, but the combination of antagonists will produce a rapid, full recovery of oxygen saturation and heart rate. Conclusions: Naloxone and yohimbine are expected to selectively reverse fentanyl-xylazine-induced hypoxia and bradycardia, and α2AR antagonists may serve as adjuncts to naloxone for faster reversal of physiological impairments associated with fentanyl-xylazine overdose.

Poster 41

Identification of New Selective Dopamine D4 Receptor Ligands for the Treatment of Neuropsychiatric Disorders

Li, Tian[1] ; Alkhatib Mohammad[2] ; Bourn, Lindsay[1] ; Rainwater, Jane K[1] ; Ramdhan, Peter A[3] , Farrington, Caitlin P[1] ; Lewis, Blake[1] ; Li, Chenglong[3] ; Keck, Thomas M[2] ; and Boateng, Comfort A[1]

[1]Department of Basic Pharmaceutical Sciences Fred Wilson School of Pharmacy High Point University; [2] Rowan University; [3] University of Florida.

The dopamine D4 receptor (D4R) is a G protein-coupled receptor (GPCR) with expression localized in brain regions critical for cognition and attention, such as the prefrontal cortex, amygdala, and hippocampus. Preclinical studies indicate that selective targeting of D4R may improve behavioral and cognitive outcomes in animal models relevant to cognitive disorders, like ADHD and Alzheimer's disease, and substance use disorders (SUDs). Despite its therapeutic potential, there are currently no FDA-approved drugs that selectively target D4R. Hence, discovery of novel compounds is a valuable tool to better understand the role of D4R signaling in neuropsychiatric conditions leading to therapeutic candidates for clinical development. In this study, we extend upon prior development of analogs of A-412997, a D4R-selective partial agonist, by exploring ligand interactions within the secondary binding pocket. We modified the alkyl chain on the phenylacetamide's benzyl ring by extending and cyclizing the alkyl chain. A series of compounds were synthesized and tested using competition radioligand binding assays on D2R, D3R, and D4R, using [3H]N-methylspiperone as the competing radioligand. Herein, we report that while increasing the chain length beyond two carbons reduced D4R affinity and selectivity, cyclizing the alkyl chain enhanced D4R affinity and maintained selectivity over D2R and D3R by 120-fold or more. Molecular modeling results suggest that the cyclized rings engage in more favorable interactions within the D4R binding pocket. These new novel compounds serve as important resources for advancing our knowledge of D4R signaling in neuropsychiatric disorders, leading to medication discovery.

Poster 42

Affective and sensory pain responses show sex differences

Little, Kaitlyn M; Lopez Arteaga, Carlos A; Franklin, Brooke E; Husainat, Meraa; Haile, Colin N; Kosten, Therese A

Department of Psychology & TIMES, University of Houston, Houston, TX

Fentanyl (FEN) is a highly potent synthetic opioid acting through mu opioid receptors and remains a major contributor to rising opioid use disorder (OUD) rates and opioid-related deaths. Sex differences in responses to psychoactive drugs, including opioids, are well documented, and circulating hormones such as estradiol influence addiction vulnerability in females. Preclinical studies show that pain elicits affective responses measurable through ultrasonic vocalizations (USVs), which are altered by opioids. However, few studies examine how opioids impact these affective responses or whether sex or hormonal state modulates them. We examined whether sex, estrous stage, or FEN differentially alter affective and sensory responses to a pain stimulus, as well as neural activation in pain-associated regions. Sensory regions included the periaqueductal gray (PAG), and affective regions included the amygdala. Adult male and female Sprague-Dawley rats were tested for: (1) locomotor activity and affective responses in an open field; (2) sensory and affective responses during FEN analgesia; and (3) neural activation to a pain stimulus through c-Fos expression. Preliminary findings indicate sex- and estrous-related differences in affective and sensory responses to FEN. In the open field, males emitted more USVs at 0.1 mg/kg FEN compared to 0.05 mg/kg and saline ($p < 0.01$), whereas females emitted more USVs at 0.05 mg/kg and minimal USVs at 0.1 mg/kg relative to males ($p < 0.05$). Females also showed greater locomotor activation at 0.05 mg/kg ($p < 0.001$). Tail flick latencies were lower in females at 0.05 mg/kg FEN, corresponding to non-proestrus phases ($p < 0.05$). FEN reduced USVs during tail flick tests in males ($p < 0.05$), with no effect in females. Analyses of c-Fos are ongoing. These outcomes clarify how sex and estrous stage shape behavioral responses to FEN and highlight key sex differences relevant to FEN-induced OUD and analgesia.

Poster 43

Characterizing binary mixtures of fentanyl and xylazine on food-reinforced behavior in rhesus monkeys

Martinez, Paul A and Maguire, David R

Department of Pharmacology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

The growing number of fentanyl overdoses along with the high prevalence of the non-opioid sedative, xylazine, in the fentanyl supply may implicate xylazine in the growing number of opioid overdoses. Subjective reports from some people who use fentanyl/xylazine mixtures suggest xylazine might enhance and/or prolong the effects of fentanyl. Behavioral effects of fentanyl/xylazine mixtures have not been well characterized, especially in primates. The current study utilized operant food-maintained behavior to examine the nature of the interaction between fentanyl and xylazine. Rhesus macaques (4 males and 4 females) responded under a fixed-ratio 20 schedule for sucrose pellets after a subcutaneous injection of fentanyl (0.0032-0.1 mg/kg) or xylazine (0.056-1.78 mg/kg) alone or a binary fixed-dose mixture. Response periods occurred every 30 minutes for 3 hours. Mixtures were constructed for individual monkeys based on the median effective doses (ED50) of fentanyl and xylazine alone which were (mean ± 95% confidence limit) 0.021 mg/kg [0.013-0.035] and 0.585 mg/kg [0.370-0.925] for fentanyl and xylazine, respectively. When mixed at a 1:1 ratio, the ED50 for fentanyl and xylazine were 0.011 [0.007-0.018] and 0.321 [0.218-0.472], respectively. To determine the nature of interaction, xylazine doses in the mixtures were converted to fentanyl equivalents and used for dose-addition analyses. The 1:1 binary mixture resulted in a mean (± 95% confidence level) potency ratio (predicted/observed) of 1.068 [0.972-1.164], suggesting the interaction is not different from additive with a 1:1 ratio. This study demonstrates an additive interaction between fentanyl and xylazine on behavior that will provide important context for subsequent studies on behavioral pharmacology. Supported by the NIH (R01DA060215 [DRM] and T32DA031115 [PAM]).).

Poster 44

Preclinical analyses of NMUR2 small compound agonist NY0128 as a potential therapeutic for cocaine use disorder

Martinez, Vena, K.[1] , Sun, Hong[1] , Fox, Robert[1] , Zhang, Cun[1] , Borzou, Ardavan[2] , Zhou, Jia[1] , Cunningham, Kathryn[1] and Hommel, Jonathan, D.[1]

[1]Center for Addiction Sciences and Therapeutics, The University of Texas Medical Branch, Galveston, Texas USA; [2] CompuFlair, Houston, Texas USA

The growing number of fentanyl overdoses along with the high prevalence of the non-opioid sedative, xylazine, in the fentanyl supply may implicate xylazine in the growing number of opioid overdoses. Subjective reports from some people who use fentanyl/xylazine mixtures suggest xylazine might enhance and/or prolong the effects of fentanyl. Behavioral effects of fentanyl/xylazine mixtures have not been well characterized, especially in primates. The current study utilized operant food-maintained behavior to examine the nature of the interaction between fentanyl and xylazine. Rhesus macaques (4 males and 4 females) responded under a fixed-ratio 20 schedule for sucrose pellets after a subcutaneous injection of fentanyl (0.0032-0.1 mg/kg) or xylazine (0.056-1.78 mg/kg) alone or a binary fixed-dose mixture. Response periods occurred every 30 minutes for 3 hours. Mixtures were constructed for individual monkeys based on the median effective doses (ED50) of fentanyl and xylazine alone which were (mean ± 95% confidence limit) 0.021 mg/kg [0.013-0.035] and 0.585 mg/kg [0.370-0.925] for fentanyl and xylazine, respectively. When mixed at a 1:1 ratio, the ED50 for fentanyl and xylazine were 0.011 [0.007-0.018] and 0.321 [0.218-0.472], respectively. To determine the nature of interaction, xylazine doses in the mixtures were converted to fentanyl equivalents and used for dose-addition analyses. The 1:1 binary mixture resulted in a mean (± 95% confidence level) potency ratio (predicted/observed) of 1.068 [0.972-1.164], suggesting the interaction is not different from additive with a 1:1 ratio. This study demonstrates an additive interaction between fentanyl and xylazine on behavior that will provide important context for subsequent studies on behavioral pharmacology. Supported by the NIH (R01DA060215 [DRM] and T32DA031115 [PAM]).).

Poster 45

Quantification of observable behaviors induced by mu- and kappa-opioid agonists in rhesus monkeys

Mastio, Justin T[1] ; Huskinson, Sally L[1,2]; Platt, Donna M[1,2]; Doyle, William S[1] ; Blough, Bruce E[3] ; Gilmore, Jackson D[4] ; Freeman, Kevin B[1,2]

[1]Program in Neuroscience, UMMC; [2] Department of Psychiatry and Human Behavior, UMMC; [3] Research Triangle Institute; [4] School of Medicine, UMMC

Kappa-opioid receptor agonists (KORAs) could serve as potential therapeutics for pain, pruritus, and substance-use disorders. Typical KORAs have side-effects like dysphoria and sedation. Atypical KORAs that are putatively G-protein biased have been reported to produce therapeutic-like effects with reduced side effects compared with typical KORAs. This study investigated HS665, an atypical, putatively G-protein biased, KORA and compared it with 2 other KORAs (i.e., U50-488h, a prototypical KORA, and triazole 1.1, a putatively G-protein biased KORA of a different structural class than HS665). Adult female (n=2-3) and male (n=3) rhesus monkeys were intravenously administered oxycodone (a mu-opioid agonist; 0.01-0.56 mg/kg), U50-488h (0.01-0.1 mg/kg), triazole 1.1 (0.1-1.0 mg/kg), and HS665 (0.01-0.32 mg/kg) across several conditions including alone, combined, and at different time points. Species-typical and drug-induced behaviors were scored by blinded observers. Oxycodone induced dose-dependent increases in scratching and facial rubbing, a putative indicator of gastrointestinal distress. U50-488h and HS665 caused dose-dependent reductions in species-typical behavior when administered alone during dose-effect determinations, while triazole 1.1 did not. When administered as mixtures with oxycodone, both HS665 and triazole 1.1 reduced scratch in a dose-dependent manner and at doses that did not affect species-typical behavior. The ability to reduce oxycodone-induced scratch dissipated within 32-100 minutes for triazole 1.1 or within 100 minutes, for HS665, suggesting a slightly longer duration of action for HS665. Our results suggest that putatively G-protein biased KORAs do not always offer more favorable side-effect profiles compared with prototypical KORAS; however, triazole 1.1 had a slightly improved profile over HS665, when considering all conditions of administration.

Poster 46

Xylazine potentiates fentanyl-induced respiratory depression

Aniah N. Matthews[1], Adriana Gregory-Flores[1], Lyndsay Krisyak[2], Shelley Jackson[2], Aidan Hampson[3], Nora D. Volkow[4], Leandro F. Vendruscolo[5], Renata C.N. Marchette[1],*, George F. Koob[1]

Xylazine, a veterinary sedative and alpha2-adrenergic agonist, has emerged as a dangerous adulterant in illicit fentanyl supplies, contributing to a rising number of opioid-related overdose deaths across the United States. Unknown is exactly how physiologically xylazine and fentanyl interact. Here we show that xylazine significantly potentiates fentanyl-induced respiratory depression in rats, as evidenced by greater reductions in minute ventilation, increased apneic pause, and prolonged relaxation time. Conversely, fentanyl also potentiates xylazine-induced respiratory depression, indicating a bidirectional additive effect. Furthermore, naloxone, while effective against fentanyl alone, only partially and transiently reverses respiratory depression induced by the fentanyl-xylazine combination, and a low dose of naloxone and atipamezole restores baseline measures. Pharmacokinetic analysis did not reveal altered fentanyl and xylazine profiles when administered together, suggesting drug-drug interactions do not underlie the additive effects observed. These findings underscore the severe and sustained respiratory compromised function caused by this drug combination, which may contribute to the high lethality observed in human polydrug overdoses involving xylazine. This work highlights the limitations of naloxone and the urgent need for novel therapeutics that can address emerging non-opioid adulterants in the illicit drug supply.

Poster 47

The Impact of Perinatal Fentanyl on Dopamine Neuron Circuitry and Behavior

McInerney, Jessica[1] ; Olusakin, Jimmy[1] ; Luján Miguel[1] ; Qamar, Bareera[1] ; Hajirnis, Surbhi[1] , Kashyap, Atul[1] , Cheer, Joseph F[1] , Lobo, Mary Kay[1]

[1]Department of Neurobiology, University of Maryland, Baltimore, Baltimore, MD USA

Use of illicit substances has reached endemic levels in the United States with over 91,000 deaths due to drug overdose occurring in 2020. This has largely affected women of childbearing age as opioid use disorder has more than quadrupled among pregnant women in the past 20 years. Both clinical and preclinical studies show that opioid exposure during gestation can lead to developmental delays, cognitive impairment, anhedonia and reduced motivation in offspring. Opioids induce neuroadaptations in the mesolimbic dopamine pathway, which is largely implicated in reward. The pathway originates in the ventral tegmental area (VTA) where dopamine neurons project to the nucleus accumbens (NAc) and other reward nuclei. How perinatal opioid exposure, including the highly potent opioid fentanyl impacts the transcriptional landscape throughout the development of the mesolimbic dopamine pathway as well as the lasting effect on motivation requires further investigation. Differential gene expression analysis of the NAc and VTA revealed PFE induces significant alterations in expression patterns of several genes important for neuronal maturation and axonal guidance, including transcription factors critical for dopamine neuron development during the juvenile time period. In addition, PFE mice exhibit reduced motivation for natural reward in both adolescence and adulthood measured through a sucrose operant task and spinning disc task which assesses motivation to exercise. In addition, PFE mice exhibit altered dopamine dynamics during increased response requirements in the sucrose operant task. These results indicate that perinatal fentanyl exposure and subsequent abstinence produce lasting transcriptional, and behavioral effects on the development and function of the mesolimbic dopamine pathway.

Poster 48

Investigating epitranscriptomic alterations in rat ventral tegmental area astrocytes following exposure to cocaine

Miller, Ashley N.[1] , Cedillo, Leonor G. [1] , Garcia, Brandon I. [1] , Fetch, Dustin R. [1] , Ramos, Angelica R.[2] , Jumamyradova, Amina[1] , Wanat, Matthew J. [1] , Soshnev, Alexey A. [1]

[1]University of Texas, San Antonio – Department of Neuroscience, Developmental, and Regenerative Biology [2] University of Illinois, Chicago – Graduate Program in Neuroscience

Ventral tegmental area (VTA) dopamine neurons regulate drug-dependent behaviors. While astrocytes are increasingly recognized as critical modulators of neuronal activity, little is known regarding if VTA astrocytes contribute to drug-dependent behavior. Our recent data demonstrate that prior drug exposure alters how VTA astrocytes regulate dopamine-dependent behavior. Specifically, chemogenetic activation of VTA astrocytes facilitates the development of a cocaine conditioned place preference (CPP) in drug-naïve animals but suppresses cocaine CPP in rats with prior cocaine experience. Long-term stability of this effect led us to hypothesize that cocaine exposure specifically alters the epigenetic landscape in VTA astrocytes.

To test this hypothesis, we analyzed chromatin accessibility changes in the VTA after repeated exposure to cocaine, using an assay of transposase-accessible chromatin followed by short-read sequencing (ATAC-Seq) [n=6]; additional transcriptomic information was categorized by cell type using single-nuclear RNA-Seq [n=5]. Cross-referencing these datasets, we aim to determine key chromosomal regulatory elements altered in VTA astrocytes following cocaine exposure. Our insights into the epitranscriptomic effects of drug exposure on VTA astrocytes are critical to revealing cellular adaptations in brain circuits that control the development of drug-cue associations.

Poster 49

Reinforcing effects of intravenous xylazine in rhesus monkeys responding under a fixed-ratio schedule

Moore, Bria[1] and Maguire, David[2]

[1]Graduate School of Biomedical Sciences, University of Texas at San Antonio, San Antonio, TX USA Department of Pharmacology and Addiction Research, Treatment & Training Center of Excellence, University of Texas at San Antonio, San Antonio, TX USA

The increasing prevalence of xylazine in the illicit opioid supply has raised significant concerns regarding its impact on opioid reinforcement, potency, and abuse liability. Xylazine is frequently detected in opioid-related overdoses and clinical data show that co-use exacerbates overdose risk and contributes to atypical withdrawal. Despite these public health concerns, whether xylazine itself contributes to drug taking or alters reinforcing effects of opioids remains to be elucidated. Although fentanyl self-administration has been well-documented by this laboratory and others, the reinforcing effects of xylazine have not been well-characterized, especially in non-human primates. This study explored potential reinforcing effects of xylazine alone in rhesus monkeys with an extensive drug self-administration history. Adult male and female rhesus monkeys (n=3) could lever-press for intravenous infusions of xylazine (0.01–1.0 µg/kg/infusion) and fentanyl (0.00032–1.0 µg/kg/infusion) alone via a chronic indwelling catheter in an operant chamber. Dose– response curves were generated separately for each drug, and xylazine dose–effect curves were determined multiple times to assess stability and reproducibility of its reinforcing effects. Fentanyl produced an inverted U-shaped dose–response curve, with peak responding at intermediate doses (0.1–1.0 µg/kg/infusion) and mean infusion levels of approximately 25–30 infusions per session, whereas xylazine produced lower and more variable responding across doses and subjects. Together, these findings suggest that xylazine alone is a weaker reinforcer than fentanyl in non-human primates.

Poster 50

Neural Mechanisms of Addiction Vulnerability: Differential PrL–DMS Circuit Activity During Punished and Effortful Cocaine Self-Administration

Morales, Jocelyn[1,2], Fogel, Peter[1,3], Espinosa, Mariana[1] , Moschak, Travis M.[1]

Department of Biological Sciences[1], ASSETS Program[2], Doctoral Program in Biological Sciences[3]

The neural mechanisms that differentiate resilient from vulnerable drug-seeking phenotypes in the face of rising behavioral costs remain poorly understood. Using in vivo calcium imaging, this study examined how the prelimbic cortex (PrL) to dorsomedial striatum (DMS) pathway contributed to cost-sensitive cocaine seeking during an intermittent-access self-administration paradigm. To test this, we incorporated intravenous cocaine self-administration and compared neural and behavioral responses across two cost manipulations: Effortful Self-Administration (ESA) and Punished Self-Administration (PSA). ESA was an effort-based cost condition in which rats had to complete increasingly demanding fixed-ratio requirements to obtain cocaine, whereas PSA was an aversive cost condition in which each cocaine infusion was paired with escalating doses of histamine to model punishment. Based on prior evidence that punishment and effort reflect distinct forms of cost and that PrL activity selectively regulates punished drug-taking, we hypothesized that PrL-DMS signaling would differentiate resilient from vulnerable phenotypes primarily under punishment, but not effort. By comparing neural activity across punishment- and effort-based costs, this study aimed to identify circuit-level markers of resilience and vulnerability that emerged specifically during punished cocaine seeking. Preliminary data suggests that PrL-DMS neural profile distribution significantly differs at three distinct levels of conflict within a punished self-administration cocaine task ($X2=25.70$, $p < 0.0001$). These findings may indicate that PrL-DMS circuitry dynamically encodes an individual's sensitivity to aversive cost, providing an early neural signature of resilience versus vulnerability.

Poster 51

Reward-Related Cues Trigger Activity in the Entorhinal Cortex

Mousavi, Seyedeh Leila; AlAdsani, Mariam Nizar; Antony, Noreen; Mirkhelker, Richa and Eagle, Andrew[1]

[1]Department of Neuroscience, University of Texas at Dallas, Richardson, TX USA

Relapse in cocaine use disorder is strongly driven by environmental cues that reactivate drug-associated memories. The lateral entorhinal cortex (LEC) is important for associative memory and sends projections to the nucleus accumbens (NAc), suggesting a role in cue–reward encoding that may drive relapse. To test this, we used fiber photometry to record calcium activity in the LEC during the presentation of natural and drug reward predictive cues. In our first experiment, adult C57Bl/6J mice were tested for LEC activation during food-predictive cues. The LEC of mice was infused with a non-cell-specific virus expressing GCaMP (pAAV.CAG.GCaMP6f). Animals were later tested across self-administration, where cues coincided with sucrose pellet delivery, and then were tested on extinction and cue-induced reinstatement. We found that these animals readily acquired, extinguished, and reinstated responding for sucrose pellets. Fiber photometry showed significantly higher calcium-dependent activity (465 nm) compared with the isosbestic control (415 nm), with event-related increases around food-predictive cue presentations. We also tested a separate cohort of mice for activation of LEC neurons that project to NAc by cocaine-predictive cues. These mice received bilateral injections of a retrograde GCaMP virus (AAVrg-syn-GCaMP7f) into the NAc and optic fiber implantation in the LEC. Mice readily acquired intravenous cocaine self-administration, reduced responding during extinction, and reinstated responding when cocaine cues were presented. Fiber photometry recordings did not reveal consistent calcium signals in this cohort, highlighting the need for improved targeting of projection-specific populations. Together, these results show that the LEC is engaged by reward-predictive cues during natural reward (and potentially cocaine) seeking and provide a foundation for future work to determine whether LEC–NAc neurons are also recruited during cue-induced cocaine relapse.

Poster 52

Structure-based cariprazine modifications to improve dopamine D3 receptor (D3R) selectivity

Nosko, Renee J.; Vogt, Caleb D.; Keegan, Bradley M. and Newman, Amy H

Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse – Intramural Research Program, Maryland, United States

Given the lack of FDA-approved treatments for psychostimulant use disorder (PSUD), there is an urgent need to develop novel therapeutics – particularly considering the prevalence and severity of comorbid PSUD and serious mental illness. One emerging candidate is cariprazine, a modestly preferential (3.6-fold) dopamine D_3 receptor/dopamine D_2 receptor (D3R/D2R) partial agonist that is FDA-approved for the treatment of schizophrenia, bipolar disorder, and more recently, major depressive disorder. We have previously demonstrated that cariprazine and a novel, more selective partial agonist ($D_3R/D_2R = 20$), ESG1-60, are effective in blocking both cocaine self-administration and cocaine-induced reinstatement to drug seeking in rats. Unlike cariprazine, ESG1-60 does not induce conditioned place aversion and, therefore, exhibits greater therapeutic potential for PSUD. The aversive behavioral effects observed with cariprazine may stem from its high affinity and low efficacy at D_2R, underscoring the need to develop additional D_3R/D_2R partial agonists to clarify how modest D_3R selectivity (approximately 20–100-fold) influences these outcomes. Acting as a bitopic ligand that engages both the dopamine D_2 and D_3 receptors, cariprazine contains a secondary pharmacophore that binds to the secondary binding pocket (SBP) – a peripheral region that is unique to D_3R and has been exploited for improving D_3R/D_2R selectivity. Using ligand-based structure design, analogs whose secondary pharmacophore were predicted to selectively interact with amino acid residues in the SBP of TM1 in D_3R were designed and synthesized. The affinities of each compound were then measured at D_2R and D_3R using radioligand binding competition assays, presenting moderate D_3R/D_2R selectivities (<100-fold).

Poster 53

Hemisphere-specific Differences in the Synaptic Properties of Inhibitory and Excitatory Connections from Pedunculopontine Tegmental Nucleus Neurons onto Substantia Nigra Pars Compacta Dopaminergic Neurons

Padilla, Kristen[1] ; Fernandez, Nathalia[2] ; Arias, Hailey[3] ; Baldwin, Alyssa[4] ; Neelala, Megha[5] ; Elfezouaty, Aaron[6] ; Rodriguez, Moraima[7] ; Penny, Dylen[8] ; Khetarpal, Ishana[9] ; Hoffman, Catherine[10]; Muzyka, Logan[11]; and Beaudoin III, Gerard M. J[12]

[1]Department of Biology, Trinity University, San Antonio, TX USA

The nigrostriatal dopaminergic pathway is essential for motivation, reward learning, and coordination. Within this pathway, the pedunculopontine tegmental nucleus (PPN) is a critical input to substantia nigra pars compacta (SNc) dopaminergic neurons and uniquely sends bilateral projections to SNc dopamine neurons. However, whether ipsilateral and contralateral PPN inputs differentially regulate SNc dopaminergic signaling remains unclear. We hypothesize that ipsilateral and contralateral PPN inputs differentially regulate SNc dopaminergic signaling in synaptic strength and neurotransmitter composition. Using adult Balb/C mice of both sexes, we utilized viral tracing, labeling techniques, and electrophysiology to further characterize SNc-PPN connectivity. Channelrhodopsin (ChR2) was virally expressed in the PPN and electrophysiological recordings from SNc dopaminergic neurons revealed that excitatory PPN inputs projected to both the ipsilateral (n = 4/6) and contralateral (n = 4/4) SNc while inhibitory inputs were observed only ipsilaterally. Unilateral retrograde injections in the SNc labeled PPN neurons both ipsilateral and contralateral to the injection site, with greater labeling ipsilaterally. Anterograde and retrograde labeling between the PPN and the SNc confirmed bilateral PPN innervation of the SNc. The characteristics of this circuitry may allow for differential regulation of dopaminergic signaling, offering novel insights into substance use disorders and addiction and permitting for future interventions.

Poster 54

Cardiorespiratory Reversal of Mixtures of Fentanyl–Medetomidine with Naloxone and Atipamezole

Puzovic, Gorana[1] ; Vazquez, Jacqueline[1] ; Shi, Yonggong[1] and Collins, Gregory T[1,2,3,4]

[1]Department of Pharmacology, University of Texas at San Antonio, San Antonio, TX USA; Departments of [2] Pharmacology and [3] Anesthesiology, University of Michigan, Ann Arbor, MI USA; [4] Ann Arbor Veterans Health Care System, Ann Arbor, MI USA.

The opioid epidemic continues to escalate, with fentanyl driving most of the nearly 23.7 per 100,000 people in the United States. Emerging α2-adrenergic receptor (α2AR) agonists such as xylazine and medetomidine (MED), veterinary sedatives that produces profound cardiorespiratory (CR) depression, may further complicate overdose presentations and reduce responsiveness to standard reversal agents. This study examined the receptors mediating the CR effects of fentanyl (FENT) and MED, the nature of their interaction, and the effectiveness of available reversal drugs. Male and female Sprague Dawley rats were implanted with venous catheters and equipped with collar-based pulse oximeters to measure heart rate (HR), blood oxygenation (SpO_2), and respiratory rate (RR). Dose–response curves for FENT (0.0056–0.56 mg/kg) and MED (0.0032–0.32 mg/kg) were established, followed by fixed-ratio mixtures (3:1, 1:1, 1:3) based on ED_{85} for HR. Naloxone (NAL), atipamezole (ATI), and combinations of NAL+ATI were evaluated for their ability to recover normal CR function. FENT produced μ-opioid receptor–mediated decreases in HR, SpO_2, and RR, whereas MED caused α2AR-mediated reductions in HR and RR. Their combined effects were largely additive. NAL rapidly reversed FENT effects but was less effective with MED present; ATI reversed MED effects but not those of FENT; and NAL+ATI improved SpO_2 but often caused rebound tachycardia and tachypnea. These results highlight the challenge of reversing overdoses involving fentanyl and α2AR agonists and emphasize the need for improved countermeasures for polysubstance exposures.

Poster 55

Comparing demand for single large infusions vs bursts of smaller infusions of heroin in rats

Rego, Felipe P; Olivero-Gamez, Claudia; Brooks, Eliza; Kearns, David N

Department of Psychology, American University, District of Columbia, USA

A recent publication suggests rats show greater preference for heroin when given the opportunity to self-administer heroin in self-controlled bursts than when only allowed one infusion at a time. The following experiments sought to test whether the essential value (EV) of reinforcers is higher when rats are allowed to take them in bursts. A behavioral economics framework was used to evaluate demand for both a non-drug reinforcer (saccharin) and heroin under conditions where rats could take a single reinforcer vs. a burst of multiple reinforcers. Experiment 1 compared demand curves between conditions where rats lever pressed for either a single 50-s period of access to saccharin or for a 5-min period wherein they could obtain up to five 10-s saccharin reinforcers. There was no significant difference in saccharin EV, indicating that bursts of saccharin reinforcers are not valued differently from single saccharin reinforcers. Experiment 2a compared demand curves between conditions where rats self-administered a single 0.1 mg/kg heroin infusion vs. a burst of up to five 0.02 mg/kg infusions. The EV of the single large infusion was significantly greater ($p < 0.05$) than the EV of the burst of smaller infusions. Experiment 2b performed the same comparison, but with the dose for burst infusions equalized with the single large infusion (0.1 mg/kg/infusion in both conditions). Now, there was no difference in EV, but there was a significant difference ($p < 0.05$) in log-Pmax, indicating subjects would continue to pay higher prices for larger total amounts of heroin. Overall, results suggest that rats do not value bursts of multiple reinforcers more than single reinforcers (whether saccharin or heroin). Instead, the total amount of heroin (but not saccharin) per reinforcer was a determinant of its value.

Poster 56

Modulation of Psilocybin's Behavioral Effects by CYP450 Inducers: Evidence for Pharmacologic Interactions in Rats

Mahfuz A. Sakib, Elmira Zolali, Yash Mehta, Jenny Wilkerson, Lance R. McMahon, and Samuel Obeng

Department of Pharmaceutical Sciences, Jerry H. Hodge School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, TX 79106

Psychedelics, especially psilocybin, are being actively investigated for their potential in treating refractory psychiatric conditions such as major depressive disorder, posttraumatic stress disorder, and substance use disorder. This study examined the acute interaction between psilocybin and the CYP3A4 enzyme inducer carbamazepine in vivo, and the prolonged interaction with the CYP3A1 inducer dexamethasone in vitro, which mimics the rat CYP3A4 isozyme. Using a drug discrimination procedure, male (n=4) and female (n=4) Sprague-Dawley rats were trained to discriminate the 5-HT2A agonist DOI (0.32 mg/kg). Both DOI (ED50 = 0.13 mg/kg) and psilocybin (ED50 = 0.45 mg/kg) elicited dose-dependent drug-appropriate responding. Pretreatment with M100907 antagonized both DOI and psilocybin effects. In contrast, co-administration with carbamazepine produced leftward shifts (10.2-fold for psilocybin; 5.8-fold for DOI), indicating enhanced discriminative stimulus effects under acute conditions. Both psilocin and testosterone showed a significant reduction in half-life when treated with dexamethasone, whereas psilocybin's half-life did not decrease. These results showed that psilocin's half-life can be modified, and we can induce faster metabolism by combining it with CYP450 inducers.

Poster 57

Maternal and Paternal Alcohol Exposures Produce Distinct and Combined Effects on Offspring Drinking, Activity, and Compulsivity

Saleh, Ahmed I[1] ; Rouzer, Siara K[2] and Miranda, Rajesh C[2]

[1]Texas A&M University College of Veterinary Medicine & Biomedical Sciences, College Station, TX; [2] Department of Neuroscience & Experimental Therapeutics, Texas A&M College of Medicine, Bryan, TX.

Background: Prenatal alcohol exposure alters offspring neurodevelopment to impact offspring behaviors across the lifespan, but most research has focused exclusively on maternal drinking. Emerging evidence shows that paternal preconception alcohol use can also influence offspring behavior, suggesting distinct and biologically meaningful paternal contributions. However, few studies have examined whether maternal and paternal alcohol exposures interact, or whether dual-parent exposure produces offspring outcomes beyond those seen with single-parent exposure. Methods: Adult C57BL/6J males and females received either water or 10% ethanol using the Drinking in the Dark paradigm. Sires were exposed for two spermatogenic cycles (70 days), and dams were exposed for 10 days before and after conception. Adult offspring were assessed on (a) operant self-administration for alcohol-seeking behavior, (b) the Open Field Test for locomotor activity and anxiety-related avoidance, and (c) the marble-burying assay for compulsive-like behavior. Results: Dual-parent exposure increased ethanol consumption relative to single-parent exposures under fixed-ratio and progressive-ratio conditions. All alcohol-exposed offspring preferred the highest ethanol concentration offered (40%). In the Open Field Test, maternal and paternal exposures increased hyperactivity and reduced center exploration, whereas dual-parent exposure did not intensify these effects. Dual-parent exposure produced the strongest compulsive-like phenotype, reflected by a higher ratio of marbles buried. Conclusion: Dual-parent alcohol exposure enhances alcohol-seeking and compulsive behaviors in offspring beyond single-parent exposure. These results highlight the importance of evaluating both parental lines in intergenerational alcohol risk and the need to investigate mechanisms underlying dual-parent effects.

Poster 58

Longitudinal Assessment of Cognitive, Behavioral, and Metabolic Changes in the 5xFAD Mouse Model of Alzheimer's Disease

Sawant Neha[1] , Buice Taylor[2] , Bergeson Susan E[2] , Bailoo Jeremy D[2]

[1]Department of Pharmacology and Neuroscience, [2]Department of Cell Biology and Biochemistry, Texas Tech University Health Sciences Center, Lubbock

5xFAD mice are one of the most widely used Alzheimer's disease (AD) mouse models. They develop hallmark amyloid pathologies, including Aβ plaque deposition, accompanied by pronounced neuroinflammation, synaptic degeneration, and neuronal loss. However, the onset of AD-related behavioral changes is highly variable across replicate between-subjects cross-sectional studies and question the reliability and translational validity of this model.
To address these inconsistencies, we are longitudinally evaluating motor–, cognitive–, and anxiety-like–behavioral changes in 5xFAD and wild-type mice in 2-month epochs, starting at 2 months of age; the animals are now 11 months old. In parallel, food and water consumption, as well as body weight were measured to identify potential metabolic contributors to behavioral variability and disease onset.

Between-subject cross-sectional studies have found that spatial learning impairment, decreased anxiety, and increased hyperactivity in 5xFAD mice emerge by 3 months of age and worsen with age. Longitudinally, our within-subjects study showed that decreased anxiety-like behavior, increased hyperactivity, and mild indications of cognitive impairment only emerged only after 6 months of age. Additionally, we observed significant differences in body weight and food consumption between WT and 5xFAD mice around six months of age, suggesting underlying metabolic alterations in the 5xFAD group that temporally coincide with the emergence of the AD-related behavioral changes and thereby highlight the necessity of longitudinal approaches for accurately characterizing disease progression in this model.
Our results highlight that understanding how disease progression occurs at the individual mouse level may improve precision and consequentially may enhance the translational relevance of preclinical models, including 5xFAD, in Alzheimer's research.

Poster 59

Conditioned withdrawal cues elicit persistent somatic and motivational responses in fentanyl-dependent rats

Neha Skandan[1] , Francesca Burton[1] , George F. Koob[1], Leandro F. Vendruscolo[1] , Courtney S. Wilkinson[1]

[1]National Institute on Drug Abuse, Intramural Research Program, Baltimore, MD, USA

Rationale: Chronic opioid exposure leads to analgesic tolerance and withdrawal-induced hyperalgesia, and cues linked to these states can promote continued opioid use through negative reinforcement. We investigated how a conditioned withdrawal cue influences somatic withdrawal signs, irritability-like behavior, and hyperalgesia during fentanyl dependence and long-term abstinence. Methods: Twenty-four male rats were implanted with fentanyl (0.6 mg/kg/day) or saline minipumps for 28 days. Rats received the preferential μ-opioid receptor antagonist naloxone (1 mg/kg, SC) or saline paired with a lemon odor to establish conditioned withdrawal or neutral cue. After conditioning, rats were exposed to the cue alone and tested for somatic withdrawal signs, irritability-like behavior, avoidance, and thermal sensitivity. Fentanyl-induced analgesia, tolerance to analgesia, withdrawal-induced hyperalgesia, and cue-induced mechanical hyperalgesia were measured using the electronic von Frey test. To determine whether the cue alone activated the HPA axis, blood was collected one hour after lemon cue exposure, 70 days after the last conditioning session, and plasma corticosterone levels were measured using ELISA. Results: Chronic fentanyl exposure induced strong analgesia but tolerance to this effect developed within three days. The withdrawal cue elicited somatic withdrawal signs, increased thermal sensitivity, and increased irritability. After minipump removal, hyperalgesia persisted for approximately 1 month. After normalization of mechanical sensitivity, the exposure to the conditioned cue reinstated hyperalgesia and increased corticosterone levels even after protracted abstinence. Conclusion: These findings demonstrate that conditioned withdrawal cues can robustly reinstate withdrawal symptoms, inducing activation of the stress system and re-emergence of hyperalgesia long into abstinence, which may contribute to relapse vulnerability in opioid use disorder. Ongoing imaging studies will identify brain circuits underlying these cue-driven states.

Poster 60

Neural Activity in the Insula–mPFC Pathway During Distress Tolerance and Its Relation to Drug-Seeking, Impulsivity, and Anxiety-Like Behavior

Smoak, Marina A.[1,3]; Batson, Serina[1]; Moschak, Travis M.[1]

[1]Department of Biological Sciences, and the [3]Graduate Programs in Biosciences; The University of Texas at El Paso, USA

Distress tolerance (DT), the behavioral ability to maintain goal-directed behavior despite psychological discomfort, is a key factor influencing vulnerability to substance use. Individuals who struggle to tolerate distress and exhibit heightened impulsivity are more prone to engage in drug-seeking and relapse, and anxiety-related behaviors often reflect similar intolerance of psychological discomfort. The insula (INS) and medial prefrontal cortex (mPFC), two regions central to the salience network, have been implicated in these behavioral vulnerabilities. However, the contribution of INS→mPFC circuitry to DT and its relationship with impulsivity, anxiety, and cocaine-seeking remains insufficiently characterized in preclinical research. We hypothesized that activity along this pathway during DT would be associated with impulsivity, anxiety, and drug-seeking behaviors, and that this circuit would exhibit altered signaling following cocaine self-administration (SA). To test this, Long Evans rats (females: n=10; males: n=10) received Cre-dependent GCaMP6s in the INS and a retrograde Cre-expressing AAV in the mPFC, enabling pathway-specific calcium imaging via a GRIN lens in the INS. Animals completed DT testing, elevated plus maze (EPM), and cocaine or water SA, followed by abstinence and re-evaluation of behaviors and neural activity patterns. Statistical analysis included ANOVAs, t-tests, and chi-square to evaluate differences in activity patterns and group-level effects. Pearson's correlations were used for changes in neural activity and behavior. Preliminary results show that although INS–mPFC neural activity tracks task events, a history of cocaine did not impact behavior. Ongoing analyses aim to further delineate how INS–mPFC signaling contributes to vulnerability factors such as impulsivity, anxiety, and drug-seeking within the context of distress tolerance .

Poster 61

Effects of psychedelics on oral furanyl fentanyl consumption and naloxone-precipitated withdrawal in male C57Bl/6N mice

Snow, Spencer[1] ; Fomin, Andriy[1] and Fantegrossi, William E[1]

[1] - Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR

Current FDA-approved medications for opioid use disorder (OUD) either maintain dependence and possess abuse liability of their own (agonist replacement drugs) or precipitate withdrawal in dependent individuals (antagonist drugs). Determining the therapeutic utility of non-opioid drugs for OUD is thus of interest, and psychedelics may be potential candidates in this regard due to their purported persistent anti-addiction effects. Our model of oral opioid consumption in mice captures an "addiction-like" phenotype characterized by induction of physical dependence and defense of opioid consumption when drug solutions are devalued, and in our previous studies with this procedure, psychedelics have elicited persistent effects on some somatic signs of opioid withdrawal. Here we used this procedure with distinct groups of mice continuously maintained on furanyl fentanyl (FF) solutions to elicit physical dependence, then treated them with saline or various doses of the psychedelics LSD, DOI or DPT. Mice were then administered the opioid antagonist naloxone to precipitate withdrawal 1 day, 4 days, and 11 days after psychedelic treatment, and naloxone-elicited weight loss and vertical jumping were quantified during each of the three withdrawal trials. None of the psychedelics altered the trajectory of FF intake across the study, suggesting a common lack of effects on ongoing opioid consumption. However, different dose- and time-dependent effects were observed for all the psychedelics on jumping and on weight loss. For example, mice receiving the largest LSD dose exhibited persistently attenuated withdrawal signs, but mice receiving the smallest DOI dose showed exacerbated withdrawal signs even 11 days after drug administration. Future studies will utilize selective agonists and antagonists to determine the specific receptor mechanisms necessary for lasting anti-withdrawal effects.

Poster 62

Characterizing Prelimbic Calcium Dynamics During Extended Waiting Periods in Impulsivity Paradigms

Sosa Jurado, Ricardo[1,2]; Espinosa Salgado, Mariana[1,3]; Galvan, Karla J[1] ; and Moschak, Travis M[1]

[1]Department of Biosciences, the [2] Graduate Program in Biosciences, and the [3] Neuroscience Undergraduate Program; University of Texas at El Paso, Texas, USA

Impulsivity is a maladaptive behavioral trait central to substance use disorders, in part by sustaining a feedback loop that escalates drug intake. The prelimbic cortex (PrL) has been strongly implicated in impulsive decision-making, yet how PrL neural populations are recruited across extended pre-cue intervals remains poorly characterized. To address this gap, we analyzed prelimbic calcium imaging data collected during performance of impulsivity tasks differing in the duration of the pre-cue interval preceding action initiation, enabling direct comparison of neural activity under short (TT) versus prolonged (LPT) waiting demands. PrL activity was processed using CaImAn for neuron extraction and deconvolution, followed by downstream analyses in NeuroExplorer. Neuronal responses during the pre-cue interval were classified as excited, inhibited, or nonphasic and compared across task conditions. Preliminary analyses revealed no significant association between task condition and prelimbic neuronal response classification, $X2$ (2, N = 251 neurons across 6 rats) = 1.97, p = .37, indicating that the overall distribution of response types was similar across conditions. These findings suggest that extending the pre-cue interval does not grossly alter the proportion of PrL response classes, motivating finer-grained analyses of temporal and ensemble-level activity patterns. Ongoing analyses continue to interrogate additional features of PrL dynamics during the pre-cue interval, including the degree to which these patterns are disrupted following cocaine exposure; all interpretations remain provisional as the dataset undergoes continued characterization.

Poster 63

Determining the role of oxytocin receptors in mediating social reward

Stall, Julia T., Leong, Kah-Chung Ph.D

Department of Psychology, Trinity University, San Antonio, TX, USA

Investigating the neural mechanisms underlying social reward is important not only to further the current understanding of what drives social interaction, but also for informing potential therapeutic strategies for disorders characterized by social dysfunction. Prior studies suggest the neuropeptide oxytocin (OXT) as a critical modulator of social behaviors, and it serves as a potential pharmacotherapeutic due to its ability to attenuate drug reward. The current study aims to elucidate how OXT may drive social reward, particularly the role of OXT receptors (OXTR) in reward-related brain structures such as the nucleus accumbens (NAc), ventral tegmental area (VTA), and lateral septum (LS). Using a social conditioned place preference paradigm, Wistar rats (n=75) were conditioned to associate one of two distinct chambers with social interaction over the course of 10 days. In experiment 1, both male and female rats established social place preference behavior, indicated by an increase in time spent in the socially paired chamber at test. In experiment 2, OXTRs were selectively knocked down through bilateral infusions of AAV-OXTR-shRNA into male rats' NAc, VTA, or LS. After the 10-day CPP paradigm, rats that received OXTR knockdown displayed diminished social place preference behavior relative to controls. These results suggest that OXTR in the NAc, VTA, or LS are independently sufficient to drive social reward. Given the role of social support as a vital component of addiction recovery and relapse prevention, these results offer potential novel applications for utilizing social intervention as a potential therapeutic strategy for substance use disorder.

Poster 64

Mechanistic Characterization of Mu Opioid Negative Allosteric Modulators

Stewart, Hannah C[1] ; Li, Mengchu[1] ; Rech, Jason C[2] and Traynor, John R[1,2]

[1]Edward F. Domino Research Center, Department of Pharmacology, University of Michigan, Ann Arbor, MI USA; [2] Department of Medicinal Chemistry, University of Michigan, Ann Arbor, MI USA

Mu-opioid receptor (MOR) agonists, such as morphine and fentanyl, are the most effective analgesics available but come with severe addiction liability, and their use can lead to opioid use disorder (OUD). One OUD treatment option, the MOR antagonist naltrexone, completely blocks opioid binding through a competitive inhibitory mechanism, and many patients relapse due to severe withdrawal. Therefore, it is of interest to identify negative allosteric modulators (NAMs) that act at a topographically distinct site on MOR to owe a noncompetitive, unsurmountable mechanism and serve as partial inhibitors to confer less severe withdrawal. We identified several promising NAMs through structure-activity studies previously, and now, characterize their mechanism of action. Radioligand competitive and saturation binding experiments show an unsurmountable effect of lead NAMs, and functional studies and Schild analysis suggest that the NAMs reach a 'ceiling' effect at high concentrations, indicative of an allosteric mechanism. Additionally, probe dependence was evaluated to elucidate the effect of NAMs on the potency of various full and partial agonists of MOR. Ongoing research involves the computational analysis of possible NAM allosteric sites through site identification, molecular docking, and molecular mechanics/generalized Born surface area (MM/GBSA) methods. These data suggest that the NAMs operate through an allosteric rather than orthosteric mechanism and therefore could serve as a better and safer treatment for OUD.

Poster 65

Effects of Novel Designer Benzodiazepines on Motor Activity

Stubbs, Quinston; Hadadnejad, Neeku; Hill, Gatch, Michael B, Forster, Michael J; and Shetty, Ritu A

Department of Pharmacology & Neuroscience, UNT Health Science Center, TX USA

Aims: Novel benzodiazepines are increasingly sold on illicit marketplaces and labeled as "research chemicals," often masquerading as FDA-approved drugs such as alprazolam. This study examined locomotor activity effects of the emerging benzodiazepines bromazolam and clonazolam compared to standard compounds midazolam and pentobarbital.

Methods: Locomotor activity was measured in male Swiss Webster mice following administration of midazolam, pentobarbital, bromazolam and clonazolam.

Results: All four compounds produced a decrease in locomotor activity at high doses. Clonazolam was the most potent (ED_{50} = 0.05 mg/kg), followed by midazolam (ED_{50} = 1.8 mg/kg), bromazolam (ED_{50} = 13.8 mg/kg), and pentobarbital (ED_{50} = 15.8 mg/kg). Mild stimulant effects were observed with low to moderate doses of midazolam and a high dose of pentobarbital but not with bromazolam or clonazolam. There was a marked increase in center-time with pentobarbital at 50 mg/kg and midazolam at 3 mg/kg, whereas a similar effect this was not evident in bromazolam and clonazolam.

Conclusion: The emerging benzodiazepines bromazolam and clonazolam differ from midazolam and pentobarbital in their anxiolytic profiles. The classic depressant effect produced by novel benzodiazepines is consistent with midazolam. However, the lack of anxiolytic effect may reflect a difference in GABAa subunit activity. In contrast, pentobarbital anxiolytic like effect would seem to align with its mechanism of enhancing channel open duration, producing deeper and longer lasting inhibitory tone. These findings provide critical comparative data for emerging benzodiazepines.

Poster 66

Establishment of GLP-1 receptor agonist Liraglutide as a discriminative stimulus in rats

Sullivan, Leslie L; Beltran, Nina M, and Serafine, Katherine

Department of Psychology, The University of Texas at El Paso, El Paso, TX USA

Glucagon-like-peptide-1 (GLP-1) receptor agonists have gained popularity as treatments for obesity and type 2 diabetes; however, it is unclear if these drugs can serve as discriminative stimuli in a drug discrimination procedure. To explore this possibility, 10 male Sprague–Dawley (n=10) rats were trained to discriminate an i.p. injection of liraglutide from saline while responding for a food reinforcer under a fixed-ratio 5 schedule, following a 4-hour pretreatment time. Training required ≥90% correct-lever responses and fewer than five incorrect responses before the first reinforcer for 5 consecutive or 6 of 7 sessions. After initial training at 0.032 mg/kg, the dose was raised to 0.056 mg/kg. After about 40 days, 8 of 10 rats met criteria to begin testing, and experiments remain ongoing. Liraglutide dose-response curves (0.0178 - 0.100 mg/kg) were generated twice, prior to substitution testing. Other GLP1 receptor agonists (e.g., semaglutide) were administered, and ongoing experiments to test other drugs (e.g., lorcaserin, morphine and cocaine) as well as antagonist combination studies are planned. To analyze results, linear regression and repeated measures ANOVAs were used. Although results are preliminary, there were no significant differences between liraglutide dose-response curve determinations when evaluating ED_{50} values. Further, semaglutide fully substituted for liraglutide, though was significantly more potent than liraglutide in this assay. Additional substitution and antagonism combination studies are in progress, and will further help to characterize the discriminative stimulus effects of liraglutide. The results of this study will further elucidate the in vivo pharmacological effects of liraglutide and can guide future experiments exploring this class of drugs for the treatment of a variety of health conditions.

K.M.S. and L.L.S were funded by NIH R16 GM149426

Poster 67

The role of organic cation transporter 3 (OCT3) in the discriminative stimulus effects of stimulants

Tangen, Simon T[1]; Daws, Lynette C[1,2] and Collins, Gregory T[1,3,4,5]

Departments of [1]Pharmacology and [2]Cellular and Integrative Physiology, University of Texas at San Antonio, San Antonio, TX USA; Departments of [3]Pharmacology and [4]Anesthesiology, University of Michigan, Ann Arbor, MI USA; 5Ann Arbor Veterans Health Care System, Ann Arbor, MI USA.

While effective for multiple neurological disorders, stimulants possess substantial abuse liability. Prescription rates, misuse, illicit use, and overdose deaths involving stimulants have continually increased over recent years with amphetamine-type stimulants (amphetamines; e.g., Adderall and methamphetamine) being the most widely misused and abused. Despite this ongoing public health crisis, no FDA-approved pharmacotherapy for amphetamine-type stimulant use disorder exists, highlighting the need to identify and validate biological targets for the development of treatments. Recent studies have indicated that reverse transport of dopamine through organic cation transporter 3 (OCT3) mediates the reinforcing effects of amphetamine, but not cocaine. However, the role of OCT3 in other abuse-related (e.g., positive subjective) effects of amphetamines is unknown. The current study tests the hypothesis that OCT3 mediates the discriminative stimulus (e.g., positive subjective) effects of amphetamines. Eight OCT3 constitutive knockout (KO) and wildtype (WT) mice were trained to discriminate cocaine (10 mg/kg) from saline (n=4/genotype/sex). Substitution curves were then generated for cocaine, amphetamine, fentanyl, and methamphetamine. Preliminary data suggests similar rates of acquisition for both OCT3 KO and WT mice. Fentanyl did not substitute for cocaine in either genotype. Amphetamine and methamphetamine did substitute for cocaine, regardless of genotype, suggesting that OCT3 does not mediate the discriminative stimulus effects of amphetamines. These early results indicate that treatments developed to inhibit OCT3 may not completely attenuate the abuse liability of amphetamines.

Poster 68

Cardiorespiratory effects of fentanyl and medetomidine: Further investigations of "tranq-dope"

[1]Thomas, Emma M.; [1]Folger, Kirsten J.; [1]Hockett, Stephanie G.; and [1]Smith, Mark A

[1] Department of Psychology and Program in Neuroscience, Davidson College, Davidson, NC USA.

A recent driver of opioid-related overdose deaths has been the adulteration of illicitly manufactured fentanyl with the veterinary anesthetic xylazine, an alpha 2 adrenergic agonist that is not approved for use in humans. Recently, reports from DEA seizures and toxicology screens indicate that other alpha 2 adrenergic agonists are increasingly being used as adulterating agents; however, little or no research has examined their toxicity when combined with fentanyl. The purpose of this study was to examine the effects of fentanyl and the alpha 2 adrenergic agonist, medetomidine, on cardiorespiratory measures that may contribute to the toxicity of these drug combinations. Male and female rats were administered fentanyl (0.1 mg/kg, iv), medetomidine (0.01 mg/kg, iv), or their combination and placed in a MouseOx® monitoring system to measure respiratory and cardiovascular functioning. When administered alone, both fentanyl and medetomidine decreased respiratory rate and heart rate relative to control. Fentanyl, but not medetomidine, decreased O2 saturation, and neither drug altered pulse distention. When administered in combination, greater decreases were seen in respiratory rate, heart rate, and O2 saturation than when either drug was administered alone, and longer durations of time were required for these measures to return to control conditions. Unlike that observed when each drug was administered alone, pulse distention was significantly decreased when these drugs were administered in combination. These data indicate that combinations of fentanyl and medetomidine produce effects that are more severe, of longer duration, and impact more aspects of cardiorespiratory functioning than either drug alone.

Poster 69

Xylazine prolongs fentanyl-induced respiratory suppression and impacts recovery with rescue agents in rats

Torgbenu, Theophilus[1] ; Zuarth Gonzalez, Julio D.[1] ; McMahon, Lance R[1] ; and Obeng, Samuel[1]

[1]Department of Pharmaceutical Sciences, Texas Tech University Health Sciences Center

Fatal opioid overdoses in the United States have nearly tripled over the past decade. Notably fentanyl, is implicated in about 92% of opioid overdose deaths. Fentanyl acts as agonist at the mu-opioid receptor. Alarmingly the lethality of illicit fentanyl has been exacerbated by the emergence of xylazine now increasingly detected as an adulterant in street drugs. This study investigated the drugs alone, in combination (1:3) and the effect of rescue agents on respiratory function. Fentanyl (0.056mg/kg, i.v.) not xylazine (0.178mg/kg, i.v.), produced 60% decrease in minute volume and reversed to baseline in 20min. Fentanyl-xylazine coadministration imitated fentanyl suppression of minute volume but reversed to baseline after 35min. Naloxone (1mg/kg, i.v.) – atipamezole (1mg/kg, i.v.) co-administration produced robust reversal of fentanyl-xylazine induced respiratory depression than either drug alone. These results suggest that presence of xylazine, prolongs respiratory compromise when combined with fentanyl making therapeutic intervention more difficult in overdose situations.

Poster 70

Role of orbitofrontal cortex circuitry in the effects of chronic stress on cognition and cue-induced reinstatement

Tuite, Kate M[1]; Maguire, David R[1]; Morilak, David A[1,2]

[1]Department of Pharmacology, UT Health San Antonio, San Antonio, TX; [2]South Texas Veteran's Health Care System, San Antonio, TX

Stress-related psychiatric disorders and substance use disorders are associated with deficits in cognitive flexibility that exacerbate and maintain these conditions. Reversal learning, a form of cognitive flexibility, is disrupted in substance use and psychiatric disorders. This form of cognitive flexibility depends on the function of the orbitofrontal cortex (OFC). OFC dysfunction is associated with deficits in reversal learning and higher rates of relapse in patients with substance use disorders. While there is significant evidence for the role of the OFC in reversal learning, the circuit-level mechanisms underlying stress-induced reversal learning deficits are not well established. Understanding how OFC circuits change under chronic stress will provide insight into how psychiatric and substance use disorders are maintained neurobiologically. Here we test the hypothesis that a projection to the OFC from the stress-responsive paraventricular thalamus (PVT) is responsible for the effects of chronic stress on reversal learning. All experiments were done in male and female Sprague-Dawley rats. We utilized ΔFosB immunohistochemistry and retrograde tracing to examine activation of the PVT-OFC pathway in non-stressed and stressed animals. In a separate cohort of animals, we used excitatory and inhibitory DREADDs in a pathway-specific manner to manipulate the PVT-OFC projection during reversal learning. Immunohistochemistry revealed that female rats have overall lower expression of ΔFosB compared to males in the PVT, but both sexes showed an increase after chronic stress. Manipulating the pathway with excitatory DREADDs in non-stressed animals disrupted reversal learning only in males and inhibiting in stressed animals reversed the effects of stress on reversal learning only in males. These results suggest the PVT-OFC pathway is involved in the effects of stress in males.

Poster 71

Thermal Pain Sensitivity Does Not Predict Punishment Sensitivity in a Preclinical Methamphetamine Model

Tumpa, Mst Afroza Alam[1] ; Basak, Kona[1] ; Madhuranthakam, Indu M[1] ; Ahmed, Shakil1 ; Uddin, Azim[1] ; Keck, Thomas M[1] ; * and Job, Martin O[1] *

Preclinical models of punishment are widely used to distinguish compulsive from noncompulsive drug taking by introducing adverse consequences, such as foot shock, during methamphetamine (METH) self-administration. In this paradigm, animals can be classified as punishment-resistant (PR) or punishment-sensitive (PS). Since METH can release endogenous opioids and potentially alter nociceptive processing, it is unclear whether individual differences in pain sensitivity influence punishment sensitivity. This study examined whether thermal pain sensitivity, measured using the hotplate test, predicts punishment sensitivity in rats trained to self-administer sucrose or METH. Male and female Long Evans rats self-administered sucrose (males: n = 22; females: n = 22) or METH (males: n = 16; females: n = 14; 0.1 mg/kg/infusion, FR1, 6-hour sessions) for 28 days. Punishment consisted of escalating foot shocks (0–1.0 mA) delivered within a single session. Thermal pain sensitivity was assessed at three time points: before self-administration, immediately prior to punishment, and after a recovery period. METH exposure did not alter pain sensitivity, and no sex differences were observed. Across all groups, punishment sensitivity was unrelated to thermal pain sensitivity. These findings indicate that individual variability in punishment-driven behavioral suppression is not explained by nociceptive sensitivity, suggesting that hotplate-measured thermal pain does not account for PR versus PS behavior in METH- or sucrose-trained rats.

Poster 72

Identification of novel ligands that target the delta opioid receptor (DOR)- kappa opioid receptor (KOR) heteromer

Vargas, Marina[1]; Diaz, Kallee C[2]; Chavera. Teresa S[1]; Wedemeyer, Michael J[1]; McHardy, Stanton F[2]; Clarke, William P[1], and Berg, Kelly A[1]

Department of Pharmacology[1], and Department of Chemistry[2], University of Texas/UT Health San Antonio, TX

Pain is a pervasive public health crisis in the United States, impacting over 100 million adults annually. Current standard-of-care analgesics for moderate to severe pain are opioids that act on mu opioid receptors in the CNS which unfortunately have dangerous adverse effects, including respiratory depression and high addiction liability. Targeting opioid receptors expressed in the periphery on pain-sensing neurons, offers a strategy to inhibit nociceptive pain that is devoid of CNS side effects. Our innovative approach involves targeting the DOR-KOR receptor heteromer by leveraging a unique receptor heteromer property known as interprotomer allosterism; an orthosteric ligand for one protomer (e.g., DOR) allosterically regulates the effect of an orthosteric ligand for the second protomer (e.g., KOR). In this study, we have focused on identifying novel ligands for DOR and KOR to obtain valuable structure-activity relationship (SAR) information facilitating rationale design of compounds. Novel analogues synthesized by the McHardy Lab, were screened using a cAMP assay in HEK cells expressing either DOR or KOR individually. Candidates demonstrating antagonist or weak agonist properties at both receptors then undergo concentration-response curve analysis to determine potency and efficacy. To date, we have screened 204 compounds and have identified 3 potential hits that will be tested for agonist activity in vivo using an animal model to determine antinociceptive efficacy. Successful compounds will serve as candidates for further characterization, optimization, and development for pain management.

Supported by NIH/NIDA R01DA057787

Poster 73

Impact of a History of Opioid Self-Administration or Opioid Withdrawal on the Positive Reinforcing Effects of Pregabalin in Rats

Varma, Harsha K.[1,3], Mijares, Abram E.[1,3], Grisham, Amanda K.[1,3], Shi, Yonggong[1,3], Bravo, Gilberto[1,3], Infante, Antonio A.[1,3], Patel, Maya N.[1,3], Das, Isaac X.[1,3], Mazhar, Talha[1,3], France, Charles P.[1-3], and Hiranita, Takato[1,3]

While the abuse potential of gabapentinoids alone is limited, their non-medical use has increased significantly among individuals with a history of opioid use. However, the extent to which opioids enhance the abuse potential of gabapentinoids remains poorly characterized. This study assessed the impact of opioid self-administration history and opioid withdrawal on the positive reinforcing effects of the gabapentinoid, pregabalin. Adult male and female rats (n = 16/sex) were trained to lever press for sucrose pellets under a fixed-ratio 1 schedule. When saline or pregabalin (0.56-17.8 mg/kg/infusion) was substituted for sucrose, doses of 1.78 and 5.6 mg/kg/infusion maintained self-administration responding slightly but significantly above saline levels in males; however, no dose of pregabalin maintained self-administration responding above saline levels in females. Rats were then transitioned into one of two experimental conditions (n= 8/sex/group). In rats trained to self-administer fentanyl (0.0032 mg/kg/infusion), 17.8 mg/kg/infusion pregabalin maintained self-administration responding above saline levels in both sexes. In the second group, opioid dependence was induced with escalating doses of morphine (10–40 mg/kg, s.c., twice daily for 4 days) and then maintained with morphine (40 mg/kg/day, s.c.) administered immediately after daily sessions. After discontinuation of morphine treatment, no dose of pregabalin maintained self-administration responding above saline levels in either sex. However, 0.001 mg/kg fentanyl maintained self-administration responding significantly above saline levels in both sexes. These results suggest that a history of opioid self-administration, but not a history of opioid dependence and withdrawal enhances the positive reinforcing effects of gabapentinoids. This study was supported by USPHS grant R01DA058018 (TH) and the Welch Foundation grant AQ-0039 (CPF).

Poster 74

A Behavioral Economic Analysis of Fentanyl and Methamphetamine Alone and in Mixtures in Nondependent and Dependent Rats

Jacqueline M. Vazquez[1] , Christina M. George[2,4], Gregory T. Collins[1,2,3,4]

[1]Department of Pharmacology, University of Texas at San Antonio, San Antonio, TX USA; Departments of [2] Pharmacology and [3] Anesthesiology, University of Michigan, Ann Arbor, MI USA; 4 Ann Arbor Veterans Health Care System, Ann Arbor, MI USA.

Polysubstance use involving opioids (e.g., fentanyl) and stimulants (e.g., methamphetamine [METH]) has increased in the United States, contributing to over 30% of all fatal overdoses in 2023. Evidence suggests that opioid withdrawal may increase the reinforcing effects of opioid and stimulant co-use. Behavioral economic analyses are particularly beneficial for comparing drugs across different classes as elasticity coefficients (α) generated from demand curves can serve as an index of the "essential" value of drugs. Our laboratory has adapted a multiple component drug self-administration procedure for demand curve analyses where the unit-dose of drug increases within a session, across four components, and the response requirement (i.e., fixed ratio) increases across sessions. We hypothesized that opioid withdrawal would increase economic demand for fentanyl alone and fentanyl + METH mixtures, but not METH alone in male and female Sprague-Dawley rats. After generating demand curves in non-dependent animals, extended access to fentanyl (i.e., 12-hour extended access) was used to establish dependence, and demand curves were re-generated during withdrawal (i.e., 8 hours after extended fentanyl access). Our results indicate that METH is a more valuable reinforcer compared to fentanyl alone with the elasticity coefficients for mixtures of fentanyl + METH increasing proportionally based on the ratio of each drug in the mixture. Demand intensity for fentanyl and METH is greater during opioid withdrawal, with similar, nonsignificant trends found for 1:3 and 3:1 fentanyl + METH mixtures. Together, these results suggest that opioid withdrawal may increase the reinforcing effects of polysubstance use involving opioids and stimulants.

Poster 75

Evaluation of Endocannabinoids in Rat Whole Blood: Insights into Blood Partitioning and Circadian Pharmacokinetics

Verma, Sarvesh kumar[1] ; Gour, Abhishek[1] ; Setlow, Barry[2] ; Neubert, John[3] ; Murphy, Niall[3] ; and Sharma, Abhisheak[1]

[1]Department of Pharmaceutics, College of Pharmacy, [2] Department of Psychiatry, College of Medicine, University of Florida, Gainesville, FL, [3] Department of Biomedical Sciences, Texas A&M University College of Dentistry, Dallas, TX

The endocannabinoid system is a widely distributed neuromodulatory network that plays a critical role in central nervous system development and in regulating diverse cognitive and physiological processes. It comprises endogenous cannabinoids (eCB), their cognate receptors, and the enzymatic pathways responsible for their synthesis and degradation. Among these lipid-derived messengers, the eCBs anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which activate cannabinoid receptors, are the most studied. Quantitative analysis of eCBs in whole blood has been challenging due to their very low circulating concentrations, often approaching assay detection limits. To address this limitation, we investigated the blood-to-plasma partitioning of eCBs and developed a sensitive LCMS/MS bioanalytical method. This method employed an optimized liquid–liquid extraction protocol alongside a range of stabilizers to prevent degradation during processing. Partitioning of 2-AG into whole blood and red blood cells increased progressively over 60 minutes, showing approximately 3- to 8-fold and 1- to 7-fold change, respectively. In contrast, AEA displayed no significant changes in partitioning over the same period. Overall, whole blood with immediate stabilization after sample collection using phenylmethylsulfonyl fluoride and acetic acid provides more reliable results for assessing circulating blood eCBs' concentrations. Using the BASi Culex system, we also monitored concentration–time profiles of eCBs in Sprague Dawley rats over a 24 h light–dark cycle to assess potential diurnal and nocturnal fluctuations. This method could be used further to evaluate effects of new chemical entities, including cannabinoids targeting endocannabinoid system.

Poster 76

The effects of dietary manipulation on sensitivity of male rats to morphine-induced conditioned place preference

Villa-Ortiz, Fernanda; Sullivan, Leslie, Perez, Adrian G. and Serafine, Katherine M

Department of Psychology, The University of Texas at El Paso, El Paso, TX USA

Eating a high fat/high carbohydrate enhances sensitivity of rats to several effects of stimulant drugs; however less is known about the impact of diet on morphine's effects. To explore if diet might impact sensitivity to morphine reward, rats ate either low-fat chow, high fat/ high carbohydrate chow, or a ketogenic chow before a conditioned place preference (CPP) experiment, using a biased design. It was hypothesized that rats the eating high fat /high carbohydrate chow would be more sensitive to morphine-induced CPP. During an initial pre-test (30 min) initial side preference was determined using a 2-compartment CPP chamber, with distinct flooring (metal bars vs. grid flooring). The next day, rats were injected with saline (i.p.) and restricted to their initially preferred compartment for 30 minutes. The next day, rats were injected with morphine (1.78 mg/kg; i.p.) and restricted to the other compartment (their initially non-preferred side) for 30 minutes. This cycle repeated for a total of 8 conditioning days (alternating drug and saline). Next, rats were injected with saline and placed in the center of the chamber, with unrestricted access to both compartments for a CPP post-test to determine preference after conditioning. CPP was determined using the following equation (time spent in the drug-paired compartment during post-test - pretest)/total session time) and converted to a percent. A two-way Analysis of Variance indicated a significant effect of dose. Specifically, rats that received morphine developed a significant CPP. However, there were no significant differences among dietary groups and only one dose of morphine has been evaluated at present. We hypothesize that dietary-induced differences could emerge when rats are conditioned with smaller doses of morphine, which are being explored currently.

This project was funded by NIH R25 DA033613 and NIH R16 GM149426

Poster 77

Social network analysis of a six unit recovery housing agency for women

Keith Warren[1] ; Taylor Harrington[2] ; Michael Broman[1] ; Gia Barboza-Salerno[1,2]; Ekansh Seth[3] ; Erin Helms[1]

[1]College of Social Work, The Ohio State University, Columbus, Ohio, USA; [2]College of Public Health, The Ohio State University, Columbus, Ohio, USA; [3]College of Arts and Sciences, The Ohio State University, Columbus, Ohio, USA.

Recovery housing for substance use disorder (SUD) is based on the social model of recovery, emphasizing mutual aid between residents. Social network analysis (SNA) is a powerful analytic tool for understanding the patterns of interaction that occur in such mutual aid based programs. While SNA has been applied to samples of individual freestanding recovery houses many houses are grouped within agencies. At this point there has been no social network study of such an agency, despite the fact that we would expect a network spanning multiple houses to show different properties than one drawn from a single house. This study consists of an analysis of the social network in an agency of six recovery houses serving women. Three social network surveys were completed over the course of eight months, using a question that asked whose opinions on recovery and other important life matters the women respected. These surveys yielded three social networks, which were analyzed using network graphs and descriptive statistics. Visual analysis of the social networks indicates a set of social network clusters with comparatively sparse connections between them. Some of the clusters span more than one house. This structure is known as a small world network, and statistical analysis confirms the small world properties of the network. Visual inspection further demonstrates that some residents receive a disproportionate number of nominations from peers, consistent with clinical theory that the presence of recovery role models is important in individual recovery from SUD. The network shows a high degree of reciprocity and triad closure, suggesting shared respect and shared beliefs about recovery among the residents. These results suggest that recovery housing agencies build social networks that support resident recovery in multiple ways.

Poster 78

14-3-3γ as a Signal-Biasing Scaffold for the Kappa Opioid Receptor

Wedemeyer, Michael, J[1]; Chavera, Teresa, S[1]; Salamango, Daniel, J[2]; Berg, Kelly, A[1]; Clarke, William, P[1]

[1]Department of Pharmacology, UT Health San Antonio, TX, USA; [2]Department of Microbiology, Immunology and Molecular Genetics, UT Health San Antonio, TX, USA

We previously identified the scaffold protein 14-3-3γ as a critical mediator for the long-term regulation of kappa opioid receptor (KOR) function by norbinaltorphimine (norBNI). Using siRNA knockdown, we demonstrated that 14-3-3γ was necessary for norBNI's long-term inhibition of KOR Gi-mediated cAMP signaling in rat peripheral pain-sensing neurons in culture and antinociception in vivo. Further, overexpression of 14-3-3γ is sufficient to inhibit KOR-mediated cAMP signaling. The inhibitory effect of 14-3-3γ is pathway dependent as KOR-mediated ERK activation is maintained, however, the underlying mechanism is unknown.

We hypothesize that, similar to β-arrestins, 14-3-3γ may form a complex with KOR to interrupt cAMP/antinociceptive signaling. Computational modeling demonstrated the feasibility of 14-3-3γ directly binding to intracellular regions of KOR, which are known phosphorylation and β-arrestin interaction sites. In support of this model, 14-3-3γ and K OR c o-immunoprecipitated in HEK293T and CHO cells. To visualize the KOR-14-3-3γ complex, we employed a bimolecular fluorescence complementation assay using split-YFP constructs. Microscopy confirmed reconstituted YFP fluorescence at the plasma membrane, providing direct evidence for a physical KOR-14-3-3γ interaction in living cells. Notably, this interaction was detected in the absence of agonist stimulation, suggesting a preformed complex that can bias KOR signaling.

Together, these findings support 14-3-3γ as a direct KOR-interacting scaffold, which selectively blocks activation of antinociceptive signaling pathways. This “scaffold-mediated signaling bias” represents a mechanistically distinct mode of signaling specificity from ligand-mediated bias, with potential implications for therapeutic targeting of scaffolding interfaces.

Poster 79

Changes in Perineuronal Net and Parvalbumin+ Interneuron Expression in the Orbitofrontal Cortex of Male Wistar Rats Following Fentanyl-Self Administration

Wernette, Chris L.[1] , Dejeux, Mariana I.[1] , Bressler, Felise J.[1] , Rojas, Kaitlyn E.[1] , Schwartz, Benjamin A.[1] , Nguyen, Jacques D.[1]

[1]Department of Psychology and Neuroscience, Baylor University, Waco, TX USA

Fentanyl is a synthetic opioid that is prescribed to manage pain, which has been shown to have a high potential for addiction and misuse. Amidst an ongoing opioid crisis, fentanyl has continued to rank as a leading cause of drug related deaths. Perineuronal nets are a mesh-like extracellular structure which encase neurons and are implicated in limiting neuroplasticity. Additionally, PNNs have been found to play a role in the maintenance of drug-related memories. Parvalbumin (PV+)- expressing interneurons can often be found encased in PNNs. The aim of our study was to investigate how the acquisition and escalation of fentanyl self-administration may alter the expression of PNNs and PV+ interneurons in the orbitofrontal cortex (OFC), a region of the brain which is involved in determining subjective value and “wanting” of drugs. To test our hypothesis, Male Wistars (~10-11 weeks) were assigned to one of four conditions (Saline, 0.625, 2.5, 10 ug/kg/inf.) and subjected to 21 daily 8 or 1-hour self-administration sessions on a FR-1 schedule. Following the completion of the 21 FR-1 sessions, animals underwent a four-day progressive ratio challenge to measure their motivation to seek out the drug at an increasing cost. Whole brain coronal slices of the OFC were stained with Wisteria Floribunda Agglutin and parvalbumin using immunohistochemistry and analyzed using ImageJ/Polygon.AI. Rats showed a significant ($p<.05$) escalation of intake throughout the 21 sessions in a dose-dependent manner. Preliminary tissue analysis suggests that fentanyl self-administration may alter PNN and PV+ interneuron expression in the OFC. Furthermore, we are currently investigating strain differences with Wistar-Kyoto rats, an endogenous model of depression. This work is supported by NIH grant DA047413.

Poster 80

Behavioral and Pharmacokinetic Implications of Synthetic Cannabinoid Receptor Agonist and Benzodiazepine Co-Administration in C57BL/6 Mice

Westphal, John H[1] ; Striednig, John T[2] ; Pressley, Justin M[3] ; Gannon, Brenda M[3] ; Ritter, Isabel L4 ; Avram, Marina[4] ; Moran, Jeffery H[3,4] and Fantegrossi, William E[3]

1- Program in Biochemistry and Molecular Biology, Hope College, Holland, MI; 2 – College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR; 3 – Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR; 4 - PinPoint Testing, LLC, Little Rock, AR

Substance use disorders are often comorbid with other psychiatric disorders, and abuse of synthetic cannabinoid receptor agonists (SCRAs) is common among those with mental illnesses. SCRAs elicit severe adverse effects which may be accentuated by drug-drug interactions when co-administered with psychiatric drugs which compete for the same Phase 1 CYP450 enzymes. We evaluated effects of co-administration of a common SCRA, 5FAPINACA, and the anxiolytic benzodiazepines alprazolam (ALP) and lorazepam (LOR) in mice. Both 5F-APINACA and ALP are substrates for CYP3A4, but LOR is not a CYP3A4 substrate. In behavioral studies, anxiogenic and aversive effects of 5F-APINACA – with or without benzodiazepine co-administration – were assessed using light / dark conflict and place conditioning tests, respectively. Separate cohorts of mice received injections of 5F-APINACA – with or without benzodiazepine co-administration – and blood samples were collected for analysis by liquid chromatography–mass spectrometry (LC–MS). Results from the light / dark conflict tests revealed CB1-mediated anxiogenic effects of 5F-APINACA which were mitigated by co-administration of both benzodiazepines. In place conditioning studies, 5F-APINACA elicited dose-dependent aversive effects which were unaffected by LOR co-administration but were flipped to a place preference with ALP. Analytical results of drug dispositions in blood will be presented to offer insights into the mechanism underlying these interactions. These studies supported in part by an ASPET SURF fellowship to JHW.

Poster 81

Allosteric dopamine transporter modulator inhibits cocaine-induced behaviors and neuronal activity

Xu, Yibin *[,1], Lewandowski, Stacia I.[1] , Mortensen, Ole Valente [1]

[1]Drexel University, Philadelphia, Pennsylvania, 19102

Dopamine (DA) is important for motivation and reward. DA is transported into presynaptic neurons by the dopamine transporter (DAT). Cocaine is an inhibitor of DAT, which causes extracellular DA levels to increase, thereby amplifying dopaminergic transmission in the mesolimbic area. This increase in DA signaling is responsible for the addictive properties of cocaine. Due to the importance of DAT, we propose that compounds that bind to DAT in a newly discovered allosteric site might impact cocaine-DAT interactions to inhibit cocaine induced behaviors and neuronal activity. KM822, a novel allosteric modulator of DAT, was previously found to decrease cocaine-induced locomotion in planarians. To test the effect of KM822 in mammals, we infused KM822 and cocaine intracranially into the nucleus accumbens (NAc) of Long Evans rats and measured changes in locomotion. We targeted the NAc for its crucial role in the mesolimbic dopaminergic pathway and high density of DAT. KM822 significantly decreased cocaine-induced hyperlocomotion without causing any locomotive changes by itself. We also investigated the impact of KM822 on cocaine's rewarding effect using the conditioned place preference (CPP) assay. KM822 pretreatment was found to inhibit development and cocaine-primed reinstatement of cocaine-induced CPP. Expression of the immediate early gene c-Fos is frequently utilized as a functional marker to investigate neuronal response to stimuli. We found that c-Fos expression was decreased in rats pretreated with KM822 prior to cocaine infusion compared to the vehicle group. In this study, the sample size for each group was at least 6 rats. When comparing between groups, unpaired t-tests were used. When comparing both between and within groups, a two-way repeated-measures analysis of variance (RM ANOVA) was used. Overall, these studies show that KM822 can inhibit cocaine-induced behaviors and neuronal activity in rats encouraging further investigations of novel allosteric DAT modulators in treating cocaine use disorder.

Poster 82

Investigating Body Mass Index (BMI) as a Potential Clinical Moderator of the Effects of Cytokines on Craving Phenotypes in Alcohol Use Disorder

You Zhang[1, 2], Lewis Nunez Severino[1, 2], Brian J. Gully[1] , Rivkah Hornbacher[1, 2], Robert M. Swift[1], [4, 5], Carolina L. Haass-Koffler [1, 4, 5, 6]

[1]Center for Alcohol and Addiction Studies, Brown University; [2]Department of Neuroscience, Brown University; [3] Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University; [4,]Department of Behavioral and Social Sciences, School of Public Health, Brown University; [5] USAVeterans Affairs Medical Center, Providence, RI; [6] Carney Institute for Brain Science, Brown University

Alcohol use disorder (AUD) is a major public health problem with limited pharmacological treatments, and growing evidence indicates that metabolic and immune dysregulation contribute to its biology. Pro-inflammatory mediators such as interleukin (IL)-18, tumor necrosis factor (TNF)-α, and C-C motif ligand 2 (CCL2) promote immune activation, whereas IL-10 dampens inflammation to maintain balance. Body mass index (BMI) is increasingly recognized as a moderator of systemic inflammation, with higher BMI driving a chronic pro-inflammatory state. Medications for weight management are currently under investigation as treatments for AUD, yet the inflammatory mechanisms by which BMI shapes alcohol-related outcomes remain poorly understood. We tested whether BMI serves as a potential moderator of the effects of cytokines on craving phenotypes, hypothesizing that elevated cytokine levels drive stronger urge to drink and craving among individuals with higher BMI. We conducted a secondary analysis of a parent clinical trial [NCT04218357] that evaluated the therapeutic potential of probenecid, a pannexin-1 channel agonist, for AUD. In a sample of participants (N= 28, 57% female), cytokines levels were measured from serum. The urge to drink alcohol and craving was assessed by the alcohol urge (AUQ) and alcohol craving (ACQ) questionnaires, respectively. For analyses, BMI was categorized into normal (25 BMI) groups. Linear regression models revealed that neither AUQ or ACQ scores were correlated with any cytokines. Conversely, we found AUQ and ACS scores were positively associated with TNF-α, CCL2, and IL-10 in the high BMI group. These results suggest that a potential immune dysregulation moderated by BMI leads to elevated urge to drink and alcohol craving. Our findings highlight the need to incorporate metabolic status when developing immune-focused precision treatments for AUD.

Poster 83

Xylazine Co-administration Prevents Fentanyl-Induced Mortality in Young Rats

Zuarth-Gonzalez, Julio[1] ; Zolali, Elmira[1] ; Metha, Yash[1] ; McMahon, Lance[1] and Obeng, Samuel[1]

[1]Department of Pharmaceutical Sciences, Texas Tech University Health Sciences Center, Amarillo, TX.

Xylazine, a veterinary sedative not approved for human use, has emerged as a common adulterant in North America's illicit opioid supply, yet preclinical studies of fentanyl-xylazine interactions have employed widely varying dose ratios, making it difficult to draw conclusions relevant to real-world exposures. Using an epidemiologically relevant ratio derived from Philadelphia's drug supply (~1:3 fentanyl:xylazine), we administered fentanyl (0.56 mg/kg, i.p.) or xylazine (1.78 mg/kg, i.p.) alone, or their combination (0.56 + 1.78 mg/kg) to drug-naive Sprague-Dawley rats at two ages: young adults (9 weeks, n=8/group) and adults (16 weeks, n=8/group). In 9-week-old rats, fentanyl alone produced 75% mortality (100% males, 50% females), whereas the fentanyl-xylazine combination resulted in zero mortality ($p=0.0023$); xylazine alone produced no adverse effects. In 16-week-old rats, neither treatment caused mortality, revealing age-dependent vulnerability. In a separate pharmacokinetic assessment, xylazine co-administration reduced plasma fentanyl concentrations 8-fold at 15 min, with apparent pattern reversal by 60 min, consistent with delayed absorption. These findings demonstrate that at epidemiologically relevant ratios, xylazine completely prevented fentanyl mortality in vulnerable young animals, suggesting that xylazine-fentanyl interactions are more complex than current models predict and that understanding actual toxicological interactions at real-world ratios is essential for evidence-based harm reduction and policy responses.

Attendees

George Adamson
National Institute on Drug Abuse
george.adamson@nih.gov

Mohammad Alkhatib
Rowan University
Alkhat76@rowan.edu

Hina Andleeb
Concordia University Wisconsin
hina.andleeb@cuw.edu

Tavishi Baidwan
Davidson College
tabaidwan@davidson.edu

Ayesha Baig
University of Texas at Dallas
Ayeshambaig2@gmail.com

Kona Basak
Rowan University
basakk33@rowan.edu

Susan Bergeson
Texas Tech University Health Sciences Center
susan.bergeson@ttuhsc.edu

Daniel Borgatti
University of Mississippi Medical Center
dborgatti@umc.edu

Felise Bressler
Baylor University
felise_bressler1@Baylor.edu

Taylor Buice
Texas Tech University Health Sciences Center
taylor.buice@ttuhsc.edu

Gopakumar Changarathil
UT Health Science Center at San Antonio
changarathil@uthscsa.edu

Ana Sofia Chavarria
University of Texas at El Paso
aschavarria2@miners.utep.edu

Kayla Chupp
University of Texas at San Antonio
kayla.chupp@my.utsa.edu

Tiffany Aguirre
University of Texas at Arlington
tiffany.aguirre@mavs.uta.edu

Sharilyn Almodovar
Texas Tech University Health Sciences Center
sharilyn.almodovar@ttuhsc.edu

Philip Antwi-Adjei
Texas Tech University Health Sciences Center
Philip.Adjei@ttuhsc.edu

Javaria Baig
Texas Tech University Health Sciences Center
jbaig@ttuhsc.edu

Jeremy Bailoo
Texas Tech University Health Sciences Center
jeremy.d.bailoo@ttuhsc.edu

Harrison Benson
Texas Tech University Health Sciences Center
Harrison.Benson@ttuhsc.edu

Nicholas Bloom
McLean Hospital, Harvard Medical School
nbloom1@mclean.harvard.edu

Hannah Bow
University of Texas at Austin
hannahbow@utexas.edu

Eliza Brooks
American University
eb2690a@american.edu

Diego Cecena
The Scripps Research Institute
dicecena@ucsd.edu

Nora Charles
University of Texas at San Antonio
Nora.Charles@utsa.edu

Teresa Chavera
UT Health Science Center at San Antonio
chaverat@uthscsa.edu

Bill Clarke
UT Health Science Center at San Antonio
clarkew@uthscsa.edu

Cristal Ahmed
East Tennessee State University
johnsonc15@etsu.edu

Olivia Anchondo
UNT Health Science Center
oliviaanchondo@my.unthsc.edu

Devon Applegate
Binghamton University
dappleg2@binghamton.edu

Aamena Baig
University of Texas at Dallas
aamenambaig@gmail.com

Kylee Bankston
University of Texas at Austin
Kgbankston@gmail.com

Kelly Berg
UT Health Science Center at San Antonio
berg@uthscsa.edu

Bruce Blough
RTI International
beb@rti.org

Gilberto Bravo
UT Health Science Center at San Antonio
bravog@uthscsa.edu

Katherine Buchanan
UT Medical Branch at Galveston
kabuchan@utmb.edu

Leonor Cedillo
University of Texas at San Antonio
leonor.cedillo@utsa.edu

Padam Raj Chaudhary
Rowan University
chaudh47@rowan.edu

Teresa Cho
Texas A&M University
tacho2248@tamu.edu

Brooke Clodgo
Med Associates
brooke.clodgo@med-associates.com

Greg Collins
University of Michigan
collinsg@umich.edu

Lynette Daws
UT Health Science Center at San Antonio
daws@uthscsa.edu

McKay Domen
Texas A&M University
mckaydomen@tamu.edu

Bill Fantegrossi
University of Arkansas for Medical Sciences
WEFantegrossi@uams.edu

Melissa Fischer
Our Lady of the Lake University
mefischer24sp@ollusa.edu

Carmella Foley
Davidson College
cafoley@davidson.edu

Michael Forster
UNT Health Science Center
michael.forster@unthsc.edu

Lindsey Galbo-Thomma
UT Health Science Center at San Antonio
galbothomma@uthscsa.edu

Brett Ginsburg
UT Health Science Center at San Antonio
ginsburg@uthscsa.edu

Jack Henningfield
Pinney Associates
jhenning@pinneyassociates.com

Kevin Honeywell
University of Arkansas for Medical Sciences
khoneywell@uams.edu

Ducel Jean-Berluche
UT Health Science Center at San Antonio
jeanberluche@uthscsa.edu

Brian Kangas
McLean Hospital, Harvard Medical School
bkangas@mclean.harvard.edu

Jeri Keitzer
UNT Health Science Center
jerikeitzer@my.unthsc.edu

Emily Cronin
Wake Forest University School of Medicine
Emily.Cronin@wfusm.edu

Emma Delgado
University of Texas at El Paso
endelgado3@miners.utep.edu

Andrew Eagle
University of Texas at Dallas
andrew.eagle@utdallas.edu

Cristiane Aparecida Favoretto
University of Mississippi Medical Center
crisafavoretto@gmail.com

Althea Floge
Wake Forest University School of Medicine
floga22@wfu.edu

Kirsten Folger
Davidson College
kifolger@davidson.edu

Charles France
UT Health Science Center at San Antonio
france@uthscsa.edu

Brenda Gannon
University of Arkansas for Medical Sciences
BGannon@uams.edu

Oliver Grundmann
University of Florida
grundman@ufl.edu

DiJon Hill
Harvard Bioscience
dhill@harvardbioscience.com

Jesse Howard
College on Problems of Drug Dependence
jhoward@parthenonmgmt.com

Alida Jimenez
Rowan University
jimene18@students.rowan.edu

David Kearns
American University
kearns@american.edu

Megan Kelly
University of Texas at Austin
megan.kelly@austin.utexas.edu

Chris Cunningham
Concordia University Wisconsin
chris.cunningham@cuw.edu

Rajeev Desai
McLean Hospital, Harvard Medical School
rdesai@mclean.harvard.edu

Soren Emerson
Vanderbilt University
soren.d.emerson@vanderbilt.edu

Carrie Ferrario
University of Michigan
ferrario@umich.edu

Shawn Flynn
University of Michigan
smflynn@umich.edu

Andriy Fomin
University of Arkansas for Medical Sciences
AFomin@uams.edu

Leonard Fu
University of Texas at Dallas
lxf220007@utdallas.edu

Erik Garcia
University of Nebraska Omaha
ejgarcia@unomaha.edu

Margaret Haney
Columbia University
meg.haney@nyspi.columbia.edu

Takato Hiranita
UT Health Science Center at San Antonio
hiranita@uthscsa.edu

Sally Huskinson
University of Mississippi Medical Center
shuskinson@umc.edu

Payton Kahanek
University of Texas at Austin
payton.kahanek@utexas.edu

Thomas Keck
Rowan University
keckt@rowan.edu

Gahyun Kim
University of Texas at Austin
gahyunk@utexas.edu

Van King
UT Health Science Center at San Antonio
kingvl@uthscsa.edu

Jenna Kramer
University of Nebraska Omaha
jkramer19@unomaha.edu

Melissa Lewis
Virginia Commonwealth University
lewism16@vcu.edu

Dan Lodge
UT Health Science Center at San Antonio
lodged@uthscsa.edu

Maia Maras
National Institute on Drug Abuse
maia.maras@nih.gov

Justin Mastio
University of Mississippi Medical Center
jmastio@umc.edu

Ashley Miller
University of Texas at San Antonio
ashley.miller@utsa.edu

Travis Moschak
University of Texas at El Paso
tmmoschak@utep.edu

Jacques Nguyen
Baylor University
jacques_nguyen@baylor.edu

Samuel Obeng
Texas Tech University Health Sciences Center
Samuel.obeng@ttuhsc.edu

Gorana Puzovic
University of Michigan
puzovic@livemail.uthscsa.edu

Kaitlyn Rojas
Baylor University
kaitlyn_rojas1@baylor.edu

Mahfuz Ahmed Sakib
Texas Tech University Health Sciences Center
masakib@ttuhsc.edu

Katherine Serafine
University of Texas at El Paso
kserafine@gmail.com

Oleg Klykov
UT Health Science Center at San Antonio
klykovo@uthscsa.edu

Nana Kofi Kusi-Boadum
UNT Health Science Center
nanakofikusi-boadum@my.unthsc.edu

Tian Li
High Point University
tli@highpoint.edu

David Maguire
UT Health Science Center at San Antonio
maguired@uthscsa.edu

Anthony Martinez
UT Health Science Center at San Antonio
martinezp3@uthscsa.edu

Aniah Matthews
National Institute on Drug Abuse
matthewsan@nih.gov

Bria Moore
UT Health Science Center at San Antonio
mooreb7@livemail.uthscsa.edu

Seyedeh Leila Mousavi
University of Texas at Dallas
leila.mousavi@utdallas.edu

Samantha Nguyen
St. Mary's University
snguyen10@mail.stmarytx.edu

Kristen Padilla
Trinity University
kpadill2@trinity.edu

Nokomis Ramos-Gonzalez
Washington University School of Medicine
nokomis@wustl.edu

Siara Rouzer
Texas A&M College of Medicine
srouzer@tamu.edu

Ahmed Saleh
Texas A&M College of Medicine
asaleh05@tamu.edu

Abhisheak Sharma
University of Florida
asharma1@ufl.edu

Mei-Chuan Ko
University of Pittsburgh
mek433@pitt.edu

Grace Le
Trinity University
gle@trinity.edu

Kaitlyn Little
University of Houston
kmlittle2@uh.edu

Susruta Majumdar
Washington University School of Medicine
susrutam@wustl.edu

Vena Martinez
UT Medical Branch at Galveston
vekmarti@utmb.edu

Jessica McInerney
University of Maryland School of Medicine
jmcinerney@som.umaryland.edu

Jocelyn Morales
University of Texas at El Paso
jmoralespe1@miners.utep.edu

Alan Myers
UT Health Science Center at Houston
Alan.L.Myers@uth.tmc.edu

Renee Nosko
National Institute on Drug Abuse
renee.nosko@nih.gov

Zachary Pierce-Messick
Johns Hopkins School of Medicine
zpierce1@jh.edu

Felipe Rego
American University
felipepazosrego@gmail.com

Aditi Rudrashetty
University of Mississippi Medical Center
arudrashetty@umc.edu

Neha Sawant
Texas Tech University Health Sciences Center
neha.sawant@ttuhsc.edu

Thomas Shellenberg
University of Kentucky
thomasshellenberg@uky.edu

Neha Skandan
National Institute on Drug Abuse
neha.skandan@nih.gov

Spencer Snow
University of Arkansas for Medical Sciences
Snowspencer@uams.edu

Julia Stall
Trinity University
jstall@trinity.edu

John Striednig
University of Arkansas for Medical Sciences
jtstriednig@uams.edu

Simon Tangen
UT Health Science Center at San Antonio
tangen@livemail.uthscsa.edu

Emma Thomas
Davidson College
emthomas@davidson.edu

Kate Tuite
UT Health Science Center at San Antonio
tuite@uthscsa.edu

Harsha Varma
UT Health Science Center at San Antonio
varmah@uthscsa.edu

Fernanda Villa-Ortiz
University of Texas at El Paso
fvillaorti1@miners.utep.edu

Chris Wernette
Baylor University
chris_wernette@baylor.edu

Yibin Xu
UT Health Science Center at San Antonio
xuy6@uthscsa.edu

Mark Smith
Davidson College
masmith@davidson.edu

Ricardo Sosa Jurado
University of Texas at El Paso
rsosa6@miners.utep.edu

Hannah Stewart
University of Michigan
hanstew@umich.edu

Quinston Stubbs
UNT Health Science Center
qstubbs@patriots.uttyler.edu

Analisa Tapia
UT Health Science Center at San Antonio
tapiaa@uthscsa.edu

Theophilus Torgbenu
Texas Tech University Health Sciences Center
ttorgben@ttuhsc.edu

Mst Afroza Alam Tumpa
Rowan University
tumpam79@rowan.edu

Jacqueline Vazquez
UT Health Science Center at San Antonio
vazquezj3@livemail.uthscsa.edu

Keith Warren
Ohio State University
warren.193@osu.edu

John Westphal
Hope College
john.westphal@hope.edu

You Zhang
Brown University
you_zhang@brown.edu

Marina Smoak
University of Texas at El Paso
mapeveto@miners.utep.edu

Amelie Soyer
Rowan University
soyer@rowan.edu

Justin Strickland
University of Maryland School of Medicine
jstrickland@som.umaryland.edu

Leslie Sullivan
University of Texas at El Paso
llsullivan@miners.utep.edu

Julia Taylor
UT Health Science Center at San Antonio
taylorj4@uthscsa.edu

Leah Truckenbrod
Harvard Bioscience
ltruckenbrod@harvardbioscience.com

Marina Vargas
UT Health Science Center at San Antonio
vargasm9@uthscsa.edu

Sarvesh Kumar Verma
University of Florida
sarvesh.verma@ufl.edu

Michael Wedemeyer
UT Health Science Center at San Antonio
wedemeyer@uthscsa.edu

Jenny Wilkerson
Rutgers University
jlw427@njms.rutgers.edu

Julio Zuarth Gonzalez
Texas Tech University Health Sciences Center
jzuarthg@ttuhsc.edu

JOHNS HOPKINS CAREY BUSINESS SCHOOL | Executive Education

INNOVATIONS FOR SUBSTANCE USE DISORDERS (I4SUD) PROGRAM

I4SUD

Duration of the Program

October 12 - December 4, 2026
(only 4 days in person)

Description of the Program

I4SUD is a selective Executive Education certificate program offered through the Johns Hopkins Carey Business School. Participants work individually or in teams to learn how pharmaceutical, digital health, or medical device innovations can be translated into viable solutions for SUDs. The program blends asynchronous and live online learning with a multi-day, in-person experience at Johns Hopkins in Baltimore, featuring workshops with expert faculty, site visits to operational SUD programs, networking with peers and NIDA program officers, and development of a commercialization plan. Participants gain preparation for follow-on funding opportunities, including the NIDA "$100,000 Start a SUD Startup" Challenge and SBIR/STTR grants. Graduates earn a Johns Hopkins Carey Business School Executive Education certificate and may compete for a cash prize through a pitch competition. Thirty U.S.-based applicants will receive fully funded scholarships supported by NIDA, covering tuition, travel, lodging, and meals. The program also accepts 20 self-funded participants who may enroll for a reduced $1,000 tuition, which includes instruction and some meals, with travel and lodging at their own expense.

Expected Commitment

- Attend **4 full days** in person in Baltimore, MD (October 20 - 23, 2026)
- Attend **three virtual sessions**, 1.5 hours each (Oct 14, Nov 4, Nov 18 / 12:00-1:30 PM)
- Attend **at least two** 30 min virtual office hour with mentors or instructors
- Engage in **3-4hrs per week** of asynchronous learning activities between October 12 and December 4, 2026, and spend time on research to develop their pitch (dependent on participant idea and stage)
- Attend and pitch in the virtual pitch competitionon December 4, 2026 from 1:00-5:00 PM with a chance to win $10,000!

Poster Index