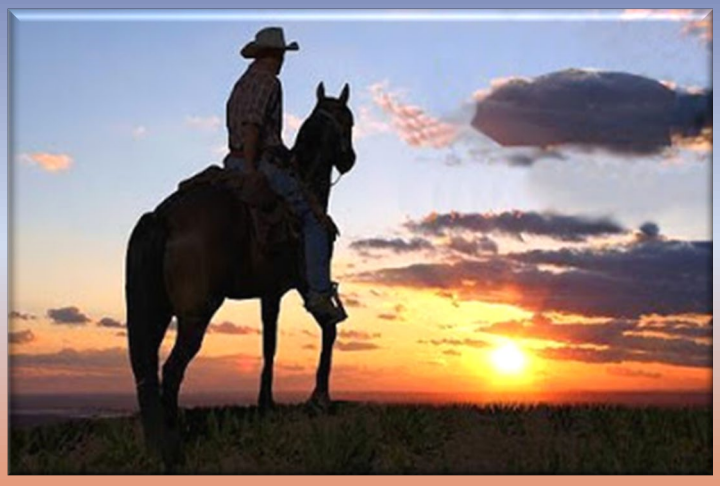
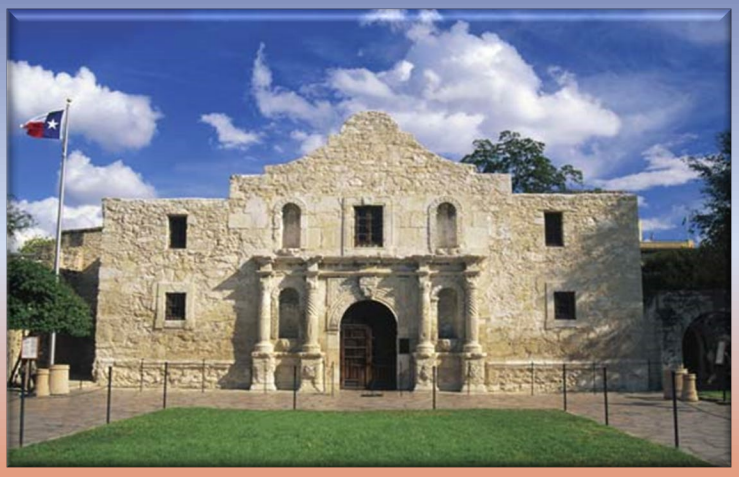
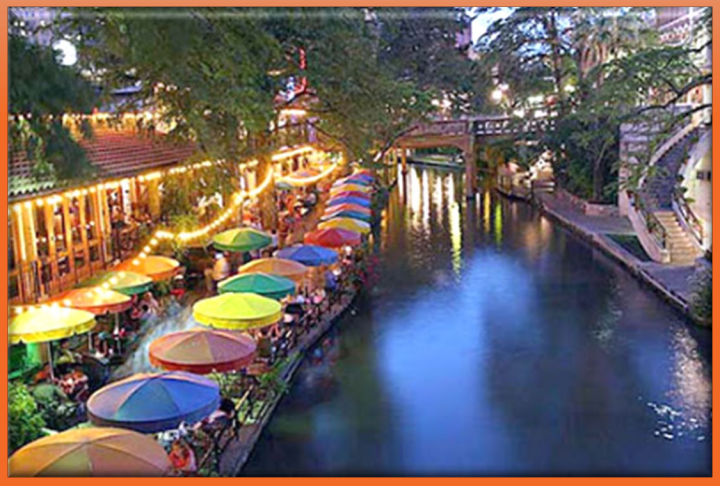
16TH ANNUAL BEHAVIOR, BIOLOGY, and CHEMISTRY:

Translational Research in Substance Use Disorders

San Antonio, Texas | Embassy Landmark | 22-24 March 2024







ARTT Addiction Research, Treatment & Training CENTER OF EXCELLENCE

NIH National Institute on Drug Abuse

UT Health San Antonio

BBC Publications

BBC 2011

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

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

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

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

BBC 2012

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

BBC 2013

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

BBC 2014

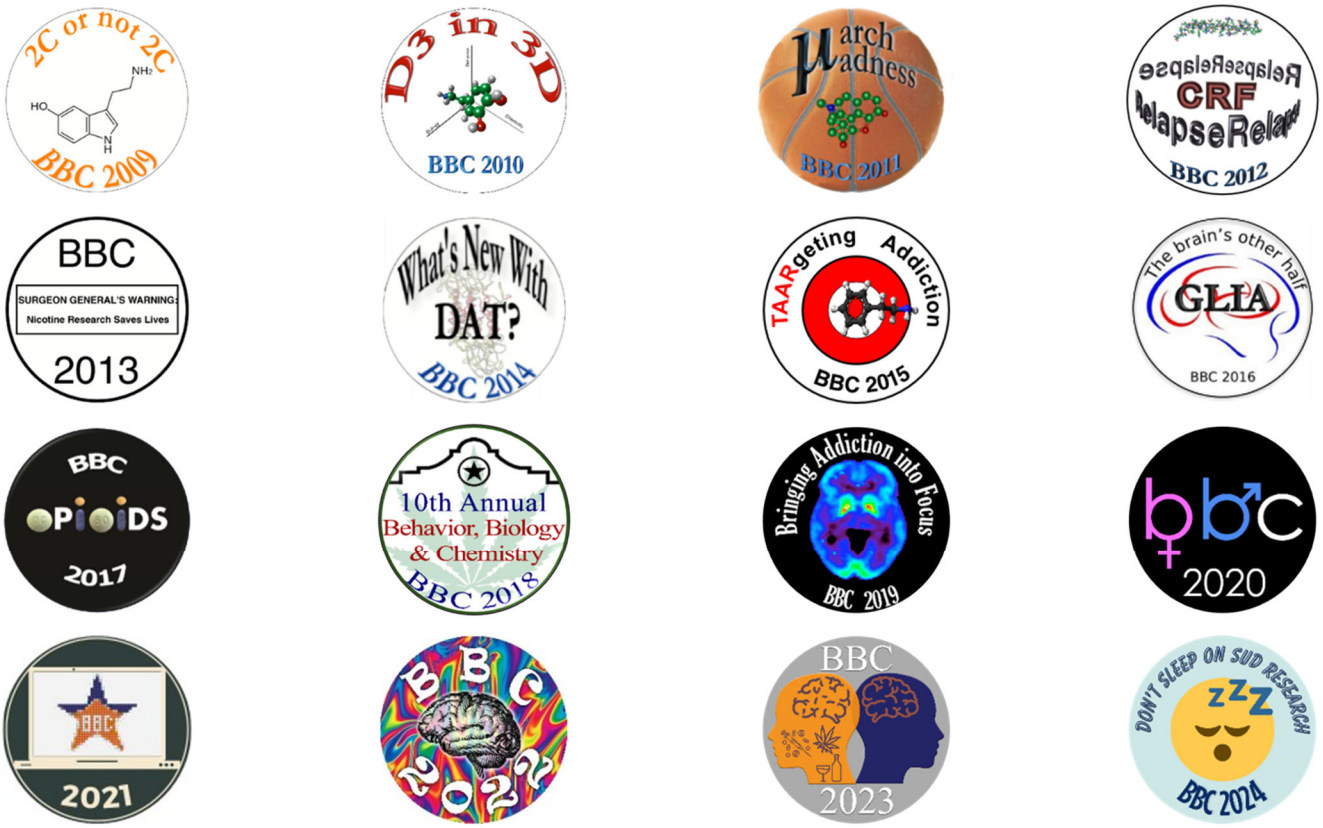
Reith ME, Blough BE, Hong WC, Jones KT, Schmitt KC, Baumann MH, Partilla JS, Rothman RB and Katz JL (2015) **Behavioral, biological and chemical perspectives on atypical agents targeting the dopamine transporter.** *Drug and Alcohol Dependence* 147, 1-19. PMC4297708

BBC 2015

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

BBC 2016

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



Acknowledgements

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- Office of the President
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- Robert A Welch Distinguished University Chair Endowment
- Addiction Research, Treatment & Training (ARTT) Center of Excellence
- Department of Pharmacology
- Department of Physiology
- Department of Psychiatry
- Center for Biomedical Neuroscience

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Alessandro Bonifazi	Brenda Gannon	Mark Smith
Gregory Collins	Brent Kisby	Zijun Wang
Rajeev Desai	Jacques Nguyen	

Presentation Judges

Lisa Baker	Lynette Daws	Takato Hiranita	Jacques Nguyen
Kelly Berg	Rajeev Desai	Sally Huskinson	Linda Perrotti
Susan Bergeson	Michael Forster	Emily Jutkiewicz	Daniel Rosenbaum
Bruce Blough	Kevin Freeman	Brian Kangas	Katherine Serafine
Stephanie Borgland	Ewa Galaj	Thomas Keck	Ritu Shetty
Deanne Buffalari	Brenda Gannon	Antoinette Maldonado-Devincci	Sunil Sirohi
Greg Collins	Mary Garner	Vanessa Minervini	Justin Strickland
Paul Czoty	Michael Gatch	Travis Moschak	Zijun Wang

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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

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

2022 – Kimberly M Holter
2023 – Gwendolyn Burgess
2024 – Cristina Rivera Quiles

Postdoctoral

2022 – Renata Christina Nunes Marchette
2024 – Laia Castell Almuni

Travel Awardees

Nadia Afrin
Harshil Aggarwal
Adesewa Akande
Hannah Alton
Miki Azuma
Amber Baldwin
Carissa Besonen
Jessica Binckley
Abigail Bowring
Payton Brabant
Rachel Burroughs
Paola Campo
Hannah Carlson
Maya Chopra

Anna Crites
Emily Cronin
Kaila Dawkins
Afua Faibille
Peter Fogel
Troy Fort
Negar Ghasem Ardabili
Nicholas Ho
Lucy Hoying
Seth Hubbard
Amaya Jenkins
Alexandra Johansen
Lida Khodavirdilou
Brent Kisby

Samuel Marsh
Farzanna Mohamed
Rohit Nambiar
Lewis Nunez Severino
Jacob Ormes
Praneetha Panthagani
Tanya Pareek
Loren Peeters
Tequila Porter
Justin Pressley
Joshua Prete
Blake Reeves
Siara Rouzer
Lauren Scrimshaw

Robert Seaman Jr
Grace Sonick
Ricardo Sosa Jurado
Leslie Sullivan
Olivia Tewell
Jessica Thrush
Akeemat Tijani
Alexandra Vargas-Elvira
Adriana Vasquez
Ymalay Vega
Caleb Vogt
Liza Wills
Kayla Wolf
Sung Joon Won
Isabel Yu

Program Overview

FRIDAY 22 MARCH 2024

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 23 MARCH 2024

8:00 AM – 8:05 AM	Welcome and Opening Remarks	
8:05 AM – 10:05 AM	Plenary Symposium:	Chair: Gregory Collins
	Targeting orexin systems for the treatment of sleep and substance use disorders	
	Daniel Rosenbaum | UT Southwestern Medical Center	
	Orexin receptor structural biology and its use in drug discovery	
	Yanan Zhang | Research Triangle Institute	
	Sleep and addiction: Development of orexin receptor modulators	
	Stephanie Borgland | University of Calgary	
	Co-release of orexin and dynorphin in the modulation of VTA dopamine neurons and opioid seeking	
	Andrew Huhn | Johns Hopkins University School of Medicine	
	Orexin antagonist effects on sleep and stress during opioid withdrawal	
10:05 AM – 11:35 AM	Poster Session and Refreshments	
11:35 AM – 12:50 PM	Lunch & Learn: Panel Discussion	Chair: Lindsey Galbo-Thomma
	Speaking up for animal research	
	Angelique Colby | University of Texas Health Science Center at San Antonio	
	James Elliott | University of Texas Health Science Center at San Antonio	
	Michael Nader | Wake Forest University School of Medicine	
12:50 PM – 2:20 PM	Open Oral Communications I	Chairs: Jacques Nguyen and Mia Allen
2:20 PM – 3:50 PM	Poster Session II and Refreshments	
3:50 PM – 5:20 PM	Open Oral Communications II	Chairs: Brent Kisby and Alessandro Bonifazi
5:20 PM – 5:30 PM	Refreshment Break	
5:30 PM – 6:30 PM	Special Lecture	Chair: Mark Smith
	Rita Valentino | National Institute on Drug Abuse	
	The neuroscience of addiction	
6:30 PM – 7:30 PM	Cocktail Hour and Poster Viewing	
7:30 PM – 9:30 PM	Dinner and Science Trivia	

SUNDAY 24 MARCH 2024

7:45 AM	Travel Awardee Group Photo	
8:00 AM – 9:15 AM	Open Oral Communications III	Chairs: Brenda Gannon and Cristina Rivera Quiles
9:15 AM – 9:25 AM	Refreshment Break	
9:25 AM – 10:40 AM	Open Oral Communications IV	Chairs: Zijun Wang and Lindsey Galbo-Thomma
10:40 AM – 10:50 AM	Refreshment Break	
10:50 AM – 11:50 AM	Special Lecture	Chair: Rajeev Desai
	Nurulain (Nur) Zaveri | Astraea Therapeutics	
	Targeting the α3β4 neuronal nicotinic acetylcholine receptors for nicotine and other substance use disorders: Rationale, preclinical validation and progress towards clinical translation	
11:50 AM – 12:05 PM	Travel and Presentation Awards	
12:05 PM – 1:15 PM	Lunch and Adjournment	

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

Program Details

Friday 22 March 2024

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 23 March 2024

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

Targeting orexin systems for the treatment of sleep and substance use disorders
(Chair: Gregory Collins)

8:05 AM – 8:35 AM **Daniel Rosenbaum** | UT Southwestern Medical Center
Orexin receptor structural biology and its use in drug discovery

8:35 AM – 9:05 AM **Yanan Zhang** | Research Triangle Institute
Sleep and addiction: Development of orexin receptor modulators

9:05 AM – 9:35 AM **Stephanie Borgland** | University of Calgary
Co-release of orexin and dynorphin in the modulation of VTA dopamine neurons and opioid seeking

9:35 AM – 10:05 AM **Andrew Huhn** | Johns Hopkins University School of Medicine
Orexin antagonist effects on sleep and stress during opioid withdrawal

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

Speaking up for animal research
(Chair: Lindsey Galbo-Thomma)

Angelique Colby | *University of Texas Health Science Center at San Antonio*
11:35 AM – 12:50 PM **James Elliott** | University of Texas Health Science Center at San Antonio
Michael Nader | Wake Forest University School of Medicine

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

(Chairs: Jacques Nguyen and Mia Allen)

12:50 PM – 1:05 PM **Adriana Vasquez** | The University of Texas at Austin
Oral hormonal contraceptives decrease amphetamine preference across extinction training in female rats

1:05 PM – 1:20 PM **Sung Joon Won** | National Institute on Drug Abuse
Building robust QSAR models of the dopamine D2 and D3 receptors' ligands using machine and deep learning approaches

1:20 PM – 1:35 PM **Mia Allen** | Wake Forest University School of Medicine
Cognitive performance as a behavioral biomarker associated with cocaine self-administration in female and male socially housed cynomolgus monkeys

1:35 PM – 1:50 PM **Laia Castell Almuni** | Johns Hopkins University School of Medicine
Dopamine D2 receptors in WFS-1-neurons regulate food-seeking and avoidance behaviors

1:50 PM – 2:05 PM **Hannah Carlson** | Davidson College
Social contact reinforces cocaine self-administration in male rats: Role of sex of social partner

2:05 PM – 2:20 PM **Jacques Nguyen** | Baylor University
Investigating neurobehavioral effects of electronic cigarette vapor inhalation in rats

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

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

Oral Communications II 3:50 PM – 5:20 PM *Bluebonnet AB*
(Chairs: Brent Kisby and Alessandro Bonifazi)

3:50 PM – 4:05 PM **Kaila Dawkins** | North Carolina A&T State University
Adolescent intermittent ethanol exposure: Sex-specific effects in alcohol drinking and c-Fos in limbic brain structures in male and female C57BL/6J mice

4:05 PM – 4:20 PM **Emily Cronin** | Creighton University
Investigating the reinforcing effects of vaporized delta-8 tetrahydrocannabinol in a rodent self-administration paradigm

4:20 PM – 4:35 PM **Hannah Alton** | National Institute on Drug Abuse
Revisiting the cannabinoid-opioid interaction hypothesis using conditional CB1 and μ opioid receptor knockout mice

4:35 PM – 4:50 PM **Jessica Thrush** | University of Arkansas for Medical Sciences
Respiratory depressant effects of synthetic cannabinoid receptor agonist 5F-ADB-PINACA in combination with fentanyl in mice: pharmacodynamic and pharmacokinetic mechanisms

4:50 PM – 5:05 PM **Brent Kisby** | Texas Tech University Health Sciences Center
Effects of Tlr3-dependent innate immune activation and chronic alcohol consumption on gene expression in brain micro-vessels

5:05 PM – 5:20 PM **Siara Rouzer** | Texas A&M School of Medicine
Prenatal alcohol and cannabinoid exposures impose distinct, sex-specific behavioral phenotypes of coordination and alcohol-seeking in adult mouse offspring.

Refreshment Break 5:20 PM – 5:30 PM

Special Lecture: Rita Valentino 5:30 PM – 6:30 PM *Bluebonnet AB*
The neuroscience of addiction
(Chair: Mark Smith)

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

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

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

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

Sunday 24 March 2024

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

Oral Communications III — 8:00 AM – 9:15 AM — *Bluebonnet AB*

(Chairs: Brenda Gannon and Cristina Rivera Quiles)

8:00 AM – 8:15 AM — **Alexandra Johansen** | National institute on Drug Abuse
The effects of orexin antagonists on economic choice between remifentanil and milk in squirrel monkeys

8:15 AM – 8:30 AM — **Cristina Rivera Quiles** | Michigan State University
Role of neuromedin s-expressing ventral tegmental area neurons in morphine behaviors

8:30 AM – 8:45 AM — **Thuy-Hien Le** | University of Mississippi Medical Center
Comparison of respiratory effects of mu opioid agonists that vary in intrinsic efficacy and reported signaling bias using whole-body plethysmography in rats

8:45 AM – 9:00 AM — **Marissa Jones** | East Tennessee State University
The deleterious effects of parental fentanyl-dependence on sleep health: Multigenerational effects on sleep architecture and cognition in adolescent rats

9:00 AM – 9:15 AM — **Sunil Sirohi** | Xavier University of Louisiana
Intermittent access of a high-fat diet differently impacts alcohol drinking in low and high-drinking male and female rats.

Refreshment Break — 9:15 AM – 9:25 AM

Oral Communications IV — 9:25 AM – 10:40 AM — *Bluebonnet AB*

(Chairs: Zijun Wang and Lindsey Galbo-Thomma)

9:25 AM – 9:40 AM — **Seth Hubbard** | National Institute on Drug Abuse
Synthesizing a novel μ-opioid-receptor-selective positron emission tomography tracer derived from the synthetic opioid etonitazene

9:40 AM – 9:55 AM — **Akeemat Tijani** | East Tennessee State University
Development of an iontophoresis-coupled microneedle skin patch of naloxone for emergency treatment of opioid overdose

9:55 AM – 10:10 AM — **Yorkiris Marmol Contreras** | University of Texas Medical Branch
The role of retinoic acid signaling in substance-use-, depression-, and anxiety-related behavior

10:10 AM – 10:25 AM — **Arpit Doshi** | Astraea Therapeutics
Bifunctional nociceptin opioid (NOP) receptor -mu opioid (MOP) receptor agonists as non-addicting analgesics for opioid use disorder: Molecular docking-assisted drug design and SAR of N3-substituted 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-ones

10:25 AM – 10:40 AM — **Zijun Wang** | University of Kansas
Prefrontal cortex to ventral tegmental area projection is responsible for early social isolation stress-induced vulnerability for heroin relapse

Refreshment Break — 10:40 AM – 10:50 AM

Special Lecture: Nurulain (Nur) Zaveri — 10:50 AM – 11:50 AM — *Bluebonnet AB*

Targeting the α3β4 neuronal nicotinic acetylcholine receptors for nicotine and other substance use disorders: Rationale, preclinical validation and progress towards clinical translation

(Chair: Rajeev Desai)

Travel and Presentation Awards — 11:50 AM – 12:05 PM

Lunch and Adjournment — 12:05 PM – 1:15 PM

See you at BBC 2025!

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

Oral Communications

Oral Communication 1-1

Oral hormonal contraceptives decrease amphetamine preference across extinction training in female rats

Vasquez, Adriana[1,2]; Antonacci, Payton E[3]; Kim, Gahyun[1]; Nguyen, Aihan[3]; Ajmal, Heba[3]; Agarwal, Rashi[3]; Dominguez, Juan M[1,2,3,4]; Monfils, Marie-H[1,3], and Lee, Hongjoo J[1,3]

[1]Dep. of Psychology; [2]Waggoner Center for Alcohol & Addiction;[3] Institute for Neuroscience; [4]Dep. of Pharmacology and Toxicology, University of Texas, Austin, TX USA.

Evidence suggests that gonadal hormones (i.e., estradiol & progesterone) are important factors in driving the maintenance of substance use disorders (SUD) in females. Further, changes in gonadal hormone levels across the menstrual cycle, as well as those induced by hormonal contraceptives (HC) among women of reproductive age, affect fear extinction. However, how HCs alter female reward-learning and extinction is yet to be determined. The current experiment investigated whether oral administration of Levonorgestrel (LNG), synthetic progestin used in HCs, would lead to a reduction in amphetamine (AMPH)-preference. To investigate this, female rats underwent AMPH-conditioned place preference and tested for their AMPH-preference for three sessions (served as extinction learning) after receiving either oral administration of LNG (250μg/rat, 500μg/rat, or 2mg/rat) or tested during an estrous cycle stage associated with higher levels of gonadal hormones (i.e., proestrus/estrus). Additionally, effects of LNG on gonadal function were assessed. All groups displayed initial AMPH-preference, however, only females that received 500μg of LNG showed significantly reduced AMPH-preference across extinction, as compared to females in proestrus/estrus. Interestingly, LNG administration did not lead to persistent estrous stages associated with lower gonadal hormone levels (i.e., diestrus/metestrus), unlike what has been previously reported. However, uterine horn width, an index of estrogen exposure, was significantly thinner in all LNG rats as compared to proestrus/estrus rats, but not significantly different from diestrus/metestrus rats, suggesting that administration of the oral contraceptive was not without consequence. Findings from this study suggest that 1. effects of LNG are dose-dependent and 2. LNG administration, in combination with extinction training (e.g., exposure therapy in humans), may be a useful tool in treating SUD's in females.

Oral Communication 1-2

Building robust QSAR models of the dopamine D2 and D3 receptors' ligands using machine and deep learning approaches

Won, Sung Joon[1]; Visayas, Benjoe R.[1] ; Lee, Kuo Hao[1]; and Shi, Lei[1]

[1]Computational Chemistry and Molecular Biophysics Section, Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse– Intramural Research Program, National Institutes of Health, Baltimore, Maryland 21224, United States.

Dysfunctions at the dopamine D2 receptor (D2) are associated with neuropsychiatric conditions like Parkinson's disease, schizophrenia, and substance use disorder. Current primary treatments for these conditions are the D2 antagonists, but these often cause motor side effects. As a result, recent research efforts have been devoted to the dopamine D3 receptor (D3) as a therapeutic target since it elicits similar effects without side effects. However, the close structural homology of the D2 and D3 makes it challenging to search for D3-selective antagonists. In this study, we aimed to establish machine and deep learning-based quantitative structure-activity relationship (QSAR) models to predict compounds' binding affinity for the D2 and the D3, as well as the D3 selectivity. We queried and collected the D2 and the D3 binding affinity training datasets from ChEMBL. We specifically developed a suite of filters to extract high-quality datasets and then manually curated them to exclude misannotated entries. We applied extreme gradient boosting (XGBoost), random forest (RF), and deep neural network (DNN) algorithms to build QSAR models. For DNN models, we developed a protocol to systematically tune the hyperparameters by exploring the feasible ranges and considering their potential dependency. Combining the prediction powers of all three algorithms into what is called the consensus resulted in significantly improved benchmarks. Finally, we collected top representative compounds and used SHAP analysis to highlight the most common chemical scaffold. Taken together, we established the D2 and the D3 QSAR models with robust power in predicting the binding affinity for each individual receptor, as well as models with prediction power in identifying D3-selective compounds.

Oral Communication 1-3

Cognitive performance as a behavioral biomarker associated with cocaine self-administration in female and male socially housed cynomolgus monkeys

Mia I. Allen[1], Bernard N. Johnson[1], Marissa B. Costa[1], Robert Gould[1], and Michael A. Nader[1]

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

Considerable research has suggested that certain cognitive domains may contribute to cocaine misuse. However, there are gaps in the literature regarding whether cognitive performance before drug exposure predicts susceptibility to cocaine self-administration and how cognitive performance relates to cocaine intake. Thus, the present study aimed to examine cognitive performance, as measured using an automated CANTAB cognitive battery, prior to and following acquisition of cocaine self-administration in female and male socially housed cynomolgus macaques. The cognitive battery consisted of measures of associative learning, behavioral flexibility, and behavioral inhibition. First, we demonstrated that animals that were less accurate on a behavioral flexibility task when drug-naïve had lower cocaine ED50 values when exposed to cocaine under a concurrent food-drug choice paradigm. Furthermore, cocaine intake was a negative predictor of accuracy on the behavioral inhibition task following chronic cocaine self-administration. Also, animals with higher cocaine intakes tended to take more trials to complete the SDR segment and made more incorrect responses during these trials. Overall, these findings suggest that levels of behavioral inhibition may not only be related to susceptibility to cocaine reinforcement but also that behavioral inhibition may be sensitive to disruptions following chronic cocaine self-administration.

Oral Communication 1-4

Dopamine D-2 receptors in WFS1-neurons regulate food-seeking and avoidance behaviors

Castell, Laia[1]; Le Gall, Valentine[2]; Cutando, Laura [3]; Petit, Chloé P[4], Puighermanal, Emma[3]; Makrini-Maleville, Leila[3]; Kim, Ha-Rang[2]; Jercog, Daniel[2]; Tarot, Pauline[3]; Tassou, Adrien[4]; Harrus, Anne-Gabrielle[4]; Rubinstein Marcelo[5]; Nouvian, Régis[4]; Rivat, Cyril[4]; Besnard, Antoine[3]; Trifilieff, Pierre[6]; Gangarossa, Giuseppe[7]; Janak, Patricia H[8]; Herry, Cyril[2]; Valjent, Emmanuel[9]

[1]IGF, Université, Montpellier, CNRS, Inserm, Montpellier F-34094, France; Department of Psychological and Brain Sciences, Krieger School of Arts and Sciences, Johns Hopkins University [2]Université, Bordeaux, Neurocentre Magendie [3]IGF, Université, Montpellier, CNRS [4]INM, Université, Montpellier [5]Instituto de Investigaciones en Ingeniería Genética y Biología Molecular, CONICET; FCEN, Universidad de Buenos Aires, Buenos Aires, Argentina; Department of Molecular and Integrative Physiology, University of Michigan Medical School [6]Université, Bordeaux, INRAE, Bordeaux INP, NutriNeuro [7]Université Paris Cité, CNRS, Unité de Biologie Fonctionnelle et Adaptative [8]Department of Psychological and Brain Sciences, Krieger School of Arts and Sciences, Johns Hopkins University; The Solomon H. Snyder Department of Neuroscience, Johns Hopkins University; Kavli Neuroscience Discovery Institute, Johns Hopkins University [9]IGF, Université, Montpellier, CNRS

The selection and optimization of appropriate adaptive responses depends on interoceptive and exteroceptive stimuli as well as on the animal's ability to switch from one behavioral strategy to another. Although growing evidence indicate that dopamine D2R-mediated signaling events ensure the selection of the appropriate strategy for each specific situation, the underlying neural circuits through which they mediate these effects are poorly characterized. Here, we investigated the role of D2R signaling in a mesolimbic neuronal subpopulation expressing the Wolfram syndrome 1 (Wfs1) gene. This subpopulation is located within the nucleus accumbens, the central amygdala, the bed nucleus of the stria terminalis, and the tail of the striatum, all brain regions critical for the regulation of emotions and motivated behaviors. Using a mouse model carrying a temporally controlled deletion of D2R in WFS1-neurons, we demonstrate that intact D2R signaling in this neuronal population is necessary to regulate homeostasisdependent food-seeking behaviors in both male and female mice. In addition, we found that reduced D2R signaling in WFS1-neurons impaired active avoidance learning and innate escape responses. Collectively, these findings identify a yet undocumented role for D2R signaling in WFS1-neurons as a novel effector through which dopamine optimizes appetitive behaviors and regulates defensive behaviors.

Oral Communication 1-5

Social contact reinforces cocaine self-administration in male rats: Role of sex of social partner

Carlson, Hannah N., Camp, Jacob D., Biancorosso, Samantha L., Smith, Mark A.

Davidson College

Previous studies have reported that social contact reinforces cocaine self-administration. The purpose of this study was to examine whether the reinforcing effects of social contact on cocaine self-administration in male rats was influenced by the sex of a social partner. To this end, gonadally intact male rats were implanted with intravenous catheters and trained to self-administer cocaine on a fixed ratio schedule of reinforcement. The reinforcing effects of social contact on cocaine self-administration was examined on a progressive ratio schedule of reinforcement under conditions in which each response-contingent cocaine infusion resulted in 30-s access to either (1) a gonadally intact male rat, (2) an ovariectomized female rat, or (3) a black-and-white sock that was the same size and coloring of another rat (nonsocial control stimulus). Social contact reinforced cocaine self-administration relative to the nonsocial control stimulus, but no differences were observed between the reinforcing effects of a male versus female social stimulus. These data support previous studies reporting the social contact reinforces cocaine self-administration in male rats and indicate that the reinforcing effects of social contact are independent of the sex of the social partner.

Oral Communication 1-6

Investigating neurobehavioral effects of electronic cigarette vapor inhalation in rats

Nguyen, Jacques D.[1] Gutierrez, Arnold[2], Jerel A. Fields[2], and Taffe, Michael A.[2]

[1]Department of Psychology and Neuroscience, Baylor University, Waco, TX USA and [2]Department of Psychiatry, University of California San Diego, San Diego, CA, USA

Electronic nicotine delivery devices (ENDS; e-cigarettes) have been marketed as a safer alternative to traditional cigarettes, primarily as a means of smoking cessation. However, these devices often contain liquids composed of psychoactive substances such as nicotine (NIC), tetrahydrocannabinol (THC), or opioids, increasing the risks for the development of substance use disorder. E-liquids also contain chemical solvents such as propylene glycol (PG). Recently developed animal models of intrapulmonary drug administration and self-administration have been useful for researchers to investigate behavioral and neurobiological mechanisms underlying drug-consumption. Male and female Sprague-Dawley rats were exposed to 10 day (twice daily) e-cigarette vapor of NIC or PG vehicle during adolescence (Post-Natal Day 31-40). Results showed increased sensitivity to locomotor-stimulating effects and volitional exposure to nicotine vapor (Fixed-Ratio 5 test) in female rats. In a separate study, 6-month-old, male, Sprague-Dawley rats were exposed to 10 day (twice daily) e-cigarette vapor of NIC, THC or PG. Brain tissue was collected and analyzed for altered gene expression of early growth receptor 2 (EGR2) and Activity-Regulated Cytoskeleton-Associated Protein (ARC), proteins which are implicated in addiction, synaptic plasticity, inflammation, processes. Propylene glycol (PG) downregulated EGR2 and ARC mRNA expression in frontal cortex, an effect which was reversed by nicotine (NIC) and THC, suggesting that PG could have a protective role against NIC and THC use. However, in vitro, PG upregulated EGR2 and ARC mRNA expression at 18 h in cultured C6 rat astrocytes suggesting that PG may have neuroinflammatory effects. PG-induced upregulation of EGR2 and ARC mRNA was reversed by NIC but not THC. Collectively, these data provide evidence that e-cigarette vapor exposure may alter addiction-associated genes in rat brains and astrocytes and further confirm that e-cigarette vapor inhalation during early life may result in lasting behavioral consequences.

Oral Communication 2-1

Adolescent intermittent ethanol exposure: Sex-specific effects in alcohol drinking and c-Fos in limbic brain structures in male and female C57BL/6J mice

Kaila Dawkins[1] and Antoniette Maldonado-Devincci, Ph.D.[2]

[1]Department of Industrial and Systems Engineering, [2]Department of Psychology, North Carolina A&T State University

During adolescence, a period associated with increased binge drinking and long-term changes in brain and behavioral outcomes, males and females are motivated to drink alcohol by different factors, i.e. stress and coping for females and sociability for males. In this experiment, we tested baseline sex differences in anxiety-like behavior during early adolescence and later tested adolescent intermittent ethanol-induced changes in voluntary alcohol drinking and subsequent withdrawal-induced changes in c-Fos, a marker for neuronal activation. During early adolescence (postnatal day (PND) 24) we observed an increased anxiety-like phenotype in females compared to males. When mice were exposed to adolescent intermittent ethanol (AIE; PND 28-44) and tested for subsequent recurrent ethanol drinking, we found that males and females showed increased ethanol drinking after AIE (PND 45-49) and after re-exposure (PND 52-73). This pattern was sustained over repeated cycles of ethanol re-exposure in males, whereas this pattern dissipated in females over time. Brains were collected and AIE withdrawal-induced changes in c-Fos were observed across different amygdalar regions. Together, these data indicate the following: adolescent ethanol exposure increased subsequent ethanol drinking, and neuronal activation in amygdala structures is altered during withdrawal from ethanol re-exposure. Future work will incorporate cell-type specific markers to determine which types of cells are implicated in these lasting sex-specific effects.

Oral Communication 2-2

Investigating the reinforcing effects of vaporized delta-8 tetrahydrocannabinol in a rodent self-administration paradigm

Cronin, Emily A; Witmer, Harrison J; Durbin, Darby J; Drobny, Beth Anne A; Pulliam, Maddy; Keith, Jordan L; Wellendorf, Claire L; and Stairs, Dustin J

Department of Psychology, Creighton University, Omaha, NE USA

Delta-8 Tetrahydrocannabinol (THC) had the largest growth in sales in the 2021 cannabinoid market. This, combined with an increased interest in delta-9 THC due to its legalization and decreasing perceptions of harm associated with use, makes the need to better understand the reinforcing effects of cannabis and its derivatives paramount. While an intravenous (I.V.) self-administration paradigm is the gold standard for studying reinforcing effects in a rodent model, there are limitations when looking at I.V. cannabis drugs. The development of a vapor self-administration paradigm may overcome some of these limitations and be more relevant to humans. The current study was designed to determine if response-contingent vapor deliveries of delta-8 THC results in reinforcing effects using a rodent self-administration procedure. Eight male Sprague Dawley rats (PND 21) had daily 75-minute sessions to lever press for vaporized concentrations of delta-8 THC (2.5, 5, 10, 15, 30mg/300µl) and vehicle (ethanol). Standard operant conditioning chambers were retrofitted with a custom vapor nozzle on the front wall, through which vapor entered the chamber when the ratio requirement was completed on the active lever. A vaporizer then aerosolized the drug and pushed a 3.6-second “puff” of vapor into the chamber. Animals had a maintenance dose of 10mg/300µl on an FR2 schedule for 12 sessions. The dose was then varied every four days to establish a dose-effect curve. Results indicated that relative to vehicle substitution, the 5mg/300µl dose of delta-8 THC resulted in significantly greater active lever responding. The current results indicate that vaporized puffs of delta-8 THC can result in reinforcing effects and vaporized self-administration may be a viable preclinical model for studying the reinforcing effects and abuse potential of cannabis drugs.

Oral Communication 2-3

Revisiting the cannabinoid-opioid interaction hypothesis using conditional CB1 and μ opioid receptor knockout mice

Alton, Hannah R[1]; Linz, Emily O[1]; Bi, Guo-Hua[1]; Soler-Cedeño, Omar[1] and Xi, Zheng-Xiong[1]

[1]Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse Intramural Research Program, Baltimore, MD USA

The roles of the CB1 receptor (CB1R) in cannabinoid effects and the μ opioid receptor (MOR) in opioid effects are well characterized. However, the possibility of an interaction between these receptors is contentious. Growing evidence indicates that co-administration of cannabinoids and opioids synergistically enhances their analgesic effect; one hypothesis is that a direct, intracellular or membrane-level interaction between CB1R and MOR underlies this phenomenon. Although numerous studies support this hypothesis, many others do not. The current study aims to address this discrepancy using conditional CB1R- or MOR-knockout mice, under the hypothesis that if CB1R and MOR directly interact, then 1) both receptors should be co-localized on the same neurons and 2) selective deletion of one receptor should alter pharmacological and behavioral responses to activation of the other. Using RNAscope in situ hybridization, we found that CB1R and MOR mRNA displayed distinct regional distributions in mouse brain (n = 2). CB1R-MOR co-localization was observed in ~50% of glutamate neurons in the paraventricular nucleus of the thalamus (PVT), ~35% of GABA neurons in the substantia nigra pars reticulata (SNr), ~25% of GABA neurons in the ventral tegmental area (VTA), and <10% of GABA neurons in the nucleus accumbens (NAc). Using conditional knockout mice (n = 8-11 per group), we found that MOR deletion from GABA or glutamate neurons failed to alter Δ^9-THC-induced tetrad (analgesia, hypothermia, catalepsy, and immobility) effects, and CB1R deletion from GABA neurons also failed to alter oxycodone-induced analgesia and hypothermia. Additionally, deletion of CB1R or MOR from GABA or glutamate neurons failed to alter conditioned place preference or aversion to oxycodone or Δ^9-THC. Together, these findings do not support the CB1R-MOR interaction hypothesis.

Oral Communication 2-4

Respiratory depressant effects of synthetic cannabinoid receptor agonist 5F-ADB-PINACA in combination with fentanyl in mice: Pharmacodynamic and pharmacokinetic mechanisms

Thrush, Jessica R[1]; Shaw, Hannah E[1]; Avram, Marina[2]; Moran JH[2] & Fantegrossi, William E[1]

[1]Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR USA; 2PinPoint Testing, LLC, Little Rock, AR USA

The exponential rise in opioid overdose fatalities in the 21st century has been linked to concurrent use of fentanyl with other drugs from multiple classes. Fentanyl is a common adulterant in synthetic cannabinoid receptor agonist (SCRA) products, SCRAs are frequent adulterants in street opioids, and fentanyl and various SCRAs have been co-detected in biological samples from drug users. Case reports describe respiratory depression following SCRA overdose in humans, suggesting that co-administered fentanyl and SCRAs may elicit exacerbated respiratory depression, increasing overdose risk. In these studies we used whole body plethysmography to characterize respiratory depressant effects of the μ-opioid fentanyl and the SCRA 5F-ADB-PINACA, alone and in combination, in NIH Swiss mice. Blood levels of both drugs and their primary metabolites were also determined. Fentanyl and 5F-ADB-PINACA elicited acute respiratory depression at similar doses, and the magnitude of the effect was similar for both drugs. Naloxone attenuated respiratory depressant effects of fentanyl, but not those of 5F-ADB-PINACA, while rimonabant attenuated the effects of 5F-ADB-PINACA, but not those of fentanyl. In combination, fentanyl + 5F-ADB-PINACA elicited an apparent additive suppression of respiration which was resistant to reversal with naloxone, rimonabant, or the combination of both antagonists. Significantly more 5F-ADB-PINACA and 5-OH-ADB-PINACA were detected in mouse blood following administration of the fentanyl + 5F-ADB-PINACA combination as compared to when 5F-ADB-PINACA was administered alone. These studies suggest that unique pharmacodynamic and pharmacokinetic mechanisms may underlie exacerbated respiratory depression following concurrent use of fentanyl and SCRAs.

Oral Communication 2-5

Effects of *Tlr3*-dependent innate immune activation and chronic alcohol consumption on gene expression in brain micro-vessels

Kisby, Brent; Bustamante, Christian; Shanmugam, Sambantham; Castro-Piedras, Isabel; Ponomarev, Igor

[1]Texas Tech University Health Sciences Center, Lubbock, TX

Chronic high alcohol (ethanol) drinking is one of the characteristics of Alcohol Use Disorder (AUD). Toll-like receptor 3 (*Tlr3*) – dependent innate immune activation in rodents contributes to escalated ethanol consumption in a sex and genotype-dependent manner. Our preliminary data suggests these effects may be mediated by *Tlr3* activation in microvasculature cell types. Micro-vessels consist of cell populations that form the blood brain barrier (BBB), including endothelial cells (ECs), smooth muscle cells, and pericytes. We hypothesize that *Tlr3* activation-induced changes in gene expression in these cell types contribute to BBB dysfunction and escalated alcohol intake. The goal of this study was to determine the effects of *Tlr3* activation and/or chronic alcohol drinking on gene expression in enriched brain microvasculature in high-drinking FVB/NJ X C57BL/6J F1 hybrid mice. Male mice were randomly assigned to receive repeated injections of Poly(I:C) (PIC), a *Tlr3* agonist, or saline (9 injections total). Mice were allowed to choose between alcohol or water every other day (17 dinking sessions) and were assigned to one of four groups: saline/water (SW), saline/ethanol (SE), PIC/water (PW), and PIC/ethanol (PE). Brains were harvested 24 hours after the final alcohol session, micro-vessels from the frontal cortex were purified using mechanical homogenization and density-gradient centrifugation, and RNA sequencing and bioinformatics was performed to compare gene expression between groups. We identified 1,588 genes differentially expressed (DEGs) between PE and SE groups at nominal p-value of less than 0.05 and 74 DEGs at 5% FDR. The top DEGs were *Rsad2*, *H2-K1*, *Slc16a1*, and *Ifi44*, which are implicated in the immune response and are cell type-specific to the brain microvasculature. Taken together, these data suggest that vascular cell types are responsive to repeated *Tlr3* activation and could contribute to excessive ethanol consumption. Supported by AA027096, AA028370 (IP), John P. McGovern fellowship and AHA Predoctoral Fellowship 24PRE1184797 (BK).

Oral Communication 2-6

Prenatal alcohol and cannabinoid exposures impose distinct, sex-specific behavioral phenotypes of coordination and alcohol-seeking in adult mouse offspring

Rouzer, Siara K[1]; Bowring, Abigail M[1]; Miranda, Rajesh C[1]

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

Children prenatally exposed to alcohol or marijuana are at greater risk of developing motor impairments and drug-seeking behaviors. However, with increasing rates of polysubstance use in humans, little is known about the effects of simultaneous alcohol and cannabinoid (SAC) exposure. We therefore investigated whether SAC augments behavioral deficits in offspring compared to single-drug exposure alone. Pregnant C57Bl/6J mice were assigned to one of four groups: drug-free control, alcohol-exposed, cannabinoid-exposed or SAC-exposed. Drug exposure occurred daily between Gestational Days 12-15. For cannabinoid exposure, dams received an intraperitoneal injection of cannabinoid agonist CP-55940 (750μg/kg), and for ethanol exposure, dams were placed in vapor chambers for 30min of inhalation of 95% ethanol. Adult male and female offspring (Postnatal Days 90+) were subsequently behaviorally assessed. All drug exposures reduced offspring coordination on a Rotarod test in males, but females were resistant to cannabinoid-associated deficits. In an open field test, SAC males spent significantly less time in the center of the apparatus compared to controls and cannabinoid-exposed offspring, an effect that is absent in SAC females. In a social drinking task, both male and female SAC offspring drank significantly more alcohol over three weeks than controls. Finally, during operant administration experiments, SAC male offspring lever-pressed for alcohol more under a progressive ratio paradigm than all other groups, indicating greater willingness to work for alcohol, and demonstrated significantly greater preference for higher alcohol concentrations (40% ethanol). This SAC effect was notably absent in female offspring. In conclusion, SAC imposes distinct and sexually dimorphic motor impairments and alcohol-seeking behaviors in offspring compared to exposure to either drug individually.

Oral Communication 3-1

The effects of orexin antagonists on economic choice between remifentanil and milk in squirrel monkeys

Johansen, Alexandra N.[1]; Hecker, Jacquelin C.[1]; Jedema, Hank P.[1]; and Bradberry, Charles W.[1]

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

Opioid use disorder is prevalent, and current medications often cause undesirable side effects (e.g., sleep disturbances). Despite technological advances in neuroscience, pre-clinical substance use research often lacks translational appeal. Reverse translating models with high postdictive and ecological validity is warranted to improve treatment outcomes. As a result, our lab designed an economic choice assay with high postdictive validity to evaluate non-opioid candidate medications to treat opioid use disorder. Recently, the literature has focused on the orexin system as a possible therapeutic target for substance use disorders. Pre-clinical rodent studies suggest that high doses of both single and dual orexin receptor antagonists may attenuate opioid self-administration, decrease opioid seeking during reinstatement, reduce opioid demand, and increase demand elasticity. The present study's primary aim is to elucidate the effects of orexin antagonists on economic choice between remifentanil and food in squirrel monkeys. Namely, we hypothesized that suvorexant and SB-334867 would dose-dependently attenuate drug choice. To this end, squirrel monkeys (n = 7) received daily intravenous pre-treatments of orexin antagonists before completing an economic choice assay. Indifference values (the point at which subjects displayed an equal probability of selecting drug or milk) served as our primary outcome of interest, such that shifts in the IV during the 5-day treatment period compared to a contemporaneous baseline denoted changes in drug preference. Effective treatments shift responding away from drug toward the non-drug alternative. Because suvorexant treats insomnia, we also examined sleep using actigraphy monitors. Suvorexant significantly increased sleep but had a negligible effect on choice; studies with SB-334867 are currently underway.

Oral Communication 3-2

Role of neuromedin s-expressing ventral tegmental area neurons in morphine behaviors

Rivera Quiles, Cristina M; Dodson, Olivia J, Alday, Milagros, and Mazei-Robison, Michelle

Neuroscience Program, Michigan State University, East Lansing, MI USA

Opioid addiction is a major health and economic burden, but our limited understanding of the underlying neurobiology limits better interventions. Alteration in the activity and output of dopamine (DA) neurons in the ventral tegmental area (VTA) contributes to drug effects, but the mechanisms underlying these changes are relatively unexplored. We used TRAP to identify gene expression changes in VTA^{DA} neurons following chronic morphine and found that Neuromedin S (NMS) is enriched in VTA^{DA} neurons, and its expression is robustly increased by morphine. However, whether all VTA^{DA} neurons express NMS, and their functional impact hasn't been determined. We hypothesize that NMS neurons represent a novel subset of VTA neurons that contribute to morphine-elicited behavior. To test this, adult male and female NMS-Cre mice and wild-type littermates were used (n=86,82; males and females combined). Cre-dependent viral vectors were injected into the VTA to allow for DREADD-mediated activation (Gq) or inhibition (Gi) of VTA-NMS neurons. Locomotor activity and conditioned place preference (CPP) were assessed. Significant differences ($p<0.05$) were determined using a repeated-measures two-way ANOVA for locomotor behavior and unpaired t-tests for CPP. NMS-Gq mice exhibit increased morphine-induced locomotor activity compared to controls while NMS-Gi mice have reduced morphine locomotor sensitization. In CPP assays, NMS-Gi mice had significantly reduced morphine- CPP while NMS-Gq mice were similar to controls. Thus, manipulation of VTA-NMS neuronal activity alters morphine-elicited behaviors including locomotion, sensitization, and CPP. Future studies will determine whether VTA-NMS neuronal activity modulates other morphine behaviors. Our data suggest that NMS expressing neurons are a functionally relevant subset of VTA neurons for morphine responses.

Oral Communication 3-3

Comparison of respiratory effects of mu opioid agonists that vary in intrinsic efficacy and reported signaling bias using whole-body plethysmography in rats

Le, T.H. Rose[1]; Pham, Loc M.T.[1]; Shabbir, Tooba[1]; Blough, Bruce E.[2]; Freeman, Kevin B.[1]

[1]Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS USA; [2]Research Triangle Institute, RTP, NC

Mu opioid receptor (MOR) agonists have been developed that purportedly produce fewer opioid-typical adverse effects such as respiratory depression due to biased G-protein signaling. However, recent studies support the interpretation that the favorable outcomes reported with biased agonists are due to partial intrinsic efficacy at the MOR. The purpose of the current study was to compare the respiratory effects of two biased MOR agonists, SR17018 and PZM21, to the full-efficacy agonists, oxycodone and fentanyl, and the partial-efficacy agonists, buprenorphine and butorphanol, in rats. A total of 4 male and 4 female rats were implanted with intravenous (i.v.) catheters, and the respiratory effects of the test compounds were measured using whole-body plethysmography with no manipulation of gas mixture (i.e., room air). A range of doses were tested for each compound, and each drug and the doses within each drug were tested in a counterbalanced order across subjects on separate days that occurred at least 48 hours apart. Significant respiratory depression was operationally defined as a 50% decrease in minute volume relative to vehicle in the corresponding time bin. Oxycodone and fentanyl produced significant, dose-dependent reductions in minute volume. No other compound significantly reduced respiration on any measure. The current results will be combined with experiments testing the same compounds in models of antinociception and self-administration that are sensitive to differences in intrinsic efficacy to determine the relative alignment of their behavioral effects between the full and partial MOR agonists.

Oral Communication 3-4

The deleterious effects of parental fentanyl-dependence on sleep health: Multigenerational effects on sleep architecture and cognition in adolescent rats

Jones, Marissa R[1]; Schmeichel, Brooke E[1]

[1]Department of Biomedical Sciences, Quillen College of Medicine, Johnson City, TN USA

Fentanyl is a potent synthetic opioid that alters sleep quantity and quality, and the deterioration of sleep quality is associated with drug abuse and relapse in humans. Adding to this complex relationship between sleep disturbances and substance use disorders, research in humans has indicated that sleep disturbances during adolescence are associated with an increased risk of future substance use. Moreover, addiction is a multifaceted condition that can negatively impact multiple generations. In recent years, there has been growing preclinical evidence to suggest that parental exposure to opioids, even before gestation, can produce cognitive impairment in subsequent generations. Therefore, our first study utilized a translationally relevant model of fentanyl dependence to demonstrate the altered sleep health in adult female and male rats following chronic intermittent fentanyl vapor during drug abstinence. Our fentanyl-dependent female and male rats showed a significant reduction in the amount of time spent in rapid eye movement (REM) sleep during the light/inactive phase following one week of abstinence. Furthermore, to demonstrate the negative multigenerational effects of fentanyl dependence on sleep health and cognition, our second study measured outcomes in the drug naïve offspring of fentanyl-dependent rats during adolescence. The drug naïve offspring of fentanyl-dependent rats exhibited a significant increase in the amount of time spent in REM and NREM sleep, and less time awake within the dark/active phase during adolescence compared to control, drug-naïve rats. Additionally, the drug naïve, adolescent offspring of fentanyl-dependent parents exhibited cognitive memory deficits, as demonstrated lower performance on a novel object recognition task. Taken together, our findings not only demonstrate the direct impact of fentanyl dependence on sleep health but also the deleterious effects on sleep health and cognition in the subsequent generation.

Oral Communication 3-5

Intermittent access of a high-fat diet differently impacts alcohol drinking in low and high-drinking male and female rats

Pham Sabrina and Sirohi Sunil

Laboratory of Endocrine and Neuropsychiatric Disorders, Division of Basic Pharmaceutical Sciences, College of Pharmacy, Xavier University of Louisiana, New Orleans, LA.

We have previously reported that intermittent high-fat diet (HFD) access reduces moderate alcohol drinking in male Long-Evans rats. However, it remained to be identified if a similar paradigm would reduce low and high-alcohol drinking. Therefore, the present study evaluated the impact of intermittent HFD access on alcohol drinking in high (P-rats) and low (Wistar) drinking male and female rats. Male and female groups of rats, matched for body weight, water, and food intake, received two weeks of intermittent (24hr, Tue and Thu; Int-HFD) access to a palatable diet (PD; ~40% high in fat) or standard chow (Controls). Water and chow were available ad libitum to all groups, and food intake was measured. Following two weeks of intermittent HFD exposure, ethanol (20% v/v) consumption was evaluated using a 2-bottle-choice alcohol drinking paradigm on the chow-only access days (Mon, Wed, and Fri) and intermittent HFD cycling continued during the alcohol testing. Consistent with the previous studies, intermittent HFD access induced a feeding pattern in which the Int-HFD group of rats significantly escalated caloric intake on HFD access days, an effect observed in both low and high-drinking male and female groups of rats. Interestingly, caloric underconsumption on the chow access days was only evident in the low-alcohol drinking group of rats. Alcohol drinking was significantly attenuated in the high-drinking male and female group of rats receiving intermittent HFD access compared to the chow controls. In contrast, alcohol intake in the low-drinking male and female Int-HFD group of rats was not significantly different compared to their respective controls. Collectively, these data highlight possible rat strain-specific differences in alcohol intake following intermittent HFD exposure.

Oral Communication 4-1

Synthesizing a novel μ-opioid-receptor-selective positron emission tomography tracer derived from the synthetic opioid etonitazene

Hubbard, Seth T[1]; Sulima, Agnieszka[1]; Davis, Abigail M[1]; Jacobson, Arthur E[1]; Gomez, Juan L[2]; Michaelides, Michael[2]; and Rice, Kenner C[1]

[1]Drug Design and Synthesis Section, Molecular Targets and Medications Discovery Branch, NIDA, Bethesda, MD USA; [2]Biobehavioral Imaging and Molecular Neuropsychopharmacology Unit, Neuroimaging Research Branch, NIDA, Baltimore, MD USA

Synthetic μ-opioid receptor (MOR) agonists have been researched extensively and utilized for their analgesic properties. Though efficacious, opiates have adverse effects, such as respiratory depression, constipation, and abuse potential. Hence, it is critical to engineer MOR agonists with diminished adverse effect profiles. By using positron emission tomography (PET) imaging, a research tool utilizing radiolabeled tracers to examine a target's biological function, a MOR-selective radiotracer would elucidate the MOR distribution in models of the central nervous system and allow further insight into their biological activity. Thus far, [^{11}C]carfentanil is the only MOR-selective PET radiotracer utilized in animal and human studies. However, [^{11}C]carfentanil has very high potency, carbon-11 isotope synthesis requires an on-site cyclotron, and carbon-11 has a shorter half-life (~20 minutes) compared to other radioactive isotopes. Thus, a novel radiotracer employing fluorine-18, which has a longer half-life (~110 minutes), with lower efficacy than [^{11}C]carfentanil would be desired. Etonitazene is a synthetic, highly selective MOR agonist, 10X less potent than carfentanil. Herein, the syntheses of a novel fluorinated etonitazene analog (*N*,*N*-diethyl-2-(2-(4-(2-fluoroethyl)benzyl)-5-nitro-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-amine) and its tosylated alcohol derivative as a precursor for [^{18}F]-labeling, are reported. This novel fluorine-18-based compound will be examined through in vivo target engagement studies to evaluate its potential as a MOR-selective [^{18}F]-labeled PET radiotracer.

Oral Communication 4-2

Development of an iontophoresis-coupled microneedle skin patch of naloxone for emergency treatment of opioid overdose

Akeemat O. Tijani[1], Ashana Puri[1], Maria J. Peláez[2], Prashant Dogra[2]

[1]Department of Pharmaceutical Sciences, Bill Gatton College of Pharmacy, East Tennessee State University, Johnson City, TN; [2]Mathematics in Medicine Program, Houston Methodist Research Institute, Houston, TX 77030, USA

The use of naloxone, for opioid overdose reversal has up till date faced challenges associated with its delivery in patients. The transdermal delivery of this drug promises the obviation of all these challenges, however passive delivery of naloxone through skin is limited due to the lipophilic skin barrier. In this work, we investigated the transdermal delivery of naloxone through polymeric rapidly dissolving microneedles (MNs), the impact of MN geometrical parameters on NAL delivery was explored and pharmacokinetic predictions were made to predict *in vivo* delivery with *in vitro* permeation profile. We also explored the influence of iontophoretically driving ionized drug content in the MN patches on cumulative permeation of NAL from the best performing MN patch.
We observed a reduction in lag time to NAL delivery to about 5-15 min with MN patches over up to 75 minutes typical with passive transdermal delivery. Increasing MN length and density made significant difference in the amount permeated and flux ($p<0.05$) over 24 h. Mathematical modeling of *in-vitro* release from best performing patch revealed the significance of needle base diameter and needle count in improving systemic pharmacokinetics of NAL from the MN patches. With this approach, an optimized design of the patch that can reproduce the clinical PK of NAL obtained with commercial devices was predicted. Findings from the iontophoresis coupled MN patches include an observation of significant elevation in the cumulative amount (12-fold) and flux (6-fold) in the first 60 minutes of application. These translated through *in vitro-in vivo* mathematical correlation studies to a 30% decrease in required drug load in a basic patch design and significant reduction in required patch size.

Oral Communication 4-3

The role of retinoic acid signaling in substance-use-, depression-, and anxiety-related behavior

Yorkiris Mármol Contreras[1,2], Nolan Dvorak M[1,2], Cynthia Tapia M[1,2,] Nikita Gupta S[1,2], Tileena E. S. Vasquez[1,2], Poonam Shah[1,2], Shyny Koshy[1,2], Dingge Li[1,2], Fernanda Laezza[1,2] and Thomas A. Green[1,2]

[1]Department of Pharmacology and Toxicology, The University of Texas Medical Branch, Galveston, TX USA; [2]Mental Health Research Group, The University of Texas Medical Branch, Galveston, TX USA

Depression, anxiety, and substance use disorders severely deteriorate the quality of life of millions worldwide and often occur comorbidly. Especially for substance use disorders, pharmaceutical treatments are scarce and vary in effectiveness greatly, highlighting an urgent need to uncover genetic mechanisms underlying SUDs that may lead to novel targets for drug development. Transcriptomic analyses have revealed enhanced expression of the retinoic acid (RA) signaling pathway in the nucleus accumbens shell (NAcSh), suggesting a role of RA signaling components in controlling emotional, motivational, and other behaviors regulated by the NAcSh. In a previous study, increasing RA levels in the cell by knocking down mRNA expression of degradation enzyme Cyp26b1 in the NacSh of male rats resulted in an addiction- and depression-susceptible but anxiety-resilient behavioral phenotype. In this study, we assessed the impact of reduced RA synthesis in the NAcSh on behavioral and cellular functions related to addiction-, depression-, and anxiety-like behaviors in rats. Compared to controls, Aldh1a1 knockdown rats exhibited decreased drug-taking and increased anxiety-related behaviors. These results were corroborated by complementary findings in electrophysiological assays. Overall, we find that RA manipulations regulate substance use and motivational behaviors bidirectionally and the RA pathway may represent a promising target for therapeutic development.

Oral Communication 4-4

Bifunctional nociceptin opioid (NOP) receptor -mu opioid (MOP) receptor agonists as non-addicting analgesics for opioid use disorder: Molecular docking-assisted drug design and SAR of *N*3-substituted 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-ones

Doshi, Arpit[1]; Yasuda, Dennis[1]; Polgar, Willma E.[1] and Zaveri, Nurulain T.[1]

[1]Astraea Therapeutics, LLC, 320 Logue Ave, Suite 142, Mountain View, California 94043, USA

We previously reported AT-121, a small-molecule NOP-MOP bifunctional agonist of the spiroisoquinolinone chemical class, as a non-addicting analgesic devoid of opioid liabilities such as respiratory depression, abuse potential, and physical dependence. Based on the *in vivo* profile of AT-121 in nonhuman primates, we rationalized that a NOP-MOP bifunctional profile can be a good strategy to develop safer, non-addicting analgesics, which can benefit the current ongoing opioid crisis. To this end, we investigated a different chemical series, the 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-ones that had previously been reported as highly selective for the NOP receptor. Here, we report molecular docking-assisted discovery and structure activity relationships (SAR) of a novel series of *N*3-substituted 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-ones that yielded new bifunctional NOP full agonists–mu opioid (MOP) receptor partial agonists, which are being currently investigated as potential non-addicting analgesics for opioid use disorder. Our SAR studies on this chemical class of NOP ligands showed that modifications at the *N*3-position substituent can affect binding and functional profile at both NOP and MOP receptors. A significant finding from the current study is that, by utilizing rational drug design principles, we designed a series of bifunctional NOP/MOP agonists starting from a highly selective NOP agonist chemical series. Further preclinical studies are under progress to assess drug-like properties of these promising lead candidates.

Oral Communication 4-5

Prefrontal cortex to ventral tegmental area projection is responsible for early social isolation stress-induced vulnerability for heroin relapse

Wang, Zi-Jun[1,2]; Wang, Yunwanbin[1]; Yue, Shuwen[1]; Singh, Archana[1]; and Li, Guohui[1]

[1]Dept. of Pharmacology & Toxicology, School of Pharmacy, University of Kansas; [2]Cofrin Logan Center for Addiction Research and Treatment, University of Kansas, Lawrence, KS, USA.

Rationale: Early life adversities persistently alter brain function and increase vulnerability for substance use disorders (SUD), including increased drug taking and relapse. Our prior study reported that early social isolation (ESI) during adolescence potentiates heroin seeking and induces prefrontal cortex (PFC) and ventral tegmental area (VTA) dysfunction. Yet, the underlying circuit and molecular mechanisms are unclear. *Hypothesis*: We posit that ESI stress and heroin convergently disrupt PFC>VTA projection function by altering transcriptional profiles within this circuit. *Methods*: Here, we used both male and female mice. ESI stress lasted from P21 to P60. Then, control and ESI mice underwent 10-day heroin self-administration followed by 14-day abstinence. Context- and cue-induced heroin-seeking test (1hr) was performed after abstinence. Circuit-specific-chemogenetic and electrophysiological tools as well as translating ribosome affinity purification (TRAP) tools were used to identify functional and transcriptional changes within PFC>VTA circuit. *Results*: We found that ESI stress aggravates heroin abstinence-induced neuronal dysfunction in PFC>VTA projection. In addition, activating PFC>VTA projection attenuated ESI-potentiated heroin seeking and recovered the neuronal firing and synaptic transmission within this circuit. Furthermore, TRAP study showed that ESI stress and heroin convergently affected the expression of genes regulating DNA damage responses, apoptosis, carcinogenesis, and axon extension within the PFC>VTA circuit. Moreover, N-acetylcysteine treatment, which alleviates DNA damage and modifies synaptic transmission, attenuated ESI-potentiated heroin seeking. *Conclusion*: Our study showed that ESI stress-induced susceptibility to heroin relapse is associated with the ESI-potentiated neuronal dysfunction in PFC>VTA projection; and that this neuronal dysfunction is accompanied by transcriptional alterations within PFC>VTA circuit.

Poster Presentations

Poster 1

Widening the opioid analgesia therapeutic window with a dual pharmacology strategy

Afrin, Nadia[1]; Nambiar, Rohit[1]; Cook, James M[3].; Fischer, Bradford D[2].; Martinez, Diana[2]; Keck, Thomas M[1].

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

Morphine, an opioid analgesic, activates μ-opioid receptors to block the nociception process in the periphery and in the central nervous system. Opioids have important side-effects, including abuse liability and potentially lethal respiratory depression. Identifying new treatment strategies for analgesia may help to address patient needs and the current opioid endemic. α2/α3 subunits-containing $GABA_A$ receptors are expressed in the spinal cord and benzodiazepine-like positive allosteric modulators (PAMs) targeting these receptors produce antihyperalgesia. We have previously established that MP-III-024, a novel α2/α3 $GABA_A$ PAM, produces antinociception when co-administered with morphine. Current follow-up studies are evaluating whether MP-III-024 affects morphine-induced side effects. This study used plethysmography testing to observe whether MP-III-024 co-administration alters morphine-induced respiratory depression effects in male CD-1 mice. Following habituation, mice received cumulative doses of morphine, MP-III-024, or morphine and MP-III-024 in a 1.00: 0.94 ratio (which produces peak synergistic analgesic effects). Morphine had a biphasic response, increasing the tidal volume (TVb) at a low dose, and dose-dependently reducing breathing rate (f) at higher doses. MP-III-024 reduced TVb at the highest tested dose. The combined delivery of morphine and MP-III-024 did not produce any significant effect on the tidal volume (TVb) or breathing rate (f). Data indicating that MP-III-024 may actually provide a protective effect against opioid-induced respiratory depression. Ongoing and future studies will investigate the neurological mechanisms that might explain this effect.

Poster 2

Alprazolam withdrawal induces sex dependent anxiety like gene signaling in mice

Aggarwal, Harshil[1]; Vardeleon, Nathan I[1] and Bolaños-Guzmán, Carlos[1]

[1]Department of Psychological and Brain Sciences, Texas A&M University, College Station, TX USA

Benzodiazepine (BZD) off-label use is a public health epidemic that has flown under the radar across the globe. The rates of non-medical BZD use has seen an upsurge, with Alprazolam (Xanax; ALP) as the most abused BZD. Despite sharp increases in BZD abuse and overdose, the understanding of the neurobiology as well as available treatment(s) for their toxicity and withdrawal are critically limited. Given that BZDs overdose continues to rise in both adult and adolescent populations, and that females are more likely to be prescribed a BZD than their male counterparts, it is surprising how little is known about the mechanistic sex- and age differences induced by BZD withdrawal. Additionally, non-seizure biomarkers of BZD induced withdrawal are not well established using rodent models. Therefore, this project seeks to investigate the neurobiological effects of ALP induced withdrawal with sex and age as biological variables to establish gene target measures that may assess the mechanisms and possible treatments for BZD induced withdrawal. Male and female C57BL/6 mice (PD28-PD90) were pretreated with either a vehicle (VEH) or an abuse dose of ALP (3.0 mg/kg) twice daily for 8 days. The mice were then given a single injection of a BZD antagonist, flumazenil (5.0 mg/kg FLZ), to induce precipitated withdrawal. 24 hours after their exposure to flumazenil, mice were sacrificed, and tissue was collected to assess anxiety and addiction related gene signaling using PCR. Our brain regions of interest include the prefrontal cortex (PFC), the nucleus accumbens (NAc), the ventral tegmental area (VTA), and the lateral habenula (LHb). Our results suggest that there are sex differences, with females being more susceptible to the side effects of withdrawal.

Poster 3

Pleiotropic effects of 10-butyl ether minocycline (BEM) as a potential medication for alcohol use disorder (AUD)

Aguilera, Monica G[1]* and Shaik, Abdul A[1]*, Panthagani, Praneetha[2], Liu, Xiaobo[2], Sanchez, Jordan N[1], Blough, Bruce E[3], Bergeson, Susan E[1].

[1]Dept. of Cell Biol. & Biochem., [2]Dept. of Pharm. & Neurosci., TTUHSC, Lubbock TX; [3]RTI International, Research Triangle Park, NC.

Target selection and drug development has been a difficult problem to solve for AUD, a biologically complex brain disease. We took a multimodal approach and established BEM as our lead molecule out of 17 minocycline analogs synthesized for loss of antimicrobial action and retention of multiple positive off-target effects. Initial data showed excellent efficacy in AUD animal models, and safety at high levels of drug. Pharmacokinetic studies of BEM in male and female mice via oral and intraperitoneal route suggests that it has good blood brain barrier permeability with a mean brain residence time of 5-8 hours. We hypothesized that non-antibiotic BEM could recapitulate the neuroprotective, immunomodulatory, and other health-positive, off-target activities of minocycline. Ames testing showed no evidence of mutagenicity but rather protection from induced mutations. To ensure that was not residual antimicrobial action, growth curve with high doses of BEM were completed. There was no difference between drug treatment and control. BEM had a 2.5-fold increase in IC_{50} over minocycline (50 vs 125 μM) from the MTT assay. BEM also showed significantly improved MMP-9 inhibition over minocycline. Confocal microscopy and Western blot analysis showed suppression of LPS mediated microglial N9 cell activation by both BEM and minocycline. BEM anti-VEGF activity was similar to minocycline in a vascular endothelial cell migration assay. Additional FDA Investigational New Drug enabling results showed BEM is a BCS class-1 molecule, exhibiting good water solubility, permeability, and a favorable safety profile. It is well-tolerated in mice, rats, and dogs. BEM, with its promising efficacy and diverse pharmacological actions, holds potential for treating various neuropsychological disorders, including AUD, providing a novel avenue for drug discovery beyond traditional antibiotic properties.

Poster 4

Development of binge alcohol self-administration in mice using 16-hour operant conditioning

Akande, Adesewa; Cain, Lauryn; Nahar, and Nam, Hyung

Department of Pharmacology, Toxicology and Neuroscience, Louisiana State University Health Sciences Center, Shreveport, LA USA

To understand the behavioral mechanism of alcohol use disorders (AUD), researchers developed alcohol self-administration strategies based on free-choice drinking in home cages or operant conditioning in chambers in order to reflect more relevant conditions for examining alcohol seeking. However, these methods alone are not ideal for binge drinking since most mice limit their ethanol consumption. Therefore, studies using high doses of alcohol administration are critical to identify the neurobiological mechanisms that promote the development of alcohol tolerance in AUD. The goal of this study is to develop an operant model of voluntary high-dose oral alcohol consumption in mice using operant parameters that could be used to estimate the reinforcing properties of alcohol in individual animals. In this study, we developed long durations of operant self-administration for a sweetened alcohol solution that can induce high-dose alcohol consumption in our mouse model. We demonstrated that 16-hour alcohol self-administration increases blood alcohol concentration (BAC) up to 110 mg/dL—higher than the legally impaired dose in humans (80 mg/dl). The model offers a valuable tool to explore neural sensitization, reinforcement, and tolerance induced by high-dose alcohol self-administration. This operant conditioning model may open avenues for future investigations into pharmacological targets that can mitigate binge-like drinking, prevent tolerance, and address alcohol-induced motor deficits and intoxication. This innovative approach may facilitate the study of the effects of alcohol on various organ systems, including the brain, heart, liver, and immune system.

Poster 5

Acute amphetamine exposure increases female rat estrus frequency

Antonacci, Payton E[1]; Vasquez, Adriana[2,3]; and Lee, Hongjoo J[1,3]

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

Female rats have increased vulnerability to developing substance use disorders. This increased vulnerability is modulated by the timing of release of gonadal hormones, such as progesterone (P4) and estradiol (E2), across the rat estrous cycle. The estrous cycle is characterized by metestrus/diestrus (low circulating levels of P4 and E2) and proestrus/estrus (high circulating levels of P4 and E2). To date, most research focuses on the role of gonadal hormones in enhancing rewarding properties of drugs, however, little research has examined the effects that drugs might have on the estrous cycle. While previous evidence suggests that chronic cocaine administration alters estrous cyclicity in females, there is no existing research examining whether acute exposure to amphetamine (AMPH) has an impact on estrous cyclicity. The present study hypothesized that female rats would enter high hormonal stages more frequently upon acute exposure to AMPH. To investigate this, Long-Evans female rats were administered two AMPH (2mg/kg) i.p. injections (separated by ~4-5 days) during proestrus or estrus. To confirm estrous stage, rats underwent vaginal lavages prior to AMPH administration. Estrus stage frequency was measured across two 10-day periods: one period immediately prior to a rat receiving the first AMPH injection and another period immediately following AMPH-injection. Results showed that females cycled into estrus more frequently after receiving AMPH injections compared to their typical cycles pre-AMPH. These findings indicate that acute administration of AMPH leads to changes in the estrous cycle, suggesting a bi-directional influence of gonadal hormones on stimulant behavioral responses AND stimulant effects on gonadal function. Future studies will investigate the effects of chronic AMPH administration on the estrous cycle and whether this effect is dose-dependent.

Poster 6

Eutylone pre-exposure has no impact on the aversive effects of cocaine and MDMA: Implications of its hybrid neurochemical mechanisms of action

Nina Ardabili, Shira Tan and Anthony L. Riley

Psychopharmacology Laboratory, Department of Neuroscience, Center for Neuroscience and Behavior, American University, Washington, DC

Recreational drugs have rewarding and aversive effects, the balance of which is critical to abuse liability. This balance is impacted by various factors, including drug history, e.g., exposure to a drug reduces its aversive effects, increasing its use The present study investigated the effects of a history with the synthetic cathinone eutylone on the aversive effects of cocaine and MDMA, drugs often used serially with the synthetic cathinones. Given that eutylone blocks dopamine and norepinephrine reuptake (reuptake inhibitor like cocaine) and stimulates serotonin release (substrate releaser like MDMA), eutylone history may alter their aversive effects due to their shared neurochemistry. Methods: 192 adult male and female Sprague-Dawley rats were injected with eutylone (20 and 10 mg/kg, respectively) or saline every 4th day for four or five injections prior to conditioning in which saccharin was repeatedly paired with vehicle, cocaine (20 mg/kg), MDMA (3.2 mg/kg) or eutylone (20 and 10 mg/kg).Results: All drugs induced significant taste avoidance in both sexes pre-exposed to the vehicle (all ps<0.05). Taste avoidance was also induced with cocaine and MDMA in subjects pre-exposed to eutylone (all ps<0.05), although avoidance induced by eutylone was significantly attenuated by the eutylone history (p<0.05).Conclusions: Despite eutylone sharing neurochemical actions with cocaine and MDMA, its history failed to attenuate avoidance induced by these substances, suggesting that eutylone's hybrid neurochemical activity may create a distinct interoceptive effect unlike that produced by either cocaine or MDMA. Eutylone's ability to attenuate its own taste avoidance suggests that this failure was not due to an inability to produce such effects. Further evaluation of eutylone history on the rewarding effects of cocaine and MDMA will also be important in understanding potential shifts in the balance between reward and aversion that could influence polydrug use.

Poster 7

Detection and quantitation of emerging designer opioids in complex matrices

Avram, Marina[1,2]; Shaw, Hannah[1]; Gannon, Brenda[1]; Moran, Jeffery[1,2]; Fantegrossi, William[1]

[1]Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR USA; [2]PinPoint Testing, LLC, Little Rock, AR USA

The recent emergence of new designer opioids and unexplained overdose cases are rapidly increasing analytical demands and creating an unstainable environment for clinical, public health, forensic, and research laboratories. A reliable analytical method that is easily validated and maintained in accredited testing laboratories is needed to adequately address this. This study follows recently published laboratory validation requirements and guidelines from the Academy Standards Board (ASB) to develop a high-throughput, liquid chromatography tandem mass spectrometry (LC-MS/MS) test kit for detection and quantitation of emerging designer opioids in blood, serum, and urine samples. A quick supported-liquid extraction (SLE) sample clean-up procedure was used for all blood, serum, and urine samples. All matrices were processed simultaneously in approximately 1 hour on a single 96-well plate to support clinical, forensic and research applications that often require the use of multiple matrices. The ASB-validated testing procedure utilizing positive mode LC-MS/MS detection met accuracy and precision specification and was tested through the evaluation of 170 blood, 174 serum, and 133 urine samples collected from adult male Sprague Dawley rats. Rats were injected intraperitoneally with doses of acrylfentanyl, fentanyl, furanyl fentanyl, methoxyacetyl fentanyl or tetrahydrofuran fentanyl, alone or in the presence of xylazine. Blood samples were collected through an indwelling intravenous catheter at 0, 20, 60, 180 and 360 min after injection. Half of each collected sample was left as whole blood, and the other half was centrifuged to collect serum only. Pooled urine samples were collected at these same times, if available, from a tray beneath each rat's mesh cage floor. Results show this streamlined testing procedure is suitable for opioid testing in multiple complex matrices, but time- and matrix-dependent factors are important in the detection of specific drugs and combinations.

Poster 8

Effects of differential rearing on reward preference and parvalbumin expression in CA1 and basolateral amygdala

Azuma, Miki C.[1], Dios, M.,[1] Cain, Mary E.[1]

[1]Department of Psychological Sciences, Kansas State University, Manhattan, KS USA

Social isolation increases the 'wanting' of a reward but surprisingly decreases the 'liking' of a reward. Rats reared in social isolation (IC) self-administer more opiates, ethanol, stimulants, and food in operant paradigms but display decreased hedonic responses for sucrose compared to rats reared in an enriched environment (EC). A region susceptible to stress that might be impacted by social isolation is the CA1 region in the hippocampus, due to parvalbumin (PV) interneurons being prone to oxidative stress. There is limited research examining the effects of differential rearing on sucrose preference and mixed evidence on the effects of social isolation on CA1 PV expression. Therefore, the current experiment examined rats' sucrose preference and measured PV expression in CA1 and basolateral amygdala (BLA). We hypothesized that EC rats would have the highest sucrose preference while IC rats would have the lowest. In addition, we hypothesized that IC rats would have the lowest PV expression in CA1 and the BLA. 24 male Long Evans rats arrived on PND 21 and were randomly assigned to the standard condition (SC), IC, or EC for 30 days. This study was within-subjects and used a 2-bottle test to examine preference for a 32% sucrose solution against water, 0.7%, and 10% sucrose solution. Each preference test was one hour daily for four days, and order of testing was counterbalanced. After testing, PV expression was quantified using immunohistochemistry. Overall, EC rats had the highest preference, consistent with taste reactivity findings. However, we did not find that differential rearing influenced PV expression in CA1. Preliminary results suggests that differential rearing does not alter PV expression in the BLA. These results suggest that enrichment increases the preference for sucrose. The increased hedonic response to sucrose in EC rats is not due to PV interneurons and therefore we are examining other putative mechanisms.

Poster 9

Exploring the therapeutic potential of the nociception/orphanin FQ-NOP receptor pathway in opioid use disorder treatment

Balaguer, Maria G.[1], Kallupi, Marsida[1], de Guglielmo, Giordano[1]

[1]Department of Psychiatry, University of California, San Diego

Approximately 25% of chronic pain patients misuse prescribed opioids and 5 to 10% developing Opioid Use Disorder (OUD). Despite our understanding of the neurobiological targets of opioids, the molecular mechanisms driving addiction-like behaviors in certain individuals remain elusive. To investigate these mechanisms, we used heterogeneous stock rats, which mimic human behavioral and genetic diversity. We characterized differences in addiction-like behaviors using an addiction index that incorporates the key criteria of OUD: escalated intake, highly motivated responding, and hyperalgesia. Our findings revealed that rats exhibiting high addiction-like behaviors (HA) displayed increased γ-aminobutyric acid (GABA) transmission in the central nucleus of the amygdala (CeA) compared to low addiction-like behavior (LA) and naive rats. Superfusion of CeA slices with nociceptin/orphanin FQ peptide (N/OFQ), an endogenous opioid-like peptide, normalized GABA transmission in HA rats. Intra-CeA levels of N/OFQ were lower in HA rats than in LA rats, and intra-CeA infusions of N/OFQ reversed the escalation of oxycodone self-administration in HA rats, but not in LA rats. This suggests the downregulation of N/OFQ levels in the CeA may be responsible for hyper-GABAergic tone in the CeA observed in individuals who develop addiction-like behaviors. We tested a novel NOP receptor-selective nonpeptide agonist on various OUD measures, such as motivation to seek heroin, withdrawal-induced hyperalgesia, and opioid-induced respiratory depression. Our results demonstrated that NOP agonism significantly reduced heroin motivation and seeking, alleviated withdrawal-induced hyperalgesia, and accelerated recovery from heroin-induced respiratory depression. Targeting the N/OFQ-NOP receptor system may represent a promising therapeutic strategy for OUD, offering improved efficacy and avoiding undesirable effects associated with traditional MOR receptor agonists.

Poster 10

Evaluation of methamphetamine vs food-choice reinforcer magnitude, cost manipulation, and behavioral strain differences between Sprague-Dawley and Long-Evans rats

Amber N Baldwin and Matthew L Banks

Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond VA USA

Methamphetamine (meth) use disorder is a significant public health issue for which there is currently no Food and Drug Administration-approved pharmacotherapies. Thus, there is a need for preclinical research using assays with a history of predictive translational utility. Due to the paucity of literature on meth-vs-food choice in rats, the aim of the present study was to conduct parametric studies of reinforcer magnitude and response requirement manipulations. Sprague-Dawley and Long-Evans rats were aseptically implanted with intravenous (IV) catheters and trained to respond for meth (0.01-0.32 mg/kg/inf) and 32% vanilla ensure under a concurrent fixed-ratio (FR) 5 schedule during daily 2h behavioral sessions M-F. Food reinforcer magnitude was manipulated every week across water, 10%, 32%, and 100% ensure concentration conditions. FR requirements were evaluated every week across FR 1, 5, 25, and 125 for either meth or ensure. Under baseline conditions (32% ensure), food was chosen over smaller meth doses and behavior reallocated towards meth at larger meth doses. Compared to 32%, when water was the alternative, there was a trend towards increased meth choice; whereas, when 100% ensure was the alternative, there was a trend toward decreased meth choice. Compared to meth FR5 conditions, decrease the meth FR1 trended towards increased meth choice, whereas increasing the meth response requirement trended towards decreased meth choice. Although studies are ongoing, no sex or strain differences were noted. Overall, these results will provide the empirical foundation to establish experimental conditions for meth-vs-food choice to evaluate candidate medications and investigate the neurobiology of meth reinforcement.

Poster 11

The effects of morphine on antinociception and gastrointestinal motility in rats eating a high fat/high carbohydrate or ketogenic diet

Beltran, Nina M[1]; Minervini, Vanessa[2] and Serafine, Katherine M[1]

[1]Department of Psychology, The University of Texas at El Paso, El Paso, TX USA; [2]Department of Psychological Science, Creighton University, Omaha, NE USA.

Eating a diet that is high in fat and carbohydrates can lead to obesity; however, it is not known if the pain-relieving or adverse effects (e.g., constipation) of morphine are impacted by dietary manipulation. To explore this, the effects of acute morphine administration were assessed in male Sprague-Dawley rats (n=8/dietary group) eating a low fat laboratory chow (17% kcal from fat), a high fat/high carbohydrate chow (60% kcal from fat), or a ketogenic (high fat/low carbohydrate) chow (90.5% kcal from fat). Morphine-induced antinociception (0.32-17.8 mg/kg IP) was assessed using the warm water tail withdrawal procedure. Gastrointestinal (GI) motility was assessed by counting and weighing fecal output hourly, following an injection of saline or morphine (1, 3.2, or 10 mg/kg IP) for male rats eating wet homogenized chows (n=2-3/dietary group). It was hypothesized that rats eating the high fat/high carbohydrate chow would be more sensitive to the effects of morphine as compared to rats eating low fat or ketogenic chow. Latencies for rats to remove their tails from warm water baths were converted to a percentage of the maximum possible effect and averaged within each dietary group. Cumulative fecal output (in boli count and in g) was collected over 6 hours. Data were analyzed using mixed model ANOVAs. Morphine significantly increased latency for rats to remove their tails from 50°C water bath and reduced fecal output for rats in all dietary conditions. There were no dietary group differences in morphine-induced antinociception; however, rats eating the eating high fat/high carbohydrate chow or ketogenic chow produced significantly less feces than rats eating the low fat chow, following saline and morphine injections. Although these experiments are ongoing, these results suggest for patients eating higher fat diets, GI motility might be generally disrupted, and opioid-induced constipation might also be more severe.

Poster 12

Precipitated withdrawal after repeated treatment with morphine:ketamine mixtures in male rats

Besonen, Carissa J.; Graham, Kate E.; Meyer, Matthew P.; Burrichter, Rachel M.; Heueisen, Rachel M.; Nikodem, Catherine C..; Minervini, Vanessa

Department of Psychological Science, Creighton University, Omaha, NE USA

Mu opioids are the “gold standard” for treating moderate to severe pain despite their well-documented adverse effects (dependence, respiratory depression). There is a need for safer, more effective treatments for pain. One strategy for improving the margin of safety of opioids is combining them with other analgesic drugs to decrease the opioid dose needed for pain relief, thereby avoiding adverse effects that occur with larger doses. The NMDA receptor antagonist ketamine has been used safely and effectively to treat pain, but only under a narrow range of conditions. Our lab has previously reported additive or super additive antinociceptive effects of morphine:ketamine mixtures. It is important to determine whether morphine:ketamine mixtures selectively enhance antinociception; therefore, the purpose of the current experiment was to compare withdrawal symptoms in male Sprague Dawley rats receiving twice daily injections of either morphine alone (3.2-56 mg/kg; n=8) or that same dose of morphine + 10 mg/kg ketamine (n=8) for 18 days. On day 18 (control), withdrawal signs were recorded 30 min after a saline injection, and on day 19 (test), withdrawal signs were recorded 30 min after an injection of the opioid receptor antagonist naltrexone (10 mg/kg). Naltrexone precipitated withdrawal in all rats. Ketamine treatment did not enhance morphine withdrawal severity. In fact, rats treated with morphine + ketamine lost less weight and recovered faster as compared to rats treated with morphine alone. The interaction between morphine and ketamine for female rats as well as for other adverse effects (e.g., respiratory depression) is unknown. Morphine:ketamine mixtures might have greater therapeutic potential than mu opioids alone for treating pain, but only if adverse effects of each drug are not enhanced. Supported by: Creighton University Department of Psychological Science

Poster 13

The CYP450 enzyme kinetics of 5F-APINACA, a synthetic cannabinoid, when co metabolized with alprazolam, a benzodiazepine

Bierbaum, Carter[1]; Zia, Muhammad[1], Da-young Eom [2], and Miller, P. Grover PhD[2]

[1]University of Central Arkansas, AR, USA; [2]University of Arkansas for Medical Sciences, AR, USA

Synthetic cannabinoid receptor agonists (SCRAs) are abused across the world, with the United States alone having synthetic cannabinoids account for over a third of its new illicit drugs being produced in 2019. Substance use disorders (SUDs) are frequently comorbid with other psychiatric disorders, as over 50% of those diagnosed with SUDs also meeting criteria for mood, personality, and psychotic disorders. It is then likely that someone taking SCRA is also taking prescription psychiatric medication. Many common psychiatric medications share metabolic pathways with SCRAs, suggesting that co-administration may potentiate adverse effects of SCRAs by increasing blood levels of the parent drug and altering metabolite profiles. In these studies, we hypothesized that alprazolam would inhibit in vitro steady-state metabolism of 5F-APINACA using human liver microsomes. Metabolism of 5F-APINACA led to oxidative defluorination of the pentyl group and hydroxylation of the adamantyl group of the drug. Alprazolam inhibited both metabolic pathways acting as a mixed inhibitor affecting both Vmax and Km. Nevertheless, the alprazolam inhibitory effect was more potent toward hydroxylation of the adamantyl group over oxidative defluorination. This observation was reasonable given evidence for CYP3A4 being almost exclusively responsible for that metabolic pathway for 5F-APINACA and alprazolam metabolism. Collectively, these in vitro findings demonstrated alprazolam would likely suppress 5F-APINACA metabolic clearance when taken in combination and thus potentially prolong the effects of the SCRA. This combination is dangerous and uncharacterized despite its common occurrence; it is also highly likely that this combination's mechanisms closely mirror other drugs of abuse, so its in-vivo effects and in-vitro kinetics serve as a perfect foundation for future studies.

Poster 14

The effects of THC on operant responding for sucrose

Binckley, Jessica L[1]; Fort, Troy D[1], and Cain, Mary E[1]

[1]Kansas State University, Manhattan, KS USA

Cannabis is now one of the most commonly abused drugs of abuse globally. As more and more states move to legalize cannabis, it's important to understand if the active psychoactive compound in cannabis, THC, can increase the hedonic value of other reinforcers. Prior literature has demonstrated that THC exposure increases both the hedonic palatability ("liking") of sucrose, as well as an increased preference for higher sucrose concentrations (Jarrett, et al., 2005). This project evaluated if synthetic THC, Dronabinol, increases the rewarding effects of other substances. Male Long-Evans rats were given chocolate wafers infused with Dronabinol prior to operant sucrose self-administration to see how and if THC may alter sucrose-taking. Animals were randomly assigned to one of three doses of Dronabinol, 0.0, 1.0, or 2.5 mg/kg. The Dronabinol was administered one hour before each 1-hour self-administration (20% sucrose) session. Rats underwent six FR-1 sessions, seven FR-5 sessions, and a progressive ratio (PR) test. We predicted that Dronabinol would dose-dependently increase the motivation to self-administer sucrose under FR-1 and FR-5 schedules. Additionally, we predicted that Dronabinol would dose-dependently increase the breakpoint for sucrose when tested under a PR schedule. Our current results do not suggest that Dronabinol significantly altered responding for sucrose under FR-1 or FR-5 schedules. However, our preliminary results suggest a potential trend for Dronabinol treatment to decrease the breakpoint for sucrose on the PR schedule. Though preliminary, these results could suggest that the THC dose range tested here may be too low to alter the motivation to self-administer sucrose under FR-1 and FR-5 schedules but could alter the effort to obtain reinforcement when tested using PR schedules.

Poster 15

Discovery of novel serotonin 5-HT2A receptor positive allosteric modulators

Bolinger, Andrew A.; Zamora, Joshua; Merritt, Christina R.; Anastasio, Noelle C.; Cunningham, Kathryn A.; & Zhou, Jia

Department of Pharmacology and Toxicology and Center for Addiction Research, The University of Texas Medical Branch, Galveston, TX, 77555

Over 104,000 drug overdose deaths occur in the US annually, being a leading cause of death among individuals under 45 years old. Despite making up less than 2% of drug users, cocaine-related deaths constituted 1 in 5 drug overdose fatalities in 2017. While behavioral interventions show promise in addressing cocaine use disorder (CUD), effective therapeutics would have a significant impact. The serotonin 5-HT_{2A} receptor (5-HT_{2A}R) localize to the brain with signaling facets that contribute to cognition, mood, learning and memory. Targeting the 5-HT_{2A}R as a strategy to suppress CUD relapse is promising but achieving selective targeting of this receptors is challenged by the similarity of 5-HT orthosteric binding pockets. We present an innovative approach to allosterically modulate 5-HT_{2A}R tone, offering valuable pharmacological tools for CUD research. Synthesizing and screening novel small molecules, we identified potent positive allosteric modulators (PAMs) of 5-HT_{2A}R. Further analysis and comparison against CNS receptors, channels, and transporters led to the identification of AB0124 a potential candidate with high specificity. This compound has demonstrated functional increases in 5-HT-induced Ca^{2+} release at the micromolar level for the 5-HT_{2A}R over other serotonin receptors. With promising *in vitro* pharmacological and physicochemical profiles, our novel 5-HT_{2A}R PAMs hold potential as neurotherapeutics for CUD.

Poster 16

Prenatal alcohol and cannabinoid exposures impose distinct, sex-specific alcohol-seeking behaviors in adult mice

A.V. Bowring, S.K. Rouzer, R.C. Miranda

Texas A&M School of Medicine, Neuroscience & Experimental Therapeutics

Background: Individuals with prenatal exposure to alcohol and/or marijuana are at greater risk of engaging in drug-seeking behaviors. Little is known about the effects of simultaneous alcohol and cannabinoid (SAC) exposure. We investigated whether SAC augments alcohol-seeking behavior in offspring compared to single-drug exposure alone. Method: Pregnant C57Bl/6J mice were assigned to one of four groups: drug-free control, alcohol-exposed (AE), cannabinoid-exposed (CE), or SAC-exposed. From Gestational Days 12-15, dams received cannabinoid agonist CP-55940 (750µg/kg) or saline via intraperitoneal injection. Dams were then placed in vapor chambers for 30min of inhalation of 95% ethanol or room air. Adult offspring (Postnatal Days 120+) were assessed for preference for 20% alcohol in a 3hr two-bottle-choice homecage assessment, and then alcohol-seeking activity within operant chambers. Results: Compared to control males, CE and SAC-exposed males drank significantly more alcohol over three weeks in a social, homecage setting, while only SAC females drank more alcohol than control females. SAC males were the only group to show preference for alcohol over water in a social setting. Operant administration experiments indicate that, compared to all other offspring, SAC-exposed male offspring lever-pressed for alcohol more under a progressive ratio paradigm, indicating greater willingness to work for alcohol, and demonstrated greater preference for higher alcohol concentrations. SAC males also persisted in lever-pressing for ethanol during a three-day extinction period, while all other groups reduced their alcohol-seeking behaviors. AE females lever-pressed for alcohol more than controls under progressive ratio and extinction paradigms. Conclusion: Prenatal SAC exposure imposes distinct, sexually dimorphic changes in alcohol-seeking behaviors compared to single drug exposure. Subsequent histological assessments will determine if behavior corresponds with changes in corticostriatal circuit histology.

Poster 17

Evaluation of dietary probiotic supplements on methamphetamine-induced impulsive action in rats maintained on a differential reinforcement of low rate schedule

Brabant, Payton, D., Steck, Kaitlyn A., and Baker, Lisa E.

Department of Psychology, Western Michigan University, Kalamazoo, MI USA

Methamphetamine Use Disorder (MUD) is a chronic, pervasive neuropsychiatric condition with overlapping symptomology and comorbidity with affective disorders. MUD and affective disorders are characterized by cognitive dysfunction, including impaired decision-making and impulsivity. Research has implicated gut microbiome alterations as a contributing factor to the pathophysiology of affective disorders. Although preclinical studies have shown psychostimulants alter gut microbiome diversity, no published studies have evaluated behavioral effects of dietary interventions on psychostimulant-induced gut microbiome changes. The present study utilized differential reinforcement of low rate responding (DRL 18 s) as a behavioral index of drug-induced impulsive action to assess if a dietary probiotic alters behavioral effects of (+)-methamphetamine. Thirty-two adult male Sprague-Dawley rats were trained for several weeks, and then assigned to two dietary treatment groups. The probiotic group received Bio-Kult Advance® in their water and the control group received standard water. Each diet group was then subdivided into two drug treatment groups receiving either injections of 1 mg/kg (+)-methamphetamine or saline for eight consecutive days. DRL 18 s sessions occurred on day 1 and day 8, and subsequently 24 h, 48 h, 96h, 8 d and 11 d after the last injection. Fecal samples were collected and microbial DNA was isolated to assess differences in gut microbiome composition. Statistically significant increases in response rate and corresponding decreases in reinforcement rate were observed in drug-treated animals compared to saline-treated animals. The probiotic group displayed a higher drug-induced increase in response rate, but reinforcement rates were comparable between diet groups, and the main effect of diet was not significant. While analysis of microbial DNA is ongoing, behavioral results indicate minimal impact of probiotics on drug-induced impulsive action.

Poster 18

Enantiomers of a novel benzofuran have distinct discriminative stimulus effects

Burroughs, Rachel L; Baggott, Matthew J[2] and Baker, Lisa E[1]

[1]Department of Psychology, Western Michigan University, Kalamazoo, MI USA; [2]Tactogen, Palo Alto, CA USA.

Methylenedioxymethamphetamine (MDMA) shows significant clinical benefits in medication-assisted psychotherapy for PTSD and will soon be FDA-approved for this use. Moderate adverse effects and diversion risk may limit its clinical use. Preclinical investigations of novel molecules with structural similarities to MDMA are in progress to develop alternative pharmacotherapies with similar clinical benefits and reduced side effects. This study employed rodent drug discrimination methods to characterize the interoceptive stimulus effects of the S- and R-enantiomers of 1-(1-benzofuran-5-yl)-2-(methylamino)propan-1-one (BK-5-MAPB), a novel benzofuran with structural and pharmacological similarities to MDMA. Substitution tests were conducted with (S)-BK-5-MAPB and (R)-BK-5-MAPB in three drug discrimination studies. In rats trained to discriminate the psychostimulant, d-amphetamine (0.5 mg/kg) from saline, both (S)- and (R)-BK-5-MAPB produced dose-dependent increases in AMPH-lever responding and full substitution at the highest dose. In rats trained to discriminate the serotonergic hallucinogen, DOM (0.5 mg/kg) from saline, (S)-BK-5-MAPB produced high partial substitution and (R)-BK-5-MAPB did not substitute. In rats trained to discriminate d-amphetamine (1.0 mg/kg) and MDMA (1.5 mg/kg) from saline using a three-lever drug discrimination procedure (S)-BK-5-MAPB produced nearly complete substitution for MDMA, whereas (R)-BK-5-MAPB produced partial substitution for MDMA or AMPH at different doses. Collectively, these findings indicate (S)-BK-5-MAPB produces interoceptive stimulus effects similar to both MDMA and AMPH, whereas (R)-BK-5-MAPB has more stimulant-like effects. These results are consistent with their differential activities at serotonin and dopamine transporters. Additional preclinical research on novel benzofuran molecules is warranted to determine their abuse liability and toxicities in comparison to MDMA.

Poster 19

Nicotinic α3β4 receptor modulates addiction-like behaviors in alcohol dependent rats

Campo, Paola[1]; Doyle, Michelle R[1]; Dirik, Selen[1]; Qiao, Ran[1]; Martinez, Angelica R[1]; Zaveri, Nurulain T[2]; Kallupi, Marsida[1]; de Guglielmo, Giordano[1]

[1]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA. [2]Astraea Therapeutics, Mountain View, CA, USA

Alcohol and nicotine co-use is a prevalent issue, particularly among individuals with alcohol dependence; therefore, developing further treatments that effectively reduce both alcohol and nicotine intake is of great importance. Previous research has demonstrated that targeting nicotinic receptors with antagonists or partial agonists can successfully decrease nicotine use, and there is emerging evidence suggesting this approach may also be beneficial for alcohol use. ATRX-52, an α3β4 nicotinic acetylcholine receptor (nAChR) functional antagonist, has shown promising results on attenuating drug + cue-primed reinstatement of nicotine-seeking behavior. In this study, we sought to investigate the effectiveness of ATRX-52 in reducing alcohol consumption under fixed ratio and progressive ratio responding as well as a cue-seeking test using a heterogeneous stock (HS) rat model. HS rats were characterized for their alcohol addiction-like behavior by pairing chronic intermittent access to alcohol vapor with measurements of self-administration and motivation for alcohol during withdrawal. Rats with high and low addiction indices (n=16/group) were treated with ATRX-52 (0.2, 0.4, 0.8 mg/kg) or vehicle injections, administered 30-min prior to self-administration sessions. The specificity of the effects of ATRX-52 were also evaluated in a separate group of rats self-administering saccharin. Our findings revealed that ATRX-52 dose-dependently decreased ethanol intake in all rats in both the fixed and progressive ratio schedules of reinforcement. Notably, the treatment was more effective in rats with high addiction indices compared to those with low addiction indices. ATRX-52 (0.4 mg/kg) also reduced cue seeking in all rats. These findings suggest that ATRX-52 may have potential as a treatment strategy for alcohol use disorders, particularly in individuals with higher vulnerability to addiction.

Poster 20

Behavior of precipitated nicotine withdrawal mice treated with α-terpineol

Chopra Maya[1], Frimpong-Manson, Kofi[1] and Wilkerson, Jenny[1]

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

Tobacco use is the leading cause of preventable death in the world. Tobacco contains nicotine, a highly addictive alkaloid. Smoking cessation leads to affective and somatic withdrawal symptoms. Cannabinoid receptor agonism may be an effective alternative treatment for smoking cessation. Previous studies by our lab found that α-terpineol may function as a cannabinoid mixed agonist with preference for cannabinoid receptor 2, and that 56 mg/kg is an analgesic dose. We hypothesized that, in a mouse model of precipitated nicotine withdrawal, α-terpineol will attenuate associated withdrawal behaviors. C57BL/6J mice (n=20 female, n=19 male) received subcutaneous nicotine (2 mg/kg, base) or saline vehicle injections, four times daily over 13 days. On day 14, 30 min after the first nicotine or saline injection mice received either α-terpineol (56 mg/kg) or vehicle intraperitoneal injections. Then, 30 min after α-terpineol injections, all mice received mecamylamine (3 mg/kg, intraperitoneal). Mice were immediately placed in locomotion chambers, and then underwent the light-dark box test. Our data demonstrates a significant effect of nicotine on time spent immobile (two-way ANOVA $p=0.012$). All mice had higher duration (s) in the dark zone of the light/dark box (two-way ANOVA $p<0.001$). Nicotine had a significant overall effect on grooming frequency (two-way ANOVA $p=0.029$). The Nicotine + Vehicle group displayed increased grooming duration compared to the Saline + Vehicle control group ($p=0.044$). Nicotine treated mice's increased immobility may indicate a depressive-like state due to nicotine withdrawal. The Nicotine + α-terpineol group displayed a strong sex-related trend for reduced total somatic withdrawal score compared to the Nicotine + Vehicle control group. The terpene α-terpineol may attenuate precipitated nicotine withdrawal on a sex-related basis. Our findings in C57BL/6J mice suggests α-terpineol, and other cannabinoid receptor agonists, may be useful therapeutics for precipitated nicotine withdrawal somatic and affective behaviors.

Poster 21

In vivo characterization of MBDB and its enantiomers in C57BL/6 and autism-like BTBR T+Itpr3tf/J mice

Clark, Mia R[1]; Shaw, Hannah E[2] & Fantegrossi, William E[2]

[1]College of Natural Sciences and Mathematics, University of Central Arkansas, Conway, AR USA; [2]Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR USA

3,4-methylenedioxymethamphetamine (MDMA) and related entactogens are being explored as potential treatments for a range of psychiatric conditions. MDMA-like entactogens elicit pro-social effects, making them candidates for treatment of social anxiety, but their effects on core temperature, motor activity, and psychedelic-like effects may be treatment-limiting. These studies used implantable radiotelemetry probes to monitor locomotor activity and core temperature within the homecage environment elicited by injections of racemic mixtures and pure R- and S- enantiomers of MDMA or its analog 3,4-methylenedioxy-α-ethylamphetamine (MBDB) in male C57BL/6 (C57) and BTBR T+Itpr3tf/J (BTBR) mice, and assessed the capacity of racemic MBDB to elicit head twitches in C57 mice. In telemetry studies, racemic MDMA and S-MDMA elicited dose- and time-dependent locomotor stimulant and hyperthermic effects in both strains, but R-MDMA did not. In contrast, racemic MBDB and both of its enantiomers stimulated activity in both strains, although the magnitude of these effects was less than that of racemic or S-MDMA. However, all forms of MBDB elicited dose- and time-dependent hypothermic effects in C57 mice, but core temperature was not affected by any dose of any form of MBDB in BTBR mice. In head twitch studies, the prototypical psychedelic R-DOI produced a robust dose-dependent head twitch response in C57 mice, but racemic MBDB did not elicit significant head twitches at any dose. These studies illustrate an unusual lack of stereospecificity for the effects of MBDB on locomotor activity in both strains, and on core temperature in C57 mice. Further, these studies suggest that it may be possible to separate pro-social effects of MDMA-like drugs from their stimulant-like, hyperthermic, and psychedelic-like effects, at least in the autism-like BTBR mouse.

Poster 22

The influences of chronic unpredictable stress in rats on voluntary salt consumption and work effort for sweet and salty reinforcers

Crites, Anna E[1]; Sonick, Grace A[1]; Hite, Allianna K[1] and Gilman, T Lee[1]

[1]Department of Psychological Sciences, Kent State University, Kent, OH USA

Stress can increase intake of palatable foods and reinforcing drugs. How stress specifically affects the incentive salience (i.e., 'wanting') of food reinforcers is less understood. Here, we measured rats' effort to work ('wanting') for palatable food reinforcers (31% sucrose and 4% NaCl (salt), w/w) and how stress affected this. We hypothesized stress would increase 'wanting' of unhealthy diets and palatable reinforcers in a diet-dependent manner. Salt was employed as a flavor enhancer and because its intake is partially regulated by opioid receptors in the brain's incentive salience network. Adult (>9 weeks old) male (N=6) and female (N=12) Wistar rats were given either low (0.4%) or high salt diets (4.0%), or provided access to both (i.e., mixed). This enabled us to detect diet preference before and after stressor exposure. Rats were trained in appetitive operant conditioning to lever-press for reinforcing food pellets. After four weeks, a chronic unpredictable stress (CUS) paradigm was employed. Rats were exposed to two mild stressors weekly, for a total of eight distinct stressors over four weeks. Data collection is ongoing, but early results (one-way ANOVAs across diet condition, sex collapsed, with Dunnett's post hocs) indicate that stress increases rats' voluntary consumption of salt, and that rats consuming low salt work harder for reinforcers than those with access to high salt. Seeking of salt after stress suggests this compound could be reinforcing even when not physiologically needed. Intake of salt and drugs are regulated by the same brain network, and there is evidence that people with opioid use disorder that are currently abstinent have increased salt intake. Combined with our findings, this indicates that future studies should examine how high salt diet affects seeking of, and abstinence from, reinforcing drugs. Also, the contribution of stress upon relapse could be explored in relation to how eating salty foods might affect stress responses, thereby indirectly influencing relapse risk.

Poster 23

Modulation of the mGlu5 receptor attenuates the enhanced reward and neural plasticity response to nicotine in a rodent model of psychosis and drug abuse vulnerability: Relevance to comorbid nicotine addiction

Cuozzo, Anthony M., Peeters, Loren D., Wills, Liza J., Ivanich, Kira L., Turney, Seth E., Bullock, Luke P., Massey, Sam R., Gass, Justin T., and Brown, Russell W.

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

Nicotine has been indicated as a prevalent drug for substance abuse comorbidities in mental illness. Our laboratory has established a model of psychosis and drug abuse vulnerability in which Sprague-Dawley (SD) rats are neonatally treated with quinpirole (NQ), a dopamine (DA) D2-like agonist from postnatal days 1-21, resulting in lifelong supersensitization of the DAD2 receptor. Increases in D2 receptor sensitivity is a hallmark of psychosis. Interestingly, the DAD2 receptor forms a mutually inhibitory heteromer in the dorsal striatum with the adenosine A(2A) and metabotropic glutamate receptor type 5 (mGlu5), such that stimulation of the A(2A) or mGlu5 receptor results in decreased D2 signaling. The present study involved 141 SD rats and was designed to analyze the role of the mGlu5 receptor in the associative aspects of nicotine in adolescence using conditioned place preference (CPP). Results revealed that NQ animals conditioned to nicotine demonstrated enhanced CPP. Groups receiving 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl) benzamide (CDPPB), a positive allosteric modulator to mGlu5 showed reduced rewarding effects of nicotine in CPP. Brain tissue was analyzed via ELISA for brain-derived neurotrophic factor (BDNF) and cadherin-13 in the ventral tegmental area, as well mTOR-dependent phosphorylation of p70S6 kinase in the nucleus accumbens. Results were attained via four-way ANOVA and Bonferroni post-hoc and revealed significant elevations of BDNF and p70S6 kinase in NQ-treated rats given nicotine, and a sex difference in cadherin-13. Changes in BDNF, p70S6 kinase as well as cadherin-13 were all blocked by CDPPB. These results elucidate mGlu5 as a target for reducing the rewarding effects of nicotine in a model of drug abuse vulnerability in psychosis.

Poster 24

Resistance of cocaine reinforcement to fixed vs. variable punishment in male and female rhesus monkeys

Doyle, William S[1]; Freeman, Kevin B[1,2]; Woods, Josh A[2]; and Huskinson, Sally L[1,2]

[1]Program in Neuroscience, University of Mississippi Medical Center, Jackson, MS 39216; [2]Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS 39216

A defining feature of substance-use disorder is persistent drug use despite negative consequences. It is possible that uncertainty of negative outcomes during drug use is one determinant of the inability of such consequences to deter drug use. In prior research, probabilistic punishment was less effective than certain punishment, however, punisher probability and punisher rate were confounded. The goal of this study was to determine whether behavior maintained by cocaine would be more resistant to uncertain punishment when rate of punishment was not a confounding factor.

A group of male (n=3) and female (n=2) rhesus monkeys self-administered cocaine (0.01 or 0.03 mg/kg/infusion) under a single-operant, variable-interval (VI) 300 s schedule. During punishment conditions, cocaine remained available under a VI 300 s schedule, and a drug punisher, histamine (0.001-0.056 mg/kg/infusion), was delivered under concurrent and independent fixed-ratio (FR) or variable-ratio (VR) 200 schedules.

In general, histamine was more effective at suppressing response rates under a VR 200 schedule compared with a FR 200 schedule. We currently are evaluating denser (FR and VR 100) and leaner (FR and VR 400) schedules of punishment to determine the generality of our findings with FR and VR 200 schedules.

Our results suggest that uncertainty in the regularity of negative outcomes may be more effective at decreasing drug-taking behavior. Prior demonstrations that probabilistic punishment was less effective at suppressing behavior than certain punishment may have resulted from an overall reduction in rate of punisher delivery rather than uncertainty.

Poster 25

Evaluation of the behavioral effects of vaporized delta-8-tetrahydrocannabinol (Δ^8 THC) in male and female rats

Durbin, Darby J[1]; Stairs, Dustin J[2]; K; Fitzgerald, Haydn A[3]; Cronin, Emily A[4]; Witmer, Harrison[5]; Pulliam, Maddy[6]; Keith, Jordan L[7]; Wellendorf, Claire E[8]; King, Julia[9]; Bhinder, Arvish[10]; Beringer, Lauren[11]; Nguyen, Kianna[12]; Hanano, Cassidy A[13]

[1]Department of Psychology, Creighton University, Omaha, NE USA

The popularity and diversity of cannabis derivatives have been increasing since the 2018 U.S. Farm Bill, which federally legalized the production of hemp products containing less than 0.3% of delta-9 tetrahydrocannabinol (THC). While some research has evaluated the abuse potential of delta-9 THC, there is far less data available for the more novel minor cannabinoids. These include compounds such as the less potent and frequently marketed secondary compound, delta-8 THC. Despite widespread availability, the behavioral effects of delta-8 THC and its impact on adolescent subjects remain relatively unexplored. The current study aimed to characterize the behavioral effects of delta-8 THC using a whole-body vapor exposure route of administration in male and female adolescent (PND 21) Sprague Dawley rats. The potential rewarding and/or adverse effects of delta-8 THC were measured using a biased Conditioned Place Preference (CPP) paradigm. Animals were given ten-second vapor exposures at two-minute intervals for ten minutes to either Vehicle, 10 mg, or 20 mg/0.300ml. After vapor exposure, conditioning trials were completed. Eight total conditioning trials were then followed by a drug-free test day to determine which subjects displayed a CPP response to the drug paired side. After the first test day, the rats completed another eight conditioning trials followed by a second drug-free test day. Results indicate that compared to males, females showed a significant CPP response following conditioning with the 10 mg dose, particularly by the second test day. Ongoing assessment of the cannabinoid effects and abuse potential is crucial to better understand emerging hemp products.

Poster 26

Lateral entorhinal cortex neuronal projections to nucleus accumbens regulate motivated behavior via contextual associative memory

Kuhn HM[1], Colon Serrano L[1], Stys G[1], Smith B[1], Speckmaier J[1], Murray BR[1], Bermudez D[1], Dawson B[1], Robison AJ[1], Eagle AL[2]

[1]Department of Physiology, Michigan State University, East Lansing, MI, USA; 2Department of Neuroscience, UT Dallas, Richardson, TX, USA

Neuron circuits onto nucleus accumbens (NAc) medium spiny neurons are critical for regulating motivated behaviors, including those underlying drug reward and aversion. The lateral entorhinal cortex (LEC) is a brain region important for associative memory and sends axonal projections to the NAc (LECNAc). This suggests that LECNAc neurons may be important for associative memory underlying reward and fear. However, the role of LECNAc neurons is currently unknown. Based on evidence that LEC is activated by cocaine-associated cues in cocaine-dependent subjects and cocaine self-administering rats, we sought to determine whether LECNAc neurons mediate contextual memories associated with positive (cocaine) and negative (footshock) stimuli. We conducted chemogenetic experiments in mice during contextual memory encoding and recall across 2 tasks: cocaine conditioned place preference (CPP) and contextual fear learning. We found that LECNAc neurons are necessary for the encoding, but not recall of a place preference for cocaine. We also showed that LECNAc neurons are necessary contextual fear memory encoding, but not recall. Activation and inhibition of LECNAc neurons during other behavioral tasks, e.g. memory, anxiety, and locomotor activity had no effect. We also examined the pattern of c-fos activation in LECNAc neurons during memory encoding and recall in both cocaine CPP and contextual fear learning. Both tasks activated LECNAc neurons, but, interestingly simple contextual exposure (i.e. without drug or footshock) also activated these neurons. The findings of this study suggest that the LECNAc circuit is necessary for contextual associative memory encoding that underlies cocaine and fear conditioning; thereby identifying a novel memory pathway in motivated behavior.

Poster 27

Design of 1,2,3-triazole-linked analogues as dopamine D4 receptor selective ligands to treat substance use disorder

Faibille, Afua[1]; Jakobs, Franziska[1]; Mohammad, Alkhatib R[2]; Hanson John N[3]; Nilson, Ashley N[3]; Sibley, David R[3], Paule, James[4]; Rais, Rana[4]; Slusher, Barbara S[4]; 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]NINDS-IRP, NIH; [4]Johns Hopkins Univ. Sch. of Med.

The dopamine D4 receptor (D4R), a G protein-coupled receptor, is predominantly expressed in the prefrontal cortex in which it plays an important role in cognition, attention, and decision making. Studies have indicated D4R-selective ligands can serve as a promising medication development to treat neuropsychiatric conditions such as substance use disorders (SUD) and ADHD. Our previous studies have identified a series of D4R-selective ligands with varying efficacies to investigate D4R function in preclinical models but were metabolically unstable. In order to improve metabolic stability, we have designed, synthesized, and pharmacologically evaluated novel D4R ligands. The new analogues were designed and synthesized by using a click chemistry reaction approach to bioisosterically replace the amide with 1,2,3-triazoles. In vitro binding affinities were determined via [3H]N-methylspiperone radioligand binding using membranes prepared from HEK293 cells expressing dopamine D2-like receptors (D2R, D3R, D4R). The ligands were also studied in β-arrestin recruitment assays for their effects on D2R-like function. We further performed in vitro and in vivo pharmacokinetic analyses with selected compounds. The pharmacological analyses indicate that the 1,2,3-triazole compounds maintain binding and functional profiles like their matching amide analogues with improved metabolic stability. The 1,2,3-triazole moiety is more stable to drug metabolism with advantageous pharmacokinetic profiles. Further in vivo analyses of these compounds may provide insights into targeted drug discovery leading to a better understanding of the role of D4Rs in neuropsychiatric disorders, such as SUD.

Poster 28

Ventilatory depressant effects of *mu* opioid receptor agonist mixtures in rats

Flynn, Shawn M[1,3] and France, Charles P[1,2,3]

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

The opioid epidemic remains a major public health challenge, with over 83,000 opioid overdose deaths reported in 2022. Over 75,000 of these deaths involved synthetic opioids, primarily fentanyl and fentanyl analogs such as carfentanil, which is ~100-fold more potent than fentanyl. Highly potent synthetic opioids such as carfentanil are primarily encountered as adulterants of other drugs, such as heroin. This study used whole-body plethysmography to determine the nature of the interactions between the ventilatory effects of the *mu* opioid receptor agonists carfentanil, fentanyl, and heroin in male and female rats. Experimental sessions began with a 30-minute acclimation period after which animals were given an infusion of carfentanil, fentanyl, heroin, or saline and ventilation was recorded for 60 minutes. First, dose-effect curves were determined for the ventilatory depressant effects of each individual drug. Then, dose-effect curves were determined for binary mixtures of *mu* opioid receptor agonists at three fixed-dose ratios (3:1, 1:1, 1:3) relative to the potency of each drug alone to suppress ventilation to 75% of baseline. Carfentanil, fentanyl, and heroin dose-dependently reduced minute volume, and increased mean apnea duration in male and female rats. Fentanyl was approximately 50-fold more potent than heroin in female rats, and 10-fold more potent than heroin in male rats. Carfentanil was ~300-fold more potent than heroin in both sexes. Dose-addition analysis of the effects of binary mixtures of the three agonists determined that interactions between the drugs did not differ from predicted additivity. These findings suggest that interactions between opioid drugs likely do not contribute to the apparent increased lethality of these mixtures in humans.

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Poster 29

Exploring varied patterns of substance use: A novel rat model of cocaine and quinine self-administration

Fogel, Peter A[1,2], Madrid, Pamela[3], Powers, Rosalie[1], Moschak, Travis M[1]

[1]Department of Biological Sciences, [2]Graduate Program in Biological Sciences, [3]Bridges to Baccalaureate Research Training Program; University of Texas at El Paso

Substances of abuse are often associated with aversive stimuli, such as the bitterness of alcohol, the taste of cigarettes, or the pain associated with injecting drugs into the bloodstream. While these aversive experiences deter many individuals from further substance use, some persist, leading to an increased risk of substance use disorder and other compromising health conditions. Cocaine is frequently utilized in studying substance use disorder where rats are taught to self-administer the drug in varying conditions. Typically, rats are initially trained to self-administer cocaine, followed by the introduction of an aversive stimulus at a later stage to observe changes in behavior or neuronal activity. However, this approach does not align with the way humans are introduced to and use drugs of abuse. Here, rats are taught to self-administer a pairing of cocaine and quinine, a bitter, aversive substance, from day 1 of self-administration. This acts to mirror the varied usage patterns observed in human drug use. Twenty-four adult Sprague Dawley rats (12 female, 12 male) underwent jugular vein catheterization, intraoral cannula installation, and recovery. Subsequently, each animal underwent a combination of 2-hr self-administration sessions and taste reactivity tests. Preliminary results reveal a significant variation in self-administration behaviors among the 24 rats ($F(3.793,75.868)=4.219, p=0.005$). Like humans, some rats consistently administered and escalated their drug usage, while others hardly administered, despite facing the same cocaine-quinine pairing. During a taste reactivity test, where quinine alone was forcibly given to the rats, there was no significant difference in aversive reactions (gapes) across any of the rats, irrespective of their prior cocaine usage. Future directions include calcium imaging of brain regions involved in drug usage to further investigate the reason for the varied drug usage.

Poster 30

Cocaine challenge in astrocytes promotes the aggregation and activation of MAVS in antiviral immunity

Fongsaran, Chanida[1,2,3]; Jirakanwisal, Krit[1,2,3]; Cisneros, Irma E[1,2,3,4]

[1]Department of Physics, Princeton University, Princeton, NJ USA; [2]Department of Physics, University of Copenhagen, Copenhagen, Denmark; [3]Department of Paleontology, Harvard University, Boston, MA USA. [1]Department of Pathology, University of Texas Medical Branch, Galveston, TX [2]Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, TX [3]Neuroinfectious Diseases, University of Texas Medical Branch, Galveston, TX [4]Center for Addiction Sciences and Therapeutics, University of Texas Medical Branch, Galveston, Texas, USA

The inflammasome signaling pathway plays a crucial role in preserving immunological balance. Within this intricate system, the mitochondrial antiviral signaling protein (MAVS) serves as a pivotal innate immune adaptor located on the outer mitochondrial membrane, acting as a switch in the transduction of immune signals in response to viral infections. Previous studies have shown that cocaine activates antiviral signaling pathways and type I interferon in response to HIV-1. In this study, we aim to understand the roles of MAVS in antiviral immunity and explore the regulatory mechanisms governing MAVS activation through cocaine-mediated astrocyte antiviral immune responses. Additionally, we demonstrate that the innate immune activation mediated by MAVS is dependent on TNF receptor-associated factors (TRAFs) and associated with the ubiquitination of E3 ligase, promoting downstream signaling and enhancing the transcription of IFNα/β. This study will provide novel insights into the role of cocaine in the potential effects of mitochondrial signaling pathways in astrocytes involved in this process.

Poster 31

The effects of fatty-acid amide hydrolase inhibition on methamphetamine relapse

Fort, Troy D[1], Azuma, Miki[1], Rigler, Jocelyn[1], & Cain, Mary E[1]

[1]Department of Psychological Sciences, Kansas State University, Manhattan, KS USA

Overdose deaths due to methamphetamine (meth) have risen significantly in last decade. Despite this increase, treatment options of mitigating cue-induced meth craving are extremely limited. One burgeoning area of therapeutic interest is the endocannabinoid (eCB) system given its involvement in reward-based processing. Specifically, the eCB, anandamide (AEA) has previously been shown to lower cue-induced cocaine craving when injected intracranially. The current project took a different therapeutic approach by inhibiting the breakdown of AEA via the fatty-acid amide hydrolase (FAAH) inhibiting drug, URB597, to examine URB597's efficacy in attenuating relapse to meth following extended-access self-administration. 48 male Sprague-Dawley rats were given the opportunity to self-administer either meth (0.1 mg/kg/infusion) or a saline control for 6 hours a day for 12 sessions. Following completion of self-administration, all animals entered a period of forced abstinence where they not exposed to meth or any meth-related cues. Rats were given daily injections of either URB597 (0.3 mg/kg or 1.0 mg/kg; ip) or a vehicle during the abstinence period. Cue-induced relapse was tested on Withdrawal Days 2 and 28 via a cue-seeking test. Following the Withdrawal Day 28 cue-test, animals were humanely euthanized, and brains were prepared for western blot analysis.
There was a significant escalation in meth intake over the course of the 12 self-administration sessions. URB597 (both the 0.3 and 1.0 mg/kg doses) was not effective in lowering relapse at either Withdrawal Day 2 or 28. These results may suggest that inhibition of FAAH via URB597 may not produce increases in AEA hypothesized to lower relapse. Although URB597 was shown to be ineffective in attenuating relapse, our ongoing western blot and AEA measurements will be critical in evaluating neurobiological changes in response to meth abstinence and treatment with URB597. These assessments will help to explore the efficacy of future therapeutics aimed at modulating AEA activity for the prevention of meth relapse.

Poster 32

A monoclonal antibody prevents fentanyl-induced ventilatory depression and selectively attenuates fentanyl self-administration in rhesus monkeys

Lindsey K. Galbo-Thomma[1], Takato Hiranita[1], Julia R. Taylor[1], David R. Maguire[1], Carly Baehr[3], Marco Pravetoni[4], Charles P. France[1,2]

[1]Departments of Pharmacology, [2]Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX; [3]Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN; [4]Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA

Nearly 70% of drug overdose deaths in 2022 were attributed to fentanyls. Vivitrol®, the long-acting formulation of the mu-opioid receptor antagonist naltrexone, is an opioid use disorder (OUD) medication that can prevent overdose and attenuate the reinforcing effects of opioids via competitive antagonism. However, non-selectively inhibiting all opioids can limit the use of opioid agonist pain medications and maintenance therapies. Highly selective fentanyl-targeting monoclonal antibodies (mAbs) may be an alternative as they bind and sequester fentanyl in the serum. In the present study, a mAb was examined for preventing fentanyl-induced ventilatory depression and attenuating fentanyl self-administration in rhesus monkeys. Using head plethysmography, baseline ventilation was established and within-session fentanyl dose-effect curves that decreased ventilation by >30% were determined (n=5). The mAb produced a ~3.5-fold rightward shift in the dose-effect curve 24 hours post-treatment; this effect decreased over 3-4 weeks. In a separate cohort of monkeys (n=4), dose-effect curves were determined for intravenous fentanyl, heroin and cocaine self-administration. The mAb was administered 15 minutes prior to a cycle in which fentanyl was available each morning and heroin or cocaine in the afternoon. The mAb selectively and significantly attenuated fentanyl self-administration, but not heroin or cocaine, for up to 30 days in some monkeys. These data demonstrate the potential use of the mAb as an overdose prevention and OUD medication. (Funding: U01DA051658, T32DA031115 and the Welch Foundation [AQ-0039]).

Poster 33

Characterization of cocaine and 3,4 methylenedioxypyrovalerone (MDPV) self-administration in male and female heterogenous stock rats

George, Christina M.[1,2], Vazquez, Jacqueline M.[1], Shi, Yonggong[1,2], Toue, Marie J.[1], Polesskaya, Oksana[3], Palmer, Abraham A.[3], Collins, Gregory T.[1,2]

[1]Department of Pharmacology, UT Health San Antonio, T.X., U.S.; [2]South Texas Veterans Health Care System, San Antonio, T.X., U.S.; [3]Department of Psychiatry, University of California, San Diego, La Jolla, CA U.S.

Rates of substance use disorder (SUD) are at an all-time high; however, factors that confer vulnerability to develop an SUD remain poorly understood. Unlike when rats have limited access to cocaine, we and others have previously found that when rats are allowed to self-administer synthetic cathinones, such as MDPV, a subset will rapidly transition to high rates of dis-regulated drug-taking, consistent with an SUD-like phenotype. To test whether genetic factors that predispose rats to high rates of cocaine-taking overlap with those that confer vulnerability to high rates of MDPV-taking, we evaluated cocaine and MDPV self-administration in two groups of heterogenous stock (HS) rats with genotypes predicted to confer low or high vulnerability to cocaine addiction (HS-low and HS-high, respectively, n=36 per group; 18m, 18f). SUD-like phenotypes were scaled using a series of endpoints: 1) area under the fixed ratio (FR) 5 dose-response curve; 2) % of responses made during post-infusion time outs (drug-seeking); 3) motivation to respond under a progressive ratio (PR) schedule; 4) escalation of intake over 14 days of extended access; 5) resistance to extinction; and 6) cue-induced reinstatement. Though HS-high and HS-low rats did not differ on all endpoints, HS-high rats reliably self-administered more infusions of MDPV and cocaine than HS-low rats, resulting in a greater FR5 AUC. Further, when the SUD-like index (average z-score for the 6 endpoints) were compared, HS-high rats self-administering MDPV were found to have a more severe SUD-like phenotype suggesting that genes associated with more robust cocaine-taking phenotypes also confer vulnerability to high rates of MDPV self-administration.

Poster 34

Self-administration of benzodiazepines in drug-naïve rhesus monkeys: Role of $GABA_A$ receptor subtypes

Gilmore, Ihle, D[1]; Piracha, Neha[2], Sharmin, Dishary[3], Cook, James, M[3], Doyle, William, S[4], Freeman, Kevin B[1,4], Rowlett, James, K[1,4], and Huskinson, Sally L[1,4]

[1]Department of Psychiatry and Human Behavior, University of Mississippi Medical Center (UMMC), Jackson, MS; [2]Medical Student Research Program, School of Medicine, UMMC, Jackson, MS; [3]Department of Chemistry & Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, WI; [4]Program in Neuroscience, UMMC, Jackson, MS

Benzodiazepines (BZs) bind to a site on the $GABA_A$ receptor located at the interface of the α and γ subunit, with $\alpha1$, $\alpha2$, and $\alpha3$ subunit-containing receptors likely involved in their reinforcing effects. Compounds that lack efficacy at the $\alpha1$ subunit-containing $GABA_A$ receptor ($\alpha1$-sparing compounds) appear to have reduced potential for misuse, though their reinforcing effects are dependent upon past drug experience. Choice procedures were used to evaluate whether drug naïve subjects would self-administer $\alpha1$-sparing compounds when substituted for food or when combined with food. Two female and two male rhesus monkeys chose between a fixed food amount on one option and on the other option, in different conditions, between increasing food amounts, drug doses, or food + drug combinations. Three compounds (YT-III-31, MP-III-24, MP-III-80) with various degrees of functional selectivity at $\alpha2$, $\alpha3$, and $\alpha5$ subunit-containing $GABA_A$ receptors were evaluated. The compounds were not self-administered on their own, suggesting that they do not function as reinforcers in drug naïve subjects, and is similar to outcomes obtained with cocaine-experienced subjects. Thus far, unlike with cocaine experience, these compounds have failed to reliably enhance food choice. These experiments will be replicated with a nonselective BZ, midazolam, and the $\alpha1$-preferring compound, zolpidem, in the same subjects. From a therapeutic perspective, $\alpha1$-sparing compounds may hold promise as treatments for anxiety or BZ use disorder with reduced potential for misuse.

Poster 35

The effects of ethanol abstinence on impulsivity in Long Evans rats

Grijalva, Sofia[1]; Sosa, Ricardo[2]; Powers, Rosalie[3] and Moschak, Travis[4]

[1]Department of Biology, University of Texas at El Paso, El Paso, TX USA; [2]Department of Biology, University of Texas at El Paso, El Paso, TX USA; [3]Department of Biology, University of Texas at El Paso, El Paso, TX USA; [4]Department of Biology, University of Texas at El Paso, El Paso, TX USA

Impulsivity refers to the difficulty to inhibit reward-driven responses and impaired choice processing. Impulsive behaviors have been related to substance use disorders and as a predictor for relapse, especially for cocaine. This study examined the role of impulsivity in ethanol-seeking behavior and its change before and after ethanol intake. We predicted that abstinence from ethanol would increase impulsivity. We adapted the intermittent access 2-bottle choice protocol and ethanol (n=10) or water (n=8) self-administration in male and female Long Evan rats. We assessed impulsivity by measuring early errors in a modified cue titration task at three timepoints: drug naïve, early abstinence (~10 days post-ethanol), and late abstinence (~28 days post-ethanol), with extinction sessions during early and late abstinence.

A within-subjects ANOVA test revealed no significant relationship in the interaction between timepoints and sex ($F(2,28)=0.156$, $p=0.856$), suggesting that regardless of sex, impulsivity remained the same in all three timepoints. We also found no significant differences in the interaction between timepoints, drug exposure, and sex ($F(2,28)=0.73$, $p=0.930$), suggesting that impulsivity is not changed after alcohol abstinence.

Our findings indicate that while impulsivity can be a useful model to explain other drug-use behaviors, ethanol does not seem to have an effect, suggesting that alcohol relapse might be influenced by different aspects, such as stress or societal factors. Future research will explore specific neural mechanisms underlying substance use disorder and optogenetic manipulation for treatment approaches.

Poster 36

Design, synthesis and biological evaluation of compounds inspired by *Mitragyna speciosa* for opioid use disorder

Gupta, Sampa;[1] Obeng, Samuel;[2] Seabra, Maria;[1] McCurdy, Christopher R.[1]

[1]Department of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, FL, 32610, USA. [2]Department of Pharmaceutical Sciences, Jerry H. Hodge School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, TX, 79106, USA

The ongoing global opioid use disorder epidemic is associated with numerous health and social problems, including an increased risk of hospitalization and death. The persistent use of opioids should be diagnosed and treated promptly. In 2022, approximately 75% of the total drug overdose deaths in the United States involved some type of an opioid.[1] The number of deaths due to an opioid overdose in 2020 is 8.5 times higher than the number of opioid overdose deaths in 1999.[2] A Southeast Asian-native plant, *Mitragynine speciosa*, or "kratom", has been used to relieve exhaustion, sustain energy, increase work efficiency, elevate mood, relieve pain, and mitigate opioid withdrawal symptoms. The most abundant alkaloid presents in the plant, mitragynine (MG), acts as a partial μ-opioid receptor (MOR) agonist with G-protein biased signaling and shows some moderate affinity towards $\alpha2$A-adrenergic ($\alpha2$A-AR) receptor.[3] This dual receptor activity is believed to play a major role in kratom's overall pharmacology for mitigating opioid withdrawal symptoms. This work is designed to introduce chemical flexibility in kratom alkaloids by creating simplified synthetic analogues of MG to understand the minimal structural requirements needed for opioid and adrenergic receptor binding. We synthesized analogs by removing the B ring and ethyl group at C-20 of mitragynine's structure and these molecules were assessed for *in vitro* affinity at $\alpha2$-AR and MOR. The synthesized compounds showed decreased affinity at MOR (>10,000 nM) and more selectivity towards $\alpha2$-AR (~15 nM). Based on these data we synthesized analogs of corynantheidine, a minor kratom alkaloid with opioid and adrenergic activity, to examine the affinities at MOR and $\alpha2$-AR. The synthesis and SAR will be presented and compared with kratom alkaloids.

Poster 37

Organic cation transporter 3: A possible link between co-morbid alcohol use and post-traumatic stress disorders?

Hammack, Robert J[1]; Shin, Sangbin[1], Toney, Glenn M[1], Daws, Lynette C[1,2]

Departments of [1]Cellular and Integrative Physiology and [2]Pharmacology

Alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD) are highly co-morbid. Selective serotonin (5-HT) reuptake inhibitors (SSRIs) are the frontline, and only FDA approved treatment for PTSD, however, their efficacy is suboptimal. SSRIs increase extracellular 5-HT by reducing its uptake via the serotonin transporter. We have shown that concurrent blockade of an alternative 5-HT uptake mechanism, organic cation transporter 3 (OCT3), greatly augments the antidepressant-like effects of SSRIs. We also made the novel discovery that ethanol inhibits 5-HT uptake via OCT3, raising the possibility that individuals with comorbid PTSD and AUD may develop the latter as a means of self-medication, i.e., by ethanol-induced inhibition of 5-HT uptake via OCT3. The basolateral amygdala (BLA) is a key hub for both reward- and fear/anxiety-related behaviors. We thus hypothesized that PTSD-related anxiety and fear behaviors are reduced by genetic OCT3 depletion in BLA. In male C57BL6 mice, we bilaterally injected into BLA a viral construct encoding an OCT3 shRNA or scrambled RNA sequence (AAV5-GFP-U6-OCT3/SC-shRNA) to assess behavioral effects of BLA OCT3 knockdown (KD). Three weeks later, mice underwent a battery of fear-associated tasks. OCT3 KD reduced anxiety-like behavior without affecting contextual fear learning or recall. Since OCT3 blockade is known to enhance antidepressant-like effects of SSRIs, the same mice underwent fear extinction learning prior to treatment with an SSRI and underwent cued fear conditioning/recall. Fear expression during memory recall was significantly impaired by the combination of BLA OCT3 KD and SSRI treatment, implicating a role for OCT3 in the development of fear memory when SERT is inhibited. Findings suggest that inhibition of OCT3 in BLA may be an effective adjunct therapy for SSRI treatment of PTSD, encouraging development of OCT3-specific inhibitors that lack the addictive properties of ethanol.

Poster 38

Does stimulant history affect the anxiety-like response to nicotine in male rats

Harman, Taylor B[1], Buffalari D[1]

[1]Department of Neuroscience, Westminster College, New Wilmington, PA USA

Amphetamine, commonly known as Adderall, is a stimulant frequently prescribed to treat Attention-Deficit Hyperactivity Disorder (ADHD). Amphetamine prescriptions have increased 2.5-fold in a decade; amphetamine is also often abused. ADHD is diagnosed in 10% of US children and is more prevalent in boys and young individuals. Those with ADHD frequently report anxiety as do over ¾ of amphetamine users. Additionally, those with ADHD smoke cigarettes at rates significantly higher than their non-diagnosed peers and experience greater reinforcing effects from smoking. The current study analyzed how a history of amphetamine exposure affected the anxiety-like response to nicotine, using (50) male Sprague-Dawley rats.

Amphetamine was administered via 14 days of repeated injection (4 mg/kg, IP), and nicotine was administered via a single injection (0.1 mg/kg, SC) 15 minutes prior to behavioral testing on the elevated plus maze (EPM), used to analyze anxiety-like behavior. Time spent in the open arms of the EPM and entries into the open arms of the EPM were measured, and ANOVA statistical testing was conducted to analyze for a significant effect of amphetamine and/or nicotine, as well as an interaction between the two. Results suggest that both amphetamine and nicotine alone may increase anxiety-like behavior. Additionally, nicotine after a history of amphetamine exposure increased anxiety-like behavior, compared to amphetamine alone. Though these results were not statistically significant, this study could provide insight into why those prescribed amphetamine are at increased risk of nicotine use, as well as anxiety. Further studies will need to be done to further assess this interaction and help correlate this drug treatment with anxiety.

Poster 39

Delivery of mitochondria-containing extracellular vesicles to the blood-brain barrier for the treatment of ischemic stroke

Hildebrand, Ella E[1], Dave, Kandarp M.[2], Manickam, Devika S.[3]

[1]Westminster College [2]Duquesne University Graduate School of Pharmaceutical Sciences, Pittsburgh, PA

Following an ischemic stroke, mitochondrial function in blood-brain barrier endothelial cells is impaired. Extracellular vesicles are naturally secreted by all cells in the body. Microvesicles (MVs), a subtype of extracellular vesicles, naturally transfer mitochondrial components between cells, raising ATP levels, therefore increasing bioenergetics and survival under conditions of cell duress. We hypothesize that mouse brain endothelial cell (bend.3)-derived MVs will increase BEC ATP levels and show neuroprotection and behavioral recovery in a mouse model of stroke. In the present study, we isolated MVs from a mouse brain endothelial (bEND.3) cell line and characterized their particle sizes and protein biomarkers. We tested ATP levels and mitochondrial transfer in MV-treated BECs under ischemic conditions. BEC-derived MVs were found to increase recipient ischemic endothelial ATP levels. Likewise, MVs transferred mitochondria to recipient BECs. Future studies will administer bEND.3 MVs in a mouse model of stroke and determine brain infarct volumes and behavioral recovery.

Poster 40

Behavioral effects of three synthetic tryptamine derivatives

Hill, Rebecca D; Shetty, Ritu A; Sumien, Nathalie; Forster, Michael J and Gatch, Michael B.

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

Aims: New synthetic tryptamine derivatives have emerged in the underground market. They act on the serotonin receptors mimicking the effects of hallucinogenic drugs such as DOM. The DEA has identified three tryptamine derivatives of concern, 5-MeO-DBT, 5-Cl-DMT, and 4-OH-MiPT.
Methods: Swiss-Webster mice were tested for locomotor activity. Discriminative stimulus effects were tested in male Sprague-Dawley rats trained to discriminate DOM (0.5 mg/kg, 30-minute pretreatment) from vehicle (0.9% saline).
Results: In the locomotor activity tests, DOM (ED_{50}= 4.8 mg/kg) produced a 40-100-minute depressant phase. 5-MeO-DBT (ID_{50}= 16.5 mg/kg; ED_{50}= 0.074 mg/kg) had a 50-minute depressant phase and a 100-minute stimulant phase. 5-Cl-DMT (ID_{50}= 12.3 mg/kg; ED_{50}= 6.1 mg/kg) produced a 20-40-minute depressant phase and a 30-minute stimulant phase. 4-OH-MiPT (ID_{50}= 5.8 mg/kg; ED_{50}=0.6 mg/kg) had a 30-130-minute depressant phase and a 50-minute stimulant phase. In the drug discrimination assay, 4-OH-MiPT (ED_{50}= 0.77 mg/kg) fully substituted while 5-Cl-DMT partially substituted for the discriminative stimulus effects produced by DOM (ED_{50}= 0.23 mg/kg). 5-MeO-DBT failed to substitute for the discriminative stimulus of DOM. 5-CL-DMT and 5-MeO-DBT decreased the response rate.
Conclusion: The locomotor depressant effects of the three synthetic tryptamine derivatives were similar to DOM, but not as potent. In the drug discrimination assay, only 4-OH-MiPT substituted fully for DOM. These results support the possibility that 4-OH-MiPT and 5-Cl-DMT have abuse liability similar to DOM, whereas 5-MeO-DBT may not.
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Poster 41

Effects of fentanyl, heroin, and *d*-methamphetamine, alone and in mixtures, on apnea duration in male rats

Ho, Nicholas P[1,3], Hiranita, Takato[1,3], and France, Charles P[1-3]

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

The number of drug overdoses and deaths has increased significantly over the past decade and co-use of opioids and stimulants is associated with greater likelihood of overdose and decreased likelihood of accessing treatment, compared with use of opioids alone. Potential adverse effects of opioid/stimulant mixtures, particularly methamphetamine, are not well characterized. Two structurally different agonists at μ-opioid receptors (MOR), fentanyl and heroin, and *d*-methamphetamine, alone and in mixtures, were assessed for their effects on apnea duration in male Sprague-Dawley rats breathing normal air. Apnea is defined as the absence of pressure changes for a period equivalent to or greater than two ventilatory cycles. Whole-body plethysmography chambers were equipped with a tower and swivel allowing infusions to indwelling intravenous catheters. Five minutes after administration of saline, fentanyl, heroin, or *d*-methamphetamine, alone and in mixtures, the opioid receptor antagonist naloxone or vehicle was injected. Fentanyl (0.0032-0.1 mg/kg) and heroin (0.1-3.2 mg/kg) dose-dependently increased apnea duration whereas *d*-methamphetamine (0.1-3.2 mg/kg) did not significantly change apnea duration. Naloxone (0.0001-0.01 mg/kg) dose-dependently attenuated apnea by fentanyl (0.1 mg/kg) or heroin (3.2 mg/kg). When combined, *d*-methamphetamine (0.1-0.32 mg/kg) attenuated apnea by fentanyl (0.1 mg/kg) or heroin (3.2 mg/kg). *d*-Methamphetamine did not alter naloxone potency to reverse apnea by fentanyl (0.1 mg/kg) or heroin (3.2 mg/kg). These studies demonstrate that *d*-methamphetamine can attenuate apnea by moderate doses of MOR agonists while not altering naloxone potency to reverse opioid apnea. Supported by USPHS grants UG3DA048387, UG3DA048387-S1, R01 DA048417, and R01DA058018 as well as the Welch Foundation (Grant AQ-0039).

Poster 42

Investigating self-administration of delta-opioid receptor agonists in morphine withdrawn rats

Hoying, Lucy R[1]; Pradhan, Amynah A[2]; Kendall, David[3]; von Mentzer, Bengt[3]; Jutkiewicz, Emily M[1]

[1]Department of Pharmacology, University of Michigan, Ann Arbor, MI USA; [2]Center for Clinical Pharmacology, St. Louis, MO USA; [3]PharmNovo AB, Lund, Sweden

For people struggling with opioid use disorder (OUD), discontinuation of mu-opioid receptor agonists produce opioid withdrawal symptoms such as body aches, hyperalgesia, anxiety, and irritability. δ-opioid receptor (DOR) agonists produce antinociceptive, anxiolytic, and antidepressant-like effects in preclinical studies, and therefore, may have potential in the treatment of opioid withdrawal. While DOR agonists are generally considered to have low abuse liability, it is important to determine whether these compounds may have abuse potential in opioid withdrawal. Therefore, the goal of the present study was to evaluate the reinforcing effects of the canonical DOR agonist SNC80 and a novel DOR agonist PN6047 in both chronically morphine-withdrawn and morphine-naive rats. Male Sprague-Dawley rats were implanted with intravenous catheters and then received twice daily saline or morphine injections for 4 days (10, 20, 20, 40 mg/kg, respectively). Then rats were allowed to self-administer remifentanil (0.0032 mg/kg/infusion) on a fixed ratio (FR) 1 schedule of reinforcement and received an injection of 40 mg/kg morphine or saline approximately 60 min after each daily self-administration session. Following stable self-administration of remifentanil, saline or different doses of PN6047 or SNC80 were substituted for at least 7 days. PN6047 (0.32 mg/kg/infusion or 1 mg/kg/infusion) did not maintain responding for any dose tested in either morphine-withdrawn or morphine-naive rats. SNC80 (0.32 mg/kg/infusion) maintained responding in morphine-naive, but not morphine-withdrawn, rats. These data suggest that SNC80 and PN6047 may have differential reinforcing effects in morphine-naive animals but likely have weak reinforcing effects overall. These findings suggest that DOR agonists have low abuse liability, even during opioid withdrawal.

Poster 43

Associations between interoceptive stimulus control and morphine self-administration

Huang, Shihui; Cerveny, Sydney E; Valsan, Anushka; Denney, Garrett G; Scott, Morgan G; Younesie, Honeyeh; Abielmona, Sasha A; Robinson, Sophie M and Riley, Anthony L.

Department of Neuroscience, American University, Washington, D.C. USA.

Clinical research has linked individual variability of interoception to differential susceptibility for dysregulated drug use, yet it remains unclear how interoceptive information is involved in regulating drug intake. Using a conditioned taste avoidance/drug discrimination learning (CTA/DDL) task, we have demonstrated that a morphine-induced interoceptive state can signal an impending aversive effect associated with saccharin, thus setting the occasion for avoidance. This task yields consistent individual variability. Here, we tested the hypothesis that rats exhibiting a strong interoceptive stimulus control would show different pattern of morphine self-administration than rats with a weak stimulus control. In 25 male Sprague-Dawley rats, individual variability was assessed in the CTA/DDL task with morphine (10 mg/kg, IP) as the interoceptive signal. Rats within the lower and upper 50% of the ranking score were designated as weak- and strong-interoceptive-control subjects (WIC and SIC) and underwent IV self-administration to assess the acquisition, escalation, and persistence of morphine intake. 30% of rats failed to acquire morphine interoceptive control, consuming comparable levels of saccharin on both morphine and vehicle sessions, while 40% of rats acquired strong interoceptive control, consuming at least 30% less saccharin on morphine relative to vehicle sessions. A mixed-model ANOVA showed that SIC rats learned to self-administer morphine more rapidly under the 2-hr access (FR1). Although other behavioral endpoints did not reach statistical significance, SIC rats displayed a greater level of active lever-pressing during 4-hr and 6-hr access (FR1), while WIC rats displayed higher breakpoints under progressive ratio assessments. The findings suggest that strong interoceptive control is associated with more rapid acquisition of morphine self-administration. It remains to be explored whether WIC and SIC would exhibit different behaviors under intermittent access, extinction, and reinstatement.

Poster 44

Insomnia treatment drug lemborexant rescues REM sleep dysfunction associated with methamphetamine vapor withdrawal

Huffcutt, Galen P[1]; Jones, Marissa R[1] and Schmeichel, Brooke E[1]

[1]Department of Biomedical Sciences, East Tennessee State University, Johnson City, TN USA

Nearly 2.5 million people abused methamphetamine (MA) in the U.S. in 2020. Chronic MA use can lead to disordered sleep, particularly during withdrawal, and clinical studies show that sleep dysfunction is a strong predictor for relapse. The neuropeptide hypocretin (HCRT) is critical in the transition to wakefulness and modulates drug reward. Enhanced HCRT signaling in the brain underlies the sleep disorder insomnia and dual-HCRT-receptor antagonist lemborexant (LEM) is prescribed for treatment of insomnia in humans. Here we characterized sleep dysfunction during MA vapor (MAV) withdrawal in rats and hypothesized that HCRT signaling contributes to poor sleep. Adult male Wistar rats (N=8) received telemetry device implants, and EEG/EMG signals were recorded for 23 hours. Rats were exposed to passive MAV for 4 weeks to induce dependence, shown by a decrease in body temperature and novel object recognition during acute drug withdrawal. Sleep/wake data were analyzed prior to MAV exposure, during withdrawal, and during protracted abstinence, with LEM administered prior to sleep recordings. After 1 week of abstinence, rats showed a decrease in rapid eye movement (REM) sleep time and number of bouts in the light cycle during withdrawal but an increase in REM sleep time during the dark cycle. LEM restored the amount of REM sleep time and the number of REM sleep bouts during the light cycle. Average NREM bout duration decreased and number of bouts increased in the dark cycle during withdrawal, indicating NREM dark cycle fragmentation. Rats showed an increase in WAKE bouts during both cycles. After 4 weeks of abstinence, REM sleep time remained reduced while number of REM bouts in the light cycle and REM sleep time in the dark cycle returned to baseline levels. These findings show that REM and NREM sleep are dysregulated during abstinence from MAV and that HCRT neurotransmission contributes to the disrupted sleep.

Poster 45

Sex-specific effects of THC vapor exposure on synaptic transmission and anxiety-like behavior following traumatic brain injury in Wistar rats

Jacotte-Simancas, Alejandra[1], Middleton, Jason[2], Henn, Sarah[1], Jahnke, Abigail[1], Molina, Patricia[1]; Gilpin, Nicholas[1]

[1]LSUHSC, Department of Physiology, New Orleans, USA; [2]LSUHSC, Department of Cell Biology and Anatomy, New Orleans, USA.

Rationale: Traumatic brain injury (TBI) leads to increases in anxiety and neuronal hyperexcitability. It is possible, but not known, whether repeated THC vapor inhalation may potentially reduce anxiety and restore neuronal hyperexcitability after TBI. Here, we hypothesized that THC vapor inhalation attenuates TBI-induced increases in neuronal hyperexcitability and excitatory synaptic transmission in the basolateral amygdala (BLA), as well as anxiety-like behavior. **Method:** Male and female Wistar rats (N= 80) were subjected to TBI followed by 10 days of THC vapor exposure (1hr/day). In Study 1, electrophysiological analysis of the ipsilateral BLA was performed. In Study 2, the elevated plus maze (EPM), open field (OF), and dark/light (D/L) test assays were used to test anxiety-like behavior. **Results:** TBI increased apnea ($p<0.01$) and reduced respiratory reflex ($p<0.01$) in females. THC reduced resting membrane potential of BLA neurons in males ($p<0.05$). In females, naïve controls showed lower resting membrane potential compared to the other groups ($p<0.05$). TBI did not alter spontaneous excitatory and inhibitory post-synaptic currents (sEPSCs and sIPSCs) in males or females, but THC produced non-significant trends toward reductions in sEPSC amplitude regardless of TBI condition, and in sEPSC frequency in females with TBI. THC did not affect anxiety-like behavior in males with TBI, but decreased the time spent in the open arms of the EPM ($p<0.05$), the time spent in the center of the OF ($p<0.05$), and the time spent in the light side of the D/L test ($p<0.01$) in females with TBI compared to TBI-control. **Conclusions:** THC vapor exposure produces sex-specific effects on synaptic transmission and anxiety-like behavior after TBI.

Poster 46

Distinguishing the prohedonic vs. anti-anhedonic effects of ketamine: Implications for self-medication and substance use disorder

Jenkins, Amaya R[1] and Kangas, Brian D[1]

[1]McLean Hospital, Harvard Medical School

Ketamine use and abuse represents an unprecedented circumstance. Given its FDA approval in 2019 for treatment-resistant depression, paired with its decades-long association with abuse liability (and front-page news lethality), the study of ketamine demands characterization of both its desirable and undesirable consequences. In particular, the high comorbidity of substance use disorder (SUD) and major depressive disorder (MDD) suggests consideration of illicit 'self-medication' hypotheses in patient populations that have been previously exposed to ketamine's licit therapeutic use. Because ketamine's profile as a drug reward has already been characterized in previous self-administration studies, the present work focused on its antidepressant-like effects to provide insight regarding its efficacy and time course related to self-medication in those with SUD and MDD. Anhedonia, an endophenotype of depression, is defined by a decrease in responsivity to previously rewarding stimuli. The present studies evaluated ketamine's effects on hedonic tone in healthy and chronically-stressed rats using the Probabilistic Reward Task (PRT), a reverse-translated assay for rodents originally designed to objectively quantify anhedonic phenotypes in the clinic. Results, using one-way repeated measures ANOVA, show in healthy (unstressed) rats, ketamine produced significant prohedonic effects that dissipated 24 hr later. In chronically-stressed rats, ketamine was associated with significant anti-anhedonic rescue of blunted reward responsivity, with a persistent time course lasting nearly one week. Taken together, the prolonged anti-anhedonic effects in stressed subjects, compared to the shorter-lived prohedonic effects in healthy subjects, could inform the ketamine experience in patients with comorbid SUD and MDD. Specifically, these data suggest that those self-medicating with ketamine might have a different experiential time course than what might be predicted by traditional assays of abuse liability.

Poster 47

Unraveling cocaine-induced neurotoxicity: Insights into mitochondrial dysfunction and astrocyte mediation

Jirakanwisal, Krit[1,5]; Fongsaran, Chanida[1,5] and Cisneros, Irma E[1,2,3,4,5]

[1]Department of Pathology, University of Texas Medical Branch, Galveston, TX USA; [2]Center for Addiction Sciences and Therapeutics; [3]Center for Biodefense and Emerging Infectious Diseases; [4]Institute for Human Infections and Immunity; [5]Neuroinfectious Diseases, University of Texas Medical Branch, Galveston, TX USA.

The abuse of cocaine remains a significant public health concern, with a myriad of neurological consequences attributed to its disorder use. This study aims to unravel the molecular mechanisms underlying the interplay between cocaine abuse, compromised mitochondrial health, and astrocyte-mediated neuroimmune responses, providing critical insights for targeted neuroimmune pharmacological interventions. Emerging evidence suggests that cocaine disrupts mitochondrial function, leading to a cascade of events that contribute to neuroimmune dysregulation. Our investigations reveal alterations in mitochondrial membrane potential and reactive oxygen species production following exposure to cocaine. Moreover, we explore the impact of cocaine-induced mitochondrial dysfunction on mitochondrial dynamics. Understanding the crosstalk between mitochondrial dysfunction and neuroinflammation is crucial for unraveling the intricate pathogenesis of cocaine-induced neurotoxicity. Importantly, we will focus on the specific consequences of cocaine-induced mitochondrial dysfunction in astrocytes, exploring their activation and the subsequent release of pro-inflammatory mediators. Furthermore, we will discuss potential pharmacological interventions targeting mitochondrial preservation, specifically in astrocytes. The modulation of astrocyte activation and the mitigation of neuroinflammatory responses represent promising strategies for attenuating the neurological consequences associated with cocaine use. Our findings will contribute to a nuanced understanding of the neuroimmune pharmacology underlying cocaine-induced neurotoxicity, paving the way for targeted interventions to alleviate the impact of cocaine abuse on neurological health.

Poster 48

Oxytocin attenuates stress-induced responding for oral oxycodone under a progressive ratio schedule in male and female rats

Kaneko, Moe[1]; Cornejo, Natalie[1]; Yates, Taylor Q.[1]; Rager-Aguiar, Ryan J.[1]; Ho, Sophia[1]; and Leong, Kah-Chung[1]

[1]Neuroscience Program, Trinity University, San Antonio, TX USA

Opioid Use Disorder (OUD) has become an epidemic in the United States, greatly disrupting the lives of patients and those around them. Notably, oxycodone stands as one of the most widely abused opioids and is often known as a "gateway drug" to more addictive substances such as heroin. Many studies show that stress is a main driving force in instigating opioid use, ultimately leading to the development of addiction and relapse. Therefore, investigations for therapeutic interventions are imperative to confront the effect of stress on OUD. Recent studies have explored the anxiolytic properties of the neuropeptide oxytocin and its ability to attenuate addiction-related behaviors. We hypothesized that oxytocin would attenuate stress-induced enhancement of oxycodone reward strength as measured through a progressive ratio test. Male and female Sprague-Dawley rats (n = 12) were first trained in an operant conditioning paradigm to orally self-administer oxycodone. Briefly, animals were trained to press an active lever for 5s access to oxycodone solution (0.1 mg/ml) using a sucrose fading paradigm until stable responding was observed. After establishing self-administration, the pharmacological stressor yohimbine (2 mg/kg, i.p.) was administered prior to a progressive ratio test, in which an animal must produce increasingly higher responses to receive a single exposure to oxycodone, resulting in enhanced oxycodone responding. A one-way ANOVA revealed that when animals were concurrently administered oxytocin (1 mg/kg, i.p.), this yohimbine-induced enhancement in oxycodone response was attenuated in both male and female rats. Overall, our study indicates that oxytocin moderates oxycodone-responding during stress in both male and female rats, proposing it as a potential therapeutic remedy to mitigate the deleterious impact of stress on oxycodone addiction.

Poster 49

The comorbidity of caffeine and nicotine on memory in Sprague-Dawley rats

Kattler, Victoria[1] and Buffalari, Deanne[2]

[1]Department of Neuroscience, Westminster College, PA USA; [2]Department of Neuroscience, Westminster College, PA USA

This study focuses on the prevalence of caffeine as an addictive substance, its effect on memory, and its comorbidity with nicotine. Studies have shown that caffeine is consumed by around 80% of the US population and is not only found in drinks but also in everyday food. When ingested, the effects of caffeine depend on the dosage, frequency of use, and tolerance of the consumer. Similarly, nicotine impacts most organs in the body and has been found to be carcinogenic. Despite the negative effects of both substances, they have been shown to enhance memory and cognitive function in certain dosages. Studies in both human and animal models have shown that low doses of nicotine and caffeine improve memory retention, while high doses have adverse effects. This study aims to understand the effects of comorbid use of caffeine and nicotine on memory in rats through behavioral testing in the radial arm maze. The study aims to explore how the two substances might interact in tests of working memory.

Poster 50

Investigating the effects of mitragynine on food-motivated behavior

Khordavirdilou, Lida[1]; Zuarth Gonzalez, Julio D[1]; Mukhopadhyay, Sushobhan[2]; Guadagnoli, Nicholas[2]; McCurdy, Christopher R[2]; McMahon, Lance R[1]; and Wilkerson, Jenny L[1]

[1]Department of Pharmaceutical Sciences, Texas Tech University Health Sciences Center; [2]Department of Medicinal Chemistry, College of Pharmacy, University of Florida

Kratom, scientifically known as *Mitragyna speciosa*, has been a subject of interest for its potential in self-treating substance use disorders (SUD), including methamphetamine addiction. The study aimed to investigate the hypothesis that mitragynine does not diminish the reinforcing effects of a natural reinforcer, such as food, in comparison to its observed impact on self-administration of methamphetamine. Male and female Sprague Dawley rats underwent training to self-administer 20 mg food pellets, during 2-hour sessions, establishing lever-pressing behavior under a fixed ratio (FR) 1 schedule of reinforcement. The reinforcement schedule gradually increased to FR5, with a maximum of 100 reinforcers allowed. After achieving stable responding over three consecutive sessions, the study evaluated the effects of pretreatment with either vehicle or mitragynine (at doses of 10, 17.8, 32, and 56 mg/kg, i.p.), with the order of doses counterbalanced. Food self-administration led to significant lever presses on the active lever compared to the inactive lever and resulted in maximum reinforcers earned. Notably, none of the administered doses led to a decrease in food self-administration. These results indicate that mitragynine does not influence natural reward-driven behavior and exhibits greater selectivity for methamphetamine-related behavior.

Supported by National Institute on Drug Abuse grants DA25267 and DA048353.

Poster 51

Impact of nicotine's autonomic effect on nicotine's overall discriminative stimulus

Kusi-Boadum, Nana Kofi[1]; Shetty, Ritu 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: As the leading cause of preventable death, tobacco smoking has inspired years of research into pharmacological targets for smoking cessation. A previous locomotor activity study in our lab showed that hexamethonium, a brain-impermeable nicotinic receptor antagonist blocks the locomotor stimulant effects of nicotine in mice. To further assess the impact of the autonomic effects of nicotine on behavior, we conducted a nicotine discrimination study. In this study, we subtracted nicotine's autonomic effects from the overall subjective effect by using hexamethonium. **Method:** Using a two-lever drug discrimination operant chamber, six male Sprague-Dawley rats were trained to discriminate 0.1 mg/kg nicotine tartrate from saline by lever pressing. Subcutaneous injections of nicotine or saline for training occurred five minutes prior to the start of the training session. On test days, rats received hexamethonium (1, 2.5, 5, 10, 25, or 50 mg/kg) intraperitoneally 25 minutes prior to subcutaneous administration of nicotine at the training dose (0.1 mg/kg). Percentage of drug lever responses and response rate were recorded to measure antagonism and analyzed using repeated measures ANOVA. **Results:** Within the dose range of 10-50 mg/kg, hexamethonium partially antagonized nicotine's discriminative stimulus effect by reducing the percentage nicotine-lever response to 42% of nicotine's maximum discriminative stimulus effect. **Conclusion:** Although full antagonism was not observed, the partial antagonism of nicotine's discriminative stimulus by a solely peripherally-acting antagonist shows that the autonomic effects of nicotine are a component of the overall subjective effect of nicotine that influences behavior. This suggests that the autonomic system contributes to the neurobiology of nicotine addiction, and thus can be considered as a pharmacological target for smoking cessation.

Poster 52

Effects of voluntary ingestion of delta-9-tetrahydrocannabinol on the hedonic responding of rewarding and aversive substances

Laux, Dylan A., Tewell, Olivia R., Polton, Tristan A., and Cain, Mary E.

Department of Psychological Sciences, Kansas State University, Manhattan, KS USA.

Human studies indicate a relationship between THC use and alcohol use, therefore preclinical models have begun to model this phenomenon in rodents. However, research on the development of co-dependency of cannabis and alcohol use is limited. Rodent models of cannabis administration have shown that cannabinoids can increase the incentive salience ("wanting") to sucrose and alcohol in operant and voluntary access paradigms (Gallate et al., 1999; Hamidullah et al., 2021). Cannabinoids also increase the hedonic value ("liking") to sucrose and quinine in the taste reactivity paradigm (Jarret et al., 2005; Jarret et al., 2006). However, other research suggests that oral THC reduces both sucrose and alcohol consumption (Nelson, et al., 2019). Due to the discrepancies in the literature and the use of doses higher than typical human consumption, the present study utilizes edible administration of lower doses of synthetic THC (Dronabinol), corresponding to human use. Male Long-Evans rats voluntarily ingested vehicle (sesame oil) or THC-containing (Dronabinol, 0.5 mg/kg,) cookies prior to testing the hedonic value of sucrose and alcohol via taste reactivity paradigm. Preliminary results suggest that Dronabinol increases hedonic reactions to sucrose (0.5M) when compared to the control group. Additionally, Dronabinol increases hedonic reactions to alcohol (40% ETOH) compared to the control group. Our preliminary results suggest that oral synthetic THC consumption increases the liking of both reinforcing and aversive substances. Further, these results may illustrate a prelusive explanation for the co-morbidity of alcohol and THC use disorder in a pre-clinical model. This research provides insight on the role of THC increasing the hedonic value of aversive and rewarding substances, while utilizing a translatable dose of THC administration in a pre-clinical model.

Poster 53

Effects of acute and repeated VU0364572 treatment on cocaine-vs-food choice in male and female rats

Marsh, Samuel A.[1]; Banks, Matthew L.[1]

[1]Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, USA

Cocaine use disorder (CUD) has been a significant public health problem since 1914 when it was outlawed by the Harrison Narcotic Act. However, despite continued scientific community efforts, there are currently no Food and Drug Administration-approved pharmacotherapies for CUD. Recent preclinical studies suggest M1 agonists may have utility as candidate CUD medications. The goal of the present study was to determine the effectiveness of the M1 agonist VU0364572 to attenuate cocaine-vs-food choice in female and male rats. Male and female Sprague Dawley rats (n=9, 3F/6M) were aseptically implanted with intravenous (IV) catheters and trained to respond for cocaine (0.032 – 1.0 mg/kg/inf) and 32 or 100% vanilla flavored ensure under a concurrent fixed-ratio 5 schedule of reinforcement during daily 2h behavioral sessions. Once cocaine choice was stable, saline or VU0364572 (0.32-10 mg/kg, IP) was administered as a 30 min pretreatment and cocaine choice was monitored for 2 weeks. Then VU0364572 was administered as a repeated 5-day daily pretreatment before cocaine choice sessions and then the VU0364572 dose was increased. Up to VU0364572 doses of 3.2 mg/kg, VU0364572 failed to significantly attenuate cocaine choice according to a two-way repeated measures ANOVA. Studies are ongoing with 10 mg/kg VU0364572 and additional environmental manipulations to demonstrate sensitivity of cocaine choice. Overall, the present results do not suggest that activation of M1 receptors with VU0364572 is a candidate medication for CUD.

Poster 54

Locomotor and discriminative stimulus effects of two synthetic cannabinoids

McDonald, Jared A[1]; Hill, Rebecca D[1]; Shetty, Ritu A[1]; Sumien, Nathalie[1]; Gatch, Michael B[1] and Forster, Michael J[1]

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

Aims: Synthetic cannabinoids are manufactured as "legal" alternatives to Δ^9-tetrahydrocannabinol (THC). These synthetic compounds act on CB_1 cannabinoid receptors and can cause major side effects such as hallucinations and death. New synthetic cannabinoids are still being found in the underground markets. The DEA has identified two synthetic cannabinoids of concern, ADB-HEXINACA and ADB-FUBIATA.
Methods: Swiss-Webster mice were tested for locomotor activity to compare behaviorally active dose ranges of each compound with THC. Discriminative stimulus effects were tested in male Sprague-Dawley rats trained to discriminate THC (3 mg/kg, 30-minute pretreatment) from vehicle (ethanol/Cremophor EL/0.9% saline (1:1:18)).
Results: In the locomotor activity test, ADB-HEXINACA (ED_{50}=0.55 mg/kg) produced robust depression lasting 70 min, whereas ADB-FUBIATA (ED_{50}= 87.7 mg/kg) produced weak effects lasting 40 min. In the drug discrimination assay, ADB-HEXINACA (ED_{50}=0.11 mg/kg) fully substituted for the discriminative stimulus effects of THC (ED_{50}=0.84 mg/kg), whereas ADB-FUBIATA produced a maximal effect of 46% drug-appropriate responding and decreased response rate following 100 mg/kg.
Conclusion: ADB-HEXINACA produced locomotor depressant effects and full substitution for THC and was 6 to 8-fold more potent, suggesting that ADB-HEXINACA may have substantial abuse liability as a substitute for THC, whereas the weak effects of ADB-FUBIATA suggest it may have a lower risk of misuse.
Support: Supported by NIDA contract N01DA-23-8936

Poster 55

The effects of gabapentinoids in rats discriminating fentanyl from saline: A sex difference comparison

Mijares, Abram E.[1,3], Flynn, Shawn M.[1,3], Grisham, Amanda K.[1,3], Murphy, Erin N.[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

The number of prescriptions for and the off-label use of gabapentinoids (gabapentin and pregabalin) to treat pain is soaring with gabapentinoids increasingly detected in opioid overdose victims, raising concerns about the health risks of this class of drugs. The effect of gabapentinoids on *mu* opioid receptor (MOR)-mediated effects and a potential sex difference in those effects is not well characterized. Male and female rats (8 per sex) discriminating fentanyl (0.0032 mg/kg, i.p.) from saline were used to test the following hypotheses: 1) gabapentinoids do not share discriminative stimulus effects with fentanyl; 2) gabapentinoids increase fentanyl potency to produce discriminative stimulus effects; 3) gabapentinoids decrease naloxone potency to antagonize the discriminative stimulus effect of fentanyl; and 4) there is no sex difference in these effects. Gabapentin (10-320 mg/kg, i.p.) and pregabalin (3.2-100 mg/kg, i.p.) did not significantly increase fentanyl-appropriate responding. Each gabapentinoid (3.2-100 mg/kg, i.p.) dose-dependently shifted the fentanyl discrimination dose-effect function to the left whereas naloxone (0.01-1.0 mg/kg, i.p.) dose-dependently shifted the fentanyl discrimination dose-effect function to the right. Each gabapentinoid (100 mg/kg, i.p.) significantly decreased naloxone potency to antagonize the discriminative stimulus effect of fentanyl. Similar presession treatment effects of gabapentinoids were observed with heroin. No significant effect of sex was found in any experiment. These results can help guide government agencies and others develop better policies for regulating gabapentinoids and treating opioid misuse and overdose. Supported by USPHS grant R01DA058018 and the Welch Foundation (Grant AQ-0039).

Poster 56

Inhibition of Gβγ signaling produces antihyperalgesia by enhancing signaling from mu-opioid and 5HT1B/D receptors

Mohamed, Farzanna A[1], Smrcka, Alan V[2] and Jutkiewicz, Emily M[2]

[1]Neuroscience Graduate Program, Rackham Graduate School, University of Michigan;
[2]Department of Pharmacology, University of Michigan Medical School, Ann Arbor, MI, USA

Although mu opioid receptor (MOR) agonists provide short-term pain relief, they also produce adverse effects and are frequently misused, increasing susceptibility for opioid use disorder (OUD). It is necessary to find alternative analgesics with low abuse liability. Previous findings have shown that an inhibitor of Gβγ protein subunits, gallein, potentiates the antinociceptive effects of morphine without altering its rewarding effects *in vivo*. Therefore, we sought to evaluate if gallein-mediated inhibition of Gβγ signaling can enhance antihyperalgesic effects produced by endogenous opioid-induced activation of MOR. We treated female and male C57BL6/N mice with the Gβγ inhibitor gallein (10 mg/kg, i.p.), morphine (10 mg/kg, i.p.), or the 5HT1B/D agonist sumatriptan (0.6 mg/kg, i.p.) 90 min after nitroglycerin (NTG, 10 mg/kg, i.p.) and measured tail withdrawal latencies from a 46°C water bath. NTG decreased tail withdrawal latencies as compared with baseline, indicating a hyperalgesic state. Gallein, like morphine and sumatriptan, reversed NTG-induced decreases in withdrawal latencies. The nonselective opioid antagonist naloxone (NLX, 3.2 mg/kg, i.p.) attenuated the antihyperalgesic effects of gallein and morphine, but not sumatriptan, suggesting that activity at opioid receptors mediate the antihyperalgesic effects of gallein. GR127935 (3 mg/kg, s.c.), a 5HT1B/D antagonist, blocked the antihyperalgesic effects of sumatriptan and gallein, but not morphine. Interestingly, these data suggest that gallein may potentiate antihyperalgesic activity of endogenous opioid peptides and serotonin acting through opioid and 5HT1B/D receptors, respectively. Future studies will evaluate the role of the other Gi/o-coupled receptors in gallein-mediated antihyperalgesia.

Poster 57

Effects of methamphetamine on mitochondrial subpopulations in dopaminergic neurons

Abigail Morgan[1,2], Ana Bock[1], Harris Blankenship[1,2], Kelsey Carter[1], Michael Beckstead[1,2], Tommy Lewis[1,2]

[1] Department of Aging and Metabolism, Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104, USA.
[2]Department of Neuroscience, Biochemistry, Molecular Biology, and Physiology, University of Oklahoma Health and Sciences Center, Oklahoma City, OK, 73104, USA.

METH abuse leads to an increased susceptibility for dopaminergic neuron degradation within the nigrostriatal pathway, thus increasing the chances of developing Parkinson's disease. Mitochondria dysfunction is thought to play a key role in this degradation, as mitochondria are vital for producing ATP and buffering Ca^{2+}. Activation of the calcium dependent CAMKK2-AMPK pathway mediates mitochondrial size by promoting fission in order to link mitochondria morphology and function with neuronal activity. This link drives the formation of compartmentalized mitochondrial morphologies across other neuronal subtypes such as observed in cortical and hippocampal neurons. Since dopaminergic neurons exhibit a high level of activity along with poor endogenous calcium buffering, and methamphetamine use increases firing rates driving an increase in calcium flux, we hypothesized that dopaminergic neurons will have a unique compartmentalization of mitochondria morphologies that renders them more susceptible to chronic METH exposure. Utilizing DAT^{Cre} mice and a suite of genetically encoded probes to specifically label mitochondria in dopamine neurons; we set out to measure mitochondria morphology, relative redox state, ATP abundance, and calcium handling in axons and dendrites. To date, our results show that within the axon of dopaminergic neurons, mitochondria are smaller and less abundant compared to dendritic mitochondria which are more elongated and occupy more volume. Interestingly, dendritic mitochondria appear to become smaller, but the opposite happens in the axon, where the mitochondria become slightly longer when treated with METH.

Poster 58

Evaluation of mitragynine amide: Synthesis, receptor binding and pharmacological characterization in opioid and adrenergic receptors

Mukhopadhyay, Sushobhan;[1] Seabra, Maria;[1] Kanumuri, Siva Rama Raju;[2] Sharma, Abhisheak;[2] McCurdy, Christopher R;[1,2]

[1]Department of Medicinal Chemistry, 2Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL, 32610, USA

Kratom (*Mitragyna speciosa*), a plant native to Southeast Asia, has gained popularity for self-medication of pain, anxiety, depression, and opioid withdrawal. The most abundant alkaloid in kratom products, mitragynine (MTG), and its metabolite, 7-hydroxymitragynine (7-OH-MTG), are partial agonists at mu opioid receptors (MORs) *in vitro*, and are suggested to be responsible for pharmacological effects of kratom.[1,2] Structure-activity relationship (SAR) investigations of mitragynine have been focused primarily on the indole-nucleus of the scaffold (mostly at C9, C11, and C12 position).[3] Krugel *et al.* demonstrated the unsaturated beta-methoxy acrylate (BMA) is a key moiety for the binding of mitragynine with the MOR, therefore this part of the molecule has been kept integral throughout most of the studies in literature.[3] Interestingly, mitragynine also interacts with alpha adrenergic receptors and it has been hypothesized that this dual pharmacology is beneficial in treating opioid withdrawal. The present work aimed at developing novel molecules derived from mitragynine which can mimic its properties by chemically modifying the ester portion of the beta-methoxy acrylate (BMA) to the bioisosteric amide functional group. Compounds were screened separately at opioid and adrenergic receptors using radioligand binding assays. Among the twenty-four synthesized analogs, most of the compounds displayed promising results. Two compounds, SUSM-522 and SUSM-523, exhibited high affinity for MOR with K_i values of 67.8±7.02 and 81.9±9 nM, respectively and approximately ten-fold higher than mitragynine 709±91.2 nM. The adrenergic receptor binding of SUSM-501 at alpha-2A K_i = 1810±91.2 nM and alpha-2C K_i = 410±110 nM compared to mitragynine alpha-2A K_i = 4090±273 nM and alpha-2C K_i = 4040±417 nM. The details of synthesis, SAR, and metabolic stability will be presented and compared with mitragynine.

Poster 59

Discriminative stimulus effects of NBOH hallucinogens in rodents

Munir, Daaniyal D[1]; Shetty, Ritu A[1]; Gatch, Michael B[1]; Sumien, Nathalie[1]; Hill, Rebecca D[1]; Priddy, Jeanne A[1] and Forster, Michael J[1]

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

Despite the efforts of the Drug Enforcement Administration (DEA) to safeguard the public from hazardous analogs of synthetic hallucinogens, they have increasingly been observed in the illicit drug market. Four substituted phenethylamine hallucinogens, 25B-NBOH, 25C-NBOH, 25E-NBOH, and 25I-NBOH were tested in the mouse locomotor assay to obtain dose ranges and time courses for their psychoactive effects. The purpose of this study was to further characterize safety and abuse liability of these compounds using a drug discrimination (DD) assay. The synthetic hallucinogens were tested for substitution using separate groups of six male Sprague-Dawley rats that had been trained to discriminate the abused prototype dimethoxy-4-methylamphetamine (DOM) (0.5 mg/kg) from deionized water, using a two-lever choice methodology. DOM substituted for itself with an ED_{50} of 0.22 mg/kg, whereas 25B-NBOH (ED_{50} = 0.0095 mg/kg), 25C-NBOH (ED_{50} = 0.096 mg/kg), and 25E-NBOH (ED_{50} = 0.072 mg/kg) substituted for the DOM discriminative stimulus with comparatively greater potency. These results confirmed abuse potential for all the substituted phenethylamines with the exception of 25I-NBOH, which showed only partial substitution for DOM in the dose range of 0.05 to 0.5 mg/kg. While 25B-NBOH increased response rates, 25C-NBOH, 25E-NBOH and 25I-NBOH suppressed responding. The failure of 25I-NBOH to fully substitute may be due to its rate decreasing effects preventing the testing of higher doses. The ability of the phenethylamine compounds to produce depression in the locomotor activity assay predicted substitution in the DOM drug discrimination assay. Funding for this study was provided by NIDA contracts N01DA-18-8908 and N01DA-23-8908. DOM was provided by the NIDA Drug Supply Program.

Poster 60

Evaluating the analgesic effects of DS-II-48 and CP-55,940, alone and in combination

Rohit Nambiar, Danya Aldaghma, Pintu Miah, Indu Mithra Madhuranthakam, Nadia Afrin, Shakil Ahmed, Bradford D. Fisher, Thomas M. Keck*

Department of Chemistry & Biochemistry, Rowan University, Glassboro, NJ 08028
Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ 08103

Opioids are effective analgesics, but have undesirable side effects including constipation, abuse liability, respiratory depression, and overdose deaths. Cannabinoids have been explored as an alternative analgesic strategy but have their own undesirable side effects including constipation, respiratory depression, and loss of consciousness. Previously we have reported that α2/α3-selective $GABA_A$ positive allosteric modulators like DS-II-48 (an HCl salt of MP-III-024) can synergistically enhance opioid analgesia without increasing opioid side effects, effectively widening the therapeutic window for opioid analgesia. This project is focused on determining whether DS-II-48 can similarly synergize with the antinociceptive effects of the synthetic cannabinoid receptor 1 (CB1) agonist CP-55,940. Herein we report that while both male and female mice have similar responses to DS-II-48 in the hot plate assay, there were substantial sex differences in response to CP-55,940. In follow-up studies using only male mice, DS-II-48 and CP-55,940 elicited dose-dependent antinociceptive effects to mechanical stimuli in the von Frey assay. Ongoing tests are evaluating the effects of concurrent administration of both DS-II-48 and CP-55,940 in males and females. These results will help us determine if simultaneous targeting of CB1 and α2/α3-containing $GABA_A$ receptors is a viable route towards improved analgesia. Discovering new analgesic treatment regimens will hopefully improve the quality of living for patients undergoing pain treatment.

Poster 61

Methamphetamine induces conditioned place preference in a sex and strain specific manner in adolescent mice

Nunez Severino, Lewis[1]; Toussaint, Andre B.[1,3]; McKenna, Grace[1]; Burghardt, Nesha S.[1,2]

[1]Department of Psychology, Hunter College, CUNY, New York, NY; [2]Psychology Program, Behavioral and Cognitive Neuroscience, The Graduate Center, CUNY, New York, NY.; [3]Zuckerman Institute, Columbia University, New York, NY

There are sex differences in the use and response to methamphetamine, with women initiating use earlier and transitioning to regular use faster than men. However, most rodent studies investigating the cellular basis of addiction only test males during adulthood. We used a conditioned place preference (CPP) paradigm to test whether there are sex differences in the rewarding effects of methamphetamine in mice of two strains (C57Bl/6 and 129Sv/Ev). CPP began during adolescence (postnatal day 41), as substance abuse in humans often begins during this period of development. To evaluate the neural basis of methamphetamine-induced CPP, mice were perfused 90 minutes after the CPP test (drug-free), and immunohistochemistry was used to label cells expressing the neural activity marker c-Fos. Behaviorally-induced upregulation of c-Fos in the nucleus accumbens (NAc) was quantified with ImageJ software. In the C57Bl/6 strain, we found that methamphetamine enhanced locomotion without producing behavioral sensitization in both sexes. However, methamphetamine induced CPP in C57Bl/6 females only. In the 129Sv/Ev strain, methamphetamine induced behavioral sensitization and CPP in males only. In both strains, CPP was associated with an increase of c-Fos+ cells in the NAc shell. These results demonstrate sex and strain differences in response to methamphetamine and are consistent with literature indicating that the NAc drives the rewarding effects of drugs of abuse. This work may provide insight into which background strain is most appropriate to use when generating transgenic mouse lines in future CPP studies.

Poster 62

Investigating the effects of Gβγ inhibition on morphine-induced antinociception across different pain modalities

Ormes, Jacob A[1]; Zhang, Hanbo[1]; Smrcka, Alan V[1] and Jutkiewicz, Emily M[1]

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

Inhibition of Gβγ subunits with the small molecule, gallein, downstream of mu-opioid receptor (MOR) agonist-induced activation has been shown to potentiate morphine-induced antinociception without enhancing opioid-related side effects. Thus, Gβγ inhibition may be a promising treatment strategy for improving the therapeutic index of MOR agonists. However, the effects of gallein to potentiate morphine-induced antinociception have only been demonstrated in the warm water tail withdrawal assay (WWTW). Therefore, the goal of the current study was to evaluate whether gallein would potentiate morphine-induced antinociceptive effects in different assays. In female and male C57BL/6 mice, gallein pretreatments (i.p. 24 h and/or i.c.v. 30 min) to morphine were evaluated in the WWTW (55°C), hotplate (HP, 52°C), and acetic acid stretch (AASA) assays. In accordance with prior findings, both i.p. (100 mg/kg) and i.c.v. (100 nmol) gallein pretreatments potentiated the effects of morphine (3.2 mg/kg, i.p.) in the WWTW. Gallein (32 mg/kg, i.p.) also induced a leftward shift in a dose-response curve of morphine (s.c.) as compared to vehicle pretreatment in the AASA. However, neither i.p. (50 or 100 mg/kg) nor i.c.v. (100 nmol) gallein potentiated the effects of morphine (10 mg/kg, i.p.) in the HP assay. Together these data suggest that gallein does not potentiate morphine-induced antinociception in all circumstances. While central administration of gallein enhances the antinociceptive effects of morphine in the WWTW assay, this was not observed in the HP assay, which measures purportedly supraspinal nocifensive responses. Future work should seek to confirm these data and evaluate how gallein affects morphine-induced antinociception in other pain modalities.

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Poster 63

Efficacy and receptor activity of mitragynine and speciogynine in attenuating cancer-induced bone pain associated mechanical allodynia

Ortiz, Yuma T.[1]; Mukhopadhyay, Sushobhan[2]; McCurdy, Christopher R.[2]; McMahon, Lance R.[1]; Wilkerson, Jenny L.[1]

[1]Hodge School of Pharmacy, Pharmaceutical Sciences, Texas Tech University Health Science Center, Amarillo, TX USA.; [2]College of Pharmacy, Medicinal Chemistry, University of Florida, Gainesville, FL USA.

Cancer patients commonly experience neuropathic pain caused by tumor metastasis to bone, known as cancer-induced bone pain (CIBP). There are currently no curative treatments for CIBP. Analgesics such as gabapentinoids, serotonin-norepinephrine reuptake inhibitors, and opioids are used to treat CIPB. These analgesics provide only temporary relief that is susceptible to breakthrough pain and have side effects that limit therapeutic windows. Novel therapeutics are needed to alleviate CIBP. The kratom alkaloid mitragynine has previously been shown in mice to alleviate chemotherapy-induced neuropathic pain. The kratom alkaloid speciogynine has previously been shown in rats to provide antinociceptive effects. Utilizing a C3H/HEJ mouse sarcoma cell CIBP model, we assessed the potential therapeutic capacity of both kratom alkaloids to attenuate pain-related behaviors associated with CIBP. Tumor metastasis produced distinct mechanical allodynia but neither cold allodynia nor thermal hyperalgesia. Mitragynine (17.8 – 100 mg/kg, i.p.) significantly ($F(1.360, 9.518) = 21.53$, $p < 0.0001$) attenuated CIBP-induced mechanical allodynia. Speciogynine (10 – 32 mg/kg, i.p.) significantly ($F(1.277, 8.939) = 21.53$, $p = 0.0008$) attenuated CIBP-induced mechanical allodynia. We sought to elucidate the receptor activity responsible for mitragynine- and speciogynine-induced mechanical allodynia attenuation via antagonism studies utilizing naltrexone, yohimbine, or WAY-100635 administered prior to the alkaloids. Results indicate opioid and adrenergic activity of the alkaloids, with additional serotonergic activity with mitragynine. Ultimately, kratom alkaloids may hold potential as novel CIBP therapeutics.

Poster 64

A multifaceted approach to evaluate BEM as a treatment for alcohol use disorder

Panthagani, Praneetha[1]; Shaik, Abdul A[2]; Liu, Xiaobo[1]; Aguilera, Monica G[2]; Sanchez, Jordan N[2]; Vega, Arlette[2]; Shanmugam, Sambantham[2]; Castro-Piedras, Isabel[1]; Kisby, Brent R[1]; Medina, Daxx[1]; Adjei, Philip[1]; Blough, Bruce[3]; Pauli, Elliot[3]; Henderson, George E[1]; Ponomarev, Igor[1]; Bailoo, Jeremy D[2]; and Bergeson, Susan E[2].

[1]Dept of Pharmacology & Neurosci., [2]Dept of Cell Biology & Biochem., Texas Tech University Health Sci. Center, Lubbock, TX 79430, [3]RTI International, Research Triangle, NC 27709

Alcohol Use Disorder (AUD) has limed treatment options. 10-Butyl Ether Minocycline (BEM) was synthesized and characterized as the lead molecule, of 17 analogs, based on its physicochemical properties, preliminary efficacy, and safety studies. Here, we test the hypothesis that BEM reduces alcohol consumption during various phases of AUD. We utilized three mouse models representing mild (Drinking in the Dark - DID), moderate (Immune-Induced Escalation - IIE), and severe (Chronic Intermittent Ethanol - CIE) AUD. Additionally, a pig model resembling severe AUD was employed. This multifaceted strategy is crucial as multiple mammalian preclinical models may better represent the complexity of human AUD. For DID, a dose-response reduction in alcohol consumption at 20, 40 and 60 mg/kg of BEM was observed. Consistent with the pharmacokinetic profile of BEM, a significant reduction in consumption at 6 hr but not at 24 hr with a dose of 60 mg/kg, i.p was noted in the IIE model. In CIE model, BEM (60 mg/kg, i.p.) reduced alcohol consumption by 80%. Both sexes were included in all tests and only IIE showed a difference in efficacy. Finally, in a non-rodent, swine model, we treated two female minipigs with a history of nearly 3 years of alcohol consumption with at least six of eleven DSM-V criteria, meeting severe AUD diagnoses. At 10 mg/kg p.o. BEM, a reduction in both alcohol consumption and preference were observed. The use of multiple models confirmed the efficacy of BEM across various stages of AUD making BEM a potential candidate for AUD treatment. Ongoing pharmacokinetic studies are also vital for FDA Investigational New Drug application approval.

Poster 65

Region-specific alterations of orexin-a neuronal densities in the hypothalamus of rhesus monkeys with chronic alcohol use

Pareek, Tanya[1]; Grant, Kathleen, A[3,4]; Platt, Donna, M[1,2]; Gisabella, Barbara[1,2.] and Pantazopoulos, Harry[1,2.]

[1]Program in Neuroscience, University of Mississippi Medical Center, Jackson, MS USA; [2]Division of Neurobiology and Behavior Research, Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS USA; [3]Division of Neuroscience, Oregon National Primate Research Center, Oregon Health & Science University, Portland, OR USA; [4]Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR USA.

The orexin system plays an integral role in reward signaling and sleep, representing a promising therapeutic target for both substance abuse and sleep disturbances in people with an alcohol use disorder (AUD). Orexin neurons are located in the lateral hypothalamic area (LHA) and the dorsomedial hypothalamus (DMH) and differentially innervate reward signaling areas. The objective of the present study was to evaluate orexin-A neurons in the LHA and DMH of rhesus monkeys with chronic alcohol use. Serial sections (n=5/monkey) of hypothalamus samples from adult, male rhesus monkeys with a history of chronic alcohol use (n=7) or no alcohol (n=5) were used. Sections were labeled with immunohistochemistry for orexin-A and counterstained with methyl green. Neurons expressing orexin-A in hypothalamic subregions were quantified with stereology-based computer assisted light microscopy, and densities of orexin-A neurons in the LHA and DMH were compared between groups using analysis of variance. Our results identified significantly greater densities of orexin-A neurons in the DMH region ($p<0.03$) in monkeys with chronic alcohol use compared to monkeys without alcohol use. In contrast, densities of orexin-A neurons were significantly decreased in the LHA region of monkeys with chronic alcohol use ($p<0.05$). The current results suggest that orexin-A alterations are region-specific, potentially explaining discrepancies in prior studies. Alterations may impact alcohol use, contributing to the relationship between sleep and alcohol consumption.

Poster 66

Epigenetic, behavioral, and neurobiological analysis of a transgenerational model of drug abuse and relapse vulnerability in psychosis

Peeters, LD[1]; Wills, LJ[1], Cuozzo, AM[1], Ivanich, KL[1], Wang, C[2], Chen, W[2], Chen, Z[2], and Brown, RW[1]

[1]Department of Biomedical Sciences, East Tennessee State University, Johnson City, TN USA; [2]Department of Basic Sciences, Loma Linda University School of Medicine, Loma Linda, CA, USA

Psychotic disorders such as schizophrenia are often accompanied by high rates of cigarette smoking, reduced quit success, and high relapse rates. However, the mechanisms underlying altered relapse-like behaviors in individuals diagnosed with psychosis are poorly understood. The present study explored epigenetic mechanisms contributing to enhanced drug abuse vulnerability in a novel heritable model of psychosis, demonstrating increased dopamine D2 receptor sensitivity, and analyzed changes in brain-derived neurotrophic factor (BDNF) response following altered relapse-like behavior. Male and female offspring of two neonatal quinpirole-treated (QQ) and two neonatal saline-treated (SS) Sprague-Dawley rats were tested on an extended CPP paradigm to analyze changes in extinction and nicotine-primed reinstatement (N=6/group). Brain tissue was analyzed for BDNF response in brain areas that mediate addiction 60 min after the last nicotine injection (N=4/group). In a separate set of male QQ and SS offspring, methyl-seq analysis was performed (N=6/group). QQ offspring demonstrated delayed extinction, more robust reinstatement, and an enhanced BDNF response to nicotine compared to SS control animals. Methyl-seq revealed region-specific changes in several pathways, including nicotine addiction, dopamine synapses, and neuron projections. These results reveal epigenetic mechanisms of heritability, and demonstrate altered relapse-like behavior consistent with a model of comorbid drug abuse and psychosis. Behaviorally, this is related to elevated activity-dependent BDNF in brain areas associated with drug reward, which persists through the extinction phase, rendering aberrantly salient drug associations resistant to extinction and enhancing relapse vulnerability.

Poster 67

Quantitative comparisons of biased mu agonists to full and partial mu agonists in measures of drug self-administration and thermal antinociception

Pham, Loc MT[1]; Pareek, T[1]; Gilmore, J[2]; Blough, Bruce E[3] and Freeman, Kevin B[1,2]

[1]Program in Neuroscience, University of Mississippi Medical Center, Jackson, MS, USA; [2]Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS, USA; [3]Research Triangle Park, RTI, NC, USA.

G-protein biased agonists at the mu-opioid receptor (MOR) are purported to produce antinociception with fewer adverse effects than typical MOR agonists. However, it has been suggested that this improved profile can be explained by partial intrinsic efficacy of the biased agonists. The objective of the current study was to compare the biased agonists, PZM21 and SR17018, to typical MOR agonists with full (fentanyl and oxycodone) and partial (buprenorphine and butorphanol) intrinsic efficacy in *in vivo* measures that are sensitive to the differences in intrinsic efficacy. In the first study, 4 female and 6 male Sprague-Dawley (SD) rats were tested in thermal antinociception using the hot-plate method set at three temperatures (48, 50, and 52.5°C). In the second study, separate groups of male and female SD rats self-administered one of the respective MOR agonists (N's vary per drug) under a progressive-ratio schedule of reinforcement. Full dose-response determinations were obtained in each study. In the antinociception study, only fentanyl, oxycodone, and SR17018 produced full antinociception at the highest temperature (52.5°C), although the other compounds were effective at the lower temperatures. In the drug self-administration study, only fentanyl and oxycodone were self-administered significantly more than vehicle. Generally, the biased agonists produced *in vivo* effects consistent with partial intrinsic efficacy with the exception of SR17108 producing full antinociception at the highest temperature. This difference may be related to yet-to-be discovered effects specific to SR17018's structural class or differences in the effects of receptor reserve on the two behavioral measures.

Poster 68

Understanding opioid rehabilitation needs for young adult black women ages 18-30

Porter, Tequila S[1]; Draughon Moret, Jessica[2]

[1]Betty Irene Moore School of Nursing, University of California, Davis; [2]Betty Irene Moore School of Nursing, University of California, Davis

The aim of this study was to explore Black women's explanatory models of their opioid use disorder and decision to engage in formal rehabilitation. In 2021, 9.2 million people reported past-year opioid misuse. Increased public health efforts have aimed to reduce opioid use disorders since 2015, yet many people are still not receiving appropriate rehabilitation care. More importantly, in 2021, roughly 1.2 million Blacks reported an opioid use disorder. Despite increased rates of opioid use among Blacks, and increased attention and treatment for people with opioid use disorders, Black women remain understudied. National surveillance provides opioid use pattern rates but data on the intersection of gender, race, and geography are missing. Thus, there is a gap in knowledge about Black women and their experiences with opioid use rehabilitation services. This social constructivist grounded theory study interviewed Black women ages 18 and older with opioid use rehabilitation experiences, within the United States. Participants were recruited via a university hosted recruitment site. Participants (N=30) completed in-depth individual interviews via Zoom between January 2023 and April 2023. Preliminary results will be presented. Black women aged 18-30 years responded to the study call. Participants reported oral opioid use, heroin use, and multi-use histories. Participants acknowledged the emotional and physical traumas which influenced initiating use, and multiple overlapping experiences of societal backlash from within Black communities. Participants described backlash for opioid use, saying "we don't do those kind of drugs"; and backlash for seeking help "Blacks don't need that kind of help"; and backlash within rehab programs "Blacks are supposed to be strong, so you don't need help". Black women might be more attracted to complete rehab if the rehab programs focus on fostering community and connections versus invalidating Black women's experiences. The societal message and internalized *need to be a Strong Black Woman* are hurting Black women's health behaviors and biasing care providers.

Poster 69

In vivo drug-drug interactions between synthetic cannabinoid receptor agonist 5F-APINACA and benzodiazepines: Effects on core temperature in mice

Pressley, Justin M[1]; Shaw, Hannah E[1] and Fantegrossi, William E[1]

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

As of October 2022, synthetic cannabinoid receptor agonists (SCRAs) continue to account for more than 25% of new abused drugs appearing on the global market. Recent US surveys report a significant increase in SCRA use among 12th graders and persistent SCRA abuse in vulnerable populations, including those with mental health disorders. Co-administration of SCRAs and commonly prescribed psychiatric medications (PSYCs) occurs frequently, because substance use disorder often co-occurs with other psychiatric disorders. Moreover, co-use of PSYCs and SCRAs is evident from clinical reports and autopsies of SCRA abusers, with the most common anxiolytic found among SCRA users being the strong CYP3A4 inhibitor alprazolam. In these studies, we used implantable radiotelemetry probes to determine a dose-effect relationship for hypothermic effects of the SCRA 5F-APINACA (which is extensively metabolized by CYP3A4), and to determine the timecourse of effects of the benzodiazepines alprazolam and lorazepam on core temperature in male C57 mice. We then chose an intermediate dose of 5F-APINACA and administered it in combination with alprazolam (where we expected a metabolic interaction) or lorazepam (where we did not). On its own, 5F-APINACA elicited robust time- and dose-dependent hypothermic effects. In combination with alprazolam, the duration of 5F-APINACA-elicited hypothermia was dramatically increased, but co-administration with lorazepam did not alter hypothermic effects. As a control experiment, we administered the SCRA JWH-018 (which is not metabolized by CYP3A4) alone or in combination with the benzodiazepines. In contrast to the findings with 5F-APINACA, neither alprazolam nor lorazepam altered hypothermic effects elicited by JWH-018. These findings illustrate that co-use of SCRAs and PSYCs may exacerbate drug effects with implications for abuse and toxicity.

Poster 70

Nonhuman primate models of cocaine-alcohol polysubstance use: Effects of chronic ethanol drinking on cocaine reinforcement

Prete, Joshua N; Collier, Miracle C; Epperly, Phillip E; Roberts, Brianna F; Czoty, Paul W

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

Cocaine use disorder (CUD) is a persistent and rapidly growing problem in the US with no candidate pharmacotherapies proving safe and effective enough to achieve FDA approval. One possible reason for this lack of progress is that, although cocaine is typically used in combination with alcohol, these drugs are studied in isolation in preclinical studies. Our laboratory has developed a nonhuman primate (NHP) model of polysubstance use (PSU) in which 12 monkeys self-administer (SA) cocaine in the morning and drink either ethanol (n=6) or a control solution (n=6) in the afternoon. In these groups, cocaine SA dose-effect curves (0.0003-0.3 mg/kg/inj, i.v.) were determined before and after 2 years of SA of 0.1 mg/kg per injection cocaine under a 30-response fixed ratio (FR30) schedule. At the latter time, cocaine SA under a progressive-ratio (PR) schedule was also compared between groups. Noting that cocaine and ethanol SA were separated in time in those studies, we also examined the effect of cocaethylene (0.1-3.0 mg/kg, i.v., 5 minutes before cocaine SA)—a cocaine-like cocaine metabolite formed in the presence of ethanol—on FR30 cocaine SA. Cocaine SA dose-response curves did not differ between ethanol-drinking and control groups under either the FR30 or the PR schedule of reinforcement. Cocaethylene shifted the cocaine SA dose effect curve to the left. Results indicate that although ethanol modifies the effects of cocaine SA on the brain, cocaine SA is not altered when cocaine and ethanol are consumed separately. Our data suggest that cocaethylene generated by consuming alcohol just before cocaine SA may be required for long-term increases in the reinforcing potency of cocaine. Preliminary studies indicate that sufficient cocaethylene is produced when ethanol drinking immediately precedes cocaine. These data are being used to refine and enhance the translational validity of our NHP nonhuman model of cocaine-ethanol PSU. Funding: DA039953.

Poster 71

Evaluation of a polypharmacy approach targeting dopamine D3 and serotonin 2C receptors to decrease drug taking in rats

Puzovic, Gorana[1]; Mason, Briana M.[1,2]; Thomas, Anona[1,2]; George, Christina M.[1,2]; Shi, Yonggong[1,2]; Cao, Jianjing[3]; Newman, Amy H.[3]; Collins, Gregory T.[1,2]

[1]Dept of Pharmacology, University of Texas Health Science Center at San Antonio; [2]South Texas Veterans Health Care System, San Antonio, TX, USA; [3]Molecular Targets and Medications Discovery Branch, NIDA-IRP, Baltimore, MD, USA

Preclinical research has demonstrated that dopamine (DA) D3 and serotonin (5-HT) 2C receptor ligands decrease stimulant and opioid self-administration; however, clinical investigations have been less promising. Improving receptor selectivity and/or developing polypharmacy methods targeting both DAD3 and 5-HT2C receptors are two approaches to advance drug development efforts. Male and female Sprague-Dawley rats were implanted with venous catheters and allowed to self-administer cocaine, methamphetamine (METH), fentanyl, or sucrose under a progressive ratio schedule of reinforcement. Inhibition functions for a DAD3 receptor-selective antagonist (VK4-116) and partial agonist (VK4-40), as well as a 5-HT2C receptor-selective agonist (CP809,101) were established for each drug alone, as well as for combinations of VK4-116 + CP809,101 and VK4-40 + CP809,101 at ratios of 3:1, 1:1, and 1:3 relative to the ID50 for each drug to reduce drug self-administration. Individually, VK4-116, VK4-40, and CP809,101 each reduced responding for to cocaine, METH, and fentanyl, with CP809,101 being most potent and effective. Combining VK4-116 + CP809,101 and VK4-40 + CP809,101 resulted in a dose dependent and complete inhibition of responding for cocaine, METH, and fentanyl. Importantly, mixtures were less potent and effective at decreasing responding for sucrose. These findings show that a polypharmacy approach targeting DAD3 and 5-HT2C receptors can effectively (and selectively) inhibit self-administration of both stimulants and opioids, suggesting that such an approach could provide a broad-spectrum strategy for treating (poly)substance use disorders.

Poster 72

Expression of behavior and extracellular matrix structures after acute or repeated oxycodone exposure and abstinence in male and female Wistar rats

Reeves, Blake A.; Dejeux, Mariana I. M.S.; Jewanee, Sarah S.; Nguyen, Jacques D. Ph.D.

Department of Psychology and Neuroscience, Baylor University, Waco, TX, USA.

Oxycodone, a potent opioid often prescribed to manage pain, can cause addiction and dependence if used nonmedically. We hypothesized that male and female Wistar rats (~10 weeks old) repeatedly injected with oxycodone would express tolerance and dependence-like behaviors in a dose-dependent manner, and that expression of perineuronal nets (PNNs), extracellular matrix proteins important to neuroplasticity and conditioning, would differ following abstinence. Subjects were randomly sorted into groups receiving a single or repeated (twice daily for 7 days) oxycodone injection (2 or 4 mg/kg, i.p.) or 0.9% saline vehicle. A thermal antinociception test was used to validate opioid intoxication, tolerance, and spontaneous or precipitated (naloxone-induced, 1 mg/kg, i.p.) withdrawal following an acute or extended (1 day vs. 4 week) abstinence period. Behavioral tests included marble burying, elevated plus maze, and opioid-withdrawal scoring. Whole brain coronal slices were collected to identify *Wisteria Floribunda Agglutinin* (WFA)-PNNs using immunohistochemistry. Significant antinociceptive effects of oxycodone and tolerance following repeated injections ($p < 0.05$) were observed in both sexes. Marble burying behavior was significantly higher in subjects that received repeated oxycodone injections followed by a naloxone injection compared to controls ($p<0.05$). Initial analysis suggests a dose-dependent and time-dependent change in PNN number in the trunk. Analysis of PNNs in the ventral tegmental area, nucleus accumbens, and amygdala is forthcoming. Ongoing experiments will determine if acute or repeated fentanyl (0.01 and 0.02 mg/kg, s.c.) will alter PNN expression. Overall, these data suggest that oxycodone administration and abstinence may alter expression of extracellular matrix structures (e.g. PNNs) that are crucial to memory, emotional regulation, and reward, following a repeated exposure with or without behavioral tolerance or withdrawal-like effects.

Poster 73

The relationship between anxiety-like behavior and methamphetamine-induced behavioral sensitization in adult rats

Roach, M.L., Nguyen, C.H., Nguyen, T.P., Lin, A., Siu, E.N., Sedillo, A.G., & Zavala, A.R.

Department of Psychology, California State University, Long Beach

Methamphetamine (METH) is one of the most abused psychostimulant drugs, which has led to an increase in overdose deaths in recent years. Repeated exposure to METH results in behavioral sensitization, and in rodents, is characterized by an increase in the behavioral response without increasing the dose of METH or an enhanced response in animals given chronic administration compared to animals given an acute injection of the drug. METH leads to locomotor sensitization after single or repeated doses. METH also results in changes in anxiety-like behavior, with some studies finding anxiolytic and others finding anxiogenic effects. Few studies have examined the relationship between sensitization and anxiety-like behavior. Thus, this study examined anxiety-like behavior after repeated METH using the elevated plus maze (EPM). We hypothesized that METH-induced sensitization would be associated with greater anxiety-like behavior. Adult male and female Sprague-Dawley rats (N = 75) were pretreated with either saline or METH (0.11–3 .0 mg/kg, SC) for 7 days, and their locomotor activity was assesed daily for 90 min. Rats were then tested in the EPM 24 h later. Five days later, behavioral sensitization was assessed with a challenge injection of METH (.33 mg/kg, SC), during which locomotor activity was assessed for 120 min. The next day, rats were again tested in the EPM. Contrary to our expectations, rats pretreated with METH exhibited a significant decrease in locomotor activity from day 1 to day 7 in all groups except the 0.33 METH group (ANOVA). During the challenge test, the 0.33 and 1.0 METH groups exhibited an increase in locomotor activity when compared to the acute group. However, no sensitization was evident after the initial 10 min. EPM data revealed no differences in any of the groups or EPM tests. The lack of locomotor sensitization may be attributed to the emergence of stereotypy, which may have masked the sensitized response. Future research will examine rearing and sniffing as measures of behavioral sensitization.

Poster 74

Study of correlation between sleep and alcohol sensitivity and tolerance in *Drosophila melanogaster*

Rodriguez-Avila, Isabela[1]; Osegueda-Delgado, Joel[1]; Martinez, Evelyn[1]; Kang, Yuan Yuan[1]

[1]Department of Natural Sciences; University of Houston-Downtown, Houston, TX

Sleep is a homeostatically-regulated process and influenced by the circadian rhythms with distinct mechanisms in vertebrates and invertebrates. Some studies showed potentially conserved mechanisms in the relationship between sleep and other phenotypes, such as life span, learning and memory, and response to alcohol. While there is evidence that drinking alcohol affects sleep duration and pattern, less is known about the vice versa, which is whether alteration in sleep correlates with changes in animals' response to alcohol. Here, we utilized a previously established inbred sleep panel of *Drosophila melanogaster* differing in their length of sleep from short to long sleep cycles. We then tested whether their sleep duration and pattern correlated with several locomotive behaviors, including exploration, negative geotaxis, and alcohol sensitivity/tolerance. We hypothesize that short sleep flies should show higher sensitivity and lower 4-hour rapid tolerance to alcohol while long sleep flies should show the opposite trends, in a Loss of Righting (LoR) reflex assay. Our preliminary results showed a clear positive correlation between sleep length and exploration and negative geotaxis, but not with alcohol sensitivity/tolerance. Through this experiment we hope to expand our knowledge regarding the correlations between sleep and alcohol sensitivity, ultimately applying these findings in search for effective therapies for alcohol disorders.

Poster 75

The enkephalinase inhibitor RB101 enhanced cocaine conditioned reinforcement in the New Response Acquisition procedure

Rysztak, Lauren G*[1] and Jutkiewicz, Emily M[1]

[1]Department of Pharmacology, University of Michigan, Ann Arbor, MI

One contributor to relapse is the ability of environmental cues that have been associated with drug to evoke drug-craving and -seeking behaviors. We sought to evaluate whether increasing the endogenous opioid peptide enkephalin, which has been shown to potentiate reinstatement behaviors, also increases responding for cocaine-paired cues in a stringent test of cocaine conditioned reinforcement (New Response Acquisition). Further, we investigated which opioid receptors mediate potential effects of enkephalins as these peptides have been shown to bind to both mu and delta opioid receptors (DORs). The procedure begins with Pavlovian Conditioning in which subjects receive five infusions of cocaine (320 ug/kg/inf) and either simultaneous (Paired) or separate (Unpaired) presentations of a light+tone stimulus per day for 10 days. Then, novel operant manipulanda are introduced into the chamber, and responses produce presentations of cues formerly associated with cocaine (Acquisition). During Acquisition, a drug pre-treatment was administered acutely before the start of the session and responding was evaluated. Consistent with previous findings, subjects in the Paired group make more active responses than inactive responses for cue presentations than Unpaired subjects. Interestingly, acute administration of the enkephalinase inhibitor RB101 (10 mg/kg intravenously), which prevents breakdown of enkephalin peptides, robustly increased responding for cocaine-paired cues. The effects of RB101 were blocked by the DOR selective antagonist naltrindole (3.2 mg/kg subcutaneously), suggesting enkephalins are acting in a DOR dependent manner. Further, selective activation of delta, but not mu or kappa, opioid receptors increased the conditioned reinforcing properties of cocaine-paired cues. These data suggest that enkephalins acting via DORs may mediate cocaine cue-controlled behaviors and provide a novel target for pharmacological interventions for relapse.

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Poster 76

Appetitive operant conditioning acquisition sex-dependently enhanced by PMAT deficiency

Scrimshaw, Lauren R[1], Hallal, Elayna M[1], Hite, Allianna K[1], Ross, Aliyah J[1], Crites, Anna E[1], Sonick, Grace A[1], Beaver, Jasmin N[1], Shafer, Amanda L[1], Gilman, T. Lee[1]

[1]Department of Psychological Sciences, Kent State University, Kent, OH

Plasma membrane monoamine transporter (PMAT, *Slc29a4*) is a low affinity, high-capacity transporter of dopamine and serotonin. Around 30% of humans have a PMAT polymorphism associated with reduced PMAT function. How reduced PMAT function affects behavior remains unknown, in part because no known drugs selectively inhibit PMAT. Thus, the objective of this study was to use genetically modified PMAT-deficient mice to investigate how reduced PMAT function impacts appetitive operant conditioning performance for a food reinforcer. So far, we've used 33 mice (8 males, 25 females). Once mice completed fixed ratio (FR) -1, -3, and -5 schedules, then reached a stable breakpoint on a progressive ratio (PR) schedule, operant behavior was paused. Mice were swum 8 weeks later, then returned to operant testing to reach a stable breakpoint again. We hypothesized PMAT knockout (KO) mice would perform better, completing FR schedules before their wildtype (WT) and heterozygous (HT) littermates, due to prolonged dopamine and serotonin signaling. Thus far, we've observed that all KO mice completed FR & PR schedules within their first 40 days, as opposed to their same sex WT counterparts requiring 100+ days. FR data were analyzed with survival curve log rank tests; PR data analyzed with two- (gene × sex) and three-way (gene × sex × stress) ANOVAs. Stress experiments are ongoing. Our findings suggest normal PMAT function attenuates operant acquisition when responding for food reinforcers. Given we have found sex-specific effects of PMAT in other dimensions of behavior, we hypothesized breakpoints would increase more after stress in PMAT-deficient males versus females. Future directions for this project include evaluating the necessity of sex hormones in these PMAT-deficient shifts, and further characterization of how stress interacts with sex and PMAT genotype to alter responding for other reinforcers (e.g., reinforcing drugs).

Poster 77

The use of single-chain variable fragments (scFv) to reverse cardiopulmonary and antinociceptive effects of fentanyl in male mice

Seaman Jr, Robert[1]; Hannon, Bryan[1]; Hicks, Dustin[2]; Baehr, Carly[2]; and Pravetoni, Marco[1]

[1]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA USA; [2]Department of Pharmacology, University of Minnesota, Minneapolis, MN USA

Opioid use disorder and opioid-related overdose deaths continue to serve as a worldwide health concern and were further exacerbated by the COVID-19 pandemic. Current FDA-approved treatments for opioid overdose are limited to opioid receptor antagonists and may produce untoward effects (e.g., opioid withdrawal, sympathetic overshoot). Immunotherapeutics have been proposed a complementary treatment for opioid overdoses. The current study investigated the potential of an anti-fentanyl single-chain variable fragment (scFv) to reverse the cardiopulmonary and antinociceptive effects of fentanyl. Male BALB/c mice (n=5 per group) were administered subcutaneous fentanyl (0.1 mg/kg) and 15 minutes later were administered either subcutaneous saline (10 ml/kg), subcutaneous naloxone (0.1 mg/kg), or an scFv (40 mg/kg) delivered intramuscularly, intravenously, or subcutaneously. Heart rate, breath rate, and oxygen saturation were quantified in 5-minute intervals, and thermal nociception in 15-minute intervals, for a total of 60 minutes. Fentanyl significantly reduced heart rate, breath rate, oxygen saturation, and thermal nociception. Intramuscular and intravenous injections of scFv rapidly reversed the cardiopulmonary and antinociceptive effects of fentanyl, returning them to baseline. Similarly, subcutaneous administration of an scFv produced a less rapid, but complete, reversal of the effects of fentanyl. Together, these data support the use of scFvs to treat opioid overdose. Future studies will determine whether scFvs produce an opioid withdrawal syndrome akin to that produced by naloxone, as well as the selectivity of this scFv to bind fentanyl relative to other structurally similar fentanyl analogs with the ultimate goal being the development of clinically effective immunotherapeutic treatments for individuals suffering from opioid use disorder and at risk of overdosing.

Poster 78

Pharmacokinetics and toxicokinetics of 10-butyl ether minocycline

Shaik Abdul A[1], Panthagani Praneetha[2], Blough, Bruce E[3], Bergeson, Susan E[1]

[1]Dept. of Cell Biol. & Biochem., [2]Dept. of Pharm. & Neurosci., TTUHSC, Lubbock TX; [3]RTI International, Research Triangle Park, NC.

Current treatment efficacy and compliance for Alcohol Use Disorder needs improvement. Out of 17 minocycline analogs, 10-Butyl Ether Minocycline (BEM) became the lead molecule based on its physicochemical properties, preliminary efficacy, and safety studies. We have established the efficacy of minocycline and BEM in reducing alcohol consumption in mice and swine models. The current study was aimed at determining the pharmacokinetics (PK) of BEM in three different model organisms: mice, rat and dogs. In addition, toxicokinetics (TK) on rats were performed. Blood and brain samples were analyzed using LC-MS for BEM and the PK/TK was subsequently modeled using non-compartmental analysis (NCA). All studies had a sampling interval of 0-, 0.5-, 1-, 2-, 4-, 8- and 24-hr time points. Both male and female mice (3 / time point) were administered with BEM at two different doses, 50mg/kg (PO, IP) and 100mg/kg (PO). Sex-differences were observed in the plasma pharmacokinetics, where females had a higher half-life (t1/2 = 9 h for 100 PO) compared to males (t1/2 = 5.9 h for 100 PO). Rats of both sexes were subjected to PK (50mg/kg PO) and TK (1000mg/kg PO) analyses (2 rats / timepoint). Plasma PK concentration-time profiles, Cmax, and AUC values were similar between males and females (F:M Cmax ratios ranged from 0.795 to 1.35 and F:M AUC0-24hr ratios ranged from 0.929 to 1.34). Two different dosing regimens were followed for TK: rising-dose [n=3 / sex] at 10 mg/kg to 1000 mg/kg and multiple-dose at 100 mg/kg to 500 mg/kg [n=5 males]. For TK, the median Tmax values was 1 hour at 100 mg/kg and 16 hours at 500 mg/kg on Day 10. For the dog PK analyses, 1 male and 1 female dog were administered with 50 mg/kg (PO) dose on two different days (day 1 and 8). Sex-differences were seen in the PK profile with a Tmax for female on day 1 at 0.5 hr and the male on day 8 at 0.5 hr. The NCA analyses revealed that BEM had favorable PK profiles for both PO and IP route.

Poster 79

Locomotor effects of MDMA-like psychostimulants in C57BL/6 and autism-like BTBR T^{+}Itpr3^{tf}/J mice

Shaw, Hannah E[1] & Fantegrossi, William E[1]

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

Locomotor stimulant effects of 3,4-methylenedioxymethamphetamine (MDMA) and related drugs have been demonstrated in multiple species, and these effects may be treatment-limiting in a therapeutic context. MDMA and its analogues are being explored as potential treatments for social withdrawal secondary to Autism spectrum disorder (ASD), but the effects of these drugs in the BTBR T^{+}Itpr3^{tf}/J (BTBR) mouse – the "gold standard" model for ASD research – have not been adequately characterized. These studies used implantable radiotelemetry probes to monitor locomotor activity within the homecage environment elicited by injections of MDMA and a series of structurally-related phenethylamines, including methamphetamine, methylone, methcathinone, α-PVP, MDPV, 5-EAPB and 6-EAPB in male C57BL/6 (C57) and BTBR mice. All drugs elicited dose- and time-dependent locomotor stimulant effects, though a full dose-effect determination for methylone could not be completed due to observation of convulsions (in both strains) and lethality (in C57s only). In all other cases, drug doses which elicited locomotor stereotypy in C57 mice (thus defining the descending limbs of their dose-effect curves) failed to do so in BTBR mice, resulting in large strain-dependent differences in locomotor AUC values. Because the drugs studied vary in their affinities for and selectivities among monoamine transporters, and because some drugs function as monoamine releasers while others function as passive reuptake inhibitors, it is likely that pervasive neurobiological and / or metabolic differences in BTBR mice mediate this apparent resistance to stereotypy. These studies emphasize the need to extensively characterize mutant mouse models in order to better interpret experimental results.

Poster 80

Renewal of alcohol-seeking in male and female rats

Simmons, Taylor A[1]; Gonzales, Rueben A[2,3]; Monfils, Marie H[1,3]; Lee Hongjoo J[1,3]

Department of Psychology[1], College of Pharmacy[2], and Institute for Neuroscience[3], University of Texas at Austin, Austin, TX 78712

Environmental cues become conditioned stimuli when associated with alcohol consumption, and facilitate alcohol-seeking, even during abstinence, leading to relapse. Extinction of a conditioned alcohol-seeking response can reduce cue-conditioned responses but often renewal occurs when the cue is presented in a different context than the extinction context. Existing research suggests sex differences whereby males exhibit more robust renewal of both appetitive and fear responses (Anderson and Petrovich, 2015; Binette et al., 2022); however, the presence of sex differences in renewal of alcohol-seeking behavior is not known. In the current study, we investigated the impact of contextual shifts and discrete environmental cues on renewal of alcohol-seeking behavior in rats. Male (n=9) and female (n=16) Long-Evans rats first underwent an induction phase: 15% unsweetened alcohol was provided MWF on a 24-hour schedule over a 5-week period. Then, Pavlovian conditioning took place in context A (standard conditioning chamber) where a 20-second light presentation was paired with a 10-second presentation of sipper containing 15% unsweetened alcohol (8 trials/session, 12 daily sessions). Subsequently, extinction (12 trials/session, 12 daily sessions) and testing (4 trials) occurred in context B consisting of smooth flooring, lemon scents, and black wall on the front and back of conditioning chambers. A 20-second light presentation was paired with a 10-second presentation of sipper without alcohol. Renewal testing (4 trials) occurred in context A. The results demonstrated successful extinction as measured by low levels of sipper contact (indicating reduced alcohol-seeking behavior) during extinction memory recall in context B. Notably, both male and female rats showed a similar increase in sipper contact when placed back in the original alcohol associated context (context A). Therefore, no sex difference was observed in renewal of alcohol-seeking behavior in Long-Evans rats.

Poster 81

Activation of 5-HT1B receptors with zolmitriptan on the acquisition of ethanol preference in adolescent female Sprague-Dawley rats

Siu, E. N., Moore, S. P., Garcia, A. K., & Zavala, A.R.

Department of Psychology, California State University, Long Beach

Activation of serotonin-1B (5-HT1B) receptors decreases the reinforcing and rewarding effects of psychostimulants and ethanol, but no studies have examined the effects of activating this receptor in adolescent rats. Thus, the present study investigated whether administering zolmitriptan, a 5-HT1B agonist, attenuates the preference for ethanol in adolescent female rats. Ethanol preference was examined using the conditioned place preference (CPP) paradigm. We hypothesized that zolmitriptan would attenuate the acquisition of ethanol-induced CPP, which was assessed across a 10-day CPP procedure. On day 1, baseline, adolescent female Sprague-Dawley rats (N = 94) had free access to both sides of a two-chamber apparatus for 15 min. During days 2–9 of conditioning, rats were injected on alternating days with saline or ethanol (0, 0.625, or 2.0 g/kg, IP) and were immediately confined to one side of the apparatus for 15 min. During ethanol-paired days, rats were initially pretreated with 10 mg/kg of zolmitriptan or vehicle. On day 10, preference for the ethanol-paired side was assessed (i.e., PD 40), during which rats again had access to both sides of the CPP apparatus for 15 min. Female rats exhibited a preference for the 2.0 g/kg dose of ethanol, as they spent significantly more time on the ethanol-paired side compared to the vehicle-saline group (ANOVA/Dunnett test). Moreover, pretreatment with zolmitriptan attenuated the preference for the 2.0 g/kg dose of ethanol, and this decrease was not associated with a decrease in locomotor activity on the test day. Interestingly, zolmitriptan alone resulted in an increased preference for the drug-paired side (i.e., without any ethanol). The latter is surprising, as preference using this dose of zolmitriptan has not been reported. Overall, however, our findings indicate that activating 5-HT1B receptors decreases the rewarding effects of ethanol in female adolescent rats. These findings add to a growing body of literature that points to this receptor as a pharmacological target for treating drug addiction.

Poster 82

Region specific neuroadaptations of CB1, but not CB2, receptors in heroin-dependent rats

Slama, Joseph[1]; Xie, Coco[1]; Burdick, Emma[1] and Galaj, Ewa[1]

[1]Neuroscience Program, Colgate University, Hamilton, NY, USA.

Chronic opioid use leads to long-term dysregulation of the systems related to reward, pain or stress. In recent years, much attention has been given to the role of endocannabinoid CB1 and CB2 receptors in opioid-driven behaviors. However, neuroadaptations of these receptors following opioid exposure is less clear. In this study, we systematically assessed CB1 and CB2 protein expressions within the cortico-mesolimbic-basal ganglia circuit in rats with a history of chronic heroin-exposure. Long Evans rats received one subcutaneous injection of saline or heroin per day for 16 days. During naloxone-precipitated withdrawal, heroin rats showed significantly more withdrawal signs including rapid weight loss, wet dog shakes, abnormal posture, genital grooming and urination than saline control rats. Although heroin rats scored higher on criteria pertaining to vocalization, defecation, jumping and profuse salivation than did saline rats, these trends did not reach statistical significance. Using Western Blotting, we found significant decreases in CB1 protein expression in the nucleus accumbens, hypothalamus, substantia nigra and pedunculopontine nucleus but no significant changes in the prefrontal cortex, insula, dorsal striatum, medial/lateral septi, amygdala, dorsal hippocampus, ventral tegmental area, and lateral tegmental nucleus. We also detected low expression of CB2 receptors in the same brain regions but found no significant changes in their expression following chronic heroin treatment. These data suggest that chronic heroin exposure leads to region-specific neuroadaptation of CB1 receptors but has no significant impact on CB2 receptors.

Poster 83

How diet affects learning and memory under stressful conditions

Sonick, Grace A[1] and Gilman, T Lee[1]

[1]Department of Psychological Sciences, Kent State University, Kent, OH USA

The average human consumes more salt than physiologically needed, leading to questions of how this affects learning and memory, particularly under stress. We are studying how dietary salt influences learning and remembering to avoid an aversive stimulus. Based on previous work, we hypothesized stress would increase consumption of high salt, and high salt diet would not influence learning to avoid a stressor but would enhance memory of that stressor. Adult (>9 weeks, N=15) female Wistar rats were randomly assigned either high salt (4.0%), low salt (0.4%; control), or mixed diet (access to both) conditions. Two weeks later, rats were trained in active avoidance, a form of aversive operant conditioning, for five consecutive days. Four weeks later, rats were tested for three days to examine long-term retention. We evaluated data with two-way repeated measures ANOVAs with Dunnett's post hocs. After the stress of active avoidance, consumption of high salt within the mixed diet group increased, while low salt intake decreased. Thus, female rats chose to consume more of an unhealthy diet after enduring stress. Rats on high salt learned fastest to avoid the shock relative to controls. However, high salt rats began reverting to escapes on their last training day, suggesting they were overtrained, or another factor was influencing their memory. Rats on mixed diet fell in between rats consuming low and high salt diets in performance, despite that during this training time, mixed rats were almost exclusively consuming low salt. Overall, we found the opposite of our hypothesis. Rats on high salt diet initially learned faster, but then deteriorated. Given abstinent people with opioid use disorder eat more salt, our findings could indicate that salt- and stress-induced memory impairments would have detrimental effects on their quality of life and may even increase relapse risk. This study will provide preliminary data that can be used to further investigate the interaction of intake of drugs and salt, and the neural structures involved in these processes.

Poster 84

Exploring the role of distress tolerance in ethanol-seeking behavior

Sosa Jurado, Ricardo[1]; Grijalva, Sofia[1]; Powers, Rosalie E[1] and Moschak, Travis M[1]

[1]Deparment of Biosciences, University of Texas at El Paso, Texas, USA

This study examined whether Distress Tolerance (DT), a key behavioral endophenotype in substance abuse – defined as an individual's persistence in goal-directed behavior while under psychological distress – predicted relapse in ethanol-seeking behavior. We assessed DT in Long Evans rats after ethanol (n=10) or water (n=8) administration, using an intermittent access 2-bottle choice protocol and evaluating DT at drug-naïve, early abstinence (~10 days post-ethanol), and late abstinence (~28 days post-ethanol) stages, along with extinction sessions.
Our analysis revealed a trending decrease in DT across all groups ($F(2,20)=3.048$, $p=0.070$), suggesting a consistent pattern of reduced distress tolerance over time, independent of substance exposure. While DT showed no significant interaction with sex or substance, these trends may hint at subtle influences that warrant further exploration.
In water consumers, we found that high or low consumption differentially affected DT ($F(2, 28) = 3.951$, $p = 0.031$), indicating that consumption behavior itself might influence DT. Specifically, at the short abstinence timepoint, high water consumers exhibited higher DT, while low consumers had lower DT ($F(2,362.632)=14.885$, $p=0.005$), suggesting an inherent difference in response to stress post-substance cessation.
In summary, this study's findings suggest that DT decreases over time in a substance-independent manner, challenging the hypothesis. The study reveals that DT's variance in addiction research extends to non-drug influences, as evidenced by the differential DT responses in water-consuming subjects, indicating a wider behavioral impact. The variable impact of ethanol on DT and the lack of a strong correlation with reward-seeking behaviors suggest that other neurobehavioral factors may be involved. Future research will delve into these aspects, exploring the neurocircuitry underlying addiction and DT.

Poster 85

Variability in phosphatidylethanol (PEth) formation rate in ex vivo whole blood

Stark, Haidyn[1]; Sanchez, Jesus J[1]; Lopez-Cruzan, M[1]; Hill-Kapturczak, N[1]; Roache, John D[1]; Javors, Marty A[1]; Simon, T[1] and Ginsburg, Brett C[1]

[1]Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX USA

Phosphatidylethanol (PEth) is a a biomarker for ethanol consumption in humans. The interpretation of PEth measurement is limited due to inter-individual variability in detected PEth concentrations. Additionally, little is known of the consistency of detected PEth levels from the same person at different blood collection timepoints. This study assesses the extent of variability in PEth formation rate across a range of ethanol concentrations in ex vivo whole blood, and the similarity of detected PEth levels in each participant about one month apart. Whole blood samples from six participants were collected intravenously, and ethanol (0-0.3% BAC) was added to individual samples. Samples were incubated at 37°C, and aliquots were taken every hour for five hours. PEth 16:0 18:1 concentration was measured using high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS), and rate of formation (ng/mL/hr) was determined. Analyses were repeated with a second blood collection for each participant about a month later. A main effect of ethanol concentration on percent change in measured PEth concentration ($F(7,389) = 2.8$, $p < 0.05$) and rate of PEth formation ($F(7,74) = 2.19$, $p < .05$) was found, with the two highest ethanol concentrations yielding significantly different PEth formation rates than baseline of no added ethanol. No effects of blood collection timepoint or interactions were detected. The results indicate PEth formation rate increases with ethanol concentration; and is similar between blood collection time points. Therefore, a single PEth measurement is likely reflective of recent alcohol consumption irrespective of physiological state of the individual. Further investigation of mechanisms of PEth formation – namely Phospholipase D – in the blood may highlight sources of variability in PEth formation rate.

Poster 86

Proimpulsive effects of acute treatment with 1-(1-benzofuran-5-yl)-2-(methylamino) propan-1-one hydrochloride (BK-5-MAPB) enantiomers in rats

Kaitlyn A. Steck[1], Payton D. Brabant[1], Matthew J. Baggott[2], & Lisa E. Baker[1]

[1]Psychology Department, Western Michigan University, Kalamazoo, MI; 2Tactogen, Palo Alto, CA

Recreational use of novel psychoactive substances (NPS) is global public health concern. Benzofurans are a popular group of NPS on the illicit drug market with comparable psychoactive effects to the entactogen, methylenedioxymethamphetamine (MDMA) and other phenethylamines. In rodent drug discrimination studies, the S- and R- enantiomers of 1-(1-benzofuran-5-yl)-2-(methylamino)propan-1-one (BK-5-MAPB) display differential effects that are likely related to differing potencies at dopamine (DA) and serotonin (5-HT) transporters. Psychostimulant drugs have pro-impulsive effects in rodent operant conditioning procedures utilizing differential reinforcement of low rate responding (DRL) schedules. Previous studies utilizing a DRL 36 s schedule showed differential effects of DA and 5-HT releasers. This study examined the acute effects of S- and R-BK-5-MAPB on responding maintained by a DRL18 s schedule of food reinforcement. Sixteen adult male Sprague-Dawley rats with an extensive training history were assessed following acute injections of saline (N=8) or S- and R BK-5-MAPB (N=8). Tests were conducted once per week with ascending doses (0.675 mg/kg, 1.35 mg/kg, 2.7 mg/kg). S-BK-5-MAPB produced dose-dependent increases in response rate and decreases in reinforcement rate, as well as a leftward shift in the inter-response time (IRT) distribution. Similar effects were observed only following the highest dose of R-K-5-MAPB. These results are consistent with drug discrimination findings that S-BK-5-MAPB produces behavioral effects comparable to MDMA, though the observed enantiomeric differences in IRT distribution changes opposed predicted outcomes based on differential potencies as DA releasers.

Poster 87

Sertraline and caffeine interactions and their effects on anxiety levels in zebrafish

Stoddard, Macy

Westminster College

Depression causes suffering for people all over the world. Antidepressants, like selective serotonin reuptake inhibitors (SSRIs), are effective in reducing the symptoms of depression by increasing the concentration of serotonin in the brain. SSRIs, like sertraline, are more tolerable than other classes of antidepressants. The most reported side effects involve sleep interruptions and fatigue. Caffeinated beverages can be used to reduce feelings of tiredness and fatigue, but use of caffeine may increase anxiety in sertraline users. The current study was designed to examine how sertraline and caffeine might interact to affect anxiety-like behavior in zebrafish. Acute exposure involved single 30-minute drug exposure followed by testing, chronic involved 10 days of 30 min exposure history. Acute exposure to sertraline or caffeine did not significantly affect measures of anxiety-like behavior. Ten days of sertraline history did not affect the response to any drug on anxiety-like behavior. Despite no significant differences, fish acutely and chronically exposed to sertraline demonstrated the fewest indicators of anxiety, so this relationship may be worth exploring further to better understand how acute and chronic sertraline might affect anxiety in treated patients.

Poster 88

The impact of fish oil and anorectic drugs on the reinforcing effects of food

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

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

Eating a high fat diet can lead to negative health consequences, such as weight gain, obesity, and insulin resistance. Previous research has also demonstrated that rats eating a high fat diet are more sensitive to the behavioral effects of drugs. Dietary supplementation with omega-3 fatty acids (i.e., fish oil) has been found to counteract this enhanced drug sensitivity in rats eating a high fat diet. This experiment extended prior findings by exploring the impact of dietary manipulation on operant responding for food alone and in combination with drugs that have known anorectic effects (i.e., cocaine, methamphetamine, quinpirole, naltrexone, liraglutide, bupropion and lorcaserin). These drugs decrease feeding and the rate of responding for food in an operant paradigm. It was hypothesized that rats eating different diets would vary in terms of their sensitivity to the response rate-reducing effects of these drugs. To test this hypothesis, male Sprague-Dawley rats (n = 5/dietary group) either ate a standard chow (17% kcal from fat), high fat chow (60% kcal from fat) or one of these diets supplemented with 20% (w/w) fish oil. Rats were trained under a fixed ratio 5 schedule of reinforcement (FR5) to earn food pellets and were tested with cumulative doses of each drug. Data were analyzed using a two-way mixed model ANOVA with dose and diet as factors. Response rate was comparable across groups of rats eating different diets following saline injections. Additionally, increasing cumulative doses of cocaine, methamphetamine, quinpirole, naltrexone, bupropion, and lorcaserin significantly, and dose-dependently, decreased response rate. Although our results are preliminary (and statistically under powered), in this paradigm the GLP-1 receptor agonist liraglutide did not decrease response rate, though next day carry over effects on feeding were observed. The results of this study will contribute to our overall understanding about the impact of dietary supplements in combination with drugs that decrease feeding and has the potential to inform the future treatment approaches for obesity and binge-eating disorder.

Poster 89

Evaluation of abuse potential of synthetic opioids using in vivo pharmacology studies

Sundar, Megana[1]; Hill, Rebecca D[1]; Shetty, Ritu A[1] and Gatch, Michael B[1]

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

Background: Synthetic opioids have played a massive role in fueling substance abuse issues and drug overdose deaths in the United States. As newer synthetic opioids are manufactured and circulated among the population, it is imperative to determine the potency and abuse potential of these compounds.
Methods: Five synthetic opioids (N-piperidinyl etonitazene, N-desethyl isotonitazene, *para*-fluoroacetyl fentanyl, *para*-bromofentanyl, N-piperidinyl isotonitazene) were tested for their ability to produce antinociceptive effects in a warm-water (50°C) tail-flick assay in Swiss-Webster mice. A cumulative dosing procedure was used to determine the peak effect of the drug. The action of these substances at opioid receptors was supported by testing the effects of naltrexone (1 mg/kg) at the peak dose of each synthetic opioid.
Results: N-Piperidinyl etonitazene (ED_{50}=0.031 mg/kg), N-desethyl isotonitazene (0.0052 mg/kg), *para*-fluoroacetyl fentanyl (0.097 mg/kg), *para*-bromofentanyl (4.01 mg/kg), N-piperidinyl isotonitazene (0.0078 mg/kg) and fentanyl (0.058 mg/kg) dose-dependently increased tail-flick latencies to maximum effect. Naltrexone antagonized all five compounds at their respective peak dose.
Conclusions: These five synthetic opioids produced antinociceptive effects via opioid receptors at a wide range of potencies. N-Desethyl isotonitazene and N-piperidinyl isotonitazene were more potent than fentanyl, suggesting these may produce substantial risks of overdose, and *para*-bromofentanyl produced substantial adverse effects, indicating a risk for toxic effects in human users. These results support the notion that these compounds have a significant potential for substance misuse.

Poster 90

The effects of voluntary ingestion of delta-9-tetrahydrocannabinol on sucrose consumption

Tewell, Olivia R., Laux, Dylan A. and Cain, Mary E.

Department of Psychology, Kansas State University, Manhattan, KS USA.

Cannabis, the most widely used illicit drug in the United States (Schulenberg et al., 2018), contains Delta-9-Tetrahydrocannabinol (THC) as its major psychoactive component. THC is commonly consumed through edibles (Barrus et al., 2018), a prevalent method due to increasing legalization. Preclinical models aim to explore cognitive and behavioral changes resulting from THC consumption. Recent studies indicate oral THC leads to behavioral and cognitive deficits (Nelson et al., 2019; Rohleder et al., 2020; Smoker et al., 2019). However, translational research often employs high THC doses not reflective of human use. Injections of THC have been shown to increase the hedonic value or "liking" of sucrose (Jarrett et al., 2005). The present study explores if low doses of oral synthetic THC enhance the preference for or consumption of sucrose. Using a translatable administration model, we examined the effects of voluntary ingestion of synthetic THC (Dronabinol) on sucrose consumption in Long-Evans adult rats. Rats voluntarily consumed THC (0.05mg/kg or 0.5mg/kg) or vehicle (control) every other day for two weeks. Following two weeks of THC consumption, three habituation sessions were performed, followed by three progressive sucrose concentration preference tests (water vs low (0.7%), low vs medium (10%), medium vs high (32%)) administered every other day, 90min after THC delivery. Statistical analysis revealed a significant difference in total sucrose consumption across the different sucrose concentrations, but no THC dose effect. Our findings suggest that voluntary low-dose edible THC consumption does not alter sucrose preference or sucrose consumption.

Poster 91

Identifying helpful research as it relates to substance use disorder treatment

Triplett, Daquane L

South Texas Veterans Health Care System, Department of Education, San Antonio, TX

Most research conducted within the field of Psychology is Quantitative in nature. For this reason, it was important to highlight helpful ways of analyzing this kind of data for those, like the author, may have received training that was geared more toward Qualitative research. The hypothesis for this endeavor is that with an efficient method of research analysis, it is possible to identify and utilize quality quantitative research as it relates to substance use disorders (SUD). A step by step research analysis guide was created in order to identify quality research as it related to SUD treatment so that it could be applied to practice. For the purposes of this analysis, quality research was defined as having practical applications to practice as an SUD treatment provider and comprises of a total of ten essential components (i.e. analysis methods are explicit, systematic, and reproducible) among others. The literature review conducted included 35 peer-reviewed articles, published during or after 2014, related to treatments for common SUDs. The results showed that the method of analysis created efficiently identified quality research. Further, these articles demonstrated similar themes such as utilizing components of “Gold Standard” treatments, using the Tolin Criteria, providing treatment recommendations, discussing the implications for both practitioners and those who they are working with; and more. This analysis along with the results demonstrated that it is possible to find quality research, common themes among high quality SUD treatments, and offer a method of exercising an important skill needed at all levels of practitioners’ careers.

Poster 92

Sex differences in anxiety-like behaviors during withdrawal from morphine

Van Dyk, Davis J[1]; Koly, Farzana[1] and Perrotti, Linda I[1]

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

Negative somatic and behavioral symptoms, such as anxiety, are known to accompany withdrawal from opioids in both humans and rodents and are primary drivers of continued opiate use. Contradictory results have been reported comparing males with females, with some studies finding that opioid withdrawal increases anxiety-like behavior in the elevated plus maze (EPM) in males compared to females, while other studies reported no difference. However, few studies, if any, have considered the estrus cycle stage with opiate withdrawal-induced anxiety. In the current study, adult male and female Long Evans rats were subcutaneously injected with escalating doses of morphine starting at 2.5 mg/kg and ending at 40 mg/kg twice a day for 10 days while controls received 0.1 ml/kg of saline. To assess morphine withdrawal-induced anxiety, all rats were tested via the EPM at 24 hours after the last morphine administration. The estrous cycle stage was monitored for females throughout the study. The behavior of all rats on the EPM was recorded over a 5-minute test period and analyzed by Noldus Ethovision software. Our analyses showed that all rats experiencing morphine withdrawal displayed increased anxiety-like behaviors. Specifically, the number of open-arm entries and the percent time spent in open arms decreased significantly. Similarly, closed-arm entries and percent time spent in closed arms were significantly increased compared to saline controls. Additionally, morphine-treated female rats in the proestrus/estrus stage of the cycle demonstrated increased anxiety-like behavior compared to morphine-treated female rats in the metestrus/diestrus stages and saline-treated females and males. Sex differences in addiction-like behaviors are observed to correspond to differences in levels of estradiol and progestins.

Poster 93

Hindbrain GLP1R and PENK neurons differentially modulate food and drug reward

Vargas-Elvira, Alexandra G.[1]; Huang, Kuei-Pin[1]; Burns, Ryan[1,2] and Alhadeff, Amber L.[1,2]

[1]Monell Chemical Senses Center, Philadelphia, PA, USA; [2]University of Pennsylvania, Philadelphia, PA, USA

It has been recently discovered that anti-obesity medications, specifically glucagon-like peptide 1 receptor (GLP1R) agonists such as semaglutide (Ozempic/Wegovy), can modulate drug craving and behavior. Though patients on these drugs report reduced motivation to consume various abused substances in addition to food, the mechanisms for this reduction in reward and motivation is not fully clear.
The hindbrain dorsal vagal complex (DVC) mediates satiety and serves as a site of action for anti-obesity medications. We therefore examined whether DVC GLP1R neurons modulate food- and drug-evoked dopamine (DA) signaling in mice. To determine whether effects are specific to GLP1R neurons or extend to other satiety-inducing populations, we also examined how DVC proenkephalin (PENK) neurons impact evoked DA. We hypothesized that activity in both satiety-inducing populations reduce DA responses to food and drugs.
We chemogenetically activated $GLP1R^{DVC}$ and $PENK^{DVC}$ neurons while monitoring DA signaling in the nucleus accumbens via in-vivo fiber photometry ($GRAB^{DA}$ sensor). Activation of either $GLP1R^{DVC}$ or $PENK^{DVC}$ neurons reduced both chow- and high-fat diet-evoked DA signaling. We next examined how activation of these populations influences DA responses to drugs. Contrary to our hypothesis, activation of $GLP1R^{DVC}$ neurons, but not $PENK^{DVC}$ neurons potentiated rather than suppressed intraperitoneal cocaine-induced DA signaling. The same pattern was observed with nicotine-induced DA signaling: $GLP1R^{DVC}$ neurons potentiated nicotine-evoked DA signaling, while $PENK^{DVC}$ neurons had no effect. Overall, our data suggest a complex interaction between hindbrain satiety neuron signaling and reward responses, where DVC satiety-inducing populations reduce DA responses to food but have divergent effects on DA responses to drugs. These findings begin to shed light on neural mechanisms that influence the effects of anti-obesity medications on motivation to consume food and drugs.

Poster 94

Differential effects of naloxone on reversal of the respiratory depressant effects of opioids and opioid/stimulant mixtures in rats

Vazquez, Jacqueline[1]; Seaman, Robert Jr.[1,2]; and Collins, Gregory[1,2]

[1]Department of Pharmacology, UT Health San Antonio; 2South Texas Veterans Health Care System, San Antonio, TX, USA

Overdose deaths from the concurrent use of opioids (e.g., fentanyl) and stimulants (e.g., methamphetamine; METH) have increased in the United States. In 2022, over 70,000 overdose deaths were attributed to synthetic opioids; more than 80% involved a stimulant. While naloxone (NarCan®) is highly effective at reversing the respiratory depressant effects of opioids, it is unclear whether it is equally potent and/or effective at reversing an overdose related to the co-use of opioids and stimulants. Using collar-based pulse oximetry, this study characterized the effects of intravenous (IV) fentanyl (0.0056-0.56 mg/kg), heroin (0.32-5.6 mg/kg), METH (0.1-1 mg/kg), or mixtures of 0.56 mg/kg fentanyl + 1 mg/kg METH or 5.6 mg/kg heroin + 1 mg/kg METH on measures of SpO_2 and heart rate in male and female Sprague-Dawley rats. To evaluate the capacity of naloxone to reverse these effects, naloxone (0.01-3.2 mg/kg; IV) or vehicle was administered 5 minutes after the opioids and stimulants alone or in mixtures. The effects of fentanyl and heroin on SpO_2 and heart rate were dose-dependently reversed by naloxone. Female rats had greater decreases in heart rate at larger fentanyl doses, however, naloxone was equipotent and effective in male and female rats. Naloxone reversal of fentanyl and heroin produced a rebound tachycardia, indicative of a sympathetic overshoot, at the two largest doses tested. There was no effect of naloxone treatment on SpO_2 or heart rate when it was administered alone or after METH. Compared to when it was administered after fentanyl, heroin, or heroin + METH, naloxone was less effective at reversing the cardiorespiratory effects of fentanyl + METH. Lethality was only observed in the fentanyl mixture condition (30.23%). As such, pharmacological interactions between fentanyl overdose reversal and stimulants may be driving deaths in polysubstance overdoses.

Poster 95

Behavioral and neuronal activity analysis in the prelimbic cortex during an impulsivity task

Vega, Ymalay A.[1]; Galvan, Karla J.[1]; Meza, Mariana[1]; Lopez, Alyssa I.[1]; Turner, Kimberly[1]; Powers, Rosalie E.[1]; Moschak, Travis M.[1]

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

The prelimbic cortex (PrL) is a crucial brain region that is involved in drug-seeking behaviors, craving, inhibitory control, and impulsivity. Studies have demonstrated that impulsivity predicts drug reinforcement and addiction. High-impulsive individuals are more likely to develop substance abuse disorders than those with low impulsivity levels. Given the role the PrL has in addiction, we investigated how it influences impulsivity. We used female (n=7) and male (n=11) Sprague Dawley rats that were exposed to a viral infusion of the GCAMP6s and lens implantation in the PrL followed by an intrajugular catheter surgery and miniscope baseplate insertion. After a recovery period, the subjects were placed into an operant conditioning chamber where they were required to press the extended lever when the cue light was active to receive a reward. Impulsivity is defined as the number of responses before the cue light period divided by the total responses. We recorded the PrL activity with endoscopic in vivo calcium imaging during the behavioral tasks to measure neuronal activity. After the recordings were analyzed, cells were classified as 'excited', 'inhibited' or 'nonphasic' depending on their activity. Neurons that were excited by the lever extending into the chamber (signaling the start of the trial) predicted impulsivity. Specifically, high impulsive rats had significantly stronger excitation on trials in which they were impulsive, while low impulsive rats had significantly stronger excitation on trials in which they were not impulsive ($t(12)=3.00$, $p = 0.011$). A similar effect was seen for neurons inhibited by the lever ($t(14) = 3.49$, $p = 0.003$), but not by neurons unaffected by the lever ($t(15) = 0.19$, $p = 0.849$). Furthermore, these patterns of neural activity significantly correlated with impulsivity (excited: $r = 0.63$, $p = 0.015$; inhibited: $r = -0.56$, $p = 0.030$). Understanding the neural mechanisms behind impulsivity may help create treatments for patients who are impulsive and more prone to developing drug abuse disorders.

Poster 96

Deconstructing vilazodone binding to the serotonin and dopamine transporters

Vogt, Caleb D.[1]; Camacho-Hernandez, Gisela Andrea[1]; Løland, Claus J.[2]; Bi, Guo-Hua[1]; Xi, Zheng-Xiong[1]; Newman, Amy H.[1]

[1]Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse–Intramural Research Program, Maryland, United States
[2]Laboratory for Membrane Protein Dynamics, Department of Neuroscience, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Vilazodone is a high affinity (K_i = 0.11 ± 0.02 nM) inhibitor of the serotonin transporter (SERT) used for the treatment of major depressive disorder. Notably, this drug also binds to the human dopamine transporter (hDAT) with nanomolar affinity (K_i = 11.1 ± 0.6 nM), which is 27-fold higher than cocaine (K_i = 300 ± 60 nM). Vilazodone is approved for the treatment of depression and has not been reported to have abuse potential. Based on these and other structural data, we hypothesized that vilazodone, in addition to being a selective serotonin reuptake inhibitor (SSRI) may also act as an atypical DAT inhibitor and, therefore, might be useful for treating psychostimulant use disorder. Nevertheless, vilazodone had no effect on cocaine self-administration in rats (FR-1 schedule of reinforcement) at doses of 3, 10, and 20 mg/kg. We conclude that its lack of efficacy stems from SERT/DAT selectivity (>100-fold). To begin exploring this hypothesis, we deconstructed the chemical structure of vilazodone into fragments of varying sizes. The affinities of these pieces were then tested at hDAT and hSERT in radioligand binding assays. Our experiments revealed that the 5-cyanindole terminus is largely responsible for SERT binding and that by replacing it with other functional groups a more balanced DAT/SERT inhibitor results. Using both small molecule structure–activity relationships and the cryoEM structure of vilazodone, we aim to design new analogues that are more DAT selective and determine if they retain an atypical inhibitor profile.

Poster 97

Deleterious neuronal activation in infralimbic cortex associated with fear extinction in a rodent model of PTSD/AUD

Wills, Liza J[1,2]; Schwartz, Britta[1], McGuffin, Bailey[1] and Gass, Justin T [1,2]

[1]Department of Biomedical Sciences, Quillen College of Medicine, East Tennessee State University, Johnson City, TN USA; [2]Mountain Home VA Medical Center, Mountain Home, TN USA.

AUD and PTSD are two of the most common mental health disorders and are highly comorbid. Additionally, maladaptive memories are implicated in these disorders, such that fear-/alcohol-related cues become disproportionally salient over non-fear-/ non-alcohol-related cues. This enhanced salience contributes to difficulty extinguishing fear/alcohol associations for people with comorbid PTSD/AUD. To gain a better understanding of the potential impact co-occurring PTSD/AUD has on neuronal activation in the IfL and PrL cortices we measured neuronal activation using immunohistochemistry and electrophysiology after the final day of fear extinction learning using a rodent model of PTSD/AUD. Wistar rats were grouped based on their exposure to the PTSD/AUD paradigm and fear conditioning (FC) task. The PTSD/AUD paradigm consisted of animals being exposed to 2h restraint stress (RS) followed by 2-weeks of chronic intermittent ethanol vapor exposure (CIE). Upon completion of CIE animals were given 10-days to recover from withdrawal symptoms prior to the commencement of the FC task. FC was used to assess future stress sensitivity by examining the acquisition of fear learning and extinction of fear behaviors. On the final day of extinction training animals were either euthanized for cfos analysis or underwent electrophysiological recordings. Brain tissue containing IfL and PrL were stained with anti-cFos and Neurotrace Nissl and imaged to assess cell colocalization in each brain region. Our results indicated that animals exposed to RS+CIE had significantly less colocalized cells in the IfL than CTRL animals, suggesting a reduction of cFos activity in these neurons. Electrophysiological recordings suggest significantly reduced neuronal activity in the IfL. The current study provides fundamental knowledge on the possible cause in the difficulty for individuals with comorbid PTSD/AUD to extinguish fear memories.

Poster 98

Consumption of furanyl fentanyl solutions elicits antinociception and physical dependence in male C57 mice: Developing a model of oral self-administration of fentanyl analogs

Wolf, Kayla[1]; Fantegrossi, William E[2] and Shaw, Hannah[3]

[1]Department of Toxicology and Cancer Biology, University of Kentucky, Lexington, KY; [2]Department of Pharmacology and Toxicology, University of Arkansas Medical School, Little Rock, AK; [3]Department of Pharmacology and Toxicology, University of Arkansas Medical School, Little Rock, AR.

In 2023, the Drug Enforcement Administration (DEA) seized more than 76.5 million capsules or tablets containing the μ-opioid agonist fentanyl or one of its synthetic analogs, and 70% of these seized oral dosage units contained what DEA describes as a "lethal" amount of drug. Despite the prevalence of oral fentanyl use, few animal studies utilize oral administration, limiting our knowledge of abuse-related and toxicological implications of this route of administration. Oral drug self-administration is challenging in rodents due to their innate neophobia, and the immediacy of aversive drug taste versus delayed pharmacological effects. The extreme potency of fentanyl analogs may result in opioid-like drug effects following consumption of dilute solutions which may not have a discriminable taste. Here we demonstrate a reliable model of consumption for both 10 and 30 μg/mL furanyl fentanyl (FF) in water provoked by a daily 2-hour period of access to the drug solutions. As compared to mice drinking water, FF solutions elicited dose-dependent increases in tail withdrawal latency from 50° and 55°C water baths, and withdrawal latency was highly correlated with individual FF intake. These antinociceptive effects were blocked by 10 mg/kg of the opioid antagonist naloxone. Consistent with physical dependence, post-session administration of naloxone elicited withdrawal-like jumping and decreased horizontal locomotor activity in mice drinking FF solutions, but not in mice drinking water. These studies pave the way towards a model of oral fentanyl analog self-administration in the mouse.

Poster 99

Differential effects of the imidazodiazepine KRM-II-81 and the benzodiazepine midazolam on opioid-induced respiratory depression in adult rats

Woodhouse, Kristen L[1]; Sharmin, Dishary[2], Cook, James M[2] and Li, Jun-Xu[1]

[1]Department of Pharmacology and Toxicology, University at Buffalo, Buffalo, NY USA; [2]Department of Chemistry and Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, WI USA

Overdose deaths attributed to both opioids and benzodiazepines have increased in recent years, and physicians have continued co-prescribing opioids and benzodiazepines despite widespread evidence of the potential for dangerous respiratory interactions. Classical benzodiazepines, such as midazolam, bind to the benzodiazepine site of α_1-, α_2-, α_3-, and α_5-subunit containing $GABA_A$ receptors. Prior studies in rodents demonstrated that centrally-administered (i.t.) benzodiazepines are analgesic, but this analgesic effect is otherwise masked by sedation. In contrast, the imidazodiazepine, KRM-II-81, preferentially binds to this site on α_2- and α_3-subunit containing $GABA_A$ receptors, and is analgesic when administered systemically (i.p.) in rats with inflammatory or neuropathic pain. Furthermore, KRM-II-81 produces additive to supra-additive interactions with fentanyl in rat models of inflammatory and neuropathic pain. However, it was unknown whether the subtype-specificity of KRM-II-81 is sufficient to avoid potential respiratory interactions with opioids. Therefore, this study examined the effects of KRM-II-81 or midazolam pretreatment on fentanyl- and morphine-induced respiratory depression using whole body plethysmography. Unlike midazolam, KRM-II-81 was found to have no significant effect on either fentanyl- or morphine-induced respiratory depression, even at a dose larger than what is needed to elicit significant antinociception. These findings suggest KRM-II-81 is safe to combine with opioids from a respiratory standpoint, and further support the potential clinical utility of combining KRM-II-81 with opioids for treating chronic pain.

Poster 100

Central amygdala protein kinase C-δ neurons are required for fentanyl withdrawal

Wooldridge, Lisa M[1,2]; Lee, Angela[2]; Wu, Jackie[2]; Mahmood, Malaika[2]; and Corder, Gregory[2]

[1]Neuroscience Graduate Group, University of Pennsylvania, Philadelphia PA; [2]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia PA

Agonists for the μ-opioid receptor, such as fentanyl, remain a frontline option for moderate to severe pain management. However, their propensity to produce dependence and withdrawal limit their long-term clinical use. Preclinical studies have associated both chronic pain and opioid withdrawal with increased activity in the central nucleus of the amygdala (CeA). In the context of chronic pain, this is seen largely in neurons expressing Protein Kinase C-δ (CeAPKCδ). The impacted cell types in opioid withdrawal are not fully understood. We hypothesized that CeAPKCδ neurons also show increased activity during fentanyl withdrawal, and that their activity contributes to the behavioral correlates of dependence. Mice were given fentanyl (0.02 mg/mL) or untreated water in their homecage drinking water supply for 8 days. Fentanyl-drinking mice developed significantly more classic murine somatic withdrawal signs after forced abstinence or naloxone administration (3 mg/kg) compared to untreated water-drinking controls (n=16/group, unpaired t-test), indicating the development of fentanyl dependence. Immunohistochemistry revealed that this fentanyl withdrawal induces robust FOS expression in CeAPKCδ neurons (n=4/group, two-way ANOVA). Fiber photometry in the CeA of PKCδ-Cre mice confirmed that these neurons show increased activity during fentanyl withdrawal, compared to opioid-naïve conditions (n=4-6/group, two-way repeated measures ANOVA). Finally, we chronically inhibited CeAPKCδ neurons via overexpression of the potassium channel Kir2.1 in the CeA of PKCδ-Cre mice. Kir2.1-overexpressing mice exhibited fewer somatic withdrawal signs compared to fluorophore-expressing control mice during spontaneous fentanyl withdrawal (n=6-12/group, one-way ANOVA). Collectively, these data support our hypothesis that the activity of CeAPKCδ neurons is both driven by fentanyl withdrawal, and drives the behavioral correlates of withdrawal.

Poster 101

Impact of chronic Δ⁹-THC exposure on methamphetamine's behavioral effects

Yu, Isabel L., Burke, Emily L., & Desai, Rajeev I.

McLean Hospital/Harvard Medical School, Belmont, MA, USA

Deaths related to stimulants, including methamphetamine (MA), have more than doubled in recent years. The number of medical emergencies related to cannabis, the most commonly self-administered psychoactive substance in the United States, have also increased drastically. Cannabis has long been considered a 'gateway drug' – 75% of users consume other drugs of abuse and have a 50% higher cumulative risk of abusing other illicit substances. Although evidence suggests that chronic cannabis use alters dopaminergic (DA) signaling throughout the brain, little is known about how this exposure affects behavioral and neurobiological responses to illicit substances. The present study examined how chronic exposure to 10 or 32 mg/kg/day Δ-9-tetrahydrocannabinol (Δ^9-THC) impacts MA-induced increases in locomotor activity and body temperature in male mice (n=8/group). Using 2-way ANOVAs, we found that chronic administration of a high dose of 32 mg/kg Δ^9-THC for 10 days dampened MA-induced increases in locomotor activity and amplified MA's hyperthermic effects in mice, whereas exposure to a 3-fold lower dose of 10 mg/kg Δ^9-THC for 10 days markedly amplified MA's locomotor stimulant effects compared to controls without altering MA-induced hyperthermia. Additional preliminary work using conditioned place preference found chronic exposure to 10 mg/kg Δ^9-THC increased preference for both 1.0 mg/kg and 3.2 mg/kg MA. Taken together, these data indicate that the history of chronic Δ^9-THC exposure is an important determinant of MA-induced behavioral effects; low or moderate doses of Δ^9-THC will amplify MA's behavioral effects without altering MA-induced hyperthermia, whereas exposure to a high dose of Δ^9-THC will dampen MA's behavioral effects thus necessitating higher MA doses that will render subjects more susceptible to MA's adverse hyperthermic effects. Future work will use in vivo microdialysis techniques to explore the how chronic Δ^9-THC exposure impacts MA-induced increases in DA levels in reward-related brain regions.

Poster 102

Enzyme enigmas: What happens when 5F-APINACA meets olanzapine in the human liver?

Zia, Muhammad[1], Crosby, Samantha[2], Miller, Grover P[2]

[1]Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, AR USA [2]Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, AR USA

Drug combinations commonly occur for those with substance use disorders and lead to increased health risks. In this study, we focused on the drug-drug interactions between a drug of abuse, 5F-APINACA, and olanzapine, which is used to treat schizophrenia and bipolar disorder, because those suffering from the psychiatric conditions are prone to substance use disorders making it likely that the drug combinations occur for users. Both drugs undergo metabolism by CYP3A4 and would presumably compete for the enzyme. We then hypothesized that olanzapine would inhibit 5F-APINACA metabolism. We tested this hypothesis using in vitro steady-state reactions with human liver microsomes when both drugs are present. 5F-APINACA undergoes metabolism down two pathways leading to hydroxylation of the adamantyl group and oxidative defluorination. In preliminary studies, olanzapine acted as a mixed inhibitor by suppressing both the 5F-APINACA OH and the 5OH-APINACA metabolic pathways. Those effects were much more significant for adamantyl hydroxylation than oxidative defluorination. These findings reveal the interactions between prescription medications and synthetic cannabinoids, presenting a critical foundation for further investigation into the complexities of drug-drug interactions. These findings go beyond immediate implications, playing a crucial role in enhancing our understanding of drug safety and efficacy. Additionally, this research catalyzes the creation of more personalized and efficient treatment plans, contributing to a broader comprehension of substance interactions within the human body and potential avenues for personalized therapeutic strategies.

Poster 103

Mitragynine as a potential treatment for methamphetamine use disorder

Zuarth Gonzalez, Julio D[1]; Ragsdale, Alexandria[1]; Mukhopadhyay, Sushobhan[2]; Guadagnoli, Nicholas[2]; McCurdy, Christopher R[2]; McMahon, Lance R[1]; and Wilkerson, Jenny L[1]

[1]Department of Pharmaceutical Sciences, Texas Tech University Health Sciences Center; [2]Department of Medicinal Chemistry, College of Pharmacy, University of Florida

In recent years *Mitragyna speciosa* (kratom) has become popular in the United States due to vast anecdotal evidence supporting its alleged effectiveness to self-treat substance use disorders, including methamphetamine use disorder. Kratom products contain numerous alkaloids, and the most abundant alkaloid is mitragynine (MG). The study aimed to test the hypothesis that MG attenuates methamphetamine self-administration. Male and female Sprague Dawley rats implanted with a jugular catheter were trained to self-administer methamphetamine (0.032 mg/kg/infusion) intravenously. Lever pressing for methamphetamine was established during 2-hour sessions, under a fixed ratio (FR) 1 schedule of reinforcement and gradually increased to FR5. The maximum number of reinforcers that could be earned was 100. Once responding was stable for 3 consecutive sessions, the effects of either vehicle or mitragynine (10, 17,8, 32, 56 mg/kg, i.p.) pretreatment were assessed. The order of the doses was counterbalanced. Methamphetamine led to significant lever presses on the active lever compared to the inactive lever. The highest mitragynine doses (32 and 56 mg/kg) attenuated methamphetamine self-administration. These results indicate that mitragynine shows promise as a potential therapeutic for methamphetamine use disorder. The effects of mitragynine should also be evaluated in non-drug reinforcers.

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Poster 104

Prenatal drug exposure predicts HPA- & synaptic plasticity-related DNA methylation

Hanson, Taena[1]; Mennenga, Sarah E[2]; Deoni, Sean CL[3]; and Lewis, Candace R[1,2]

[1]Department of Psychology, Arizona State University, Tempe, AZ, USA; [2]School of Life Sciences, Arizona State University, Tempe, AZ, USA; [3]School of Engineering, Brown University, Providence, RI, USA

Prenatal alcohol exposure (PAE) can have detrimental impacts on mental health outcomes during development. For example, PAE predicts problem behaviors such as internalizing/externalizing in children and adolescents, two measures that predict later mental health problems. Studies have investigated DNA methylation (DNAm) as a potential mechanism by which PAE impacts behavior. However, these studies primarily utilize epigenome-wide analyses, which often fail to pull small-effect-size predictors and do not target genes related to behaviors of interest. The purpose of this study is to perform a candidate-gene investigation on the impact of prenatal alcohol and drug exposure on DNAm of stress-related genes previously associated with problem behaviors in a developmental cohort. Participants were a subset of an Environmental Influences on Child Health Outcomes (ECHO) cohort (N=51, Mage=24.8mo, SDage=38.2mo). Three genes were selected for DNAm analyses: NR3C1 has been implicated in various int/externalizing disorders and is highly linked to maternal stress pre-pregnancy; IGF2 is highly tied to development and has DNAm profiles shown to differ in PAE mice compared to controls; finally, GAPDH is a common housekeeping gene is therefore utilized as a control gene. ANCOVA group comparisons controlling for sex, age, and cell count revealed that prenatal drug exposure significantly predicts DNAm of NR3C1 [$F(2,45)=156$, $p<0.0001$] and IGF2 [$F(2,45)=104$, $p<0.0001$], but not GAPDH [$F(2,45)=1.29$, $p=0.29$]. These results suggest a significant relationship between PAE and DNAm of both alcohol- and stress-related genes, shown to be gene-specific due to a lack of significance in GAPDH. Importantly, post-hoc results suggest that differences in DNAm are not only due to PAE, but also to other drugs, such as nicotine, marijuana, or opioids.

Attendees

Nadia Afrin
Rowan University
afrinn49@students.rowan.edu

Harshil Aggarwal
Texas A&M University
harshilaggarwal23@tamu.edu

Monica Aguilera
Texas Tech University Health Sciences Center
monica.aguilera@ttuhsc.edu

Adesewa Akande
LSU Health Sciences Center Shreveport
adesewa.akande@lsuhs.edu

Mia Allen
Wake Forest University School of Medicine
mia.allen@my.com

Hannah Alton
National Institute on Drug Abuse
hannah.alton@nih.gov

Payton Antonacci
University of Texas at Austin
pantonacci@utexas.edu

Nina Ardabili
American University Washington DC
ng7086a@american.edu

Marina Avram
University of Arkansas for Medical Sciences
mavram@uams.edu

Miki Azuma
Kansas State University
caseymiki@ksu.edu

Lisa Baker
Western Michigan University
lisa.baker@wmich.edu

Maria Balaguer
University of California San Diego
mbalaguer@health.ucsd.edu

Amber Baldwin
Virginia Commonwealth University
anbaldwin@vcu.edu

Nina Beltran
University of Texas at El Paso
nmbeltran@miners.utep.edu

Paige Bensing
Trinity University
pbensing@trinity.edu

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

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

Carissa Besonen
Creighton University
carissabesonen@creighton.edu

Carter Bierbaum
University of Central Arkansas
cgbierbaum@gmail.com

Jessica Binckley
Kansas State University
binckleyj@ksu.edu

Bruce Blough
RTI International
beb@rti.org

Andrew Bolinger
University of Texas Medical Branch
aaboling@utmb.edu

Alessandro Bonifazi
National Institute on Drug Abuse
alessandro.bonifazi2@nih.gov

Stephanie Borgland
University of Calgary
s.borgland@ucalgary.ca

Abigail Bowring
Texas A&M School of Medicine
abigail.bowring@tamu.edu

Payton Brabant
Western Michigan University
payton.d.brabant@wmich.edu

Deanne Buffalari
Westminster College
buffald@westminster.edu

Rachel Burroughs
Western Michigan University
rachel.l.burroughs@wmich.edu

Bobbi Bushey
Med Associates Inc
Bobbi.Bushey@med-associates.com

Paola Campo
University of California San Diego
p3campo@health.ucsd.edu

Hannah Carlson
Davidson College
hacarlson@davidson.edu

Laia Castell Almuni
Johns Hopkins University School of Medicine
lcastel9@jh.edu

Maya Chopra
Texas Tech University Health Sciences Center
maya.chopra@ttuhsc.edu

Mia Clark
University of Central Arkansas
miaclark1214@gmail.com

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

Brook Clodgo
Med Associates Inc
brooke.clodgo@med-associates.com

Jeffrey Coira
Coira Psychotherapy & Associates, PLLC
jeffrey@severancetherapy.com

Greg Collins
UT Health Science Center at San Antonio
collinsg@uthscsa.edu

James Cook
University of Wisconsin-Milwaukee
capncook@uwm.edu

Anna Crites
Kent State University
acrites8@kent.edu

Emily Cronin
Creighton University
eac12140@creighton.edu

Anthony Cuozzo
East Tennessee State University
cuozzoa@etsu.edu

Paul Czoty
Wake Forest University School of Medicine
pczoty@wakehealth.edu

Kaila Dawkins
North Carolina A&T State University
kcdawkins@aggies.ncat.edu

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

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

Katherine Dixon
Trinity University
kdixon1@trinity.edu

Arpit Doshi
Astraea Therapeutics
arpit@astraeatherapeutics.com

William Doyle
University of Mississippi Medical Center
wdoyle@umc.edu

Elizabeth Drobny
Creighton University
elizabeth.drobny@gmail.com

Darby Durbin
Creighton University
djd00800@creighton.edu

Andrew Eagle
UT Dallas
andrew.eagle@utdallas.edu

Afua Faibille
High Point University
afaibill@highpoint.edu

Haydn Fitzgerald
Creighton University
haf05893@creighton.edu

Shawn Flynn
UT Health Science Center at San Antonio
flynns@livemail.uthscsa.edu

Peter Fogel
University of Texas at El Paso
pafogel@miners.utep.edu

Chanida Fongsaran
University of Texas Medical Branch
chfongsa@utmb.edu

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

Troy Fort
Kansas State University
tfort1346@ksu.edu

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

Kevin Freeman
University of Mississippi Medical Center
kfreeman@umc.edu

Ewa Galaj
Colgate University
egalaj@colgate.edu

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

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

Michael Gatch
UNT Health Science Center
michael.gatch@unthsc.edu

Christina George
UT Health Science Center at San Antonio
Georgec3@uthscsa.edu

Ihle Gilmore
University of Mississippi Medical Center
igilmore@umc.edu

Kate Graham
Creighton University
keg03200@creighton.edu

Sofia Grijalva
University of Texas at El Paso
sdgrijalvat@miners.utep.edu

Sampa Gupta
University of Florida
sampa.gupta@ufl.edu

Robert Hammack
UT Health Science Center at San Antonio
hammackr@livemail.uthscsa.edu

Taylor Harman
Westminster College
harmtb52@westminster.edu

Rachel Heueisen
Creighton University
rachelheueisen@creighton.edu

Ella Hildebrand
Westminster College
hildee52@westminster.edu

Rebecca Hill
UNT Health Science Center
darbi.hill97@gmail.com

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

Nicholas Ho
UT Health Science Center at San Antonio
Lake Erie College of Osteopathic Medicine - Bradenton
NHo07127@med.lecom.edu

Lucy Hoying
University of Michigan
lrhoying@umich.edu

Shihui Huang
American University
sh3116a@american.edu

Seth Hubbard
National Institute on Drug Abuse
seth.hubbard@nih.gov

Galen Huffcutt
East Tennessee State University
huffcutt@etsu.edu

Andrew Huhn
Johns Hopkins University School of Medicine
ahuhn1@jhu.edu

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

Alejandra Jacotte-Simancas
LSU Health Sciences Center
mjacot@lsuhsc.edu

Amaya Jenkins
McLean Hospital, Harvard Medical School
arjenkins@mclean.harvard.edu

Krit Jirakanwisal
University of Texas Medical Branch
krjiraka@utmb.edu

Alexandra Johansen
National Institute on Drug Abuse
alex.johansen@nih.gov

Marissa Jones
East Tennessee State University
jonesmr8@etsu.edu

Emily Jutkiewicz
University of Michigan
ejutkiew@umich.edu

Moe Kaneko
Trinity University
mkaneko@trinity.edu

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

Victoria Kattler
Westminster College
kattve52@westminster.edu

Thomas Keck
Rowan University
keckt@rowan.edu

Lida Khodavirdilou
Texas Tech University Health Sciences Center
lida.khodavirdilou@ttuhsc.edu

Brent Kisby
Texas Tech University Health Sciences Center
brent.kisby@ttuhsc.edu

Farzana Akter Koly
University of Texas Arlington
fxk1516@mavs.uta.edu

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

Dylan Laux
Kansas State University
dlaux@ksu.edu

Thuy-Hien Le
University of Mississippi Medical Center
Thuyhien.le17@gmail.com

Kah-Chung Leong
Trinity University
kleong@trinity.edu

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

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

Antoinette Maldonado-Devincci
North Carolina A&T State University
amdevinc@ncat.edu

Yorkiris Marmol Contreras
University of Texas Medical Branch
yomarmol@utmb.edu

Samuel Marsh
Virginia Commonwealth University
smarsh3@vcu.edu

Elizabeth Martinez
UT Health Science Center at San Antonio
martineze39@uthscsa.edu

Jared McDonald
UNT Health Science Center
jaredmcdonald@my.unthsc.edu

Abram Mijares
UT Health Science Center at San Antonio
mijaresa@uthscsa.edu

Vanessa Minervini
Creighton University
vanessaminervini@creighton.edu

Farzanna Mohamed
University of Michigan
famohame@umich.edu

Abigail Morgan
OU Health and Science Center
abigail-morgan@ouhsc.edu

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

Sushobhan Mukhopadhyay
University of Florida
smukhopadhyay@ufl.edu

Daaniyal Munir
UNT Health Science Center
daaniyalmunir@my.unthsc.edu

Mike Nader
Wake Forest University School of Medicine
mnader@wakehealth.edu

Rohit Nambiar
Rowan University
nambia72@students.rowan.edu

Christina Nguyen
California State University, Long Beach
nguyenchristina0614@gmail.com

Jacques Nguyen
Baylor University
jacques_nguyen@baylor.edu

Catherine Nikodem
Creighton University
ccn66104@creighton.edu

Lewis Nunez Severino
Hunter College, CUNY
lewis26nz@gmail.com

Jacob Ormes
University of Michigan
jormes@umich.edu

Yuma Ortiz
Texas Tech University Health Sciences Center
yuortiz@ttuhsc.edu

Praneetha Panthagani
Texas Tech University Health Sciences Center
praneetha.panthagani@ttuhsc.edu

Tanya Pareek
University of Mississippi Medical Center
tpareek@umc.edu

Loren Peeters
East Tennessee State University
peeters@etsu.edu

Linda Perrotti
University of Texas at Arlington
perrotti@uta.edu

Loc Pham
University of Mississippi Medical Center
lpham@umc.edu

Tequila Porter
University of California, Davis
tporter@ucdavis.edu

Justin Pressley
University of Arkansas for Medical Sciences
JMPressley@uams.edu

Joshua Prete
Wake Forest University School of Medicine
jprete@wakehealth.edu

Gorana Puzovic
UT Health Science Center at San Antonio
puzovic@livemail.uthscsa.edu

Blake Reeves
Baylor University
blake_reeves1@baylor.edu

Cristina Rivera Quiles
Michigan State University
riveraqu@msu.edu

Madison Roach
California State University, Long Beach
madi.roach@att.net

Isabela Rodriguez
University of Houston-Downtown
Rodriguezavi1@gator.uhd.edu

Daniel Rosenbaum
UT Southwestern Medical Center
dan.rosenbaum@utsouthwestern.edu

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

Lauren Rysztak
University of Michigan
lrysztak@umich.edu

Lauren Scrimshaw
Kent State University
lscrimsh@kent.edu

Robert Seaman
University of Washington
rwseaman@uw.edu

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

Abdul Shaik
Texas Tech University Health Sciences Center
Abdul.Shaik@ttuhsc.edu

Nima Shariatzadeh
UT Health Science Center at San Antonio
shariatzadeh@uthscsa.edu

Hannah Shaw
University of Arkansas for Medical Sciences
HShaw@uams.edu

Ritu Shetty
UNT Health Science Center
ritu.shetty@unthsc.edu

Taylor Simmons
The University of Austin at Texas
tsimms121@utexas.edu

Sunil Sirohi
Xavier University
ssirohi@xula.edu

Emily Siu
California State University, Long Beach
emily.siu01@student.csulb.edu

Joseph Slama
Colgate University
jslama@colgate.edu

Mark Smith
Davidson College
masmith@davidson.edu

Grace Sonick
Kent State University
gsonick@kent.edu

Ricardo Sosa Jurado
University of Texas at El Paso
rsosa4@utep.edu

Dustin Stairs
Creighton University
dustinstairs@creighton.edu

Haidyn Stark
UT Health Science Center at San Antonio
starkh@uthscsa.edu

Kaitlyn Steck
Western Michigan University
kaitlyn.a.steck@wmich.edu

Benjamin Stinson
UT Health Science Center at San Antonio
stinsonb@livemail.uthscsa.edu

Macy Stoddard
Westminster College
macystod@gmail.com

Megana Sundar
UNT Health Science Center
meganasundar@my.unthsc.edu

Olivia Tewell
Kansas State University
ort@ksu.edu

Daquane Triplett
South Texas Veterans Health Care System
daquane.triplett@va.gov

Alexandra Vargas-Elvira
Monell Chemical Senses Center
avargas@monell.org

Ymalay Vega
University of Texas at El Paso
ymalay.vega@gmail.com

Claire Wellendorf
Creighton University
cew20761@creighton.edu

Kayla Wolf
University of Kentucky
wolfkaylaj@gmail.com

Lisa Wooldridge
University of Pennsylvania
lisawool@pennmedicine.upenn.edu

Arturo Zavala
California State University, Long Beach
arturo.zavala@csulb.edu

Muhammad Zia
University of Arkansas for Medical Sciences
muhammadzia1064@gmail.com

Justin Strickland
Johns Hopkins University School of Medicine
jstric14@jhmi.edu

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

Jessica Thrush
University of Arkansas for Medical Sciences
JRThrush@uams.edu

Rita Valentino
National Institute on Drug Abuse
valentinorj@nida.nih.gov

Adriana Vasquez
University of Texas at Austin
avasquez97@utexas.edu

Caleb Vogt
National Institute on Drug Abuse
caleb.vogt@nih.gov

Liza Wills
East Tennessee State University
willslj@ETSU.edu

Sung Joon Won
National Institute of Drug Abuse
sungjoon.won@nih.gov

Coco Xie
Colgate University
cxie@colgate.edu

Nurulain Zaveri
Astraea Therapeutics
nurulain@astraeatherapeutics.com

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

Akeemat Tijani
East Tennessee State University
tijaniao@etsu.edu

Davis Van Dyk
University of Texas at Arlington
djv9281@mavs.uta.edu

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

Zijun Wang
University of Kansas
zjwang@ku.edu

Harrison Witmer
Creighton university
harrisonwitmer@gmail.com

Kristen Woodhouse
University at Buffalo
kwoodhou@buffalo.edu

Isabel Yu
McLean Hospital, Harvard Medical School
isyu@mclean.harvard.edu

Yanan Zhang
RTI International
yzhang@rti.org

Hanson, Taena
Arizona State University
taenahanson@gmail.com

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Maharaj ("Raj") Ticku, PhD

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

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

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

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

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