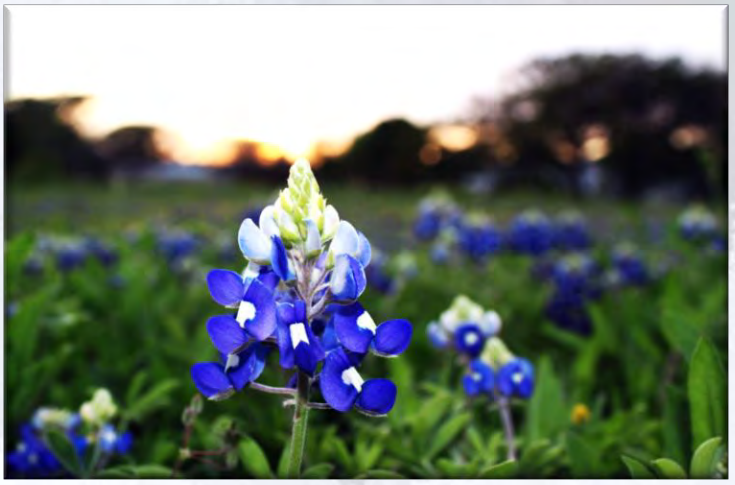
12TH ANNUAL BEHAVIOR, BIOLOGY, and CHEMISTRY:

Translational Research in Addiction

San Antonio, Texas | Embassy Landmark | 29 February – 1 March 2020



ARTT
Addiction Research, Treatment & Training
CENTER OF EXCELLENCE

UT Health San Antonio

San Antonio Life Sciences Institute

NIH National Institute on Drug Abuse

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

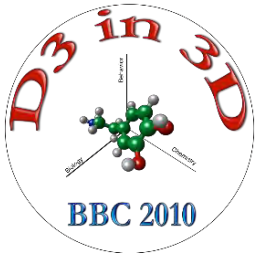
Reith ME, Blough BE, Hong WC, Jones KT, Schmitt KC, Baumann MH, Partilla JS, Rothman RB and Katz JL (2015) **Behavioral, biological and chemical perspectives on atypical agents targeting the dopamine transporter.** *Drug and Alcohol Dependence* 147, 1-19. PMC4297708

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

Sponsors

National Institute on Drug Abuse

University of Texas at El Paso

UT Health San Antonio

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

San Antonio Life Sciences Institute

Med Associates

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

Additional Donations From

Comfort Boateng
Carlos Bolanos
Gregory Collins
James Cook
Andrew Coop
Juan Dominguez
William Fantegrossi
Kevin Freeman
Chad Johnson
Thomas Kosten
Therese Kosten
Hayley Manke
Katharine Nelson
Linda Perrotti

Organizing Committee

Charles P France (Chair)

William P Clarke
Cindal C Dominguez
Brett C Ginsburg
Therese A Kosten
David R Maguire
Gregory T Collins
Rheaclare Fraser-Spears
Wouter Koek
Richard J Lamb
Katherine M Serafine

Program Committee

Gregory T Collins (Chair)

Wouter Koek
Stephen J Kohut
T Celeste Napier
Janet L Neisewander
Katherine M Serafine

Travel Awards Committee

Brett C Ginsburg (Chair)

Eddie Castaneda
Christopher W Cunningham
David N Kearns
Thomas M Keck
Thomas E Prisinzano

Session Chairs

Lisa E Baker
Gregory T Collins
James M Cook
Fernando B de Moura
Suzette M Evans
T Lee Gilman
Chad R Johnson
Thomas M Keck
Therese A Kosten
John D Roache

Poster Judges

Comfort Boateng
Kathleen Borgmann
Andrew Coop
Rebecca Craft
Lynette Daws
Rajeev Desai
Juan Dominguez
Bill Fantegrossi
Kevin Freeman
Michael Gatch
Lisa Gerak
Lee Gilman
Georgianna Gould
Takato Hiranita
Yuanyuan Kang
David Kearns
Thomas Keck
Therese Kosten
David Maguire
Lance McMahon
Michael Nader
Samuel Obeng
Linda Perrotti
Katherine Serafine
Mark Shapiro
Keith Warren

Oral Presentation Judges

Paul Czoty
Brian Kangas
Cassandra Gipson-Reichardt
Sally Huskinson

Administrative and Technical Support

Fermin C Barrera
Christopher Cruz
Cindal C Dominguez
Ashleigh S Morgan

Maharaj Ticku Memorial Travel Fellowship for New Investigators

2012 – Jun-Xu Li

2013 – Kevin B Freeman

2014 – Christopher W Cunningham

2015 – Brian D Kangas

2016 – Clinton E Canal

2017 – Thomas M Keck

2018 – Comfort A Boateng

2019 – Stephen J Kohut

2020 – T Lee Gilman

Travel Awardees

Dalal Alkhelb

Ross Armant

Francisco Battiti

Madeline Beasley

Jasmin Beaver

Nina Beltran

Sanaya Bharadia

Joshua Bilbrey

Adam Brandner

Harley Buechler

Astrid Cardona-Acosta

Erika Carlson

Samuel Castillo

Catherine Conway

Pierpaolo Cordone

Bryan Cruz

Monica Dawes

Fernando de Moura

Marie Doyle

Madeline Elsey

Sophie Elvig

Veronika Espinoza

Ewa Galaj

Lindsey Galbo

Kayla Galindo

Anghelo Gangano

Israel Garcia-Carachure

Priscilla Giner

Rajan Giri

Emma Gogarnoiu

Adriana Gregory-Flores

Bernard Johnson

Saurabh Kokane

Anjali Kumari

Kendyl Lewis

Jingfei Li

Charlotte Magee

Hayley Manke

Peter Manza

Renata Marchette

Michelle Martínez

Liliana Maynez-Anchondo

Christina Norman

Atiqur Rahman

Morgan Reeves

Harmony Risca

Andrea Rodriguez-Crespo

Hudson Roth

Lauren Rysztak

Oscar Sandoval

Karl Schmidt

Jessica Sharp

Omar Sial

Mousumi Sumi

Anapaula Themann

Aaron Tryhus

Andres Vasquez

George Ward

Kristen Woodhouse

Ruyan Wu

Program Overview

FRIDAY 28 FEBRUARY 2020

4:00 PM – 7:00 PM	Registration – Embassy Landmark
3:00 PM – 5:00 PM	**Pathways to Careers in Science Workshop** – UT Health Campus
7:00 PM – 10:00 PM	**BBC Opening Reception, Embassy Landmark**

SATURDAY 29 FEBRUARY 2020

7:00 AM – 5:00 PM	Registration
8:00 AM – 9:05 AM	Poster Session I
9:05 AM – 9:10 AM	Welcome and Opening Remarks
9:10 AM – 11:30 AM	Plenary Symposium: *Sex Differences in Addiction* (Chairs: Gregory T Collins and Therese A Kosten)
	Cora Lee Wetherington; *Sex as a biological variable in addiction research: past, present and future and why it matters*
	Rebecca M Craft; *Sex differences in behavioral effects of opioids and cannabinoids*
	Suzette M Evans; *Sex differences in the behavioral responses to drugs of abuse: translational evidence from human and non-human primate laboratory studies*
	Sherry A McKee; *Considering sex differences in treatment development for smoking*
11:30 AM – 1:00 PM	Lunch
11:45 AM – 1:00 PM	Panel Discussion: *Patient advocate perspectives*
	Jennifer S Potter (Moderator) **Valerie McDonald**
	Yolanda Huff **Doug Smith**
1:15 PM – 3:15 PM	Open Oral Communications I (Chairs: Suzette M Evans and Chad R Johnson)
3:15 PM – 3:30 PM	Coffee Break
3:30 PM – 5:15 PM	Open Oral Communications II (Chairs: T Lee Gilman and Thomas M Keck)
5:15 PM – 5:30 PM	Coffee Break
5:30 PM – 6:30 PM	Special Lecture (Chair: John D Roache)
	Roland R Griffiths; *Psilocybin: history, neuropharmacology, and implications for treatment of drug addiction and other psychiatric disorders*
6:30 PM – 7:30 PM	Poster Session and Cocktail Hour
7:35 PM – 9:30 PM	Dinner
	Science Trivia and Entertainment

SUNDAY 1 MARCH 2020

7:45 AM	Travel Awardee Group Photo
8:00 AM – 9:10 AM	Poster Session II
9:10 AM – 11:10 AM	Open Oral Communications III (Chairs: Lisa E Baker and Fernando B de Moura)
11:10 AM – 11:25 AM	Coffee Break
11:25 AM – 12:25 PM	Special Lecture (Chair: James M Cook)
	Bruce E Blough; *The Evolution of releaser stimulants from natural products to bath salts*
12:25 PM – 12:30 PM	Travel and Presentation Awards
12:30 PM – 1:30 PM	Adjournment and Lunch

Maharaj Ticku Memorial Travel Fellowship for New Investigators

Travel Awardee

Program Details

Friday 28 February 2020

Registration	4:00 PM – 7:00 PM	*Bluebonnet Foyer*
Pathways to Careers in Science Workshop	3:00 PM – 5:00 PM	*UT Health Campus*
Opening Reception	7:00 PM - 10:00 PM	*Lantana Ballroom*

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

Saturday 29 February 2020

Poster Session I (odd posters judged)	8:00 AM - 9:05 AM	*Bluebonnet C/Foyer*
Welcome and Opening Remarks	9:05 AM - 9:10 AM	*Bluebonnet AB*
Plenary Symposium; *Sex Differences in Addiction*	9:10 AM – 11:30 AM	*Bluebonnet AB*

(Chairs: Gregory T Collins and Therese A Kosten)

Substance use is common among both males and females; however, mounting evidence suggests that biologic sex can impact the age of onset, trajectory, and severity of substance use disorders. This symposium brings together leading experts in the field to discuss the importance of studying sex as a biological variable in substance use disorder, as well as cutting-edge research into sex-related differences in the abuse-related effects of opioids, cannabinoids, stimulants, and nicotine. Ultimately, this symposium aims to highlight key sex-related differences in the behavioral and neurobiological effects of abused drugs, and demonstrate how this information can be exploited to develop novel and effective pharmacotherapies for substance use disorders.

9:10 AM – 9:45 AM	**Cora Lee Wetherington;** National Institute on Drug Abuse *Sex as a biological variable in addiction research: past, present and future and why it matters*
9:45 AM – 10:20 AM	**Rebecca M Craft;** Washington State University *Sex differences in behavioral effects of opioids and cannabinoids*
10:20 AM – 10:55 AM	**Suzette M Evans;** Columbia University *Sex differences in the behavioral responses to drugs of abuse: translational evidence from human and non-human primate laboratory studies*
10:55 AM – 11:30 AM	**Sherry A McKee;** Yale University *Considering sex differences in treatment development for smoking*

Lunch	11:30 AM – 1:00 PM	*Lantana Ballroom*
Panel Discussion; *Patient advocate perspectives*	11:45 AM – 1:00 PM	*Bluebonnet AB*

Attendees are invited for a frank and friendly moderated panel discussion about the challenges of overcoming a substance use disorder, and efforts being made to help those struggling with a substance use disorder. Significant time will be provided for audience questions and participation.

Jennifer S Potter	UT Health San Antonio (Moderator)
Yolanda Huff	Judge, Bexar County Specialty Courts Coalition
Valerie McDonald	Freedom House Recovery Clinic
Doug Smith	Texas Criminal Justice Coalition

Oral Communications I — 1:15 PM – 3:15 PM — *Bluebonnet AB*

(Chairs: Suzette M Evans and Chad R Johnson)

1:15 PM – 1:30 PM — **Francisco Battiti**, National Institute on Drug Abuse
Clearing the path to selective dopamine D3 receptor agonists one bitopic ligand at a time

1:30 PM – 1:45 PM — **Brent Kisby**, Texas Tech University Health Science Center
Alcohol dependence in rats is associated with global changes in gene expression in central amygdala

1:45 PM – 2:00 PM — **Jingfei Li**, University of Chicago Pritzker School of Medicine
Subjective factors predicting amphetamine-choosing behavior in healthy adults

2:00 PM – 2:15 PM — **Marie Doyle**, Michigan State University
SGK1 activity in VTA dopamine neurons regulates cocaine and morphine reward behaviors

2:15 PM – 2:30 PM — **Michelle Doyle**, UT Health San Antonio
Effects of sex and access condition on cocaine self-administration in rats

2:30 PM – 2:45 PM — **Lauren Russell**, University of Arkansas for Medical Sciences
Structure-activity relationships for locomotor stimulant effects of substituted amphetamines and cathinones

2:45 PM – 3:00 PM — **Saurabh Kokane**, University of Texas at Arlington
Activation of ERK1/2 underlies estradiol mediated sex differences in cocaine reward

3:00 PM – 3:15 PM — **Robert Seaman**, UT Health San Antonio
Neurocognitive effects of extended access methamphetamine, cocaine, and MDPV self-administration in rats

Coffee Break — 3:15 PM – 3:30 PM

Oral Communications II — 3:30 PM – 5:15 PM — *Bluebonnet AB*

(Chairs: T Lee Gilman and Thomas M Keck)

3:30 PM – 3:45 PM — **Peter Manza**, National Institute on Alcohol Abuse and Alcoholism
Intravenous but not oral methylphenidate systematically tunes brain activity in association with subjective 'high'

3:45 PM – 4:00 PM — **George Ward**, National Institute on Drug Abuse
An improved synthesis of tamoxifen analogs and the effect on methamphetamine induced neurotoxicity

4:00 PM – 4:15 PM — **Renata Marchette**, National Institute on Drug Abuse
Sex differences in the involvement of the dynorphin/kappa opioid receptor system in heroin withdrawal-induced hyperalgesia

4:15 PM – 4:30 PM — **Karl Schmidt**, Davidson College
The role of progesterone and estradiol on opioid self-administration in female rats

4:30 PM – 4:45 PM — **Jessica Sharp**, Davidson College
The effects of estrous cycle and ovarian hormones on heroin and sucrose self-administration

4:45 PM – 5:00 PM — **Drew Townsend**, Virginia Commonwealth University
Effect of sex and opioid withdrawal on opioid reinforcement under a fentanyl vs. food choice procedure in rats

5:00 PM – 5:15 PM — **Fernando de Moura**, Harvard Medical School/McLean Hospital
Sex differences and the impact of alternative reinforcers on oxycodone self-administration and reinstatement in squirrel monkeys

Coffee Break — 5:15 PM – 5:30 PM

Maharaj Ticku Memorial Travel Fellowship for New Investigators — Travel Awardee

Special Lecture: Roland R Griffiths 5:30 PM – 6:30 PM *Bluebonnet AB*

Psilocybin: history, neuropharmacology, and implications for treatment of drug addiction and other psychiatric disorders

(Chair: John D Roache)

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

Dinner 7:35 PM – 9:30 PM *Bluebonnet AB*

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

Science Trivia and Entertainment *Bluebonnet AB*

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

Sunday 1 March 2020

Travel Awardee Group Photo — 7:45 AM — *Bluebonnet C/Foyer*

Poster Session II (even posters judged) — 8:00 AM – 9:10 AM — *Bluebonnet AB*

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

(Chairs: Lisa E Baker and Fernando B de Moura)

9:10 AM – 9:25 AM	**Lee Gilman**, Kent State University *Pharmacobehaviorally evaluating the contribution of plasma membrane monoamine transporter function to monoamine clearance*
9:25 AM – 9:40 AM	**Chad Johnson**, University of Maryland, Baltimore *A potential muscarinic antagonist antidepressant that lacks cognitive deficits*
9:40 AM – 9:55 AM	**Ewa Galaj**, National Institute on Drug Abuse *Substantia nigra reticulata GABA neurons: newly identified targets involved in opioid reward and relapse*
9:55 AM – 10:10 AM	**Cassandra Gipson-Reichardt**, Arizona State University *Chemogenetic inhibition of accumbens cholinergic interneurons inhibits nicotine seeking and associated transient, synaptic plasticity*
10:10 AM – 10:25 AM	**Comfort Boateng**, High Point University *Molecular determinants of D4R-selective antagonist and partial agonist efficacy*
10:25 AM – 10:40 AM	**Kathleen Borgmann**, University of North Texas Health Science Center *Assessing sex differences in the functional responses of primary human astrocytes*
10:40 AM – 10:55 AM	**Samuel Obeng**, University of Florida *Investigation of the in vitro binding, pharmacokinetic, antinociception and substitution properties of selected indole-based kratom alkaloids*
10:55 AM – 11:10 AM	**Keith Warren**, The Ohio State University *Tightly bound: the relationship of network clustering coefficients and reincarceration at three therapeutic communities*

Coffee Break — 11:10 AM – 11:25 AM

Special Lecture: Bruce E Blough — 11:25 AM – 12:25 PM — *Bluebonnet AB*

The evolution of releaser stimulants from natural products to bath salts

(Chair: James M Cook)

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

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

See you at BBC 2021!

Maharaj Ticku Memorial Travel Fellowship for New Investigators

Travel Awardee

Oral Communications

Oral Communication 1-1

Clearing the path to selective dopamine D3 receptor agonists one bitopic ligand at a time

Battiti, Francisco O.[†]; Cemaj, Sophie L.[†]; Guerrero, Adrian M.[†]; Adhikari, Pramisha[‡]; Yano, Hideaki [‡]; Sanchez, Julie [§]; Lane, J. Robert [§]; Shi, Lei[‡]; Newman, Amy Hauck[†]; Bonifazi, Alessandro[†]*

[1]Department of Psychology, University at Buffalo, SUNY, Buffalo, NY USA
† Medicinal Chemistry Section, Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse-Intramural Research Program, National Institutes of Health, 333 Cassell Drive, Baltimore, Maryland 21224, United States; ‡ Computational Chemistry and Molecular Biophysics Unit, Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse-Intramural Research Program, National Institutes of Health, 333 Cassell Drive, Baltimore, Maryland 21224, United States; § Centre for Membrane Proteins and Receptors, Nottingham University, Nottingham, NG7 2RD, UK

Small molecules that act as selective agonists at the D2-like dopamine receptor subtypes have long been sought after due to their therapeutic potential in treating pathologies characterized by dopamine dysregulation. Despite significant effort, the high homology between the D2R and D3R subtypes has impeded the development of highly subtype selective agonists. Inspired by promising results shown by bitopic GPCR ligands in achieving high affinities and subtype selectivities, we sought to develop a new generation of D3R selective agonists with bitopic structures. Making use of the known (+)-PD128,907 and PF-592379 scaffolds as primary pharmacophores, to recognize the orthosteric binding site (OBS), we conducted an extensive SAR investigation to identify the optimal linker and secondary pharmacophores that would translate to improved D3R subtype selectivity. Several lead compounds were identified that demonstrate some of the highest D3R/D2R selectivities, in cell-based binding assays, for agonists reported to date. Moreover, the agonist functional profile of these compounds was determined by Bioluminescence Resonance Energy Transfer assays (BRET) and showed agonist profiles that were in agreement with the binding data obtained and predicted via our optimized agonist radioligand binding protocol. The degree of structural complexity and enantioselectivity of these compounds make them promising substrates for computational studies to provide insight on ligand-receptor interactions and the receptor conformations responsible for the observed selectivity. Further, in vivo investigation of our lead compounds will guide medicinal chemistry efforts toward therapeutic application.

Oral Communication 1-2

Alcohol dependence in rats is associated with global changes in gene expression in central amygdala

Kisby, Brent R.[1]; Farris, Sean P[2]; McManus, Michelle[1]; Varodayan, Florence[3]; Roberto, Marisa[3]; Harris, R. Adron [2,4]; Ponomarev, Igor[1]

[1]Texas Tech University Health Science Center, Lubbock, TX; [2]University of Texas at Austin, Austin, TX; [3]The Scripps Research Institute, La Jolla, CA; [4] Waggoner Center for Alcohol and Addiction Research, Austin, TX

The current Diagnostic and Statistical Manual of Mental Disorders (DSM-5) integrates the two DSM–IV disorders, alcohol abuse and alcohol dependence, into a single disorder called Alcohol use disorder (AUD). AUD is a chronic, relapsing disease that affects approximately 16 million individuals in the USA. Alcohol dependence is evident in most severe AUD cases and is associated with adverse consequences of alcohol (ethanol) use. Currently, one of the most widely used rodent models for assessing alcohol dependence is the chronic intermittent ethanol (CIE) vapor model. The central nucleus of the amygdala (CeA) plays a critical role in the development of alcohol dependence. Here we used an RNA-Seq approach to identify 1,837 genes differentially expressed in CeA of rats exposed to ethanol vapor compared to air controls (nominal p≤0.05). Different cell types and gene ontologies were over-represented, including, but not limited to the, astrocyte (e.g., *Mmp14*), oligodendrocytes (e.g., *Mbp, Mobp*), stress-related genes (*Crh,Crhbp*), extracellular matrix (e.g., *Mmp14, Col1a1, Col3a1*), and immune-related genes (e.g., *Nfkbib, Il6r)*. Our results demonstrate further insight into molecular mechanisms of alcohol dependence in rats. These molecular targets may be used in future studies to develop therapeutics to treat AUD.

Oral Communication 1-3

Subjective factors predicting amphetamine-choosing behavior in healthy adults

Li, Jingfei[1]; Weafer, Jessica J PhD[1] and de Wit, Harriet PhD[1]

[1]Human Behavioral Pharmacology Lab, University of Chicago, Chicago, IL, USA

While amphetamines are widely prescribed today as therapy for certain conditions, their psychoactive properties pose an inherent risk for abuse. However, it is unclear why certain users are more likely to abuse amphetamines than others. This study attempted to determine if subjective drug effects experienced while on amphetamines could predict future amphetamine-choosing behavior in healthy adults.
In this study, 112 adults completed five session choice study, consisting of four 5-hour drug and placebo sampling sessions followed by a choice session. On the first four sessions they received 20mg of d-amphetamine or placebo in alternating order under double blind conditions. They filled out validated questionnaires detailing their subjective response to the drug at regular intervals. On the fifth session, they had the option of choosing either placebo or amphetamine, whichever they preferred. For this analysis, subjects were grouped by their drug or placebo choice, and their subjective responses to the drug were compared using Student's t-tests.
Participants who subsequently chose amphetamine reported significantly higher stimulant and euphoric effects during the amphetamine sessions, compared to while on placebo. They also differed significantly in liking the drug more, wanting more of the drug, and were willing to pay more for the drug compared to placebo choosers. The groups did not differ in how much they reported feeling the drug or how "high" they felt during the session.
These results suggest that the ability of amphetamines to induce euphoria and stimulating effects in an individual may predict that individual's likelihood to use amphetamines again. Furthermore, while users may report feeling the effects of amphetamines equally, those that like the effect and want more of it are more likely to use amphetamines again.

Oral Communication 1-4

SGK1 activity in VTA dopamine neurons regulates cocaine and morphine reward behaviors

Doyle, Marie[1]; Bali, Vedrana[2]; Williams, Elizabeth[3]; Stark, Ali[1]; Robison, AJ[1,2]; and Mazei-Robison, Michelle[1,2]

[1]Neuroscience Program, Michigan State University; [2]Department of Physiology, Michigan State; [3]Pharmacology and Toxicology Department, Michigan State University

Drugs of abuse are known to regulate activity of the mesolimbic dopamine (DA) system. Specifically, drug-induced changes in ventral tegmental area (VTA) cellular activity and gene regulation contribute to behavioral outputs associated with addiction. Our previous work has determined that serum- and glucocorticoid-inducible kinase 1 (SGK1) catalytic activity is increased by chronic administration of cocaine or morphine. Furthermore, I have shown that viral overexpression of SGK1 mutants in the VTA of adult mice produce behaviorally relevant effects on drug reward. Specifically, intra-VTA infusion of a catalytically inactive SGK1 mutant (K127Q) significantly decreases cocaine conditioned place preference (CPP) and morphine preference in a two-bottle choice task, suggesting that decreasing VTA SGK1 activity is sufficient to decrease drug reward. To more fully understand the role of VTA SGK1 in behaviors relevant to addiction, I am now manipulating SGK1 expression in a cell type-specific manner to determine whether SGK1 activity in DA or GABA neurons drives the observed behavioral effects. Utilizing novel Cre-dependent viral constructs, I have found that decreased SGK1 activity in VTA DA neurons significantly decreases cocaine CPP, while this same manipulation in VTA GABA neurons has no effect. Moreover, preliminary data suggests that SGK1 activity may regulate cocaine IV self-administration. These studies will allow for identification of the specific cells and circuits that are critical for SGK1-mediated effects on drug reward and intake, a necessary step in assessing the feasibility of SGK1 inhibition as a novel therapeutic avenue for addiction.

Oral Communication 1-5

Effects of sex and access condition on cocaine self-administration in rats

Doyle, Michelle R.[1,2]; Sulima, Agnieszka[3]; Rice, Kenner C.[3]; and Collins, Gregory T.[1,2]

[1]Dept of Pharmacology, UT Health, San Antonio, TX, USA; [2]South Texas Veterans Health Care System, San Antonio, TX, US; [3]Molecular Targets and Medications Discovery Branch, NIDA-NIAAA-IRP, Bethesda, Maryland, USA.

Despite decades of research, the behavioral, pharmacological, and neurobiological determinants of one's vulnerability to develop a substance use disorder are not well understood. When rats are allowed to self-administer cocaine under short-access conditions, patterns of drug intake tend to be well regulated; however, it is thought that manipulating drug access conditions (e.g., long- or intermittent-access) can produce neurobiological and behavioral changes related to addiction. The current studies used male and female Sprague Dawley rats self-administering cocaine (0.32 mg/kg/infusion) to test the hypothesis that rats with 21 days of long- and intermittent-access to cocaine will exhibit higher levels of drug taking, greater levels of responding when drug is not available, and reduced sensitivity to punishment by foot shock (i.e., addiction-like behaviors) compared to rats with 21 days of short-access to cocaine. Female rats appear to be less sensitive to punishment by foot shock than male rats; however, there were no apparent sex differences in drug intake or responding during periods of signaled drug unavailability. Though long- and intermittent-access produced some changes in patterns of drug-taking and resulted in different levels of cocaine intake, manipulating access condition did not systematically alter the addiction-like behaviors. These results suggest that long- and intermittent-access self-administration may not produce long-term and robust behavioral changes thought to be related to addiction, and these effects do not differ as a function of sex.

This work was supported by NIH/NIDA (R01 DA039146; GTC) and NIDA- and NIAAA-IRPs (KCR).

Oral Communication 1-6

Structure-activity relationships for locomotor stimulant effects of substituted amphetamines and cathinones

Russell, Lauren[1]; Landavazo, Antonio[2]; Blough, Bruce[2]; Baumann, Michael[3]; Fantegrossi, William[1]

[1]College of Medicine, University of Arkansas for Medical Science, Little Rock, AR USA; [2]Research Triangle Institute, Research Triangle Park, NC USA; [3]National Institute on Drug Abuse, Intramural Research Program, Baltimore, MD USA

In these studies, we compared 12 structurally-analogous substituted amphetamines and cathinones from amphetamine to 4-chloroethcathinone to assess structure-activity relationships for locomotor stimulant and lethal effects in mice. Automated photobeam chambers were used to record various aspects of mouse locomotor activity. Full dose-effect curves were determined for each compound, starting with a dose that produced saline-like distance traveled, and increasing in half-log units until distance decreased from that drug's peak, or until lethal effects were observed. The addition of a ketone group at the beta-carbon of the ampehtamines decreased maximal horizontal distance traveled and increased time spent in stereotypy. Addition of a chlorine at the 4 position increased effectiveness for horizontal activity but also induced lethality. Additionally, the functional activity of the compounds at DAT, NET, and SERT were observed utilizing uptake and release experiments. For the substituted amphetamines, increasing the length of the side chain increased SERT affinity, and 4-Cl substitution further increased SERT activity essentially creating non-selective transporter blockers/substrates. 4-Cl ethyl amphetamine and cathinone were inactive in DA release assays, but robustly released 5-HT. All 4-Cl compounds produced lethality at doses on the ascending limb of the dose-effect curve for distance traveled. 4-Cl substituted amphetamines and cathinones pose a significant health risk in a drug abuse setting as lethal effects emerge at doses eliciting only minimal stimulant effects, most likely via serotonin syndrome related complications. Supported by DEA, NIDA IRP, RTI, and T32 DA022981.

Oral Communication 1-7

Activation of ERK1/2 underlies estradiol mediated sex differences in cocaine reward

Kokane, Saurabh S.[1]; Butler, Brandon; Antonio, Josimar H.; Perrotti, Linda I.[1]

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

Previous research has shown that increased vulnerability of women and female animals to the subjective effects of cocaine and hypersensitivity to cocaine-associated cues is mediated by estradiol (EB). In males, ERK-mediated neuroadaptations in the mesolimbic pathway during early cocaine exposure lead to cocaine reward and development of cocaine-cue associations. However, research demonstrating sex differences in cocaine hypersensitivity, involvement of EB during early cocaine exposure, and its effect on ERK-mediated cocaine reward and cocaine-cue associations is severely lacking. The goal of the present study was to - a) determine EB-mediated sex differences on cocaine-cue associations and b) determine the effect of EB on ERK1/2-mediated cocaine reward and cocaine-cue associations. Using a three-day conditioning procedure, intact adult male, female, and ovariectomized (OVX) Long Evans rats were conditioned to associate one of two large chambers of a conditioned place preference apparatus with one of four doses of cocaine (0, 5, 10, or 15mg/kg). OVX female rats were treated with either EB (5 µg) or peanut oil 30 min prior to the start of each daily cocaine-conditioning session. Expression of cocaine-CPP was assessed under a cocaine- and hormone-free state 24h following the last conditioning session. Immediately after the cocaine-CPP test, rats were euthanized and brain tissue comprising VTA, NAc, dorsal striatum, and medial PFC was isolated. ANOVAs were used to statistically analyze all data. Results demonstrate that females have higher preference for cocaine at lower doses compared to males. EB-treatment during the conditioning phase of CPP potentiates cocaine-CPP. Moreover, intact and EB-treated females demonstrate increased levels of phosphorylated ERK1/2 protein in VTA, dorsal striatum, and NAc shell after cocaine-CPP. In conclusion, the increased sensitivity of females to cocaine may be due to the potentiation of cocaine-cue associations by EB and this may be mediated by increased activation of ERK1/2 signaling. Funding support: NIH/NIDA R15DA040809 (LIP).

Oral Communication 1-8

Neurocognitive effects of extended access methamphetamine, cocaine, and MDPV self-administration in rats

Seaman Jr, Robert W.[1,2]; Sulima, Agnieszka[3]; Rice, Kenner C.[3]; Collins, Gregory T.[1,2]

[1]UT Health San Antonio, TX USA; [2]South Texas Veterans Health Care System, San Antonio, TX USA; [3]NIDA/NIAAA Intramural Research Programs, Bethesda, MD USA.

Over 18 million people in the United States are classified as having a substance use disorder. Given the chronicity of these disorders, it is crucial to gain a better understanding of the toxicity associated with prolonged drug use. Regarding stimulants, monoamine releasers (e.g., methamphetamine) rather than monoamine uptake inhibitors (e.g., cocaine) are typically associated with neuroinflammatory and neurodegenerative effects that are thought to underlie neurocognitive dysfunction. Interestingly, recent data suggest that a synthetic cathinone, MDPV (a monoamine uptake inhibitor), has neurotoxic effects; however, the neurocognitive consequences of MDPV self-administration remain largely unexplored. The current study aims to investigate the degree to which self-administered MDPV can induce deficits in recognition memory compared to methamphetamine and cocaine. Rats were allowed 90-min or 12-h access to grain pellets on one lever and an infusion of either 0.032 mg/kg MDPV, 0.1 mg/kg methamphetamine, 0.32 mg/kg cocaine, or saline on the other lever (n=8/group) for 6 weeks. Rats that had 12-h access to MDPV or methamphetamine exhibited deficits in the novel object recognition assay relative to rats given access to saline. No deficits were observed in rats that self-administered cocaine. The total exploration time of objects remained comparable among all groups. These data suggest that unlike cocaine, the prototypical monoamine uptake inhibitor, MDPV is capable of producing memory deficits often associated with neuroinflammation and/or neurodegeneration. Future studies will evaluate markers of neurodegeneration and neuroinflammation in these rats and explore pharmacological avenues to mitigate stimulant-induced neurocognitive deficits.
Supported by NIH/NIDA (R01DA039146; GTC) and the IRPs of NIDA and NIAAA (KCR).

Oral Communication 2-1

Intravenous but not oral methylphenidate systematically tunes brain activity in association with subjective 'high'

Manza, Peter[1]; Tomasi, Dardo [1]; Yuan, Kai[1] ; Wang, Gene-Jack [1]; Volkow, Nora [1,2]

[1]National Institute on Alcoholism and Alcohol Abuse, National Institutes of Health, Bethesda, MD; 2National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD

There is great interest in understanding how dopamine alters human brain function and behavior; e.g., following drug intake, how does dopamine release at different timescales change brain function to contribute to the subjective experience of 'high'? These measures are very challenging to capture simultaneously *in vivo* in humans. *Methods*: We used simultaneous PET-fMRI with oral and IV methylphenidate (MPH) drug challenges to measure "dopamine release" (difference in Raclopride binding between placebo and MPH conditions), brain network function, and subjective high ratings in ten healthy adults (5 male, 5 female; Age 34 ± 10 years; double-blind, placebo-controlled, within-subject design) in real time. We compared pre-drug levels of brain activity with dynamic changes in activity in association with dopamine release and subjective 'high' across a 90-min PET-fMRI scan. That is, we computed voxelwise spatial correlations of whole-brain activity (pre-drug baseline vs. dynamic PET-fMRI session) in each individual and used paired *t*-tests comparing correlation coefficients for placebo vs. drug conditions). *Results*: MPH increased subjective 'high' and elicited dopamine release, and the effect was more dramatic for IV than oral MPH, replicating prior work (IV vs. Placebo: t's > 5.0, p's < .001; Oral vs. Placebo: t's > 3.0, p's < .05). Subjective 'high' was associated with a systematic change in activity across the brain: regions with greater activity at baseline showed decreased activity with increasing 'high', and vice versa, in the IV ($t(9) = 3.389$, $p = .008$) but not oral MPH condition ($t(9) < 1.0$, $p > .05$). No systematic change in activity was observed in association with dopamine release (t's < 1.5, p's > .05). *Conclusion*: These data demonstrate unique brain functional changes that occur with IV (but not oral) MPH in association with 'high', which may help explain why faster modes of drug intake are more addictive than slower ones.

Oral Communication 2-2

An Improved synthesis of tamoxifen analogs and the effect on methamphetamine induced neurotoxicity

Ward, George W.[1]; Zestos, Alexander[3]; Riley, Anthony[3]; Sulima, Agnieska[1]; Perez, Mariana A.[2]; Kuhn, Donald M.[2]; Jacobson, Arthur[1]; Rice, Kenner C.[1]

[1]Drug Design and Synthesis Section, Molecular Targets and Medications Discovery Branch, Intramural Research Program, National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Department of Health and Human Services, 9800 Medical Center Drive, Bethesda, MD 20892-3373.
[2]Department of Psychiatry & Behavioral Neurosciences, Wayne State University School of Medicine & John D. Dingell VA Medical Center, 4646 John Rd, Detroit, MI 48201.
[3]Psychopharmacology Laboratory, Center for Behavioral Neuroscience, American University, Washington, DC 20016.

For many years, tamoxifen has been used as a treatment for a variety of breast cancers. Recently, it has been found to also have effect on protein kinase C (PKC) which decreases dopamine efflux, and this appears to decrease manic symptoms in bi-polar patients. It is also known that the neurotoxic effects of methamphetamine can be reduced by tamoxifen analogs. We decided to explore the modification of the molecular structure of tamoxifen with the hope of increasing its effect on PKC and reducing the neurotoxicity of amphetamine-like compounds in vivo. In previous studies SAR analysis was used to establish a small collection of analogs with improved PKC inhibition and dopamine transporter efflux inhibition. In this study, we have improved the synthesis of tamoxifen analogs with new structural motifs both in overall yield and purity of final compounds. With a common late stage intermediate, a wide range of different analogs containing an interesting array of molecular structures can be easily accessed in rapid succession. Additional studies with these new compounds are ongoing.

Oral Communication 2-3

Sex differences in the involvement of the dynorphin/kappa opioid receptor system in heroin withdrawal-induced hyperalgesia

Marchette, Renata C.N.[1]; Gregory-Flores, Adriana[1]; Carlson, Erika R.[1]; Tunstall, Brendan J.[1]; Sulima, Agnieszka [2]; Rice, Kenner [2] ; Vendruscolo, Leandro F.[1]; Koob, George F.[1]

[1]Neurobiology of Addiction Section, Integrative Neuroscience Branch, NIDA IRP, NIH, Baltimore, MD; [2]Drug Design and Synthesis Section , NIDA IRP, NIH, Bethesda, MD.

Although opioids are potent analgesics, chronic opioid use leads to hyperalgesia that is observed during withdrawal and is hypothesized to contribute to opioid seeking and taking. There is evidence supporting the involvement of dynorphin and kappa opioid receptors (dyn-KOR) in hyperalgesia in chronic pain models and dynorphin expression is upregulated in rodent models of opioid dependence. However, the involvement of this system in opioid withdrawal-induced hyperalgesia remains to be investigated. We tested the hypothesis that increased dynorphin/KOR signaling plays a functional role in opioid withdrawal-induced hyperalgesia. Hyperalgesia was induced in male and female Wistar rats by daily injections of heroin (2-6 mg/kg, s.c.). Mechanical sensitivity was measure by an electronic von Frey filament device 4-6 h into heroin withdrawal. Treatment with the KOR antagonists 5'-guanidinonaltrindole (GNTI, 30 mg/kg, s.c.) or nor-binaltorphimine (norBNI, 30 mg/kg, s.c.) reversed heroin withdrawal-induced hyperalgesia in rats of both sexes, an effect that lasted longer in females. Additionally, we tested mice lacking the pro-dynorphin gene (pDyn KO) in heroin withdrawal-induced hyperalgesia. pDyn KO mice had higher baseline paw withdrawal thresholds and were resistant to hyperalgesia development. These findings suggest that the dynorphin/KOR system is functionally involved in the development of withdrawal-induced hyperalgesia and represent a potential target for the understanding of the relationship between pain and opioid addiction.

Oral Communication 2-4

The role of progesterone and estradiol on opioid self-administration in female rats

Schmidt, Karl T.[1]; Sharp, Jessica[1]; Ethridge, Sarah[1]; Pearson, Tallia[1]; Zhang, Huailin[1]; Ballard, Shannon[1]; Casimir, Alexander[1]; Potter, Kenzie[1]; Robinson, Andrea[1]; Smith, Mark[1]

[1]Department of Psychology, Davidson College, Davidson NC USA

We previously reported that heroin intake decreases during the proestrus phase of the estrous cycle in female rats. The purpose of this study was to (1) replicate these findings in Long-Evans (LE), Lewis (LEW) and Sprague-Dawley (SD) rats, (2) determine the hormonal mechanisms mediating proestrus-induced decreases in heroin intake by testing the effects of exogenous estradiol and progesterone on heroin intake in ovariectomized female rats, and (3) determine whether chronic administration of exogenous hormones decreases opioid intake in intact female rats. In Experiment 1, the estrous cycle of intact, female LE, LEW, and SD rats was tracked daily and heroin intake was examined. In Experiment 2, separate groups of ovariectomized female LE rats were treated chronically with estradiol, progesterone, estradiol + progesterone, or vehicle, and heroin intake was examined. In Experiment 3, separate groups of intact female LE rats were treated chronically with either a low dose of estradiol, a high dose of estradiol, or vehicle, and heroin and remifentanil intake was examined. Heroin intake decreased significantly during proestrus in all three rat strains under at least one dose condition, and these effects were most robust in LE rats. In Experiment 2, estrogen-treated rats self-administered less heroin than any other group and significantly less heroin than rats treated with progesterone. In Experiment 3, chronic administration of estradiol non-significantly decreased heroin intake and significantly decreased remifentanil intake in intact female rats. These data indicate that heroin intake decreases significantly during proestrus across rat strains and that these effects are likely mediated by estradiol. These data also indicate that chronic estradiol administration decreases opioid intake in intact female rats, suggesting that an estrogen-based pharmacotherapy may represent a novel treatment approach for women with opioid use disorder. NIH Grants DA045364, DA031725, and DA045714.

Oral Communication 2-5

The Effects of Estrous Cycle and Ovarian Hormones on Heroin and Sucrose Self-Administration

Sharp, Jessica [1]; Schmidt, Karl[1]; Ethridge, Sarah[1]; Zhang, Huailin[1]; Marcus, Madison[1]; Potter, Kenzie[1]; Robinson, Andrea[1]; Smith, Mark[1]

[1]Department of Psychology, Davidson College, Davidson NC USA

We previously reported that heroin intake decreases during the proestrus phase of the estrous cycle in female rats. Estradiol and progesterone rise and fall in rapid succession during proestrus, and therefore it is not known which of these two hormones contribute to the decrease in heroin intake observed during proestrus. The purpose of this study was to examine the effects of estradiol and progesterone on heroin self-administration and to determine if proestrus-induced decreases in responding extended to a nondrug reinforcer.
In Experiment 1, the estrous cycle of intact female rats was tracked daily and either the estrogen-receptor antagonist, raloxifene, the progesterone-receptor antagonist, mifepristone, or their combination was administered 30 minutes prior to a heroin self-administration session. In Experiment 2, an artificial proestrus state was experimentally induced in ovariectomized rats by administering estradiol (or vehicle) 22 hours and progesterone (or vehicle) 30 minutes before a heroin self-administration session. In Experiment 3, the effects of the estrous cycle on responding maintained by sucrose was examined. In Experiment 1, raloxifene, but not mifepristone, significantly blocked proestrus-induced decreases in heroin intake in female rats. In Experiment 2, estradiol administered 22 hours before a test session significantly decreased heroin intake in ovariectomized rats, and this effect was independent of progesterone administration. In Experiment 3, responding maintained by sucrose did not decrease during proestrus in intact female rats. These data indicate that responding maintained by heroin, but not a nondrug reinforcer, significantly decreases during proestrus in female rats, and that these effects are mediated by estradiol but not progesterone. NIH Grants DA045364, DA031725, and DA045714

Oral Communication 2-6

Effect of sex and opioid withdrawal on opioid reinforcement under a fentanyl vs. food choice procedure in rats

Townsend, Andrew E.[1]; Banks, Matthew L.[1]

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

AIM: Clinical evidence suggest that men are more sensitive than women to the abuse-related effects of mu-opioid agonists. In contrast, preclinical studies suggest the opposite sex difference. In addition, the effect of sex on opioid withdrawal-associated changes in opioid vs. food choice are unknown. The aim of the present study was to clarify this discrepancy using a fentanyl vs. liquid food choice procedure to assess sex differences in opioid reinforcement.
METHODS: Sex differences in intravenous (IV) fentanyl self-administration were examined under 1) a fixed-ratio (FR5) schedule, 2) a behavioral economic analysis, and 3) a concurrent (choice) schedule of fentanyl and liquid food (18% Ensure®) reinforcement in under male and female rats (n=18 male, 18 female). Fentanyl vs. liquid food choice was assessed under opioid dependent and non-opioid dependent conditions.
RESULTS: The fentanyl dose-effect function under the FR5 schedule was significantly shifted upward in females compared to males. Similarly, the reinforcing effectiveness of both fentanyl (3.2 and 10 µg/kg/inj, IV) and liquid food (18 and 56%) were greater in females than males as assessed using behavioral economic analysis, irrespective of dose or concentration. However, under a fentanyl vs. food choice procedure, non-opioid dependent males chose 3.2 µg/kg/inj fentanyl injections over 18%, but not 56%, liquid food at a higher percentage compared to females. Opioid-withdrawn male, but not female, rats exhibited increased opioid choice.
CONCLUSION: These results suggest the expression of sex differences in opioid reinforcement depends upon the schedule of reinforcement and state of opioid dependence. In addition, these findings suggest that preclinical opioid vs. food choice procedures may provide for a more translationally relevant experimental endpoint (i.e., behavioral allocation vs. rates of responding), as the non-opioid dependent choice data are consistent with the direction of sex differences reported in the clinical literature.

Oral Communication 2-7

Sex differences and the impact of alternative reinforcers on oxycodone self-administration and reinstatement in squirrel monkeys

de Moura, Fernando B.[1,2]; Kohut, Stephen J.[1,2]

[1]Behavioral Neuroimaging Laboratory, McLean Hospital, Belmont, MA USA; [2]Department of Psychiatry, Harvard Medical School, Boston, MA USA

The extent to which the availability of alternative reinforcers that vary in magnitude will differentially impact preference for, intake of, or reinstatement of oxycodone self-administration between males and females has yet to be established. Squirrel monkeys (n=8; 4 males, 4 females) responded under concurrent second-order FR3(FR5:S);TO45s schedules of reinforcement for intravenous oxycodone (0.001-0.1 mg/kg) and sweetened condensed milk (10, 20, 30% v/v in water) or water. Reinstatement tests (i.e., drug-seeking) were conducted by administering either a dose of 0.1 or 0.32 mg/kg oxycodone intramuscularly 10-min prior to sessions in which saline was available on the drug-associated lever. At all milk concentrations, self-administration of oxycodone in males and females engendered a prototypical inverted U-shaped curve; however, the peak self-administered oxycodone dose was up to 100-fold more potent in females and, at low doses, oxycodone intake (mg/kg/day) was up to 3x more in females when compared to males. Varying the magnitude of the alternative reinforcer, decreased the potency of oxycodone preference by less than 2-fold in males. In contrast, preference for oxycodone in females was approximately 5- and 10-fold more potent when 10% milk was available compared to 20% or 30% milk, respectively. During reinstatement tests, milk concentration significantly impacted reinstatement of oxycodone self-administration in males - i.e., subjects responding on the drug-associated lever for a shorter duration when 30% milk was available compared to 10 or 20%. In females, milk concentration did not appreciably impact drug-seeking, and females responded on the drug lever for a longer duration compared to males regardless of alternative reinforcer. These results support the hypothesis that females are more sensitive to the reinforcing effects of oxycodone.

Oral Communication 3-1

Pharmacobehaviorally evaluating the contribution of plasma membrane monoamine transporter function to monoamine clearance

Gilman, T. Lee[1,2]; Beaver, Jasmin N.[1]; Vitela, Melissa[2]; and Daws, Lynette C.[2]

[1]Department of Psychological Sciences, Kent State University, Kent, OH USA; [2]Department of Cellular & Integrative Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX USA.

Psychostimulant drugs of abuse (e.g., cocaine, amphetamine) primarily exert their pharmaco-behavioral effects by blocking clearance of monoamines at their low capacity transporters (i.e., dopamine transporter [DAT], serotonin transporter [SERT], norepinephrine transporter [NET]). Plasma membrane monoamine transporter (PMAT) can clear dopamine, serotonin, *and* norepinephrine, and PMAT has a much higher transport capacity than DAT, SERT, or NET. However, there are currently no selective inhibitors of PMAT, and mice genetically deficient in PMAT exhibit no overt behavioral phenotypes at baseline. Only during conditions of elevated monoamine transmission (e.g., acute stress) has the impact of impaired PMAT function become evident. In the present experiments, we started to piece apart the contribution of PMAT to dopamine, serotonin, and norepinephrine clearance in the presence (tail suspension test, TST) and absence (locomotor assay) of acute stress. To initially minimize potential confounds of reinforcing effects, we used the SERT inhibitor escitalopram, and the DAT/NET inhibitor bupropion, both frequently prescribed as antidepressants. Mice with intact (+/+), reduced (+/-), or ablated (-/-) PMAT function were given one of two doses of these inhibitors or vehicle (saline) prior to testing. Female and male PMAT-deficient mice displayed augmented and attenuated responses, respectively, to escitalopram in TST. The latter could be partially attributable to a hypolocomotive effect of escitalopram in male PMAT -/- mice. We also observed a diminished locomotor response to bupropion in female PMAT-deficient mice compared to female PMAT +/+. Parallel experiments examining cocaine response in these mice are ongoing (see Beaver et al. poster), and future studies will examine how PMAT function affects the reinforcing components of psychostimulant exposure.

Oral Communication 3-2

A potential muscarinic antagonist antidepressant that lacks cognitive deficits

Johnson, Chad[1]; Jutkiewicz, Emily[3]; Kangas, Brian[4]; Coop, Andy[1]; Bergman, Jack; Winger, Gail[2]; Woods, James[2]

[1]Department of Pharmaceutical Sciences, University of Maryland, Baltimore; [2]Department of Pharmacology, University of Texas Science Center at San Antonio; [3]Department of Pharmacology, University of Michigan; [4]McLean Hospital, Harvard University.

Approximately 16% of Americans are diagnosed with major depressive disorder, a mental disorder thought be caused by a combination of characterized by genetic, biological, environmental, and psychological factors. While counseling and antidepressant medication can be effective treatments, current selective serotonin re-uptake inhibitors (SSRI's) take weeks before therapeutic effects are observed. This "delay" period of action is not well understood and presents a significant challenge for medical professionals in the management of major depression.

Mechanisms of anti-depressants have been a major focus of both current/past research in hopes of developing more effective and faster acting drugs. Directly related to this, clinical data that oral and intravenous treatment with the muscarinic cholinergic antagonist scopolamine had rapid anti-depressant effects in humans, likely mediated through an antimuscarinic effect (nimh.nih.gov). Unfortunately, scopolamine can produce cognitive impairment including memory disturbances due to its anticholinergic properties.

It is our goal to identify a muscarinic antagonist that may be able to relieve depression without disrupting cognitive effects. In order to probe the orthosteric site of the mAChRs we designed a large library of compounds and evaluated them via a battery of pharmacological assays to confirm both their antidepressant and cognitive effects. This resulted in the identification of lead compound (CJ2100) that showed potent antidepressant activity without cognitive impairment. (Supported by NIMH Grant 107499)

Oral Communication 3-3

Substantia nigra reticulata GABA neurons: newly identified targets involved in opioid reward and relapse

Galaj, Ewa[1]; Xi, Xiong-Zheng[1]

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

The neural mechanisms underlying opioid reward and addiction are not fully understood. Opioid reward has been traditionally thought to involve GABA-mediated disinhibition of midbrain dopamine neurons. However, this hypothesis has been challenged by reports that the rewarding effects of opioids rely on mu opioid receptors (MORs) expressed in other brain regions. Notably, the substantia nigra reticulata (SNr), a brain region with high expression of MORs on GABA neurons, has been largely ignored. Using transgenic and optogenetic approaches, we investigated the role of SNr GABA neurons in opioid reward and relapse. Optogenetic inhibition of SNr GABA neurons was found to produce rewarding effects in vGAT-cre mice, as assessed by optical intracranial self-stimulation and real-time place preference. On the other hand, optogenetic stimulation of SNr GABA neurons produced significant compensatory increases in heroin self-administration and reductions in drug-primed reinstatement of heroin seeking, suggesting a critical role for these neurons in opioid reward and relapse. These findings have been corroborated by additional findings that intra-SNr microinjections of naloxonazine (a MOR antagonist) produced similar effects in rats. However, intra-SNr naloxonazine did not disrupt motivation for heroin, as measured in a progressive ratio schedule of reinforcement paradigm. Our findings expand our understanding of the neurobiological mechanisms underlying opioid addiction, pointing to the SNr GABAergic neurons as a key player in some aspects of heroin-related behaviors.

Oral Communication 3-4

Chemogenetic inhibition of accumbens cholinergic interneurons inhibits nicotine seeking and associated transient, synaptic plasticity

Gipson, Cassandra[1]; Leyrer-Jackson, Jonna[2]; Newbern, J.[3]; Olive, M.F.[2]

[1]Department of Family and Community Medicine, University of Kentucky, Lexington, KY USA
[2]Department of Psychology, Arizona State University, Tempe, AZ USA
[3]School of Life Sciences, Arizona State University, Tempe, AZ USA

Nicotine is the primary addictive substance in tobacco and is widely abused. While previous studies have shown that increased glutamate release from prelimbic afferents targeting the nucleus accumbens core (NAcore) contributes to cue-induced reinstatement, the role cholinergic interneurons (ChIs) within the nucleus accumbens in mediating nicotine-seeking behavior is unknown. The principle hypothesis for the conducted studies is that cue-induced glutamate release from prefrontal cortical projections into the NAcore, activates ChIs within the NAcore, and this induces acetylcholine (ACh) release through activation of nicotinic acetylcholine receptors (nAChRs). We hypothesize that ChIs modulate glutamatergic signaling, transitioning drug craving to drug seeking. Using choline acetyltransferase (ChAT)-Cre transgenic rats, ChIs were bi-directionally manipulated prior to cue-induced reinstatement using chemogenetics. Prior to self-administration, cannulae were placed into the NAcore, and Cre-dependent inhibitory, excitatory and control DREADD vectors packaged in AAVs were then bilaterally infused into the NAcore allowing for chemogenetic control of NAcore ChIs. Rats underwent nicotine self-administration (0.02 mg/kg/infusion), in which an infusion was paired with a compound stimulus (discrete lights + tone) for 10 sessions. Rats were then placed into daily extinction sessions for 14 days. Prior to cue-induced reinstatement, intra-NAcore clozapine-N-oxide (CNO) was administered. Following reinstatement, whole-cell electrophysiology was conducted from medium spiny neurons (MSNs) within the NAcore to identify changes in synaptic plasticity (measured via AMPA/NMDA ratio). Results show that chemogenetic inhibition of ChIs inhibits cue-induced reinstatement. Ongoing studies are identifying the effects of chemogenetic activation of ChIs on cue-induced reinstatement and the changes in MSN synaptic plasticity. The results of the current study will uncover the role of ChIs in nicotine relapse and may provide mechanisms beneficial for therapeutic development for treatment of nicotine addiction.

Oral Communication 3-5

Molecular determinants of D_4R-selective antagonist and partial agonist efficacy

Boateng, Comfort A[1]; Placide, Rebekah[1]; Free, R. Benjamin[3]; Brown, Sonvia L.[1]; Newman, Amy H.[4]; Sibley, David R.[3] and Wu, Chun[2] and Keck, Thomas M.[2]

[1]Basic Pharmaceutical Sciences, Fred Wilson School of Pharmacy Department, High Point University; [2]Rowan University; [3]NINDS-IRP, NIH; [4]NIDA-IRP, NIH

Dopamine D_4 receptor (D_4R) is enriched in the prefrontal cortex where it plays important roles in cognition, attention, decision making and executive function. Novel D_4R-selective ligands have promise in medication development for neuropsychiatric conditions, including Alzheimer's disease and substance use disorders (SUD). To identify new D_4R-selective ligands, and to understand the molecular determinants of agonist efficacy at D4R, we report a series of eighteen novel ligands based on the classical D_4R agonist A-412997 (2-(4-(pyridin-2-yl)piperidin-1-yl)-N-(m-tolyl)acetamide). Compounds were profiled using radioligand binding displacement assays, β-arrestin recruitment assays, cAMP inhibition assays, and molecular dynamic computational modeling. We identified several novel D_4R-selective (Ki ≤ 4.3 nM and >100-fold vs. other D_2-like receptors) compounds with diverse partial agonist and antagonist profiles, falling into three structural groups. These compounds highlight receptor-ligand interactions that control efficacy at D_2-like receptors and may provide insights to targeted drug discovery leading to a better understanding of the role of D_4Rs in neuropsychiatric disorders such as SUD.

Oral Communication 3-6

Assessing sex differences in the functional responses of primary human astrocytes

Borgmann, Kathleen[1]; Proulx, Jessica[2]; Edara, Venkata Viswanadh[2]; Stacy, Satomi[1]

[1]Department of Pharmacology and Neuroscience, [2]Department of Microbiology, Immunology and Genetics, University of North Texas Health Science Center, Fort Worth, TX USA

Over the last quarter century, the contributions of astroglia to the pathogenesis of addiction and neurodegenerative disease have become an accepted, yet under studied phenomenon. Astrocytes directly support neurons metabolically and regulate their function *via* intercellular signaling with calcium, glutamate and neurotrophic factors. However, astroglia also propagate neuroinflammation during infection and normal aging. They potentiate excitotoxicity by failing to clear neurotransmitters sufficiently during disease. While many studies have investigated the various roles of astrocytes *in vitro*, none have characterized specifically sex as a biological variable in primary human astrocyte cultures. Primary human astrocytes were isolated from conceptual tissues in accordance with all federal, state and NIH statutes. Cultures were maintained in complete media, in the absence of either estrogens or androgens. Cultures were characterized for purity, morphology, metabolic activity and replication rates after several passages. Cultures were treated with the prototypical inducer of gliosis interleukin 1 beta, methamphetamine or infected with an HIV activity reporter virus. Astrocyte functional responses, including chemokine expression, glutamate clearance, mitochondrial respiration and HIV latency, were compared between sexes. In all, the functional characteristics of human astrocyte cultures were similar across sexes. Variation between cultures was donor dependent and was not attributable to sex. Treatment induced responses such as increased chemokine expression and decreased glutamate clearance were comparable between male and female astrocytes. Therefore, *in vitro* evaluation of these fundamental astrocyte functional responses permits generalization across sexes in design and analysis as long as neither sex is excluded from experimentation. Refinement of culture methods to include sex hormones could enhance sex-associated differences in astrocyte functional responses for future investigations.

Oral Communication 3-7

Investigation of the *in vitro* binding, pharmacokinetic, antinociception and substitution properties of selected indole-based kratom alkaloids

Obeng, Samuel[1,2]; Kamble, Shyam H.[3,4]; Reeves, Morgan, E.[1]; Restrepo, Luis, F.[1]; Patel, Avi[1]; Behnke, Mira[1]; Chear, Nelson J-Y[5]; Ramanathan, Surash[5]; Sharma, Abhisheak[3,4]; León, Francisco[2]; Hiranita, Takato[1]; Avery, Bonnie A[3,4]; McMahon, Lance R[1] and McCurdy, Christopher R.[2,4]

[1]Department of Pharmacodynamics, [2]Medicinal Chemistry, [3]Pharmaceutics, [4]Translational Drug Development Core, Clinical and Translational Sciences Institute, College of Pharmacy, University of Florida, Gainesville, FL USA; [5]Centre for Drug Research, Universiti Sains Malaysia, Penang, Malaysia.

The use of *Mitragyna speciosa* (kratom) has recently increased in the US and hence, the need to comprehensively characterize the pharmacology and pharmacokinetics of all the kratom alkaloids to inform policy makers regarding any potential use regulations. Mitragynine was found to have a higher affinity at opioid receptors (K_i = 161 nM) than at adrenergic receptors (K_i = 2320 nM). While the vice-versa was observed for corynantheidine. Speciociliatine was identified as a dual mu and kappa opioid ligand. Energy minimization of the 3D structures of the kratom alkaloids revealed that planar alkaloids favor binding to adrenergic over opioid receptors and the vice-versa. *In vitro* functional assays showed that 7-ydroxymitragynine and speciociliatine may be opioid agonists. The hydroxylated kratom alkaloids ($t_{1/2}$ = 170 - 181 min) were found to be resistant towards oxidative metabolism in human liver microsomes than the non-hydroxylated indole alkaloids corynantheidine ($t_{1/2}$ = 6.1- 41.8 min). 7-hydroxymitragynine produced antinociception (0.1-10 mg/kg, i.p.) in the hotplate test and fully substituted for morphine while mitragynine and corynantheidine (3.2 - 56 mg/kg, i.p.) failed to produce antinociception or substitute for morphine. The present results show that 7-hydroxymitragynine may have opioid like effects but not the other kratom alkaloids.
This work was supported by NIDA grants UG3 DA048353, R01 DA25267.

Oral Communication 3-8

Tightly bound: The relationship of network clustering coefficients and reincarceration at three therapeutic communities

Warren, Keith[1]; Campbell, Benjamin[2]; Cranmer, Skyler[2]; Weiler, Mackenzie[2]; Doherty, Fiona[1]

[1]The Ohio State University College of Social Work [2]The Ohio State University Department of Political Science

Previous work (Campbell, Cranmer, Doogan & Warren, 2019) has indicated that TC residents whose social networks include a higher percentage of closed triads as measured by the clustering coefficient (Wasserman & Faust, 1994) are less likely to be reincarcerated following discharge. While this finding is consistent with empirical findings in the social network literature that triads exert greater influence on individuals than other network configurations (Wellman & Frank, 2001), longstanding TC clinical concern regarding resident cliques that may undermine treatment (De Leon, 2000) suggests that this finding requires replication.

In this study we analyzed large social networks of affirmations drawn from three corrections based TCs, two of which include both men's and women's units and one of which housed only men. Clustering reduced the hazard of reincarceration for women at both facilities (β = -3.274, 95% CI = -4.298 - -2.250; β = -18.235, 95% CI = -32.059 - -4.410) and for men at two of the facilities (β = -0.911, 95% CI = -1.221 - -0.600; β = -1.393, 95% CI = -1.826 - -0.959). However, clustering increased the hazard of reincarceration for men at one facility (β = 5.563, 95% CI = 4.130 - 6.996).

Thus, while clustering predicts outcomes at all of these facilities, the direction of the correlation is inconsistent. Future research should analyze the predictors of prosocial clustering in TCs.

Poster Presentations

Poster 1

Female rats display greater neuronal activation in the interpeduncular nucleus during nicotine withdrawal than males

Espinoza, Veronika E.[1]; Matos, Felix[1]; Correa, Paola[1]; Correa, Victor[2]; Carcoba, Luis M.[1]; Iniguez, Sergio D.[1]; Zavala, Arturo R.[3] and O'Dell, Laura E.[1]

[1]Department of Psychology, University of Texas at El Paso, El Paso, TX USA; [2]National Institute of Mental Health, Bethesda, MD USA; [3]Department of Psychology, California State University Long Beach, Long Beach, CA USA.

Pre-clinical studies in male rodents established that the medial habenula-interpeduncular nucleus (MHb-IPN) pathway modulates negative affective states produced by nicotine withdrawal. Previous work has also revealed that female rats display greater anxiety-like behavior during withdrawal as compared to males. Despite profound behavioral differences, the role of the MHb-IPN pathway in modulating sex differences in nicotine withdrawal remains unexplored. Thus, the present study compared neuronal activation via Fos expression in the IPN of female and male rats during nicotine withdrawal. Briefly, adult male and female rats received an osmotic pump that delivered nicotine (3.2 mg/kg/day) and controls received sham surgery. Fourteen days later, rats received the nicotinic receptor antagonist mecamylamine (3.0 mg/kg, sc) to precipitate withdrawal. In order to examine the role of the stress peptide, corticotropin-releasing factor (CRF) in withdrawal-induced activation of the IPN, a separate cohort was pre-treated with the CRFR1 antagonist antalarmin (20 mg/kg, ip) ninety minutes before withdrawal induction. Ninety minutes after mecamylamine administration, rats were euthanized and the brains were processed for Fos immunofluorescence. The results revealed that controls did not display sex differences in Fos expression in the IPN. However, females displayed significantly more Fos-positive cells in the ventral portion of the IPN as compared to males. The withdrawal-induced increase in Fos was reduced in females that were pre-treated with antalarmin. These data suggest that CRFR1 receptors in the IPN modulate sex differences in nicotine withdrawal.

Poster 2

Nicotine treatment buffers negative behavioral consequences induced by exposure to physical and emotional stress in adolescent male mice

Parise, Lyonna F.[1,2]; Sial, Omar K.[1]; Parise, Eric M.[2]; and Bolaños-Guzmán, Carlos A.[1]

[1]Department of Psychological and Brain Sciences, Texas A&M University, 4325 TAMU. College Station, TX 77843, USA; [2]Fishberg Department of Neuroscience, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai. 1 Gustave L. Levy Place, New York, NY 10029, USA.

Early life stress influences adult psychopathology and is associated with an increase the propensity for drug use/seeking throughout the lifespan. Animal models corroborate that stress exposure exacerbates maladaptive reactivity to stressful stimuli while also shifting the rewarding properties of many drugs of abuse, including nicotine (NIC), a stimulant commonly misused by adolescents. Interestingly, NIC treatment can also normalize some stress-induced behavioral deficits in adult rodents, however, little is known about NIC's therapeutic efficacy following stress experienced during adolescence. The goal of the following experiments was to elucidate NIC's ability to buffer the negative consequences of stress exposure, and to further assessed behavioral responsivity while on the drug. Given that stress often occurs in both physical and non-physical forms, we employed the vicarious social defeat stress (VSDS) model which allows for investigation of both physical (PS) or emotional stress (ES) exposure. After 10 days, exposure to PS and ES decreased interaction with a social target in the social interaction test (SIT), confirming social avoidance. Groups were further divided and given NIC (0.0 or 160 mg/L) in their drinking water. After 1 month of NIC consumption, the mice were exposed to the SIT, elevated plus maze (EPM), and the forced swim test (FST), respectively. NIC-treated mice showed a reversal of stress-induced deficits in the EPM and FST. Surprisingly, the mice did not show improvement in the SIT regardless of treatment condition. Together, these data confirm NIC's ability to normalize some stress-induced behavioral deficits, however NIC's effects on social behavior needs further investigation.

Poster 3

The sigma1 receptor antagonist CM304 does not enhance the discriminative stimulus effects of the cannabinoid receptor agonist THC in rats

Patel, Avi[1]; Obeng, Samuel[1,2]; Burns, Mallory[2]; Intagliata, Sebastiano[2]; Mottinelli, Marco[2]; Reeves, Morgan E[1]; Behnke, Mira[1]; Restrepo, Luis F[1]; Ho, Nicholas P[1]; Gamez Jimenez, Lea R[1]; Williamson, Morgan R[1]; McCurdy, Christopher R[2]; McMahon, Lance R[1] and Hiranita, Takato[1]

Departments of Pharmacodynamics[1] and Medicinal Chemistry[2], College of Pharmacy, University of Florida

Studies conducted in our laboratory have shown that the sigma$_1$ receptor (σ_1R) antagonist CM304 may enhance the antinociceptive effects of the cannabinoid agonists in mice and rats. The present study compared the pharmacological effects of the σ_1R antagonist CM304 alone and in combination with THC in Sprague Dawley rats discriminating 3.2 mg/kg THC i.p. from vehicle under a fixed ratio (FR) 10 schedule of food delivery. THC produced dose-dependent increases in drug-lever responding with an ED_{50} value of 1.48 mg/kg. The cannabinoid CB_1 receptor agonist CP55,940 (0.0056 – 0.56 mg/kg) fully substituted for THC, whereas CM304 (10 – 56 mg/kg) i.p. produced a maximum of 27 % THC-lever responding at 17.8 mg/kg. CM304 at 32 mg/kg decreased response rate to below 25%. No dose of BD1063 (10 – 56 mg/kg, σ_1R antagonist), rimonabant, SR144528 (5.6 – 17.8 mg/kg, cannabinoid CB_2 receptor antagonist), morphine (1.78 – 32 mg/kg, μ-opioid receptor agonist), or naltrexone (opioid antagonist) produced greater than 30% THC-lever responding. Pretreatment with rimonabant (1.78 mg/kg) produced a rightward shift in the dose-effect function of THC (4.5-fold) and CP55940 (4.5-fold) while pretreatment with CM304 (10 mg/kg), BD1063 (32 mg/kg), SR144528 (5.6 mg/kg), and naltrexone (1 mg/kg) had no significant effect on the THC dose-effect function.
The present results may support the development of a σ_1R antagonist as an adjunct to cannabinoids for treatment of acute pain without enhancing the abuse potential of THC.
This work was supported by National Institute on Drug Abuse grants DA23205, DA47855 and DA48353.

Poster 4

The effects of eating high fat chow on sensitivity of rats to ethanol

Galindo, Kayla I.; Serna Castillon, Alex; and Serafine, Katherine M.

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

Eating a diet that is high in fat or sugar can impact dopaminergic systems, the same pathways targeted by drugs of abuse. Rats eating high fat laboratory chow are more sensitive to the behavioral effects of drugs of abuse, including cocaine and methamphetamine. However, it is not known if eating high fat chow also enhances sensitivity of rats to alcohol. To address this gap in knowledge two experiments were conducted. In Experiment 1, 24 female Sprague-Dawley rats eating either standard (18% kcal from fat) or high fat (60% kcal from fat) chow for 5 weeks were trained to drink ethanol solution. Training consisted of 28 daily 4-hour sessions. Following training, two bottles were presented (one containing 8% w/v ethanol and one containing water) while animals had continuous access to food. Average ethanol consumption was analyzed using a 2-way repeated measures ANOVA with diet, and day as factors. In Experiment 2, the development of locomotor sensitization to once weekly cumulative doses of 15% ethanol (0.5-2.0 g/kg; i.p.) was studied in 16 female Sprague Dawley rats eating high fat or standard chow. Results (dose-response curves for distance traveled, as well as area under the curve to examine changes in locomotion across weeks of testing) were analyzed using 2-way repeated measures ANOVAs with Tukey's post hoc comparisons where appropriate. In Experiment 1, rats eating high fat chow consumed more ethanol on average daily than rats eating standard chow; however, this difference was not significant when body weight was taken into consideration. In Experiment 2, rats eating high fat chow were slightly, though not significantly, more sensitive to the locomotor effects of ethanol, as compared to rats eating standard chow. These results suggest that the consumption of a diet that is high in fat, might impact individual sensitivity to the rewarding effects of alcohol, which could therefore impact abuse vulnerability. Future research will include males to investigate potential sex differences.

Poster 5

Two new sigma-1 receptor-selective ligands discovered by scaffold-hopping

Gangano, Anghelo J.[1]; Saldaña-Shumaker, Savanah L.[1] and Cunningham, Christopher W.[1]

[1]Department of Pharmaceutical Sciences, Concordia University Wisconsin School of Pharmacy, Mequon, WI USA.

"Scaffold-hopping" is a drug design strategy based on the idea that replacing one core scaffold with a structurally related group will maintain pharmacologic activity at a given target. Conceptually, 3-aminopyrrolidine and piperazine are two ring-constrained diamines with a 2.9 Å distance between basic amine groups that could function as interchangeable core scaffolds. We are developing functionalized *N*-benzyl-3-aminopyrrolidines as cannabinoid CB1 and dopamine D4 receptor probes. Preliminary binding experiments (Psychoactive Drug Screening Program, PDSP) indicate that our two lead compounds 1a,b also exhibit affinity for sigma-1,2 receptors. We synthesized two piperazine analogs of 1a,b (2a,b) to test the hypothesis that hopping from the 3-aminopyrrolidine to a piperazine core scaffold would not substantially impact receptor binding profile. Preliminary binding studies (PDSP) indicate that this structural modification was detrimental for D4 receptor binding: 1a Ki(D4) = 22 nM, 2a Ki(D4) = 206 nM; 1b Ki(D4) = 6.5 nM, 2b Ki(D4) = 445 nM. Unexpectedly, compounds 2a,b exhibited low-nM affinity for sigma-1 receptors (2a Ki(sigma-1) = 14 nM; 2b Ki(sigma-1) = 5.1 nM) and high selectivity over sigma-2 receptors (> 700-fold for 2a, > 800-fold for 2b). Virtual docking experiments (Glide, Schrödinger, Inc.) suggest that 2b binds sigma-1 via a similar molecular mechanism as the sigma receptor probe, 4-IBP. Future experiments are needed to determine the sigma-1 receptor efficacy of 2a,b, and whether these agents are pharmacologically active *in vivo*. Taken together, compounds 2a,b are new sigma-1 receptor-selective probes.

Poster 6

Female and male rats display similar increases in the reinforcing effects of nicotine and food in rodent models of diabetes

Rodriguez-Crespo, Andrea[1]; Cruz, Bryan[1]; Ortegon, Sebastian[1]; Barraza, Diana L[1]; Matos, Felix[1]; and O'Dell, Laura E.[1]

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

The present study assessed sex differences in the reinforcing effects of food and nicotine in rodent models of Type 1 and Type 2 diabetes. In Study 1, rats received administration of vehicle or streptozotocin (45 mg/kg, STZ), a drug that is toxic to insulin-producing cells and elevates glucose levels. In Study 2, rats received a regular diet or a high-fat diet (HFD) regimen for 8 weeks. A subset HFD fed rats also received a low dose of STZ (25 mg/kg) in order to induce insulin resistance more rapidly as compared to rats that received the HFD alone. Following these treatment regimens, all rats were given extended access to intravenous self-administration (IVSA) using an escalating dose regimen of nicotine (0.015, 0.03, and 0.06 mg/kg/0.1mL infusion/FR1). Each nicotine dose was delivered for 4 consecutive days with 3 intermittent days of drug abstinence. The results of Study 1 revealed that both female and male STZ-treated rats displayed an increase in plasma glucose levels and a reduction in body weight as compared to vehicle-treated controls. Study 1 also revealed that both female and male STZ-treated rats displayed a similar increase in nicotine and food intake as compared to their respective controls. Study 2 revealed that both female and male HFD-fed rats displayed insulin resistance and an increase in body weight relative to their respective controls. Study 2 also revealed that female and male HFD-fed rats displayed a similar increase in nicotine intake. However, food intake was lower in female versus male HFD-fed rats that received the low dose of STZ. In summary, diabetic rats in both studies displayed higher food and nicotine intake relative to their respective controls. However, there was no major sex differences in the enhanced reinforcement processes observed in diabetic rats. These studies suggest that diabetes enhances reinforcement processes in via similar mechanisms in female and male rats.

Poster 7

Sex differences in patients with chronic low back pain prescribed opioids

Paschali, M.[1]; Lazaridou, A.[1]; Dorado, K .[1]; Papianou, L. [1]; Burzinski, C. [2]; Garland, E. [3]; Zgierska, A [2]; Edwards, R. R. [1]

[1] Brigham and Women's Hospital/Harvard Medical School, Department of Anesthesiology, Perioperative, and Pain Medicine, [2] University of Wisconsin-Madison, School of Medicine and Public Health, Department of Family Medicine and Community Health, [3] University of Utah, College of Social Work

There is increasing concern among healthcare providers and pain clinics about the use of opioids for chronic pain. The aim of this study was to investigate sex differences in patients prescribed opioid medication for chronic pain. A sample of one hundred sixty (N = 160) patients prescribed opioid analgesics for chronic back pain were recruited. Participants completed measures of depression (HADS), opioid misuse (COMM), disability (ODI), pain interference and intensity (BPI), as well as a quantitative sensory testing battery (QST). Independent t-tests were conducted to explore sex differences in pain sensitivity and psychological factors. This study found robust differences in pain thresholds and psychological factors between male and female patients prescribed opioids. Male participants demonstrated decreased pain intensity, as well as higher pain thresholds (right/left trapezius muscles, low back muscle, right/left thumb) compared to female participants ($p<0.001$). In addition, male participants demonstrated increased depression, less pain interference, less disability, and higher opioid doses compared to female participants prescribed opioid medication for pain. This study demonstrates the importance of exploring sex variability in chronic pain patients who are prescribed opioid medication for pain. These results suggest that pain sensitivity may be associated with opioid-related problems to a greater extent for females than males. Continued research is needed to examine how these sex differences may impact clinical treatment for opioid-related problems.

Poster 8

Assessment of the aversive effects of methylone in male Sprague-Dawley rats

Manke, H.N.[1]; Nelson, K.H.[1]; Imanalieva, A.[1]; Rice, K.C.[2] and Riley, A.L.[1]

[1]Department of Psychology, American University, Washington, D.C. USA; [2] Drug Design and Synthesis Section, National Institute on Drug Abuse (NIDA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), Bethesda, MD USA

Synthetic cathinones, commonly known as "bath salts", are phenethylamine derivatives recently introduced as legal alternatives to other drugs of abuse. Methylone, a first-generation bath salt, was originally synthesized as an antidepressant, but has emerged as a drug of abuse under the trade name "explosion". Methylone is similar in structure and pharmacology to MDMA (ecstasy), and its rewarding effects have been well characterized. However, little is known about its aversive effects, a property reported to modulate the intake of most abused drugs. In this context, the present study investigated the aversive effects of methylone (vehicle, 5.6, 10 or 18 mg/kg, IP) using conditioned taste avoidance, hyperthermia and hyperactivity. Relative to controls, methylone induced significant dose-dependent conditioned taste avoidance and dose- and time-dependent hyperthermia (all ps < 0.05). Methylone also induced significant ambulation in comparison to vehicle (all ps < 0.05), although the onset and duration of this hyperactivity was dose dependent. Finally, methylone induced significant stereotypies at all three doses compared to controls (all ps < 0.05) Similar to work with other synthetic cathinones, methylone has aversive effects as indexed by taste avoidance and hyperthermia and hyperactivity (two characteristics of "excited delirium" toxicity in humans). These findings with methylone parallel prior work with related bath salts, e.g., MDPV and α-PVP, although the specific mechanisms of action for these compounds differ, e.g., reuptake inhibition (MDPV and α-PVP) vs. substrate releaser (methylone) of the brain amines. Given that drug intake appears to be a function of the balance of its rewarding and aversive effects, understanding both of these effects of methylone and the factors impacting them may provide insight into predicting its abuse potential.

Poster 9

Sex differences in cocaine-induced activity of the rostromedial tegmental nucleus

Armant, Ross J.[1]; Perrotti, Linda I.[1]

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

Addiction is a brain disease that results from chronic enhanced activation of brain structures of the mesolimbic dopamine reward pathway by drugs of abuse. This results in long term functional changes in the brain's reward pathway. Sex differences in behavioral responses and neuroadaptations resulting from chronic drug use have been established. These sex differences are associated with fluctuating ovarian hormone levels during the reproductive cycles of females. For example, in female rodents, estradiol influences dopamine activity within the mesolimbic reward system such that drug-directed behaviors are enhanced. The rostromedial tegmental nucleus (RMTg), also known as the tail of the ventral tegmental area (tVTA), is an important regulator of dopamine activity within the mesolimbic reward pathway. Previous studies have characterized the activity of RMTg cells after cocaine administration in male animals. The present study was conducted to determine if cocaine also activates this nucleus in female rodents and identify sex differences in such neural activation. Adult male and female experimentally naive Long Evans rats were treated with cocaine or saline, and standard immunohistochemical techniques were used to identify c-Fos positive neurons in the RMTg. Overall, cocaine-treated males and females expressed higher levels of c-Fos positive cells compared to saline-treated controls. Cocaine-treated female rats had fewer c-Fos positive cells compared to cocaine-treated males. Further analyses are currently underway to confirm these initial findings and to extend our results to include estrous cycle data. The RMTg may be an ideal target for further preclinical, clinical, and pharmacological research for developing better addiction treatments.

Poster 10

The effects of the M_1 muscarinic acetylcholine receptor positive allosteric modulator VU0486846 on cognitive performance in aged nonhuman primates

Norman, Christina L.[1]; Gould, Robert W.[1]; Bragg, Chrystal[1]; Lindsley, Craig W.[2-4]; Jones, Carrie K.[2]; Nader, Michael A.[1]

[1]Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, NC; [2]Vanderbilt Center for Neuroscience and Drug Discovery;[3]Department of Chemistry, [4] Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, TN

There remains a critical unmet need to understand and identify novel therapeutic strategies to address age-related impairments in arousal, cognitive function, and sleep architecture. Recently we successfully optimized a novel series of M_1 positive allosteric modulators (PAMs), represented by VU0486846. The goal of the present study was to provide the first characterization of the effects of an M_1 PAM on cognitive performance in aged nonhuman primates. For these studies, 16 aged (> 20 years old) female and male (N=8/sex) cynomolgus monkeys were trained under two different cognitive tasks. Eight monkeys (N=4/sex) were trained under a delayed match-to-sample (DMS) task. The other monkeys were trained under an attention task, the multiple-choice serial reaction time (MCSRT) task. All monkeys were tested with the following compounds, administered 60-min before the session: donepezil (0.1-0.56 mg/kg, IM); VU0486846 (1.0-5.6 mg/kg, PO) and *d*-amphetamine (0.01-0.056 mg/kg, IM). The effects of donepezil were variable across monkeys. In contrast, VU0486846 improved working memory. As a positive control, *d*-amphetamine also improved cognitive performance. Regarding MCSRT, at doses that improved working memory, VU0486846 did not affect reaction time, while donepezil slowed reaction times. These promising preliminary data will be extended in order to examine sex-specific and age-related effects of chronic VU0486846 and the consequences of the M_1 PAM and donepezil on sleep architecture in aged nonhuman primates.

Supported by NIH grant AG054622

Poster 11

Studies using von Frey testing and hot plate technique to evaluate the effects of opioids, novel benzodiazepine-like drugs, and their combinations

Rahman, Mohammad A.*[1]; Keck, Thomas M.[1]; Cook, James M.[3]; and Fischer, Bradford D.[2]

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

Opioids act in the nervous system to produce feelings of pleasure and pain relief, however addiction to these compounds can cause social and life-threatening health problems, including the risk of overdose. These issues have been highlighted during the recent opioid epidemic and together call for the development of new analgesics. The purpose of this study was to establish standard von Frey and hot plate testing parameters in order to test the analgesic effects of opioids, novel benzodiazepine-like drugs, and their combinations. Results from these studies may lead to the development of new novel opioid compounds with improved analgesia and limited side-effects including abuse liability. In von Frey test, Zymosan A was administered into the plantar surface of the footpads of male CD-1 mice to induce an inflammatory response that enhances mechanical sensitivity. 24 h later, monofilaments of differing forces (0.02-300 g) were applied. The hot plate test assesses acute, cutaneous pain sensitivity. The hot plate analgesia meter is maintained at 56°C on an aluminum surface, which will induce nociceptive behaviors, including paw licking, flutter, and jumping; increased response latencies following drug administration are interpreted as an antinociceptive response. A series of tests were performed measuring nociceptive responses to morphine and novel α2/α3 subunit-containing GABA-A receptor positive allosteric modulators, including HZ-166, MP-III-024, and MP-III-080. In the von Frey procedure, each compound produced dose- and time-dependent increases in mechanical sensitivity, whereas only morphine was effective on the hot plate. Ongoing studies are assessing drug combinations to determine effects that are either additive or deviate from additivity.

Poster 12

Role of GABA-A receptor subtypes in respiratory depression induced by benzodiazepines alone and combined with fentanyl

Haddad, Ghali G[1]; Majure, David C[1]; Cook, Jemma E[2]; Rüedi-Bettschen, Daniela[2]; Knutson, Daniel K[3]; Li, Guanguan[3]; Cook, James M[3]; Freeman, Kevin B[2] and Platt, Donna M[2]

[1]Medical Student Research Program, University of Mississippi Medical Center (UMMC), Jackson, MS USA; [2]Department of Psychiatry & Human Behavior, UMMC, Jackson, MS USA; [3]Department of Chemistry & Biochemistry, University of Wisconsin, Milwaukee WI USA

Benzodiazepines (BZs) are prescribed as anxiolytics, sleep aids, muscle relaxants, and seizure abortives. BZs are safe, but their lethality is increased greatly when combined with opioids. BZs modulate GABA-A receptors, which are Cl^- ion channels comprised of 5 subunits (2 alpha, 2 beta, 1 gamma). Each subunit has several isoforms and the alpha isoform appears to dictate the pharmacology of the receptor. Understanding the role of different alpha subunit-containing GABA-A receptors in the respiratory depressant effects of benzodiazepines may allow for the development of compounds with improved safety profiles when combined with opioids. Respiratory depressant effects of alprazolam (nonselective BZ), zolpidem (alpha1-preferring BZ), YT-III-31 (alpha3-selective BZ), and MP-III-022 (alpha5-selective BZ), alone and combined with the opioid fentanyl, were evaluated in male Sprague-Dawley rats (n=8) using whole body plethysmography. Alone, all BZs decreased minute volume; an effect driven primarily by decreases in breath frequency. Only alprazolam decreased tidal volume, whereas MP-III-022 produced a compensatory increase in tidal volume. Combined with fentanyl, alprazolam resulted in a significant decrease in minute volume driven by decreases in breath frequency. In contrast, while the selective BZs did reduce breath frequency when combined with fentanyl, they also increased tidal volume resulting in no net change in minute volume. Thus, selectivity for alpha1, 3, or 5 subtypes appears to provide some protection from respiratory depression (alone or with opioids). Alprazolam's less favorable profile may be due to its affinity for multiple subtypes and/or its positive modulation of alpha2 GABA-A subtypes.

Poster 13

Investigating the effects of nicotine vapor exposure on impulsive choice

Giner, Priscilla[1]; Flores, Rodolfo J.[1]; Miramontes, Tania G.[1]; O'Dell, Laura E.[1]; Alshbool, Fatima Z.[2] and Mendez, Ian A.[2]

[1]The University of Texas at El Paso, Department of Psychology, [2]The University of Texas at El Paso, School of Pharmacy

Studies with humans have shown that nicotine cigarette smokers exhibit increased impulsive choice relative to non-smokers. Some pre-clinical studies investigating the effects of nicotine on impulsive choice in rodents have also demonstrated that nicotine injections increase impulsive choice. Surprisingly, research investigating the effects of nicotine vapor exposure on impulsivity has not been conducted. The goal of this study was to investigate the effects of nicotine vapor exposure on decision-making, using the delay discounting task. Twenty-four adult male rats were trained on the delay discounting task, in which rats were allowed to choose between a small immediate reward or a larger food reward with delayed deliveries. After training in the delay discounting task for 24 days, rats were passively exposed to vapor containing either 0, 12, or 24 mg/ml of nicotine for 10 days, using a novel nicotine vapor exposure system. Blood samples were collected on selected exposure days 1, 5, and 10, and ELISA was used to assess serum cotinine levels. Following nicotine vapor exposure, rats were retrained until stable performance was achieved in the discounting task and the effects of nicotine vapor on choice preference in the discounting task were assessed. Analysis of blood serum levels revealed significantly higher cotinine in the 12 and 24 mg/ml nicotine groups when compared to the 0mg/ml group. Results also demonstrate that 24 mg/ml nicotine vapor exposure shifts choice preference towards the small immediate reward (increases impulsive choice) immediately following acute exposure. These findings suggest that exposure to nicotine vapor can cause short-term changes in decision making. Additional research on the effects of nicotine vapor exposure on the brain and behavior is necessary, as electronic cigarette use has now surpassed traditional cigarette use in adolescents.

Poster 14

Genetic deficiency in plasma membrane monoamine transporter function sex-selectively influences locomotor response to cocaine

Beaver, Jasmin N.[1]; Vitela, Melissa[2]; Daws, Lynette C.[2]; and Gilman, T. Lee[1,2]

[1]Department of Psychological Sciences, Kent State University, Kent, OH USA; [2]Department of Cellular & Integrative Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX USA.

Plasma membrane monoamine transporter (PMAT) can transport monoamines, such as dopamine and serotonin, much faster than the more selective dopamine transporter (DAT) or serotonin transporter (SERT), though PMAT has a lower affinity for these substrates than either DAT or SERT. Consequently, PMAT function is hypothesized to predominantly emerge when DAT or SERT function is impaired, under conditions of either heightened release in response to stressors, or pharmacological blockade. However, the contribution of PMAT function to behavioral responses to drugs of abuse that impair monoamine uptake (e.g., cocaine, amphetamine) has not been investigated. Given that no selective inhibitors of PMAT are available, we employed mice constitutively deficient in PMAT to explore this question. We hypothesized that, relative to wildtype controls (+/+), mice with reduced (+/-) or ablated (-/-) PMAT function would exhibit augmented locomotor responses to cocaine. Cocaine does not block PMAT function, but inhibits function of DAT, SERT, and norepinephrine transporter (NET). Blockade of these higher affinity monoamine transporters by cocaine permits the contribution of the lower affinity PMAT function to be unmasked. Surprisingly, cumulative doses of cocaine did not elicit any PMAT genotype-specific differences in females, but male PMAT +/- and -/- mice displayed attenuated locomotor responses to cocaine compared to PMAT +/+ males. This suggests compensatory upregulation of an as-yet unidentified monoamine transporter in male PMAT-deficient mice, a conclusion supported by our preliminary chronoamperometry data using bupropion, a DAT/NET inhibitor. Future investigations will examine if the rewarding effects of cocaine are altered in PMAT-deficient mice, and explore responses to amphetamine.

Poster 15

Antinociceptive effects of G-protein biased mu opioid receptor agonists in male and female rats with chemotherapy-induced neuropathy

Patel, T.R.[1]; Zamarripa, C.A.[1]; Blough, B.E.[2]; and Freeman, K.B.[1]

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

Aim: Mu-opioid receptor (MOR) agonists are often prescribed for the treatment of chemotherapy-induced neuropathy (CIN). Recent drug development strategies have focused on opioids with signaling profiles that "bias" activation of specific intracellular pathways (e.g., G-protein signaling) over others with the aim of increasing therapeutic selectivity. However, it is unknown if the variances in these signaling profiles at the MOR differentially modulate the antinociceptive effects of MOR agonists against neuropathic pain. In the present study, we tested a series of MOR agonists of varying G-protein signaling bias in a rat model of CIN. Methods: CIN was induced in male and female rats with injections of paclitaxel (PTX; N=10, 5 per sex) and compared to PTX-vehicle treated rats (N=10, 5 per sex). Antinociception was measured using the von Frey procedure with intravenous fentanyl (0.0018-0.01 mg/kg), oxycodone (0.1-0.56 mg/kg), SR14968 (0.0056-0.32 mg/kg), or SR17018 (0.18-1.0 mg/kg) in a counterbalanced order. ED_{50} values and 95% confidence intervals were calculated using linear regression to compare potencies between the agonists. To confirm that the antinociceptive effects were mediated by opioid receptors, the dose that produced 80% of the maximum effect for each agonist was tested before and after pretreatment with naltrexone. Results: All drugs were equi-effective but varied in potency, yielding a potency order of: Fentanyl > SR14968 > Oxycodone = SR17018. Additionally, no sex differences in efficacy or potency occurred for any drug. The antinociceptive effects of all agonists were blocked by naltrexone. Conclusion: This study confirms that biased MOR agonists produce antinociception in a neuropathy model that is typical of the MOR agonist drug class.

Poster 16

The dopamine D4 receptor antagonist L-745,870 does not affect alcohol reward or self-administration

Sumi, Mousumi*[1]; Buechler, Harley[1]; DiGiorgio Jr., Frank[1]; Fischer, Bradford D.[2]; Keck, Thomas M.[1]

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

Alcohol use disorder (AUD) affects more than 15 million people in the United States. Current pharmacotherapeutic treatments for AUD are only modestly effective, necessitating the identification of new targets for medications development. The dopamine D4 receptor (D4R) is a target of interest in the development of medications for psychostimulant addiction but has been unexplored for AUDs. In this study, we investigated the effects of the D4R antagonist L-745,870 in rodent models of alcohol addiction using adult male mice. Initial control studies with L-745,870 indicated that the doses tested (1.5 and 3.0 mg/kg, i.p)—doses that alter cocaine-mediated behavior—did not significantly disrupt locomotor activity, rotarod coordination, or food self-administration. L-745,870 was then tested for its effects in ethanol conditioned place preference and oral ethanol self-administration. Food-restricted mice were trained in operant chambers to nose poke for delivery of rewards, trained on ascending concentrations of alcohol with descending concentrations of Ensure and water, until the mixture self-administered was 8% w/v ethanol in water. L-745,870 did not significantly attenuate ethanol self-administration. Further testing determined that L-745,870 pretreatment during conditioned place preference training did not affect the rewarding value of 2.0 g/kg ethanol using a three-compartment chambered apparatus. These results suggest that D4R antagonism does not alter the rewarding value of ethanol. Future studies may explore whether D4R antagonism affects relapse-like responding in reinstatement models.

Poster 17

Acute effects of buprenorphine and buprenorphine analogs on cocaine-induced reinstatement

Rysztak, Lauren G.[1]; Sears, Bryan F.[2]; Hillhouse, Todd [2]; Olson, Keith[2]; Husbands, Stephen M.[3]; Traynor, John R.[2]; and Jutkiewicz, Emily M.[2]

[1]Neuroscience Graduate Program, [2]Department of Pharmacology, University of Michigan, Ann Arbor, MI [3]Department of Pharmacy & Pharmacology, University of Bath, Bath, United Kingdom

One current pharmacological treatment for opioid use disorders is buprenorphine, an opioid ligand with complex pharmacology. Buprenorphine is a partial agonist at mu opioid receptors (MOR), opioid receptor like-1 receptors (ORL1), an antagonist at delta opioid receptors (DOR) and kappa opioid receptors (KOR). Studies suggest buprenorphine suppresses cocaine intake and seeking, potentially mediated by ORL1. Because MOR agonists are associated with addiction liability, the potential for buprenorphine as an effective therapeutic is limited. Therefore, we evaluated the effects of novel buprenorphine analogs BU10119 and BU12004 on reducing cocaine seeking in a conditioned place preference (CPP) paradigm in male C57BL/6 mice. *In vitro* data show BU10119 and BU12004 lack agonist activity at MOR. Mice were conditioned over 2 days to associate cocaine with one side of a CPP chamber. Following a period of extinction, we recorded the time spent in the previously cocaine-paired chamber following an injection of saline or 15 mg/kg cocaine. The effects of buprenorphine, naltrexone, ORL1 agonist SCH221510, BU101119, and BU12004 on cocaine- or cue-induced reinstatement were evaluated. Our results show that buprenorphine, BU10119, and SCH221510 dose-dependently reduced cocaine-induced reinstatement. Naltrexone and BU12004 did not have any behavioral effects on drug seeking in either cocaine- or cue-induced reinstatement. These data suggest agonist activity at ORL1 may mediate the effects of buprenorphine and BU10119 to block cocaine-induced reinstatement. Because BU10119 is unlikely to have abuse liability on its own, it is an improvement on buprenorphine and could be a potential therapeutic to treat relapse to cocaine use disorder.

Poster 18

Antagonism of the ventilatory depressant effects of fentanyl by methocinnamox: impact of route of administration on duration of action in rats

Jimenez Jr, Victor M.[1,2]; France, Charles P.[1,2]

[1]Department of Pharmacology and [2]Addiction Research, Treatment & Training Center of Excellence, University of Texas Health Science Center, San Antonio, TX, USA

Opioid use disorder affects over 2 million Americans with an increasing number of deaths due to overdose from the synthetic opioid fentanyl and its analogs. Opioid toxicity is due, in large part, to the suppression of ventilatory function. Methocinnamox (MCAM) is a selective, pseudoirreversible *mu* opioid receptor antagonist with a long duration of action. Previous research has indicated MCAM (subcutaneous, s.c) prevents the ventilatory-depressant effects of heroin in nonhuman primates and attenuates the antinociceptive effects of fentanyl in rats. However, the effects of MCAM administered intravenously (i.v) in antagonizing the ventilatory depressant and antinociceptive effects of opioids, including fentanyl, has not been examined. This study further characterized the pharmacology of MCAM administered i.v or s.c, by examining fentanyl-induced ventilatory depression and antinociception in rats. Male Sprague-Dawley rats (N = 8) received MCAM (10 mg/kg i.v or s.c) or vehicle, and on subsequent days were challenged with 0.178 mg/kg fentanyl (i.v) and ventilatory parameters were recorded using whole-body plethysmography. In a different group of rats (N = 4), antinociceptive effects of fentanyl (0.01 – 0.1 mg/kg) were tested before and after a single infusion of MCAM (10 mg/kg i.v) using a warm water (50°C) tail withdrawal procedure. Both i.v and s.c MCAM administration attenuated the ventilatory depressant effects of 0.178 mg/kg fentanyl after 1 day, and only the s.c route beyond 1 day for up to 21 days after MCAM was administered. MCAM administered i.v or s.c antagonized the antinociceptive effects of fentanyl for 13 or 45 days, respectively. This study identified differences in the duration of MCAM antagonism for ventilatory suppression and antinociception by two different routes of administration (i.v or s.c). MCAM administered s.c or by a means pharmacokinetically similar, may provide a useful treatment option for the current opioid crisis, including toxicity from fentanyl and related highly potent analogs. Supported by NIH (R01DA005018 and R01DA048417) and the Welch Foundation (AQ-0039).

Poster 19

Behavioral phenotypes and kappa opioid receptor availability related to cocaine self-administration in socially housed female and male monkeys

Johnson, Bernard[1]; Czoty, Paul[1]; Gould, Robert[1]; Coller, Michael[1]; Odom, Jillian[1]; Nader, Susan[1]; Solingapuram Sai, Kiran[2]; Huang, Yiyun[3] and Nader, Michael[1,2]

[1]Department of Physiology and Pharmacology; [2]Department of Radiology, Wake Forest School of Medicine, Winston-Salem, NC USA; [3]Yale PET Center, Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, CT, USA.

The dynorphin/kappa opioid receptor (KOR) system is implicated in the regulation of aversive states, stress and substance abuse. A recent positron emission tomography (PET) study with KOR agonist tracer [^{11}C]EKAP in humans reported that lower social status was associated with higher KOR availability; sex differences were noted. Differences in KOR availability have also been shown with PET to correlate with cocaine choice in CUD subjects. This ongoing study aims to extend the characterization of the dynorphin/KOR system utilizing socially housed male and female cynomolgus monkeys (N=16/sex, naïve and with cocaine history) in a highly homologous model of CUD. Monkeys with drug history were trained under a concurrent cocaine (0.01-0.1 mg/kg/inj) vs. food (1-pellet) choice paradigm, while naïve monkeys under a 1- vs. 3-food pellets conditions; delay discounting was studied in both groups, and the indifference point (IP), or delay that results in 50% choice, calculated. Executive function was also assessed using two different cognitive tasks. Finally, all naive monkeys received a [^{11}C]EKAP PET scan to examine the relationship between KOR availability and social rank. Preliminary data indicates that when a non-preferred, cocaine dose was available and food was delayed, dominant females had higher IPs compared to dominant males (140-s vs 45-s), suggesting less "impulsivity". Preliminary comparisons suggest no relationship between IP and errors in cognitive tasks, indicating that we are assessing non-overlapping cognitive domains that, along with PET data (not yet analyzed), may prove to be sensitive biomarkers for decreasing cocaine SA. Supported by DA017763

Poster 20

Empirical validation of a touchscreen probabilistic reward task in rats

Luc, Oanh T.[1]; Wooldridge, Lisa M.[1]; Kangas, Brian D.[1,2]

[1]Cognition Biology Laboratory, McLean Hospital, Belmont, MA USA; [2]Department of Psychiatry, Harvard Medical School, Boston, MA USA.

Anhedonia, the loss of sensitivity to previously rewarding activities, is a cardinal feature of major depressive disorder (MDD) and is implicated in several other neuropsychiatric conditions. Historically, assessment of anhedonia in humans has relied on questionnaires, whereas rodent models typically involve forced swim or sucrose preference tests. However, a behavioral assay of anhedonia that is functionally and topographically similar across species is advantageous. One such approach is the Probabilistic Reward Task (PRT), a computerized task that requires humans to make numerous line length visual discriminations across trials. Probabilistic contingencies are implemented where correct responding to one alternative is rewarded more often (rich) than correct responses to the other alternative (lean). Healthy control subjects show a larger response bias (i.e., a preference for the rich alternative) than do participants with MDD, confirming blunted reward sensitivity. A reverse-translational approach in rats similarly uses touchscreen technology to train visual discriminations of lines that differ in length. This study parametrically examined probabilistic reward contingencies and line-length stimuli, as well as amphetamine (0.32-3.2 mg/kg), scopolamine (0.1-1.0 mg/kg), and oxycodone (0.1-1.0 mg/kg), for their ability to alter response bias. Results revealed an orderly relationship between response bias and the asymmetry in probabilistic schedule, and between discriminability and the differential in line length. In addition, drugs known to enhance reward sensitivity—amphetamine and scopolamine but not oxycodone—increased response bias, verifying pharmacologic sensitivity of the task. In sum, these findings validate the rodent PRT as a reliable assay with high preclinical value as an objective and quantitative characterization of reward sensitivity.

Poster 21

The CB1 negative allosteric modulator PSNCBAM-1 has a general anhedonic effect in mouse models of alcohol addiction

Buechler, Harley M. *[1]; Sumi, Mousumi[1]; DiGiorgio, Jr., Frank[1]; Fischer, Bradford D.[2]; and Keck, Thomas M.[1]

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

Alcohol use disorder (AUD) affects more than 15 million people in the United States. Current pharmacotherapeutic treatments for AUD are only modestly effective, necessitating the identification of new targets for medications development. The cannabinoid receptor type 1 (CB1) is a target of interest for development of medications for drug addiction, but CB1 antagonists/inverse agonists (e.g., rimonabant) have important side effects that limit their clinical utility, including anhedonia. Recent development of CB1 negative allosteric modulators (NAMs), including PSNCBAM-1, may provide an alternative mechanism of attenuating CB1 signaling with reduced side effects. PSNCBAM-1 has not yet been evaluated for effects in models of AUD. In this study, we investigated the effects of the CB1 NAM PSNCBAM-1 in rodent models of AUD using adult male mice. PSNCBAM-1 dose-dependently attenuated oral ethanol self-administration (8% w/v ethanol in water), significantly reducing ethanol rewards at a dose of 30 mg/kg but not at 10 or 18 mg/kg. PSNCBAM-1 also dose-dependently attenuated palatable food self-administration (diluted vanilla Ensure), significantly reducing food rewards at 18 and 30 mg/kg PSNCBAM-1. These results suggest PSNCBAM-1 produces a non-specific anhedonic effect that may preclude its use in AUD or other neuropsychiatric conditions.

Poster 22

Orexin and dopamine response to amphetamine among female orienteers

Hilz, Emily N.[1]; Monfils, Marie H[1,2]; and Lee, Hongjoo J.[1,2]

[1]Department of Psychology, The University of Texas at Austin, Austin USA, [2]Institute for Neuroscience, The University of Texas at Austin, Austin USA,

Cue-directed behavior is thought to indicate enhanced motivational processing of conditioned stimulus information and has been shown to predict drug-seeking behavior (Flagel et al., 2007; 2011). Females are at increased risk for drug addiction (Becker & Hu, 2008) and the gonadal hormone estradiol plays an important role in female drug-seeking behavior (Becker, Molenda, & Hummer, 2008) due in part to its up-regulatory relationship with dopamine (Becker, 1990). We recently investigated conditioned orienting (OR; a form of cue-directed behavior) as a phenotype which predicts drug-proclivity in female rats (Hilz et al., 2019). Females which express the OR phenotype (termed, 'Orienters') were shown to be more consistent in drug-seeking behavior in an amphetamine conditioned place preference (CPP) paradigm compared to females which did not (termed, 'Nonorienters'). The current experiment attempts to examine the neuromechanism responsible for individual differences in amphetamine CPP extinction. As a first step, we will examine the response of orexin and dopamine cells (via FOS labeling) to either single or multiple exposures of amphetamine given the role of orexin in OR behavior (Wheeler et al., 2014), appetitive extinction (Keefer et al., 2016), and drug-seeking (Aston-Jones, 2010); in addition to dopamine's established relationship with sign-tracking and drug-seeking (Flagel et al., 2007; 2011; Flagel, Akil, & Robinson, 2009). Preliminary results suggest that OR phenotype does not influence FOS+ORX expression in the lateral hypothalamus after single or multiple amphetamine exposures; however, in accordance with Anderson et al., (2012), the perifornical region of the LH expressed more ORX than the medial or lateral LH. The pattern of dopamine expression between Orienters and Nonorienters will be forthcoming.

Poster 23

Aggression modulates responses to mood-related stimuli in male CD-1 mice

Themann, Anapaula[1]; Gonzalez, Alejandra[1] and Iñiguez, Sergio D.[1]

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

Maladaptive aggressive behavior has been linked to a wide array of psychiatric disorders. Although the relationship between maladaptive aggression and psychiatric dysfunction is not thoroughly understood, recent evidence indicates that aggressive-displays towards conspecifics may be perceived as rewarding– and that this hedonic experience may be similar to other rewarding experiences, such as food, sex, and drugs of abuse. Nevertheless, the relationship between aggression and mood-related illnesses has not been thoroughly assessed using preclinical affect-related models. To address this issue, we examined whether displays of aggressive behavior result in changes in sensitivity to the rewarding properties of cocaine and sucrose. Specifically, male (retired breeder) CD-1 mice were subdivided into aggressive (AGG) and non-aggressive (NON-AGG) groups, based on their latency to attack an intruder male C57BL/6 mouse into their homecage, during a three-day screening paradigm. Mice were considered AGG if they displayed attack latencies below 10 sec across the three screening days, while animals with attack latencies greater than 30 sec (or not attacking at all) were classified as NON-AGG. One hour after aggressive screening (day 3), responsivity to cocaine conditioned place preference or a two-bottle choice sucrose (1%) test was conducted in separate groups of experimental mice. We found that AGG mice display increased preference for a cocaine-paired environment and a 1% sucrose solution. These findings indicate that aggressive behavior is associated with increases in preference for reward-related stimuli.

Poster 24

Deletion of the GHS-R ghrelin receptor exhibits a protective effect against diet-induced obesity in male but not female rats

Gregory-Flores, Adriana[1,2]; Marchette, Renata CN[2];Koob, George .F[2]; Vendruscolo, Leandro F.[2]; Leggio, Lorenzo[1]

[1]Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, National Institute on Alcohol Abuse and Alcoholism Division of Intramural Clinical and Biological Research, NIH, Bethesda, MD, USA; [2] Neurobiology of Addiction Section, National Institute on Drug Abuse Intramural Research Program, NIH, Baltimore, MD, USA.

Obesity is a chronic disease affecting over 39% of adults in the United States. This disease is associated with serious health risks, increasing costs of health care and decreasing life expectancy. The mechanisms underlying the development and maintenance of obesity are only partially understood, hence there is a critical need to investigate novel, potential mechanisms and neurobiological pathways related to this chronic disease. Ghrelin is a stomach-derived orexigenic hormone known to be implicated in feeding, stress and addictive behaviors by acting on the growth hormone secretagogue receptor 1a (GHS-R1a). We have recently developed a novel GHS-R1a CRISPR/Cas9 knockout (KO) Wistar rat model that shows decreased body weight compared to controls. The current study investigated the effect of a high-fat diet (a model of diet-induced obesity [DIO]) on body weight gain in GHS-R1a-KO and wild-type (WT) rats. We hypothesized that GHS-R1a-KO rats will be resistant to DIO. Our preliminary results suggest that GHS-R1a-KO male rats exposed to DIO gained significantly less weight compared to WT rats while consuming the same number of calories per day. No group differences were found in male rats maintained in a regular chow diet. Additionally, we found male GHS-R1a-KO rats show higher brown adipose tissue (BAT) thermogenesis when compared to WT rats regardless of diet. For females, no differences in body weight gain or body temperature were found in GHS-R1a-KO and WT rats eating either regular chow or high-fat diet. In conclusion, these findings suggest a sex-specific protective (likely via metabolism change) effect of GHS-R1a deletion against DIO.

Poster 25

Insulin restores the neurochemical effects of nicotine in the mesolimbic pathway of diabetic rats

Cruz, Bryan[1]; Carcoba, Luis M.[1]; Flores, Rodolfo J.[1]; Nazarian, Arbi[2]; and O'Dell, Laura E.

[1]Department of Psychology, The University of Texas at El Paso, El Paso, TX, USA; [2]Department of Pharmaceutical Sciences, Western University of Health Sciences, Pomona, CA, USA.

This study examined whether insulin modulates the neurochemical effects of nicotine in the mesolimbic pathway of diabetic rats. Rats received vehicle or streptozotocin (STZ) to induce hypoinsulinemia. A subset of STZ-treated rats was implanted with insulin pellets that normalized glucose levels. Two-weeks later, dialysis probes were implanted into the nucleus accumbens (NAc) and ipsilateral ventral tegmental area (VTA). The next day, dialysate samples from both regions were collected during baseline and then following systemic administration of two doses of nicotine. Dialysate levels of dopamine, acetylcholine (ACh), GABA, and glutamate were assessed using liquid chromatography/mass spectrometry (LC/MS) methods. The results revealed that vehicle-treated rats displayed a nicotine-induced increase in NAc dopamine that was accompanied by a decrease in VTA GABA and increase in VTA glutamate levels. In contrast, STZ-treated rats did not display any changes in NAc dopamine following nicotine administration, an effect that was likely related to a concomitant increase in VTA GABA and decrease in VTA glutamate levels. With regard to ACh, vehicle-treated rats displayed a nicotine-induced increase in NAc ACh levels, an effect that was lower in STZ-treated rats. There were no group differences in VTA ACh levels following nicotine administration. Importantly, in STZ-treated rats insulin supplementation normalized all of the neurochemical effects of nicotine in the NAc and VTA to vehicle-treated levels, with the exception of ACh levels in the VTA. These data suggest that insulin modulates the neurochemical effects of nicotine in the mesolimbic pathway of STZ-treated rats.

Poster 26

Enduring behavioral consequences from sub-chronic juvenile administration of synthetic and endogenous cannabinoid receptor agonists or antagonists to male mice

Gould, G.G.[1]; Ferreira L.F.[1]; Bordas B.[1]; Leonard M.E.[1]; Witt N.[1]; Pathapati N.[1]; and Schultz S.T.[1]

[1]Department of Cellular and Integrative Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX USA

Marijuana is a mixture of compounds including 60 that target cannabinoid receptors (CNBRs) with a range of pharmacological actions and affinities. To uncover contributions of CNBR agonists and antagonists to persistent behavior deficits seen after juvenile marijuana use, male mice 25-28 days old were given CNBR agonists, antagonists, or indirect agonists by intraperitoneal (ip) injection once daily for four days. Ten each of BTBR and C57BL/6J mice comprised treatment groups. Mice were monitored for changes in mean cognitive, anxious, or impulsive behaviors from postnatal day 35 to 90 by analysis of variance of data from tests of: sociability preference, marble burying, light/dark box, social dominance, tail suspension and reversal learning in the water T maze. None of the treatments impaired the social interaction preferences of C57BL/6J mice, but juvenile treatment of BTBR with N-arachidonyldopamine (NADA) or endocannabinoid uptake inhibitor AM404 enhanced interaction preference. The social novelty preference of BTBR mice was enhanced by AM404, the fatty acid amide hydrolase (FAAH) inhibitor URB597, and CNBR agonist WIN55,212-2. BTBR marble burying was increased by NADA and URB597 treatments, while for C57BL/6J mice acetaminophen (ACM) or URB597 treatments reduced burying. WIN 55,212 and NADA increased C57BL/6J social dominance, while URB597 and AM404 increased the duration of dominance matches. CNBR antagonist AM251, NADA, AM404 and ACM reduced the immobility of C57BL/6J mice in tail suspension tests. NADA enhancement of social interaction preference in three chamber tests and reduction of behavioral despair in the tail suspension test in BTBR mice was unexpected. Based on these findings the potential of NADA to ameliorate mood and social interaction preference is of interest for further study.

Poster 27

The role of TAAR1 in nicotine addiction

Wu, Ruyan; Liu, Jianfeng; Huang, Yufei; and Li, Jun-Xu

Department of Pharmacology and Toxicology, University at Buffalo, Buffalo, NY USA

Nicotine addiction is a chronic and relapsing disorders which puts heavy burden on family and society. Current therapies remained limited efficacy which highlights the urgent need to develop novel medications. Trace amine-associated receptor 1 (TAAR1) is widely suggested as a modulator in dopamine transmission. Our previous study has shown that activation of TAAR1 negatively mediates the addiction-like behavior in rats. However, less study has examined the effect of repeated treatment of TAAR1 agonist on nicotine intake, extinction and reinstatement in rats. Moreover, it remained unclear whether activation of TAAR1 could affect the withdrawal symptoms of nicotine. Here, we examined the effect of repeated administration of TAAR1 agonist RO5263397 in rats. We found that there was no difference among all groups during the training session. Repeated treatment of RO5263397 significantly reduced nicotine intake during the 2-week period, and this difference started from first day. Moreover, there was no difference in wash-out period and extinction sessions among all groups. Rats with history of repeated RO5263397 did not differ from control group both in cue- and drug-induced reinstatement. We also found that acute TAAR1 activation significantly attenuated the withdrawal symptoms in rats with a history of long-access nicotine training, as shown by the decreased somatic signs, increased central time in EPM test and prolonged paw withdrawal threshold in von Frey filament test. All these results suggested that TAAR1 agonist negatively mediated nicotine-induced addiction-like behaviors and might serve as a safe and well-tolerated target for the treatment of nicotine addiction.

Poster 28

Quantification of the relative potencies of mu opioid receptor agonists of varying G-protein signaling bias in a rat model of thermal antinociception

Yi, J. N.[1]; Zamarripa, C.A.[1]; Pareek, T.[1]; Blough, B. E.[2]; and Freeman, K.B.[1]

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

Aim: Mu-opioid receptor (MOR) agonists are highly effective for the treatment of pain but have significant side effects. Recent strategies in drug development have focused on opioids with signaling profiles that favor activation of specific intracellular pathways (e.g., G-protein activation) over others with the aim of increasing therapeutic selectivity. Establishing whether signaling bias improves therapeutic selectivity for a MOR agonist requires quantitative relations between a drug's potency to produce a therapeutic effect (e.g., antinociception) and an unwanted side effect (e.g., abuse liability). Here, we determined the relative potencies of MOR agonists of varying G-protein signaling bias in a test of thermal antinociception in male and female rats (N = 4 males, 5 females). Methods: Using a hot-plate assay, Sprague-Dawley rats received intravenous injections of fentanyl (0.0018-0.01 mg/kg), oxycodone (1.0-5.6 mg/kg), SR14968 (0.1-0.56 mg/kg), or SR17018 (1.8-10.0 mg/kg) in a counterbalanced order, and response latencies were measured by a blinded observer. ED_{50} values and 95% confidence intervals were calculated using linear regression to compare potencies between the agonists. To verify that the effects were mediated by opioid receptors, each drug was retested in subsequent sessions after naltrexone pretreatment. Results: All drugs were equi-effective but varied in potency, yielding a potency order of: Fentanyl > SR14968 > Oxycodone = SR17018. Additionally, no sex differences were observed for any drug. Pretreatment with naltrexone blocked the antinociceptive effects of all test drugs. Conclusion: This study demonstrates that a novel series of biased MOR agonists produces thermal antinociception in rats that is typical of the MOR agonist drug class. Moreover, the results provide quantitative information that will be used to establish therapeutic selectivity.

Poster 29

Synthesis and stability studies of a deuterated analog of a heroin vaccine hapten

Makarova, Mariia[1]; Sulima, Agnieszka[1]; Rodell[2,3]; Torres, Oscar B.[2,3]; Matyas, Gary R.[2,3]; Jacobson, Arthur E.[1]; Rice, Kenner C.[1]

[1]Department of Health and Human Services, NIH, NIDA, Drug Design and Synthesis Section, Bethesda, MD USA; [2]U.S. Military HIV Research Program, Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD USA; [3]U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD USA.

At the present time opioid addiction is considered to be a United States national public health crisis. The number of heroin-related deaths has increased five-fold from 2010 to 2017. Besides traditional pharmacological treatments for opioid abuse, immunopharmacotherapy has recently been developed as a potential treatment agent. The problem of heroin abuse was addressed in our group and in 2017 a heroin vaccine hapten was designed and synthesized. The anti-heroin vaccine containing our hapten will be subjected to a phase I clinical trial next year. In this work, we prepared a deuterated analog of this hapten that will allow the study of the stability of the hapten and protein conjugate by means of mass spectrometry. We have designed and prepared it in a nine-step synthesis. The synthesis used a derivative of hydrocodone as the base molecule and deuterium was introduced into the molecule after initial demethylation of the nitrogen functionality followed by methylation with deuterated iodomethane. After *O*-demethylation, the key synthetic step required Buchwald-Hartwig cross coupling to introduce a C-3 amido group. Reductive amination allowed the transformation of the C-6 oxo functionality to the amine, and the COMU-mediated coupling furnished the desired deuterated hapten.

Poster 30

The effects of eating a high fat or a ketogenic diet on sensitivity of female rats to methamphetamine

Elsey, Madeline K.; Beltran, Nina M.; and Serafine, Katherine M.

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

Ketogenic diets (which are high in fat and low in carbohydrates) have been used for the treatment of epilepsy and have been investigated for weight loss. In contrast, traditional high fat diets (which are not low in carbohydrates) can lead to obesity and weight gain, suggesting these two diets might produce opposing effects. Eating a high fat laboratory chow enhances the sensitivity of rats to the behavioral effects of drugs of abuse (i.e., methamphetamine); however, it is not known if ketogenic chow impacts drug sensitivity. To test the hypothesis that diet would impact sensitivity of rats to methamphetamine-induced locomotion and sensitization, rats eating standard chow (17% kcal from fat, 58% kcal from carbohydrate, 25% kcal from protein), high fat chow (60% kcal from fat, 21% kcal from carbohydrate, 18% kcal from protein), or ketogenic chow (90.5% kcal from fat, 0.3% kcal from carbohydrate, 9.2% kcal from protein) were tested once weekly with cumulative doses of methamphetamine (0.1-3.2 mg/kg; i.p.). Dose-response curves and Area Under the Curve (AUC) were analyzed using two-way repeated measures ANOVAs using Tukey's multiple post-hoc comparisons tests where appropriate. After 4 weeks, rats eating high fat chow were more sensitive to the locomotor-stimulating effects of methamphetamine at smaller doses (e.g., 0.32, 1.0 mg/kg) than rats eating standard chow. Rats eating ketogenic chow were also more sensitive than rats eating standard chow to the locomotor-stimulating effects of methamphetamine, but only at the largest cumulative dose studied (3.2 mg/kg). These results suggest that traditional high fat diets and ketogenic diets do not always produce identical effects and add to the growing literature demonstrating that diet can impact drug sensitivity. Future research will investigate the impact of these diets on sensitivity of rats to other drugs of abuse.

Poster 31

Synthesis and evaluation of new 2'/6'-substituted 1-phenylbenzazepines as D1R/D5R ligands

Giri, Rajan [1,2]; Harding, Wayne [1,2]

[1]PhD Program in Chemistry, The Graduate Center, City University of New York, NY, USA
[2]Chemistry Department, Hunter College, NY, USA

There is a paucity of ligands that are selective for the D1 receptor (D1R) over the D5 receptor (D5R) or vice versa. The benzazepine scaffold has been found to produce highly potent and selective D1R/D5R agonists. Currently available benzazepine D1R/D5R agonists bear a catechol motif which presents pharmacokinetic liabilities. This project is focused on identifying novel benzazepine-based and benzazepine-inspired D1R and D5R ligands that lack a catechol moiety, as leads for drug discovery efforts towards useful neuroactive tools and drugs. A series of 1-phenylbenzazepines with halogen substitutions at the *ortho* (2'/6') positions of the 1-phenyl ring were synthesized and evaluated to test their affinity towards dopamine receptors. Binding affinity results affirmed the ability of these compounds to maintain D1R/D5R selectivity over D2R with good affinity. Notably, 2',6'-dichloro substituted analogues showed modest D5R versus D1R selectivity. Analogs with 8-hydroxy-7-methoxy substitution pattern displayed higher D1R and D5R affinity than their catechol (7,8-dihydroxy) counterparts and exhibited D1R antagonist activity. N-methyl substitution seems to be favored over N-allyl or N-unsubstituted motifs in the assayed analogues for D1R/D5R affinity. In summary, our study indicates that further derivatization of the classical 1-phenylbenzazepine scaffold by varying the catechol motif and the 2' and 6' substituents may lead to the identification of D5R subtype selective and potent ligands.

Poster 32

Provider-level treatment philosophy for HIV and substance use: a qualitative analysis

Mulgaonker, Rithi[1]; Pondugula, Nishita[1]; Maguire, Rylee[1]; Kioumarsi, Avat[1]; Claborn, Kasey[1]

[1]University of Texas at Austin Dell Medical School

Aim: Treatment retention for people living with HIV (PLWH) and people who use drugs (PWUD) remains a significant public health concern. Existing literature does not adequately address organizational-level factors affecting patients' retention in care. In particular, there is a lack of qualitative research that aims to explore the HIV and substance use clinical culture at the provider level. **Methods:** This analysis used emergent data from a larger HIV treatment study that explored clinician perspectives on PLWH's linkage to substance use (SU) care and vice versa. Data from 29 semi-structured individual interviews (16 HIV and 13 SU clinicians) recruited in New England in 2015, were analyzed using thematic analysis. **Results:** Overall, 3 themes emerged assessing HIV and SU providers' treatment philosophy: 1) expectations of patient responsibility; 2) scope of treatment; and 3) level of collaboration amongst interdisciplinary healthcare professionals. HIV clinicians tended to step outside their expertise to support patient life needs, while SU clinicians were more focused on patient SU problem. **Conclusions:** Our results indicated the differences in perspectives on HIV and SU treatment philosophy. These results highlight the need for clinician-level interventions to improve retention in care and treatment outcome for highly vulnerable patient populations.

Poster 33

Environmental context is a modifier of neuroimmune activation after amphetamine experience in male and female rats

Mason, Briana M.[1]; Calhoun, C.A.[1]; Rich-Plotkin, B.[1]; Valencia, C.[1]; Herrera, M.[1]; Donaldson, S.T.[1]
[1] Department of Psychology, University of Massachusetts Boston, Boston, MA

The upregulation of proinflammatory chemokines has been shown to facilitate amphetamine-induced neuroplasticity in areas essential for learning and reward. Recent studies have focused on understanding the relationship between proinflammatory chemokines and the behavioral effects of amphetamine; however, little is known about interactions between chemokines and environmental aspects of drug dependence. Thus, the current research aimed to define alterations in chemokine levels in adult male and female Long Evans rats (n=50) after repeated amphetamine administration across distinct contexts. D-amphetamine sulfate (4.0 mg/kg AMPH or equivalent saline/SAL) was administered once per day over four testing days (48 h between doses) in either a context-dependent (CD; locomotor activity chamber) and context-independent (CI; home cage) locations with salient contrasts in appearance. A 4-day withdrawal period followed testing, after which all rats were injected with a dose of 1.0 mg/kg AMPH. Rats were then sacrificed and brain tissues were punched and stored at -80 C until processing by polymerase chain reaction (PCR). Female rats exposed to AMPH showed the greatest behavioral response on challenge, with CD females showing the largest increase in movement from baseline. These findings are consistent with literature reports that the CD setting can augment the sensitizing effect of AMPH after withdrawal in a sexually dimorphic manner. In addition, a divergent upregulation of the proinflammation-related CXC chemokine ligand 12 and C X C chemokine receptor 4 genes was observed after AMPH experience between male and female rats respectively. Thus, this research indicating that surrounding environment is a critical modulator of amphetamine engendered neuroimmune activation.

Poster 34

Role of M-type (KCNQ, Kv7) K+ channels in control over firing properties of dopaminergic neurons in the VTA, and the response to psychostimulants of abuse

Vigil, Fabio[1]; Magnon, Alexa[2]; Oliva, Idaira[2]; Carver, Chase M[1]; Wanat, Matt[2] & Shapiro, Mark S [1]

[1]Dept of Cell and Integrative Physiology, UTHSA, and [2]Dept of Biology, Section of Neurobiology, UTSA

M-type (KCNQ, Kv7) K^+ channels play fundamental roles throughout the nervous system in control of excitability, spiking and limiting hyper-excitability. A number of pharmacological "openers" of M channels have been developed as anti-convulsants and other neurological dysfunctions. Although expression of I_M has been documented in dopaminergic neurons of the VTA and the SN, this target has not been explored as a therapeutic intervention for psychostimulant abuse. We are testing the hypothesis that pharmacological augmentation of I_M in VTA dopaminergic neurons blunts extensive bursting, as is produced by methamphetamine and cocaine. We are also determining whether VTA dopaminergic neurons express M-channels dominated by KCNQ4 subunits, rather than KCNQ2&3, an issue having ramifications for pharmacological development, as a variety of subunit-specific compounds are now available.

Using patch-clamp brain-slice electrophysiology under voltage- and current-clamp on dopaminergic neurons identified by their signature low tonic firing rate, or expression of the GCaMP6f Ca^{2+} reporter behind DAT-Cre, we performed "loose cell-attached" patch recording or whole-cell recording. In the former, neurons tonically fired at ~2 Hz in normal ACSF (3 mM K^+). To mimic phasic bursting as during a physiological reward stimulus, we perfused slices with ACSF containing 40 mM [K^+]. Upon recording sustained phasic bursting, addition to that high-[K^+] ACSF of an M-channel opener specific for KCNQ2/3 channels eliminated bursting, reverting the neurons to the tonic bursting pattern, as if they were in normal ACSF. In whole-cell brain-slice experiments, we visually saw many neurons expressing GCaM6f flashing at 1-2 Hz. Current-clamp of those indeed revealed the expected 1-2 Hz firing, and under voltage clamp, robust M-type current was observed. This M current was totally TEA^+ insensitive, consistent with a composition of subunits other than KCNQ2. DHPG, an agonist of type 1 $G_{q/11}$-coupled mGluRs, depressed I_M by ~50% under voltage clamp and increased firing by ~50% under current clamp. Immunostaining revealed strong expression of KCNQ3 subunits. Finally, we performed *in vivo* cocaine cue-reinstatement assays, and stereotaxic injection of a KCNQ2/3-specific opener into the VTA. Results were variable and more cohorts will need to be studied to draw conclusions. We did observe a possible reduction in anxiety by such injection, as assayed by the "zero-maze" behavioral assay. Supported by a Pilot Grant from the ARTT at UTHSA.

Poster 35

The effects of probiotic supplementation on high fat diet-induced enhanced sensitivity to the behavioral effects of methamphetamine

Sandoval, Oscar; 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 obesity, insulin resistance, and dopamine system dysfunction. For example, rats eating high fat laboratory chow are more sensitive than rats eating standard chow to the behavioral effects of drugs that act on dopamine systems (i.e., methamphetamine). Dietary supplementation with probiotics (including a combination of lactobacillus and bifidobacterium) has been shown to aid in digestion and decrease depressive-like behavior among rats consuming a high fat chow. It is not known if probiotic supplementation can similarly decrease the effects of eating high fat chow on sensitivity of rats to the behavioral effects of dopaminergic drugs. To test the hypothesis that dietary supplementation with probiotics prevents high fat diet-induced enhanced sensitivity to methamphetamine, rats eating standard chow (17% kcal from fat), high fat chow (60% kcal from fat), or eating standard or high fat chow with daily probiotic (1 billion CFU) supplementation were tested once weekly using cumulative doses of methamphetamine (0.1-3.2 mg/kg; i.p). Dose-response curves were analyzed using two-way repeated measures ANOVAs using Tukey's multiple post-hoc comparisons test where appropriate. After 4 weeks of testing, there were no significant differences in drug sensitivity to methamphetamine among rats eating different diets. Although the experiment is ongoing, previous literature suggests that sensitivity to methamphetamine will increase with continued testing (e.g., sensitization) and that rats eating high fat chow will be more sensitive to this effect than rats eating standard chow to drugs that act on dopamine systems. Since the experiment is still ongoing, the effects of daily dietary supplementation with probiotics on sensitivity of rats to methamphetamine remain unclear.

Poster 36

Contribution of 7-Hydroxymitragynine, a metabolite of the primary kratom (*mitragyna speciosa*) alkaloid mitragynine, to the μ-opioid activity of mitragynine in rats

Hiranita, T.[1]; Sharma, A.[2]; Kamble S.H.[2]; Leon, F.[3]; Obeng, S.[1,3]; Reeves M.E.[1]; Gamez Jimenez, L.R.1; Restrepo L.F.[1]; Patel A.[1]; Ho, N.P.[1]; McCurdy, C.R.[3]; and McMahon, L.R.[1]

Departments of Pharmacodynamics[1], Pharmaceutics[2], and Medicinal Chemistry[3], College of Pharmacy, University of Florida.

Relative to the major alkaloid mitragynine (Mit) in kratom, its metabolite 7-hydroxymitragynine (7-OH) is a more potent and effective agonist at the μ-opioid receptor (MOR). Here, we investigated if Mit is a prodrug that exerts opioid agonist activity, in part, through metabolic conversion to 7-OH. The binding affinity of 7-OH at the human MOR (Ki=78 nM, [^{3}H]DAMGO) was 9-fold higher than Mit but 22-fold lower than morphine. The % maximum GTPγS stimulations of 7-OH and morphine at the MOR were 45% and 90% (≤30 μM, each), respectively. In contrast, Mit (≤100 μM) did not significantly stimulate GTPγS. As a measure unrelated to their pharmacokinetic properties in rats, the kratom alkaloids were injected intravenously in a hotplate assay at 52°C. Cumulative injections of 7-OH (0.032-3.2 mg/kg) produced robust antinociception (ED_{50}: 1.9 mg/kg) whereas Mit (3.2-17.8 mg/kg) was inactive. Following p.o. administrations of Mit (55 mg/kg), the plasma Cmax value (UPLC-MS/MS) of 7-OH (85 ng/mL) was 14-fold less than that of Mit. The Tmax values (p.o.) of 7-OH and Mit were 30 and 84 minutes, respectively. The % metabolite ratio [($AUC_{7\text{-}OH}/AUC_{Mit}$)*100] was 8% (p.o.). Yields of Mit and 7-OH in lyophylized kratom tea (100 mg) were 0.75% and 0.01%, respectively. Following p.o. administration of kratom tea (3,200 mg) and Mit (178 and 320 mg/kg) in rats, no robust antinociception was observed up to 180 minutes after gavage (≤27%). In rats discriminating morphine (3.2 mg/kg, i.p.) from vehicle, Mit (≤178 mg/kg, p.o., 90' prior) and kratom tea (1,780 and 3,200 mg/kg, p.o., 60' prior) produced 76% and 47% morphine-lever responding (ED_{50}=51 mg/kg), respectively. Despite the low conversion rate and the low yield of 7-OH in kratom, the conversion may contribute to the *in vivo* MOR activity of Mit and kratom. Supported by NIDA grants UG3 DA048353, R01 DA25267.

Poster 37

Eating a high fat diet enhances sensitivity of rats to serotonin syndrome

Beltran, Nina M.[1]; Landavazo, Antonio[2]; Blough, Bruce E.[2]; Serafine, Katherine M.[1]

[1]Department of Psychology, The University of Texas at El Paso, El Paso, TX USA; [2]Center for Drug Discovery, Research Triangle Institute, Research Triangle Park, NC, USA.

Drugs that act on serotonin (5-HT) systems are important for the treatment of many conditions, including anxiety, depression, and obesity. One potential adverse effect of these drugs is the development of 5-HT syndrome. Animal models of 5-HT syndrome include lower lip retraction, flat body posture, forepaw treading, and penile erections. Diet (e.g., type and amount of food consumed) has been shown to directly impact sensitivity of rats 5-HT syndrome. For example, food restriction decreases sensitivity of rats to lower lip retraction and flat body posture induced by 8-OH-DPAT, a 5-HT_{1A} receptor agonist. In contrast, eating high fat chow increases sensitivity of rats to 8-OH-DPAT-induced lower lip retraction; however, it is not known if eating high fat chow also impacts sensitivity of rats to other 5-HT syndrome behaviors or other 5-HT receptor agonists. To test the hypothesis that eating high fat chow enhances the sensitivity of rats to 5-HT syndrome, male rats eating high fat (60% kcal from fat) or standard (17% kcal from fat) chow were tested once weekly with cumulative doses of 8-OH-DPAT (0.01-1.0 mg/kg, s.c.), and two different 5-HT_{2C} receptor agonists (lorcaserin [1.0-32.0 mg/kg, i.p.], and WAY 163909 [1.0-32.0 mg/kg, i.p.]). After several weeks, two-way partially repeated measures ANOVAs and Tukey's post hoc comparisons (where appropriate) revealed that rats eating high fat chow were more sensitive than rats eating standard chow to 8-OH-DPAT-induced lower lip retraction and to forepaw treading induced by 8-OH-DPAT, lorcaserin, and WAY 163909. These results suggest that individuals with a history of eating a high fat diet (e.g., patients diagnosed with obesity) might be especially sensitive to the therapeutic and adverse effects of drugs that act on 5-HT receptors. Future studies will include examining the impact of diet on sensitivity of female rats to 5-HT syndrome, as well as the investigation of potential sex differences.

Poster 38

A comparative study of the discriminative-stimulus effects of the cannabinoid CB1 agonists AM8936 and AM2201 in rats.

Dalal AlKhelb[1], Spiros P. Nikas,[1] Alexandros Makriyannis[1], Rajeev I. Desai [1,2]

[1]Neurochemistry and Behavioral Pharmacology Laboratory, Center of Drug Discovery, Northeastern University;[2] Preclinical Pharmacology Laboratory, McLean Hospital, Harvard Medical School.

The present studies were undertaken to characterize the discriminative-stimulus effects of two distinct highly potent and selective CB_1 agonists AM8936 and AM2201 in rats. Using standard two-lever drug discrimination procedure, separate groups of rats (n=8) were trained to discriminate i.p. injections of 0.1 mg/kg AM8935 or 0.1 mg/kg of AM2201 from saline on a fixed-ratio-10 response schedule of food reinforcement. Results show that rats acquired AM8936 and AM2201 discriminative-stimulus control after approximately 55 and 70 training sessions, respectively. Time course data shows that 0.1 mg/kg AM8936 engendered 38.8 %, >80%, and <10% responding on the drug-lever at, respectively,10, 60, and 180 min after injection. In contrast, 0.1 mg/kg AM2201 produced >80%, 60%, ~50%, and, <10% drug-lever responding 10, 90, 360, and 1440 min after injection, respectively. Thus far, results show that: a) the CB1 agonists THC and CP55,490 substituted fully for 0.1 mg/kg AM8936 and AM2201's discriminative-stimulus effects; b) AM8936 fully substitutes for AM2201 but not vice versa; and c) the inverse CB_1 agonist rimonabant dose-dependently blocked the discriminative-stimulus effects of AM2201. Overall, results show that both AM8936 and AM2201 can effectively serve as a robust discriminative-stimulus. Although the stimulus effects of both drugs appear to be similar, some subtle differences also have emerged including, onset and offset of action and asymmetrical cross-generalization between AM8936 and AM2201, raising the possibility that different mechanisms may contribute to their discriminative-stimulus effects.

Poster 39

The effects of ketoconazole, a CYP3A inhibitor, on mitragynine, the major kratom (*mitragyna speciosa*) alkaloid, in rats discriminating mitragynine or morphine

Crowley, M.L.[1]; Kamble, S.H.[2]; Obeng, S.[1,3]; Leon, F.[1]; Reeves, M.E.[3]; Restrepo, L.F.[3]; Gamez Jimenez, L.R.[3]; Patel, A.[3]; Ho, N.P.[3]; Williamson, M.R.[3]; Zuarth Gonzalez, J.D.[3]; McCurdy, C.R.[1]; McMahon, L.R.[3]; Sharma, A,[2]; and Hiranita, T.[3]

Departments of Pharmacodynamics[1], Pharmaceutics[2], and Medicinal Chemistry[3], College of Pharmacy, University of Florida

Mitragynine (MG) is reported to produce its μ-opioid receptor (MOR) activity through a metabolic conversion to 7-hydroxymitragynine (7-OH) by human CYP3A4 *in vitro*. Here, we investigated if ketoconazole (KTC), a rat CYP3 inhibitor, can increase plasma levels of MG and potentiate MOR activity of MG in rats. Following p.o. administrations of MG (100 mg/kg), the plasma Cmax value (UPLC-MS/MS) of 7-OH (12.3 ng/mL) was 40-fold less than that of MG. The % metabolite ratio [($AUC_{7\text{-}OH}$/AUC_{MG})*100] was 2.2%. KTC (30 mg/kg, p.o.) increased the Cmax values for MG and 7-OH (1.7- and 1.5-fold, respectively) but did not affect the % metabolite ratio. The binding affinity of KTC at the human MOR (Ki=54,100 nM, [^{3}H]DAMGO) was 77- and 694-fold lower than MG and 7-OH, respectively. In rats discriminating MG (32 mg/kg, i.p.) from vehicle, KTC (56 mg/kg, i.p.) shifted the dose-effect function of MG discrimination to the left 3.1-fold. In rats discriminating morphine (3.2 mg/kg, i.p.) from vehicle, however, KTC did not affect the dose-effect function of morphine discrimination. In contrast to the training drug morphine, KTC potentiated MG discrimination 5.6-fold. KTC also shifted to the left the dose-effect function of 7-OH substitution for morphine. We have shown here that CYP3 metabolizes both MG and 7-OH. However CYP3 does not mediate the conversion of MG to 7-OH in rats. Supported by NIDA grants UG3 DA048353 and R01 DA25267.

Poster 40

Effects of nicotine vapor on risky decision making

Maynez-Anchondo, Liliana; Rastegari, Amir; Herrera, Herrera; Blanco, Marisol; Gardezi, Maham; Towers, Shelby and Mendez, Ian A.

The University of Texas at El Paso, School of Pharmacy

Previous studies have repeatedly shown that acute nicotine administration increases cost-benefit decision making. Pre-clinical studies on the effects of nicotine on risky choice have produced mixed findings; with some showing that nicotine does in fact increase risky choice. However, pre-clinical research investigating the effects of nicotine vapor consumption from electronic nicotine delivery systems (i.e., e-cigarettes) on the brain and behavior has been very limited. The goal of this study is to investigate the effects of e-cigarette nicotine vapor exposure on risky decision-making. Eight food deprived adult male rats were food restricted and trained to respond to a food reward (grain food pellet) in a risk discounting task. To test the effects of acute nicotine vapor exposure on risky choice rats were passively exposed to 100 puffs of 0 and 24 mg/ml nicotine e-cigarette vapor on 2 separate days with tests in the risk discounting task occurring immediately after exposures. To assess the effects of stress from general vapor exposure a 3rd test was conducted after a 5 day habituation to 0 mg/ml nicotine vapor in the chambers. Acute exposure to 24 mg/ml nicotine vapor increased risky choice during all 3 tests, relative to baseline measures. Interestingly, exposure to 0 mg/ml also increased risky choice during test 1 and 2, but this effect subsided for test 3, after the rats were habituated to the vapor chambers for 5 days. Both acute exposure to nicotine vapor and stress appear to increase risky choice in the risk discounting task. Findings highlight the need for future studies to habituate rats to vapor exposure chambers and procedures, to eliminate stress as a confounding factor in experiments assessing the effects of drug vapors on decision making. Finally, future studies will aim to identify neurobiological mechanism of the effects of nicotine vapor on risky choice, such as alpha4beta2 cholinergic receptors, as well as investigate these effects in both adolescent and female rats.

Poster 41

Use of fentanyl to investigate regulation of drug reward by VTA SGK1

Stark, Ali R.[1]; Doyle, Marie A.[2]; and Mazei-Robison, Michelle S.[1,2]

[1]Department of Physiology, Michigan State University, East Lansing, MI USA; [2]Neuroscience Program, Michigan State University, East Lansing, MI USA

According to the National Institute on Drug Abuse, over 130 people per day die of an opioid overdose. Opiate abuse in part results from neuroadaptations in the ventral tegmental area (VTA), and our lab has previously demonstrated that chronic morphine exposure increases catalytic activity and phosphorylation of the protein serum- and glucocorticoid-regulated kinase 1 (SGK1). Furthermore, VTA injection of a catalytically inactive version of SGK1 reduces opioid reward behavior in the morphine two-bottle choice test (TBC). However, the necessary use of quinine as a bitter taste control in the morphine TBC test presents a confounding variable, as quinine on its own is aversive. One strategy to reduce this potentially confounding effect is the use of fentanyl, another opioid 50-100 times stronger than morphine. Much lower concentrations of fentanyl could be used in the TBC test, eliminating bitter taste as a confounding variable. In order to test this, I will run mice through a single fentanyl TBC test with escalating doses in order to establish a dose response curve. In parallel, I will perform Western blots on VTA tissue from mice that have undergone chronic intraperitoneal (IP) fentanyl injections. I predict that chronic fentanyl will induce increases in VTA SGK1 phosphorylation and catalytic activity similar to our established findings in morphine-treated mice. The results of this project will expand our knowledge of SGK1's involvement in opioid reward behaviors and could present SGK1 as a potential therapeutic target for opioid addiction treatments.

Poster 42

Enduring effects of juvenile ketamine exposure for the rewarding properties of cocaine and sucrose in mice

Garcia-Carachure, I.; Preciado-Piña, J.; and Iñiguez, S.D.

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

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has shown rapid antidepressant efficacy in adolescent treatment-resistant depressed patients. However, the potential enduring side effects of ketamine exposure during early development have not been explored. Thus, using male and female C57BL/6 mice, we examined whether exposure to ketamine during adolescence, alone (Experiment 1) or in combination with stress (Experiment 2), results in long-lasting changes in sensitivity to the rewarding properties of cocaine and sucrose in adulthood. Specifically, in Experiment 1, mice received either ketamine (20 mg/kg) or saline (VEH) for 15 consecutive days during adolescence (Postnatal Day [PD] 35-49). Twenty-one days after ketamine exposure, once mice reached adulthood (PD70), we assessed their behavioral responsivity to a two-bottle choice sucrose (1%) test, or a cocaine (0, 5, 10 mg/kg) place preference (CPP) experiment. Our results showed that adult mice pre-treated with ketamine during adolescence displayed an enhanced preference for sucrose and environments paired with cocaine in male, but not female, mice. Thus, in Experiment 2, using male mice only, we evaluated whether adolescent ketamine exposure (PD35-44), in combination with social defeat or the vicarious defeat stress paradigms, would influence responses to sucrose or cocaine preference later in life (PD70). Here, no long-term differences in sucrose or cocaine preference were evident as a function of juvenile stress-and-ketamine pretreatment, in male mice. Together, our findings suggest that in the absence of social stressors, juvenile exposure to ketamine alters sensitivity to the rewarding properties of non-drug (sucrose) and drug (cocaine) reward-related stimuli, in a sex dependent manner, later in life.

Poster 43

Sex-dependent changes in voluntary ethanol consumption in adult C57BL/6J mice following intermittent ethanol exposure during adolescence

Kumari, Anjali[1]; Robinson, Victoria[2]; Jones, Myracle C.[2]; Shobande, Mariah[3]; Hall, Nzia I.[1]; and Maldonado-Devincci, Antoniette M.[2]

[1]Department of Biology, [2]Department of Psychology, [3]Department of Chemical, Biological, and Bioengineering, North Carolina A&T State University, Greensboro, NC 27411

With alcohol readily accessible to adolescents, its consumption leads to many adverse effects, including impaired learning, attention, and motor behavior. Adolescents report higher rates of binge drinking compared to adults. Accompanying increased binge drinking rates, adolescents are more prone to substance use disorder (SUD) during adulthood due to physiological changes during the adolescent developmental period. We use C57BL/6J mice to investigate the lasting impact of binge alcohol exposure during adolescence on voluntary alcohol intake in young adulthood. The present experiment was divided into three stages: (1) chronic intermittent vapor inhalation exposure, (2) abstinence, and (3) voluntary ethanol intake. During adolescence, mice are exposed to air or ethanol using a vapor inhalation model with repeated binge ethanol exposure from postnatal day (PND) 28-42. Following this exposure, mice underwent abstinence from PND 43-69. Beginning on PND 70-97, mice were assessed for intermittent voluntary ethanol consumption using a two-bottle drinking procedure. The mice were exposed to a repeated two-day drinking procedure for 28 days, containing two water tubes for 24 hours followed by 24 hours access to one tube containing 20% unsweetened ethanol and the other water. Male mice that were exposed to ethanol during adolescence showed increased ethanol consumption in adulthood, while the females showed decreased ethanol consumption. These data demonstrate a sexually divergent shift in ethanol consumption following binge ethanol exposure during adolescence. We are currently investigating these drinking patterns following a shorter withdrawal period. These data highlight sex-dependent vulnerability to developing SUD in adulthood.

Poster 44

Impact of commodity definitions on e-cigarette demand

Strickland, Justin C.[1]; Vsevolozhskaya, Olga A.[2]; and Stoops, William W.[3]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD USA; Department of Behavioral Science, University of Kentucky, Lexington, KY USA; [3]Department of Behavioral Science, University of Kentucky, Lexington, KY USA.

Behavioral economic demand provides a multidimensional understanding of reinforcement. Commodity purchase tasks are an efficient method for measuring demand in human participants. One challenge in translating these procedures to e-cigarette use is defining commodity units given the lack of standardization in the e-cigarette marketplace. The purpose of this study was to directly compare common ways of operationalizing e-cigarette use (i.e., puffs, cartridges, and mLs fluid) using a within-subject design. Participants (N=132) reporting past week e-cigarette use were recruited using crowdsourcing methods. All participants completed two purchase tasks that operationalized e-cigarette units as 1) puffs and 2) cartridges. A subset of participants (N=59) also completed a follow-up approximately 2 months later with e-cigarette units operationalized as 1) puffs and 2) mLs. Bivariate associations supported convergent and discriminant validity of each task with more robust correlations observed for the puff version. Only puff demand was associated with clinical outcomes (e.g., time to first daily e-cigarette use). Moderation models indicated that JUUL preferences moderated the relationship between time-to-first use and cartridge demand with large effect size correlations among persons reporting JUUL preferences, but weak relationships among persons reporting other device preferences. Puff demand showed modest test-retest reliability (r_{xx} > .38) at the 2-month follow-up. This study demonstrates the relevance of commodity definitions for e-cigarette behavioral tasks. Puffs may provide improved flexibility for studying e-cigarette demand in general populations, whereas more tailored or personalized approaches like cartridge or mL-based tasks may be helpful when studying specific and known sub-groups of persons reporting e-cigarette use.

Poster 45

Synthesis of novel dopamine D_2/D_3 antagonists/partial agonists based on the Cariprazine scaffold for the treatment of substance use disorders

Gogarnoiu, Emma; Shaik, Anver. B.; Bonifazi Alessandro; Newman, Amy H.

Medicinal Chemistry Section, Molecular Targets and Medications Discovery Branch, NIDA-IRP, 333 Cassell Drive, Baltimore, MD 21224, United States

The development of highly selective dopamine D_3R receptor antagonists/partial agonists has generated great interest due to the role of this D_2 receptor subtype in substance abuse and other neuropsychiatric disorders. The greatest challenge in developing selective compounds stems from the high degree of receptor homology within the D_2-like receptor family. In addition to subtype selectivity, binding kinetics is pivotal to therapeutic efficacy in this class of compounds and to date has been understudied in terms of structure kinetic relationships (SKR.) Further, comorbidities of bipolar disorder and substance use disorders (SUD) has not been adequately addressed therapeutically. Hence developing new molecules to potentially treat this patient population is a goal of this investigation. Cariprazine, an FDA approved drug for treatment of schizophrenia and bipolar disorder, is a high affinity D_2R/D_3R partial agonist, but with poor selectivity for D_3R (D_2R K_i:0.783 nM, D_3R K_i: 0.216 nM, D_2R/D_3R: 3.63), limiting its therapeutic potential to treat SUD. The design and synthesis of bitopic cariprazine analogs was initiated with the goal of increasing selectivity for D_3R while maintaining high affinity and also developing SKR within this class of molecules. This series of compounds was designed through the modification of cariprazine's bitopic molecular components: the primary pharmacophore (PP), secondary pharmacophore (SP) and the linker. The PP of cariprazine was replaced with substituted phenyl piperazines known to increase D_3R selectivity in the VK series of D_3R ligands (Kumar et al 2016). The SP was modified with aromatic heterocycles. These novel compounds have affinities ranging from 0.2 to 75 nM and D_2R/D_3R selectivity ranging from 2-18-fold. Additional functional and binding studies will determine the effects of these modifications on efficacy and kinetics.

Poster 46

Interactions between impulsivity and MDPV self-administration in rats

Abbott, Megan S.[1]; Doyle, Michelle R.[2,3]; Seaman Jr., Robert W.[2,3]; Rice, Kenner C.[4]; and Collins, Gregory T.[2,3]

[1]Long School of Medicine, and [2]Dept. of Pharmacology, UT Health San Antonio; [3]South Texas VA Health Care System; [4]NIDA-IRP

Synthetic cathinones, such as MDPV, are recreational drugs of abuse that have been shown to maintain unusually high levels of self-administration in rats as compared to other stimulant drugs, such as cocaine. Previous work suggests that behavioral phenotypes (e.g. locomotor response to novelty, saccharin preference, etc.) associated with high levels of cocaine self-administration do not predict the development of high levels of MDPV self-administration. This study aims to test the hypothesis that rats that engage in high levels of trait impulsivity (e.g. inability to withhold responding for a sucrose reward) will be more likely to engage in high levels of MDPV self-administration compared to rats with low levels of trait impulsivity. 10 female and 10 male Sprague-Dawley rats were mildly food restricted prior to assessing impulsive action (i.e. premature responding) in the 1-choice serial reaction time test (1CSRTT). Next, rats were implanted with an intravenous catheter and allowed to self-administer MDPV (0.032 mg/kg/inf) or cocaine (0.32 mg/kg/inf) under a fixed ratio (FR) 1 schedule of reinforcement. After rats acquired self-administration, full dose-response curves for MDPV (0.001-0.1 mg/kg/inf) or cocaine (0.01-1 mg/kg/inf) were generated under a FR5 schedule of reinforcement. Finally, after a history of self-administering MDPV or cocaine, baseline measures of impulsivity, as well as the effects of MDPV (0.032-0.32 mg/kg) or cocaine (0.1-1.78 mg/kg) on impulsivity, were determined by the 1CSRTT. Although MDPV and cocaine both increased measures of impulsivity, this study failed to identify an interaction between initial measures of impulsivity and high levels of drug self-administration, or between high levels of drug self-administration and subsequent measures of impulsivity.
Research supported by R01DA039146 (GTC)

Poster 47

Stereoselective effects of α-pyrrolidinopentiophenone (α-PVP): neurochemistry, hyperthermia, and locomotor activity in male Sprague-Dawley rats

Nelson, Katharine H.[1]; López-Arnau, Raúl[2]; Manke, Hayley N.[1]; Imanalieva, Aikerim[1]; To, Peter[1]; Raiten, Zachary E.[3], Rice, Kenner C.[4]; and Riley, Anthony L.[1]

[1]Department of Psychology, American University, Washington, DC, USA; [2]Department of Pharmacology Toxicology and Therapeutic Chemistry Pharmacology Section and Institute of Biomedicine (IBUB) Faculty of Pharmacy and Food Science, University of Barcelona, Barcelona, Spain; [3]Penn State University, University Park, PA, USA [4]Drug Design and Synthesis Section, National Institute on Drug Abuse (NIDA), Bethesda, MD, USA.

Work with a variety of psychostimulants report that different stereochemistry may produce different behavioral, therapeutic and/or pharmacological effects. α-PVP's mechanism of action and effects on temperature and activity (indices of human toxicity) have not been assessed in terms of stereoselectivity. To address this, we examined the ability of S-, R- and racemic α-PVP to block the reuptake of DA and NE at their respective transporters (DAT and NET) using rat brain synaptosomes derived from the striatum and frontal cortex of 18 experientially naïve adult male Sprague-Dawley rats (Experiment 1). In Experiment 2, adult male Sprague-Dawley rats (n = 80) were injected (IP) with vehicle or 1.5, 3 or 6 mg/kg of S-, R- or racemic α-PVP and assessed for changes in body temperature and activity. Both racemic and S-α-PVP were more potent than R-α-PVP in inhibiting DA and NA uptake [DA uptake IC_{50} value (nM) 129.3 ± 7.3; 44.0 ± 11.3; 430.8 ± 29.8; NE uptake IC_{50} value (nM) 18.8 ± 0.6; 8.1 ± 0.6; 113.0 ± 5.8 for racemic, S- and R-α-PVP, respectively; all ps < 0.05)]. S-α-PVP and the racemate induced significant dose- and time-dependent hyperthermia and increased ambulation and stereotypies (all ps < 0.05; no effect with R-α-PVP). The effects of α-PVP appear stereoselective across several behavioral and physiological endpoints via DA/NE reuptake inhibition (which is also stereoselective). Knowledge of such enantioselectivity may be important for prevention and treatment of α-PVP use and abuse.

Poster 48

A history of ketogenic diet prevents escalation of alcohol drinking during dependence

Elvig, Sophie K.[1]; Smith, Caroline J.[1]; Vendruscolo, Janaina C.M.[1]; Wiers, Corinde[2]; Volkow, Nora D[2]; Koob, George F.[1]; and Vendruscolo, Leandro F.[1]

Neurobiology of Addiction Section, Integrative Neuroscience Research Branch, NIDA IRP; [1]National Institute on Drug Abuse, National Institutes of Health, USA.; [2]National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, USA.

Alcohol use disorder is the most prevalent substance use disorder around the globe and is characterized by escalated alcohol drinking. Heavy drinking leads to a shift from glucose to acetate metabolism. During withdrawal, there is a deficit in acetate, which may contribute to escalated alcohol drinking and withdrawal symptoms. Replenishing the body's supply of acetate through a ketogenic diet may reduce these withdrawal symptoms, thus decreasing alcohol intake. We hypothesized that rats on a ketogenic diet will exhibit decreased alcohol drinking compared to a control diet. Male Wistar rats were trained to orally self-administer alcohol and water, then were assigned to ketogenic or regular diet groups. Twice weekly, rats were allowed to self-administer alcohol (10%, w/v). After 8 weeks on the diet, all animals were given normal chow and half were placed in alcohol vapor chambers (14 h on/10 h off) to induce alcohol dependence. The rats continued to have twice weekly operant self-administration sessions during withdrawal. The ketogenic diet and control rats consumed the same amount of alcohol before exposure to alcohol vapor. However, during alcohol vapor exposure, the control rats escalated their drinking, whereas the ketogenic diet rats decreased their alcohol intake. In summary, a history of a ketogenic diet reduced alcohol intake in rats that were made dependent on alcohol.

Poster 49

Alprazolam exposure during adolescence dysregulates reward sensitivity and second messenger signaling in adulthood

Cardona-Acosta, A.[1]; Parise, L.F.[1]; Sial, O.K.[1]; Vieregg, E.L.[1]; Rozofsky, J.P.[1]; and C.A. Bolaños-Guzmán[1]

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

Benzodiazepine-related emergency room visits have increased in the US within the past two decades and despite concerns surrounding their use, there has been a substantial increase in benzodiazepine's prescription rate. Benzodiazepines are commonly abused concurrently with opioids, resulting in increased comorbidity. There is evidence of increased use and abuse of benzodiazepines during adolescence, yet most available neurobiological evidence has been based on studies using adult organisms. This study was designed to investigate whether exposure to alprazolam during adolescence also potentiates the behavioral and biochemical effects of opiates such as morphine. Adolescent C57BL/6J male mice were treated with alprazolam (0.25, 0.5 and 1.0 mg/kg) or saline, once daily. Changes in behavioral responsiveness to morphine (0.5, 1.0 and 5.0 mg/kg), using the conditioned place preference paradigm (CPP), and gene expression changes within the ventral tegmental area (VTA), using qPCR, were assessed both 24 h and one-month after the end of drug treatment. Our results show that the alprazolam pre-treated mice developed strong preference to the compartment paired with a threshold dose of morphine (0.5 mg/kg), and this effect was still present a month after alprazolam exposure. We then measured whether extracellular signal-regulated kinase 1/2 (ERK)-signaling would be affected by alprazolam pretreatment, given ERK's role in mediating drug-induced behaviors. Preliminary results show a decrease in ERK2 gene expression when compared to controls. Overall, these findings suggest that exposure to alprazolam during adolescence potentiates the rewarding effects of opiates such as morphine, and that alprazolam exposure during this period result in persistent changes of ERK-signaling within the VTA, a brain region implicated in both drug-reward and mood-related disorders in adulthood.

Poster 50

Combination treatment with fluoxetine and aripiprazole leads to decreases in cocaine-seeking behavior in adult female C57BL/6 mice

Castillo, Samuel A.[1]; Pardo, Diamond I.[1]; and Iñiguez, Sergio D.[1]

[1]Department of Psychology, University of Texas at El Paso, El Paso, TX

Major depressive disorder (MDD) is a highly debilitating illness affecting millions across the globe. The first line of defense against this disorder is fluoxetine (FLX), a selective serotonin reuptake inhibitor. Unfortunately, FLX does not alleviate MDD symptoms in most patients – with close to 50% being resistant to this pharmacotherapeutic treatment. A current alternative approach for treatment resistant-MDD is the prescription of FLX in combination with the atypical antipsychotic aripiprazole (ARIP). This is surprising, given that the long-term consequences of this combination treatment (FLX+ARIP) have not been thoroughly assessed at either the clinical or preclinical level. To make things worse, females are often excluded in studies that assess potential long-term consequences of drug exposure, despite making up more than half of the clinically depressed population. Thus, the purpose of this study is to examine if FLX+ARIP exposure influences reactivity to anxiety-inducing situations, as well as drug-seeking behavior, in later life. To achieve this, adult (postnatal day [PD] 70) female C57BL/6 mice were administered either vehicle (DMSO) or FLX (10 mg/kg) with aripiprazole (0.03 mg/kg) for 15 consecutive days (PD70-84). Twenty-one days later (PD105+), mice were tested on the light/dark box, elevated plus maze, or cocaine (5 mg/kg) conditioned place preference (CPP) paradigm. The results showed that animals pretreated with FLX+ARIP displayed greater sensitivity to anxiety-inducing situations, and spent significantly less time in cocaine-paired environments, when compared to DMSO-treated controls. Collectively, these data indicate that the combination treatment of FLX+ARIP induces an enduring anxiogenic-like behavioral profile along with reward-related deficits, in female mice. Of concern, this enhanced sensitivity to anxiety-inducing environments and reduced sensitivity to reward-related stimuli may reflect general dysfunction(s) of brain reward systems.

Poster 51

Evaluation of the discriminative stimulus effects of two novel synthetic cannabinoid compounds

Tourigny, A. A.; Forster, M. J.; and Gatch, M. B.

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

Aims: Newly emerging synthetic cannabinoid (SC) compounds have become increasingly common as a dangerous substance in the designer drug market. They are often targeted as a "legal high" alternative to traditional cannabinoids via "darknet" markets. Although the chemical structure remains similar to natural cannabis products, the potency of new SCs are becoming a growing concern internationally. The purpose of this study was to determine whether two SCs exhibited similar discriminative stimulus effects as Δ^9-THC.

Methods: 32 single-housed, adult male Sprague-Dawley rats were trained to discriminate between IP injections of Δ^9-THC (3 mg/kg) and 1:1:18 ECS. The rats were trained to identify these treatment conditions in a double-alternating pattern (i.e.: day 1-2: drug; day 3-4: saline), then tested under an FR10 schedule when they achieved 85% treatment-appropriate lever responding in 9 out of 10 sessions (in first reinforcer and total session). Following successful treatment identification, substitution tests for 4-CN-CUMYL-BUTINACA (4-cyano-cumyl-butinaca) and 5F-CUMYL-P7AICA (5-fluoro cumyl-P7AICA) were conducted.

Results: 4-CN-CUMYL-BUTINACA and 5F-CUMYL-P7AICA each fully substituted for the discriminative stimulus effects of the training dose of Δ^9-THC.

Conclusion: Rodents exposed to both compounds produced similar stimulus effects as those produced by Δ^9-THC. Therefore, humans are likely to experience similar subjective effects when exposed to these compounds and could be abused in the same way as Δ^9-THC.

Poster 52

Correlates of prefrontal cortex activity during morphine-induce risk-taking behavior in rats

Vasquez, Andres[1,2]; Quave, Cana[2]; Engelke, Douglas[2]; and Fabricio, H. Do Monte[2]

[1]Department of Neuroscience, Rice University, Houston, TX USA; [2]Department of Neurobiology and Anatomy, The University of Texas Health Science Center, Houston, TX USA

Drug overdoses have drastically increased in number in recent years with most cases being attributed to opioid misuse. While opioid misuse is associated with deficits in risk-related decision-making, it remains unclear how opioids affect the brain and alter motivated behavior during conflict situations. To address this question, we used a rat model of conditioned place preference wherein opioid administration was paired with a specific context, in which a fear-inducing stimulus (cat saliva) was later presented (conflict test). Additionally, we recorded *in vivo* electrophysiological activity from prelimbic cortex (PL) neurons at various time points throughout the experiment. The 10-day conditioning period included alternating between drug pairings (fentanyl, morphine, or saline) in the side of the chamber least preferred at baseline and saline pairings (saline only) in the opposite side. Repeated opioid exposure resulted in an increased preference for the drug-paired side after a 72-hour forced abstinence period, an effect not observed in the saline group. During the subsequent conflict test, both saline- and fentanyl-treated animals avoided the drug-paired/cat saliva side of the chamber and exhibited increased freezing responses. Interestingly, morphine-treated rats failed to display a similar aversion to the predator odor as demonstrated by the negligible difference in the amount of time rats spent in the drug paired/cat saliva side of the chamber. Furthermore, while acute administration of either morphine or fentanyl reduced the spontaneous firing rate of PL neurons, repeated administration of these same opioids increased PL activity, an effect that persisted after 72 hours of forced drug abstinence. Taken together, our results indicate that repeated exposure to opioids induces hyperexcitation of PL neurons which is associated with increased risk-taking behavior.

Poster 53

Evidence for insurmountable antagonism of μ opioid receptors by methocinnamox

Ghodrati, Saba[1]; Gerak, Lisa R.[1] and France, Charles P.[1,2]

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

Methocinnamox (MCAM) is a novel opioid receptor antagonist that might be useful for treating for opioid overdose and abuse. It is thought to bind pseudoirreversibly to μ opioid receptors, which would be expected to produce long lasting and insurmountable antagonism at sufficiently large doses. While MCAM blocks the antinociceptive effects of morphine for several weeks, the antagonism is surmountable, perhaps suggesting that effects of very large doses of morphine (560 mg/kg) are mediated by receptors other than μ opioid receptors. The current study examined the contribution of μ opioid receptors to these antinociceptive effects by giving 10 mg/kg MCAM one day before determination of morphine dose-effect curves using a warm water tail withdrawal procedure. Immediately before morphine was administered, 4 rats received saline, 4 rats received a small dose of the opioid receptor antagonist naltrexone (0.056 mg/kg) that is acts selectively at μ opioid receptors and shifts the morphine dose-effect curve 3-fold rightward in otherwise untreated rats, and 4 rats received a large dose of naltrexone (1 mg/kg) that acts at multiple types of opioid receptors. MCAM antagonized the antinociceptive effects of morphine, shifting the morphine dose-effect curve 100-fold rightward 1 day after MCAM administration; under these conditions, 0.056 mg/kg naltrexone had no effect on the morphine dose-effect curve whereas 0.1 mg/kg naltrexone shifted the morphine dose-effect curve downward. Thus, in MCAM-treated rats, the antinociceptive effects of large doses of morphine appear to be mediated by opioid receptors other than μ opioid receptors. These data are consistent with pseudoirreversible binding of MCAM to and insurmountable antagonism at μ opioid receptors. A drug with these pharmacologic properties could be particularly beneficial in preventing opioid overdose and relapse to drug use. Supported by NIH (R01DA005018 and R01DA048417) and the Welch Foundation (AQ-0039).

Poster 54

Discrete cue-induced relapse to opioid seeking after punishment in a rat model

Ye, Qiying; Ruiz, Christina M.; and Mahler, Stephen V.

Department of Neurobiology and Behavior, University of California Irvine, Irvine, CA USA

Drug-addicted individuals lose control over drug intake despite adverse consequences, a defining feature of addiction. Classic drug abuse/relapse rodent models generally fail to incorporate negative consequences associated with addiction. Here we model opioid relapse after punishment-induced abstinence, in which rats voluntarily cease remifentanil self-administration due to the negative consequence (lever-press contingent footshock). Currently it is unknown whether drug-associated discrete cues or contexts provoke relapse in opioid-seeking behavior after voluntary, punishment-imposed abstinence. Five female Long-Evans rats were trained to self-administer i.v. remifentanil on an ascending variable interval schedule in Context A. Abstinence training then commenced in Context B, where lever-presses yielded remifentanil infusions, and 50% chance of concurrent footshock. Individual rats varied markedly on their pressing in the face of punishment. Reinstatement of remifentanil seeking was then tested under four conditions: Context A with response-contingent cues, Context A without cues, Context B with cues, and Context B without cues. Our initial results show that discrete cues in Context A elicited robust reinstatement relative to Context A alone, or context B with or without cues, indicating that a combination of drug-associated discrete cues and contextual elements evoke robust relapse-like behavior. In addition, rats that showed the most punishment resistance during drug taking also displayed greater cue-induced drug seeking than punishment sensitive rats. Our results validate the use of this voluntary abstinence/reinstatement model with an opioid drug. Moreover, our results show individual differences in punishment resistance which predict subsequent relapse-like behavior. We will next employ this translationally-relevant protocol to explore the neural circuit mechanisms of relapse-like behavior after voluntary abstinence.

Poster 55

Sex differences in estrogenic preoptic efferents to the ventral tegmental area: implications for sex differences in drug response

Martz, Julia M.[1,3]; Vasquez, Adriana[1]; and Dominguez, Juan M.[1,2,3]

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

Males and females respond differently to drugs of abuse; this difference is in part due to the influence of gonadal hormones such as estradiol. The medial preoptic area (mPOA) in the hypothalamus is an important integrator of neuroendocrine signaling and a key regulator of both natural and drug-induced reward. Although the mPOA is a sexually dimorphic structure and is implicated in several behavioral sex differences, it remains unclear how the mPOA influences the brain's reward circuitry in a sexually distinct manner. Using iontophoretic injections of the retrograde tract tracer fluorogold into the ventral tegmental area (VTA) of male and female rats (n=20), we examined sex differences in the neural projections from the mPOA to the mesolimbic reward pathway. In addition, we examined sex differences in the sensitivity of those projections to estrogen signaling. Results indicate that although males and females send a comparable number of projections from the mPOA to the VTA, female projections contain significantly more estrogen receptors ($P<.05$). Taken together with previous reports, these findings suggest that the mPOA may be an important regulator of the endocrine mediated sex differences in reward response.

Poster 56

Influence of adolescent Δ9-tetrahydrocannabinol exposure on locomotor-stimulating activity of cocaine in adult rats

Bharadia, Sanaya S.; Ajlen, Aaron; Jutkiewicz, Emily M.

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

In light of the recent trends in marijuana legalization, there is concern for increased marijuana usage among adolescents. Repeated use of marijuana during adolescence may alter development and produce long-lasting changes in the brain. For example, our laboratory recently demonstrated that adolescent exposure to the active ingredient in marijuana, Δ9-tetrahydrocannabinol (THC), increased sensitivity to the reinforcing effects of cocaine. This current study investigated the effects of chronic adolescent THC exposure on the locomotor stimulating effects of cocaine in adult rats. Male Sprague-Dawley rats were given daily intraperitoneal injections of either vehicle or 1 mg/kg THC during adolescence (P28-P45).Between P80-85, rat were implanted with intravenous (i.v.) catheters, and the effects of cocaine (0.1-3.2 mg/kg, i.v., 30 min between doses) on locomotor activity were evaluated every 72-hr between P90-99. In adulthood, cocaine produced dose-dependent increases in activity levels. An increase in cocaine-induced locomotor activity was observed between the first and fourth session. In general, the locomotor-stimulating effects of acute and repeated cocaine were not altered by adolescent THC exposure. In summary, adolescent THC exposure enhanced the reinforcing effects of cocaine but did not alter the locomotor-stimulating or sensitizing effects of intravenous cocaine. One important difference between these studies is that subjects in the cocaine self-administration studies were food-restricted, which has been shown to enhance the dopamine reward pathway. Therefore, future studies will evaluate the effects of adolescent THC exposure on cocaine-induced locomotor activity in food-restricted, adult rats.

Poster 57

The effects of sex and differential rearing on cue-induced amphetamine craving

Fort, Troy D.[1]; Moser, Theodore J[1]; and Cain, Mary E.[1]

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

Environmental enrichment (EC) has been shown to reduce amphetamine (AMP) self-administration (SA) and cue-induced relapse when compared to isolated rearing conditions (IC). Stronger cue-induced craving has been shown in females, suggesting sex differences in the propensity for cue-induced relapse. The current study used 6-hr SA procedures to elucidate the effect of differential rearing and sex on AMP SA, relapse following an abstinence period, and the extent to which relapse can be mitigated by treatment with *N-acetylcysteine* (NAC). We hypothesized that enrichment would protect against escalations in drug intake and relapse when compared to IC and standard condition (SC) animals. Male and female Sprague-Dawley rats arrived on PND21. EC rats were raised communally with daily handling and novel objects. IC rats were single-housed without objects or handling. SC rats were pair-housed, lacked novel objects, and were handled once a week. After 30 days of rearing, rats were implanted with a jugular catheter. Rats then underwent 12, 6-hr FR-1 sessions for amphetamine (0.1 mg/kg/infusion) paired with cue light presentation. After 12 sessions, all animals were given 14 daily treatments of NAC (100 mg/mL; ip) during the abstinence period while remaining in their respective environments. All animals were then placed back into the operant chambers for a 2-hr cue-induced relapse test. Enrichment significantly lowered overall AMP SA and cue-induced relapse compared to both ICs and SCs. Interestingly, cue-induced relapse was significantly lower for males than females. Analyses of inter-response times (IRTs) for AMP SA sessions indicated significantly longer IRTs for ECs than ICs or SCs and a significant shortening of IRTs across the 12 SA sessions. Enrichment produced significantly longer IRTs during the cue-test. Taken together, our results indicate that enrichment offers a neuroprotective role in lowering drug intake and cue-induced relapse. We hypothesize that rearing-induced differences in IRTs are due to differential attention to drug-associated cues.

Poster 58

Effect of prior alcohol exposure on cocaine self-administration in rhesus monkeys

Tryhus, Aaron M.[1]; Galbo, Lindsey K.[1]; Epperly, Phillip M.[1]; Davenport, April T.[1]; George, Brianna E.[1]; and Czoty, Paul W.[1]

[1]Wake Forest School of Medicine, Department of Physiology and Pharmacology

Most cocaine users also abuse alcohol, but little is known about the mechanisms that promote co-abuse. These studies in rhesus monkeys compared the acquisition of cocaine self-administration in monkeys with or without a history of chronic, binge-like alcohol drinking. Involvement of dopamine D_3 receptors in initial cocaine sensitivity was assessed using a quinpirole-induced yawning assay. One group of six male monkeys drank a sweetened, 4% ethanol (EtOH) solution five days per week while another group drank an equivalent volume of sweetened water; all monkeys self-administered food pellets under a fixed-ratio schedule. EtOH access was provided 2-3 hours after the operant session. After six months of EtOH drinking, saline or single doses of cocaine (0.001-0.3 mg/kg/injection, i.v) were substituted for food pellets in ascending order. Once a dose was reached that functioned as a reinforcer (number of injections significantly greater than during saline availability), a full cocaine dose-response curve was constructed. When the two groups were compared, no significant differences were found in the dose at which monkeys acquired cocaine self-administration, the ED_{50} of the initial cocaine dose-response curve, or total cocaine intake across the range of cocaine doses. ED_{50} values of quinpirole-induced yawning curves were negatively correlated with the dose of cocaine self-administration acquisition (r=-0.78). These results suggest that alcohol exposure—even at binge-like levels of consumption—does not affect initial sensitivity to cocaine. A strong negative correlation between D_3 receptor availability and the dose at which monkeys acquired the cocaine self-administration behavior contrasts with the view that D_3 receptor stimulation enhances cocaine reinforcement. Future studies will continue the assessment of cocaine-EtOH interactions as monkeys self-administer one or both drugs over one year and will assess longitudinal changes in D_3 receptor availability via the quinpirole assay.
Supported by: R01 DA39953

Poster 59

Development of a nonhuman primate model of drinking despite punishment

Galbo, Lindsey K.[1]; Flynn, Shawn M.[1]; Husbands, Steve M.[2]; and Czoty, Paul W.[1]

[1]Wake Forest School of Medicine, Department of Physiology & Pharmacology, Winston-Salem, NC 27157; [2]Department of Pharmacy & Pharmacology; University of Bath; Bath, UK

Continued alcohol drinking despite negative consequences is a hallmark of alcohol use disorder (AUD). Persistent drinking in the presence of a punishing stimulus, such as the bitter tastant quinine, defines a vulnerable phenotype that can be characterized, and may aid in the identification of pharmacotherapies to suppress compulsive drinking. In the present study, we extended this model, developed in rodents, to nonhuman primates. Effects of quinine were determined in 5 female rhesus monkeys with >5 years of experience drinking ethanol. Monkeys were given free access to a 4% ethanol solution 3 hours per day. Once ethanol consumption was stable (+/- 0.5 g/kg the mean of the previous three days) a concentration of quinine (0.03-3.0 g/L) was added to the ethanol for one day. Quinine dose-dependently decreased ethanol consumption as has been observed in rodents. Preliminary results suggest a greater resistance to the aversive effects of quinine in the absence of ethanol. Finally, the acute effects of a mixed mu opioid and nociception/orphanin FQ (NOP) receptor agonist, BU08028, were examined using the aversion-resistant model. BU08028 is an analog of buprenorphine with higher efficacy at the NOP receptor and has shown promise as an AUD treatment in rodent and monkey models. When administered in the presence of the quinine-ethanol solution, BU08028 enhanced the suppressive effect of quinine. In conclusion, our laboratory has established a nonhuman primate model of persistent ethanol drinking despite punishment. Preliminary data demonstrate that quinine is less effective in decreasing drinking of water compared to ethanol drinking. Future studies will fully characterize the ability of BU08028 and other potential treatments of AUD to suppress compulsive ethanol consumption in this model.

Poster 60

Evaluation of sex as variable in conditioned place preference with low dose mixtures of 3,4-methylenedioxypyrovalerone (MDPV) and 3,4-methyleneidoxymethamphetamine (MDMA) in rodents

Risca, Harmony I.; and Baker, Lisa E.

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

As a popular constituent of illicit psychoactive “bath salts”, MDPV poses serious health risks. Despite the likelihood of concomitant use of MDPV with other drugs of abuse, the combined behavioral effects of these substances have not been evaluated rigorously. The current study examined the combined effects of MDPV and 3,4-methylenedioxymethamphetamine (MDMA) using an eight-day biased conditioned place preference (CPP) procedure with male and female Sprague-Dawley rats. Rats were randomly assigned to the following treatment groups: saline, MDPV (1 or 3.2 mg/kg), MDMA (3 mg/kg), 1 mg/kg MDPV + 3 mg/kg MDMA, or 3.2 mg/kg MDPV + 3 mg/kg MDMA. Difference scores were calculated by subtracting time spent in the drug-paired chamber pre-conditioning from time spent in the same chamber post-conditioning to assess CPP. Activity levels during drug conditioning trials were highest among the 3.2 mg/kg MDPV-treated animals. A two-way ANOVA of difference scores indicated a statistically significant treatment effect. Although difference scores were higher in all MDPV and MDPV+MDMA treatment groups compared to the saline control groups, only the females treated with 3.2 mg/kg MDPV + 3 mg/kg MDMA exhibited statistically significant evidence for CPP. Interestingly, 3 mg/kg MDMA appeared to attenuate the locomotor stimulant effects of 3.2 mg/kg MDPV but increase its effects on conditioned reward. These findings suggest that females may be more sensitive to the rewarding effects of MDPV and these effects are enhanced by co-administration of MDPV and MDMA. In consideration of these findings, concurrent use of MDPV and MDMA may pose an enhanced risk for abuse, particularly in females. Further research is warranted to evaluate the contribution of sex as a biological variable in the behavioral and neurochemical effects of MDPV and related drugs.

Poster 61

Intermittent vs. long access: spiking drug levels or behavioral adaptation to constraint?

Beasley, Madeline; Jones, Robby; Gunawan, Tommy; Tripoli, Chris; Kearns, David

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

A number of recent studies have shown that intermittent access to cocaine produces more addiction-like behavior (e.g., increased progressive ratio breakpoints) than long access to cocaine (e.g., Algallal et al., 2019; Kawa et al., 2019). This is thought to be due to spiking levels of drug concentration in the brain produced by intermittent access. However, it is unknown whether similar increases in addiction-like behavior might occur after intermittent access to non-drug reinforcers. This present study compared rats' (12 female Long-Evans) behavior after intermittent access (IntA) or long access (LgA) to a saccharin reinforcer. After learning to lever press for saccharin, rats were assigned to either an IntA or LgA group (n = 6 per group). For both groups, sessions were six hours long. LgA rats could lever press for saccharin for the full six hours (i.e., the lever was continuously available). IntA rats had a five-minute period to lever press for saccharin, followed by a 25-minute timeout period where the lever was retracted. This cycle of five minutes of lever insertion followed by 25 minutes of lever retraction repeated for the full six hours. The two groups were trained on the LgA or IntA procedures for ten sessions. The IntA group significantly ($p < 0.05$) increased the number of saccharin reinforcers obtained over sessions, whereas no escalation was observed in the LgA group. Then, each rat was given a progressive ratio test, where the number of lever presses necessary increased with each reinforcer. The IntA group exhibited significantly ($p < 0.05$) higher breakpoints than the LgA group. The finding that IntA also increases breakpoints for a non-drug reinforcer suggests that the increases in addiction-like behavior observed after IntA as compared to LgA self-administration may be due more to behavioral adaptation to constraints on availability than to spiking drug levels in the brain.

Poster 62

Behavioral Effects of *d*-Methamphetamine and *in vivo* microdialysis in rats

Dawes, M.[1]; Honrao, C.[2]; Ma, X.[2]; Solakidou, E.; Makriyannis, A.[2], Bergman, J.[1]; Desai, R.I.[1]

[1]McLean Hospital, Harvard Medical School, Belmont, MA, USA [2]Center for Drug Discovery, Northeastern University, Boston, MA, USA

The present studies were conducted to examine the relationship between locomotor stimulant effects of *d*-methamphetamine (*d*-MA) and its ability to increase extracellular concentrations of *d*-MA, its active metabolite *d*-amphetamine (*d*-AMP), dopamine (DA), serotonin (5-HT), norepinephrine (NE), γ-aminobutyric acid (GABA), and glutamate (GLU) in the rat nucleus accumbens (nAcc) shell. First, the effects of cumulatively administered *d*-MA (0.3–5.6 mg/kg, i.p.) on locomotor activity were determined. In other studies, *in vivo* microdialysis and LC/MS analysis were used to determine the effects of cumulatively administered *d*-MA (0.3–5.6 mg/kg, i.p.) on extracellular levels of *d*-MA, *d*-AMP, DA, 5-HT, NE, GABA, and GLU in the nAcc shell. *d*-MA produced dose-related effects on locomotor activity, characterized by an inverted-U dose-response curve. Results from microdialysis studies show that levels of *d*-MA in the nAcc shell increased in a dose- and time-dependent manner. An increase in *d*-AMP was also observed after 0.3–5.6 mg/kg *d*-MA; peak levels of d-MA and *d*-AMP were detected 20 min after 5.6 mg/kg administration. *d*-MA produced dose- and time-dependent increases in DA, 5-HT, and NE efflux in the nAcc shell. In contrast, *d*-MA did not produce significant changes in GABA or GLU levels. Analysis shows that increases in *d*-MA levels after 0.3–3.0 mg/kg are concordant with increases in DA, 5-HT, and NE efflux. However, levels of *d*-MA after 5.6 mg/kg appear to reflect increases in DA and 5-HT but not NE. Correlation analysis revealed an inverse relationship between *d*-MA-induced increases in locomotor activity and extracellular levels of 5-HT and *d*-AMP. Taken together, the ability to detect and correlate the presence and clearance of *in vivo* brain levels of *d*-MA, and its active metabolite *d*-AMP in the nAcc shell of rats to neurochemical and behavioral effects can provide insight into the neuropharmacological effects of *d*-MA.

Poster 63

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

Vanderhoof, Samantha[1,2]; Latsko, Maeson[1,2]; Halcomb, Carly[1,2], Jasnow, Aaron[1,2]

[1]Department of Psychological Sciences, Kent State University, Kent, Ohio, USA; [2]Brain Health Institute, Kent State University, Kent, Ohio, USA.

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

Poster 64

Methcathinone and 3,4-methylenedioxypyrovalerone differentially affect vesicular monoamine transporter-2 function

Magee, Charlotte P.[1,2]; Le, BaoMinh D.[2]; Siripathane, Yasmeen H.[2] and Fleckenstein, Annette E.[1, 2]

[1]Interdepartmental Program in Neuroscience, University of Utah, Salt Lake City, UT USA; [2]School of Dentistry, University of Utah, Salt Lake City, UT USA.

Methcathinone (MCAT) and 3,4-methylenedioxypyrovalerone (MDPV) are abused synthetic cathinones with differing neurotoxicity profiles. Repeated high-dose administrations of MCAT cause persistent dopaminergic deficits in rodent models, and MCAT abuse is associated with severe long-term motor deficits in humans. In contrast, preclinical data suggest minimal or no dopaminergic toxicity as a consequence of MDPV exposure. Dysregulation of monoamine transporters like the vesicular monoamine transporter-2 (VMAT-2) can contribute to, or protect against, drug-induced dopaminergic deficits. Accordingly, the hypothesis that MDPV and MCAT differentially alter VMAT-2 function was investigated. For statistical analyses, a Student's t-test was utilized for 2-, and ANOVA was utilized for 3- or 4-group experiments. Results revealed that a single MDPV administration (2.5 mg/kg, s.c.) rapidly increased [^{3}H]dopamine uptake, as assessed *ex vivo* in synaptic vesicles prepared from rat striatum. MDPV likewise increased VMAT-2 immunoreactivity within this vesicle-enriched subcellular fraction; an effect that was D2 receptor-mediated. In contrast to the upregulation after MDPV, repeated high-dose MCAT administrations (3 x 30 mg/kg, s.c., 2-h intervals) rapidly decreased [^{3}H]dopamine uptake, and was not D2 receptor-mediated. These data support the hypothesis that the MDPV-induced increase in VMAT-2 function may protect against, whereas the MCAT-induced decrease in VMAT-2 function may contribute to, persistent dopaminergic deficits.

Poster 65

Pharmacological characterization of corynantheidine, minor alkaloid in mitragyna speciosa, at the μ-opioid receptor

Zuarth Gonzalez, Julio D.[1]; Sharma, Abhisheak[2]; Obeng, Samuel[1,3]; Leon, Francisco[3]; Reeves, Morgan E.[1]; Restrepo, Luis F.[1]; Patel, Avi[1]; Gamez Jimenez, Lea R.[1]; Ho, Nicholas[1]; Williamson, Morgan R.[1]; Crowley, Morgan L.[3]; McCurdy, Christopher R.[3]; McMahon, Lance R.[1] and Hiranita, Takato[1]

Departments of Pharmacodynamics[1], Pharmaceutics[2], and Medicinal Chemistry[3], College of Pharmacy, University of Florida

Mitragyna speciosa (kratom) has been used for centuries in Southeast Asia and has recently gained worldwide attention due to its opioid pharmacology. The present study focuses on corynantheidine, a minor alkaloid of kratom. The affinity of corynantheidine at the human μ-opioid receptor [Ki=118 (SEM: 12) nM] was 28-fold lower than that for morphine. Following p.o. administration of corynantheidine (20 mg) in rats, its Cmax and Tmax values were 206 (SEM: 43) ng and 8 hours. In contrast i.v. administration of corynantheidine (2.5 mg) had the maximum concentration of 786 (SEM: 41) ng at 5 minutes. Cumulative i.v. injections of corynantheidine (1.0-32 mg/kg, i.v.) or morphine (1.0-10 mg/kg, i.v.) produced robust antinociceptive effects (ED_{50} values: 17.9 and 4.8 mg/kg) in a hotplate assay at 52°C; the major kratom alkaloid mitragynine (3.2-17.8 mg/kg, i.v.) was inactive. In rats discriminating morphine (3.2 mg/kg, i.p.) from its vehicle, corynantheidine (5.6-56 mg/kg, i.p., 15 minutes prior to session) produced up to 25% morphine-like discriminative-stimulus effects; 56 mg/kg markedly decreased the rates of responding. In the rats discriminating morphine, no dose of corynantheidine was active in the hotplate assay. When pretreated, corynantheidine (17.8 mg/kg, i.p.) decreased the discriminative-stimulus effects of morphine (3.2 mg/kg) by 47%. However, naltrexone (0.032 mg/kg, i.p., 30 minutes prior to session) fully blocked the discriminative-stimulus effects of morphine. Thus, the present result suggests corynantheidine as a long-active antagonist at the μ-opioid receptor. Supported by UG3 DA048353 and R01 DA25267.

Poster 66

Developing new dopamine D2 receptor agonists and partial agonists for Parkinson's disease and schizophrenia

Keck, Thomas M.*; Nguyen, Catherine; Ricchezza IV, Joseph; Bohn, Stephanie; Crowthers, Raymond; Kurtyan, Emily; Tharakan, Jaslin; Briaguez, Wendy; Pino, Michael; Brunt, Dylan; Sullivan, Holli-Joi; Wu, Chun

Rowan University, Glassboro, NJ 08028

Current medications for Parkinson's disease (PD) and schizophrenia target the dopamine D_2 receptor (D_2R). Adverse side effects associated with these medications significantly reduce quality of life and drug compliance, thus new therapeutic strategies are clearly needed. D_2R activation by agonists can activate cAMP and ß-arrestin signaling pathways in neurons. Current evidence suggests that biased D_2R agonism and D_2R partial agonism are strategies that may provide greater treatment specificity while avoiding side effects. The objective of this project is to identify and investigate new D_2R ligands with novel chemical scaffolds, with the long-term goal of producing more effective medications for neuropsychiatric disorders. An initial virtual screen of a ZINC lead-like library with >3.6 million molecular structures was performed using models of the D_2R crystal structure refined into unbiased agonist and G protein-biased agonist biding modes via molecular dynamics simulations. Following this *in silico* screen, 8 potentially novel D_2R ligands were purchased and tested in radioligand competition binding screens using [^{3}H]N-methylspiperone and [^{3}H]7-OH-DPAT. 6 of 8 purchased compounds (A01, A02, A03, A08, B03, B06) have detectable affinity for D_2R (K_i = 0.75-51 μM), demonstrating the feasibility of our approach. New molecular dynamics simulations have been completed to expand *in silico* screens to include partial agonist and β-arrestin-biased agonist binding modes, and to evaluate a larger ZINC library (>17.9 million structures). Studies are ongoing to determine K_i values at D_3R and D_4R, and to characterize compound efficacy in cAMP and β-arrestin signaling pathways for each hit compound. Collaborations are in development to build initial analogue libraries of each compound. Each hit compound is a new structural entity with no previously known dopaminergic activity. The identification of new chemical entities with D_2R activity will build the foundation for future research to optimize pharmacological parameters for preclinical medications development.

Poster 67

Effects of repeated nicotine vapor exposure on withdrawal and anxiety-like behavior

Martínez, Michelle[1]; Flores, Rodolfo J[1]; Lira, Omar[1]; Uribe, Kevin P.[1]; Matos, Felix[1]; Espinosa, Veronika[1]; Giner, Priscilla[1]; O'Dell, Laura E.[1]; and Mendez, Ian A.[2]

[1]The University of Texas at El Paso, Department of Psychology, [2]The University of Texas at El Paso, School of Pharmacy

In recent years, there has been an increase in electronic nicotine delivery system use, especially in adolescents and young adults. Pre-clinical studies have previously investigated the rewarding and withdrawal effects of nicotine through injections and osmotic minipumps that continuously release nicotine. However, there is limited research investigating the effects of nicotine vapor on reward and withdrawal. Furthermore, understanding underlying neural and behavioral mechanisms driving the effects of nicotine vapor on the brain and behavior will aid in addressing factors that contribute to relapse. The goal of this study is to assess nicotine withdrawal signs and increases in anxiety following exposure to nicotine vapor in rats. Fifty-six male rats were exposed to either 0, 12, or 24mg/ml of nicotine for 16 days. Separate groups of rats received daily injections of either 0.8mg/kg of nicotine or saline, and another group received no nicotine vapor exposure for 16 days (homecage controls). For all groups, blood samples were collected on days 1 and 6 of vapor exposure to assess nicotine metabolite levels. Physical withdrawal signs and anxiety-like behavior following i.p. injections of the nicotinic receptor antagonist mecamylamine were assessed on day 7 and day 9 of vapor exposure, respectively. An increase was seen in physical withdrawal and anxiety signs during withdrawal days in the groups exposed to nicotine vapor relative to those that were not. A similar pattern was seen in cotinine levels in the groups exposed to nicotine. The findings suggest that there are similar findings in nicotine vapor, to those seen with various other administration techniques such as injections and osmotic minipumps. Additional research of intermittent vapor exposure would aid in understanding its behavioral effects and generalize results to e-cigarette use seen in adolescent and young adult populations.

Poster 68

Evaluation of the discriminative stimulus effects of six novel psychedelic substances

Hoch, A. C.; Forster, M. J. Gatch, M. B.

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

Aims: Novel psychedelic substances (NPS) are available via cryptomarket forums which facilitate the anonymous exchange of unregulated analogues putatively eliciting subjective effects similar to known psychedelics (e.g., LSD, DMT, DOM). The purpose of this study was to evaluate whether six NPS have similar discriminative stimulus effects as the scheduled psychedelic, 2,5-dimethoxy-4-methylamphetamine (DOM).

Methods: Singly-housed, adult male Sprague-Dawley rats were trained to discriminate DOM (0.5 mg/kg, ip.) from saline under an FR10 schedule. Rats were tested once they achieved 9 of 10 sessions at 80% treatment-appropriate lever responding for both the first reinforcer and total session. Training sessions occurred on separate days in a double-alternating pattern (i.e., drug-drug-saline-saline) until training was complete. Afterwards, substitution tests for 4-AcO-DET (4-acetoxy-N,N-diethyltryptamine), 4-AcO-DiPT(4-acetoxy-N,N-diisopropyltryptamine), 4-AcO-DMT (4-acetoxy-N,N-dimethyltryptamine), 4-AcO-MiPT (4-acetoxy-N-methyl-N-isopropyltryptamine), 4-OH-DET (4-hydroxy-diethyltryptamine), and 4-OH-MET (4-hydroxy-N-methyl-N-ethyltryptamine) were conducted.

Results: Full substitution for the discriminative stimulus effects were observed in the following compounds: 4-AcO-DET, 4-AcO-DiPT, 4-AcO-DMT, 4-AcO-MiPT 4-OH-DET, and 4-OH-MET.

Conclusion: These six compounds produced behavioral effects similar to those of DOM and are thus likely to elicit similar subjective effects in humans.

Poster 69

Evaluating combination therapies for treatment of chronic inflammatory pain: a GABAA approach

Woodhouse, Kristen L.[1]; 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.

Approximately 20% of U.S. adults suffer from chronic pain. Current therapies for treatment of chronic pain are limited, ineffective for a large number of patients, and often produce undesirable side effects. Though not used clinically to treat pain, benzodiazepines alleviate pain when administered into the spinal canal. This analgesic effect is due to their action at α2 and α3 subunits of the GABAA receptor: since α2/α3 subtype-selective GABAA positive allosteric modulators (PAMs) act specifically at these subunits, they produce analgesia without eliciting side effects typically seen with classical benzodiazepines, such as sedation or cognitive impairment. This study evaluates the analgesic efficacy of combinations of two α2/α3 subtype-selective PAMs (KRM-II-81 and NS16085) with the NSAID acetaminophen and two opioids (fentanyl and buprenorphine) in a rat model of chronic inflammatory pain (complete Freund's adjuvant). We used a fixed ratio approach to evaluate combinations of drugs, assessing both mechanical pain (von Frey) and thermal pain (Hargreaves), in order to visualize the onset and duration of action of each of these drugs alone and in combination. We found that combining KRM-II-81 (4.0 mg/kg) and buprenorphine (0.048 mg/kg) produced greater analgesia than either of these drugs alone at comparable doses. These data are among the first to systematically examine the performance of α2/α3 subtype-selective GABAA PAMs in combination with other analgesics, and are an important step towards developing novel therapies for treating chronic pain.

Poster 70

Activation of the claustrum-BLA pathway reduces fear retrieval

Liu, Jiafeng[1]; Maren, Stephen[1]

[1]Department of Psychological and Brain Sciences and Institute for Neuroscience, Texas A&M University, College Station, Texas 77843-3474

The claustrum is a subcortical structure that connects with a broad range of cortexes and some subcortexes including the basal lateral amygdala (BLA). Previous studies have demonstrated the role of the claustrum (CLA) in attention and Activation of the claustrum-PFC pathway reduced methamphetamine-induced impulsivity. However, the function of the CLA and its projections into the subcortical area remains unclear. Here, we examined effects of activation of the CLA->BLA pathway on fear retrieval. We microinjected the AAV expressing hM3Dq DREADDs into the CLA and placed cannulae into the BLA in rats. Fear conditioning (day1) was conducted five weeks after virus microinjection. Cued fear and context fear were tested with a counterbalance design through days 2 to 5. Vehicle (0.5μl/side) and CNO (1mM; 0.5μl/side) were administered through cannulae before behavioral tests. We found that activation of the claustrum-BLA pathway by CNO significantly reduced retrieval of both cued and context fear, suggesting that the claustrum-BLA pathway might regulate fear memory and anxiety. Our future experiment will test whether the activity of claustral neurons projecting into the BLA would be associated with fear retrieval by calcium imaging.

Poster 71

Extended protection by methocinnamox (MCAM) of the ventilatory depressant effects of fentanyl in awake, unrestrained rats

Castaneda, Gabriel[1]; Jimenez Jr., Victor M.[1,2]; France, Charles P.[1,2]

[1]Department of Pharmacology and [2]Addiction Research, Treatment & Training Center of Excellence, University of Texas Health Science Center, San Antonio, TX, USA

Opioid-related overdose deaths have reached epidemic levels in the United States with an increasing number of deaths due to the synthetic opioid receptor agonist fentanyl. Opioids, including fentanyl can induce overdose and death, primarily through significant ventilatory depression. The opioid receptor antagonist naloxone (e.g. Narcan®) is used currently to reverse opioid-induced ventilatory depression; however, naloxone has a short duration of action of about 1 hour in humans and is reportedly less effective to reverse the effects of fentanyls compared to other opioids. Methocinnamox (MCAM) is a selective, pseudoirreversible *mu* opioid receptor antagonist with a long duration of action that may reverse and provide long-term protection from the ventilatory-depressant effects of opioids, including fentanyl. The intent of the current study was to compare the effectiveness of naloxone and MCAM to reverse fentanyl-induced ventilatory depression and subsequently protect from ventilatory depression beyond 24 hours after initial reversal. Male Sprague-Dawley rats (N = 8) received fentanyl (0.01-0.178 mg/kg i.v) or vehicle and ventilatory parameters were recorded utilizing a whole-body plethysmograph. Fentanyl produced dose-dependent decreases in minute volume with 0.178 mg/kg fentanyl decreasing minute volume to 35% of control. Within 1 minute after i.v. administration, naloxone (10 mg/kg) and MCAM (10 mg/kg) fully reversed the ventilatory depressant effects of fentanyl. The next day, the ventilatory depressant effects of 0.178 mg/kg fentanyl were fully attenuated in rats that had received MCAM but not in rats that had received vehicle. Extended protection by MCAM could provide a useful treatment option for the current opioid crisis, including toxicity from fentanyl and related potent analogs. Supported by NIH (R01DA005018 and R01DA048417) and the Welch Foundation (AQ-0039).

Poster 72

The adrenergic α_2 receptor-mediated discriminative-stimulus effects of mitragynine, the primary alkaloid in kratom (m*itragyna speciosa*) in rats

Reeves, Morgan E.[1]; Obeng, Samuel[1,2]; Leon, Francisco[2]; Behnke, Mira[1]; Restrepo, Luis F.[1]; Patel, Avi[1]; Ho, Nicholas P.[1]; Williamson, Morgan R.[1]; Gamez Jimenez, Lea R.[1]; McCurdy, Christopher R.[2]; McMahon, Lance R.[1]; and Hiranita, Takato[1]

Dept of Pharmacodynamics[1] and Medicinal Chemistry[2], College of Pharmacy, Univ. of Florida

The primary kratom alkaloid mitragynine has received attention due to its opioid pharmacology whereas the antinociceptive effects of mitragynine were blocked by an α_2 antagonist. The present study examined the opioid and α_2 pharmacology of mitragynine with radioligand binding in cell membranes and drug discrimination in rats. The affinity of mitragynine at the μ-opioid receptor (Ki=706nM) was 2- to 10-fold higher than its affinity at the κ- and δ-opioid, and α_{2A} and α_{2C} receptors. In rats discriminating mitragynine (32mg/kg, i.p.), its ED_{50} value to produce mitragynine-lever responding was 16mg/kg. The δ-, κ-, and μ-opioid receptor agonists SNC80, U69593, and morphine, respectively, produced no greater than 60% mitragynine-lever responding. The α_2 agonist lofexidine produced 74% mitragynine-lever responding; the α_2 antagonist yohimbine produced 40% mitragynine-lever responding. Yohimbine (3.2mg/kg) and naltrexone (0.032mg/kg) antagonized the mitragynine discriminative stimulus, i.e., increased its ED_{50} by 2- and 5-fold, respectively. Lofexidine (0.1mg/kg) reduced the ED_{50} of the mitragynine discriminative stimulus by 9-fold. In separate groups of rats discriminating either morphine (3.2mg/kg) or lofexidine (0.032mg/kg), mitragynine produced 72% morphine- and 100% lofexidine-lever responding (ED_{50}s=11 and 15mg/kg). In a separate group of rats discriminating the cannabinoid agonist THC (3.2mg/kg), mitragynine produced only 36% THC-lever responding. Mitragynine had comparable binding affinity at opioid and α_2 receptors in the micromolar range *in vitro*, and appeared to exhibit comparable μ-opioid and α_2 receptor agonist activity *in vivo*. By combining two separate pharmacologies in a single drug entity which otherwise requires treatment with two or more FDA approved drugs (e.g., methadone and lofexidine), mitragynine and its analogs may represent a useful approach for treating opioid use disorders. Supported by NIDA grants DA23205 and DA48353.

Poster 73

New D3R partial agonists with an aryl linker motif

Cordone, Pierpaolo[1,5]; Gadhiya, Satish[1,4]; Reci, Dajana[1]; Gallicchio, Emilio[2,4,5]; Pal, Rajat K.[2,5]; Kurtzman, Tom[3]; and Harding, Wayne W.[1,4,5]

(1) Hunter College, New York, NY, USA (2) Brooklyn College, Brooklyn, NY, USA (3) Lehman College, New York, NY, USA (4) Ph.D. Program in Chemistry, The Graduate Center, City University of New York, NY, USA (5) Ph.D. Program in Biochemistry, The Graduate Center, City University of New York, NY, USA

The dopamine D3 receptor (D3R) is one of the most studied receptors involved in drug addiction. One of the most common strategies to treat substance use disorders is via D3R antagonism. The majority of the D3R antagonists synthesized so far have poor pharmacokinetic properties and/or lack selectivity toward D3R. A new series of D3R ligands was designed and synthesized. This series contains a classical D3R pharmacophore comprising an amine-containing "head" moiety, a hydrocarbon linker "body" and an arylamide "tail" region. Variations in the tetrahydroisoquinoline-containing "head" motif and the arylamide "tail" region were examined. Meanwhile, in the hydrocarbon linker region an aryl ring was introduced. This series of analogues was subjected to binding and functional activity assays at dopamine receptors (D1R-D5R) in vitro. Data from this structure-activity relationship (SAR) study indicates that the introduction of an aryl moiety in the linker portion was beneficial for D3R affinity. D3R affinity was found to be sensitive to substitutions in the tail region and in the head region. A number of ligands with high D3R affinity (K_i = 1-5 nM) and selectivity (>20-fold) versus other dopamine receptors were identified. TANGO functional assays showed that these compounds function as D3R partial agonists. These compounds are interesting leads for further development as potent, selective and bioavailable experimental therapeutics that target D3R.

Poster 74

Tolerance to opioid-induced respiratory depression in female and male rats

Carlson, Erika R.[1]; Marchette, Renata C.N.[1]; Vendruscolo, Janaina C.M.[1]; Lewis, Stephen J.[2]; Hampson, Aidan[3]; Volkow, Nora D.[4]; Koob, George F.[1]; and Vendruscolo, Leandro F.[1]

[1]Neurobiology of Addiction Section, Integrative Neuroscience Branch, NIDA-IRP, Baltimore, MD USA; [2]Department of Pediatrics, Case Western Reserve University, Cleveland, OH USA; [3]Division of Pharmacotherapeutic Development, NIDA, Rockville, MD USA; [4]Laboratory for Neuroimaging, NIAAA-IRP, Bethesda, MD USA.

Respiratory depression is a dangerous effect of opioid misuse, and the main cause of death in cases of overdose. Therefore, we sought to characterize the respiratory depression induced by heroin and fentanyl in male and female rats. Catheters were implanted in the right jugular vein of Long-Evans rats. After recovery, rats were tested via whole-body plethysmography, a non-invasive procedure to measure multiple breath-by-breath respiratory parameters in awake, freely moving animals. After habituation to the plethysmography chambers, rats received a single intravenous bolus infusion of heroin (600 µg/kg) or fentanyl (25 µg/kg). We recorded respiration for 90 min post-infusion. This test was repeated two and five weeks later to test for the development of tolerance. Heroin induced a prolonged (60 min) respiratory depression characterized by an increased inspiratory time, decreased tidal volume (volume of air inhaled per breath) and decreased minute ventilation (volume of air inhaled per minute) compared to baseline values in both males and females. Fentanyl produced the same changes in respiration, but with a significantly shorter duration (30 min). Development of tolerance to the respiratory depression induced by opioids was observed in both sexes during the repeated tests, but the effect was less prominent in females. These results suggest that a single infusion of heroin and fentanyl produced a robust respiratory depression. With repeated infusions, the respiratory depression is subject to tolerance development.

Acknowledgements: This work was funded by NIDA-IRP.

Poster 75

Acute and sub-chronic effects of LSD in preclinical assessments of anxiety behavior

Conway, Catherine N. [1]; Baker, Lisa E. [1]

[1]Department of Psychology, Western Michigan University, Kalamazoo, MI USA

Recent developments in clinical research indicate positive psychotherapeutic effects of psychedelic drugs in some instances of severe anxiety or treatment-resistant depression. Although preclinical investigations with animal models are a necessary component to characterizing and predicting therapeutic drug effects, few studies have investigated psychedelics in established animal models predictive of anxiety. The current study implemented a light/dark test to assess the acute effects of LSD and an elevated plus maze (EPM) to assess the effects of brief intermittent LSD treatment. It was hypothesized that acute treatment would produce anxiogenic effects, particularly at higher doses, but that intermittent treatment with low doses might produce anxiolytic effects. Forty-eight adult male Sprague-Dawley rats were randomly assigned to receive a single acute injection of saline or one of three LSD doses (0.02, 0.04, 0.08 mg/kg) 15 min prior to placement into a light/dark test chamber for 5 min while entries into and time spent in each compartment were automatically recorded. Rats continued to receive the aforementioned treatments every other day for a total of six injections. Following a 48 or 72 hour drug washout, each rat was assessed in the EPM for 5 min. Videorecorded EPM tests were analyzed with Anymaze®. Acute LSD effects in the light/dark box were indicative of anxiogenic effects. EPM test results indicate a nonsignificant decrease in both closed and open arm entries following LSD treatment and do not support the hypothesis that brief intermittent exposure to LSD has anxiolytic effects. Findings are consistent with a recent report of mild anxiogenic effects following subchronic intermittent microdoses of psilocin and ketamine in the EPM test. In consideration of positive therapeutic effects in clinical trials with psychedelic drugs, development of appropriate preclinical models is essential to understanding the behavioral and biological mechanisms underlying their putative therapeutic effects.

Poster 76

Evidence of perturbed sleep architecture during alcohol withdrawal in a rodent model of alcohol dependence

Brandner, Adam J.[1]; Vendruscolo, Leandro F.[1]; Koob, George F.[1]; and Schmeichel, Brooke E.[1]

[1]Neurobiology of Addiction Section, Integrative Neuroscience Research Branch, National Institute on Drug Abuse, Baltimore, Maryland 21224.

Alcohol acts as a sedative, resulting in shortened sleep onset latency (SOL), increased slow – wave sleep (or non – rapid eye movement; NREM) and suppression of REM sleep. Sleep disturbances observed with chronic use of alcohol include extended SOL, decreases in quality of restful NREM sleep and increases in fragmented REM sleep. Sleep disruptions are higher among people with alcohol use disorders (AUD) compared to non-AUD, particularly during alcohol withdrawal. The present study sought to evaluate the effects of chronic alcohol exposure on sleep architecture during acute and protracted withdrawal in an animal model of alcohol dependence. Eight male and four female, Wistar rats were implanted with radio telemetry devices and subsequently made dependent to alcohol via chronic, intermittent alcohol vapor exposure. Electroencephalogram (EEG) and electromyogram (EMG) data were collected during the light cycle (12h total) before alcohol exposure (baseline), during acute withdrawal (6 – 12hr post-vapor) and through protracted abstinence (4 wk post-vapor). Alcohol-dependent male and female rats showed a significant reduction in percent time spent in REM sleep during acute withdrawal compared with baseline. Concurrently, the percent of time spent in Wake increased during acute withdrawal compared with baseline only in alcohol-dependent male rats. Percent of time spent in REM sleep recovered to baseline levels following protracted abstinence in both male and females, and percent time spent in wake only recovered to baseline levels in males. An increase in REM onset latency during acute withdrawal was also observed compared with baseline in males. Finally, there was an overall increase in activity during the acute withdrawal period when compared to baseline and protracted abstinence in both males and females. The overall quality of sleep resulting from chronic alcohol exposure during acute withdrawal was significantly perturbed.

Poster 77

Individual differences in chronic pain patients with high and low opioid misuse risk

Lazaridou, A.[1]; Paschali, M.[1]; Dorado, K .[1]; Papianou, L. [1]; Burzinski, C. [2]; Garland, E. [3]; Zgierska, A [2]; and Edwards, R. R. [1]

[1] Brigham and Women's Hospital/Harvard Medical School, Department of Anesthesiology, Perioperative, and Pain Medicine, [2] University of Wisconsin-Madison, School of Medicine and Public Health, Department of Family Medicine and Community Health, [3] University of Utah, College of Social Work

There is increasing concern among healthcare providers and pain clinics about the use of opioids for chronic pain. The aim of this study was to investigate the psychological factors and sensitivity to pain in patients at risk of misusing their opioid medication. One hundred sixty (N = 160) patients with chronic low back pain taking opioids for pain were recruited into the study. All patients completed baseline psychological measures including the HADS-anxiety, HADS-depression, Pain Catastrophizing Scale (PCS), MAAS (Mindful Attention Awareness Scale), Brief Pain Inventory (BPI) and Current Opioid Misuse Measure (COMM). In addition, patients underwent Quantitative Sensory Testing (QST) using punctuated pressure probes. Patients were divided into two groups based on their report of current opioid misuse (high COMM score >9). Independent group tests (Mann-Whitney tests) were used to explore differences between the groups. Patients with high COMM scores had increased depression, anxiety, pain catastrophizing, pain interference, decreased trait-mindfulness ($p<0.001$), and lower pain thresholds during QST ($p<0.05$) compared to low COMM patients. This study demonstrates the important role of monitoring psychological factors among patients with chronic pain who are prescribed opioid medication for pain. In addition, QST might be a valuable tool assessing objective pain thresholds in patients at high risk of abusing their opioid medication. Future longitudinal studies should explore the day-to-day fluctuations of psychological factors and pain thresholds as a function of opioid use.

Poster 78

The impact of alcohol on aggressive displays in *Betta splendens*

Lewis, Kendyl C.; Driver, Emma E.; Drives, Maddie; Guerrant, Carly; Hughes, Ava; Purcell, Jessica; and Dandy, Kristina L.

Department of Psychology, Georgia College & State University, GA USA

The aggressive displays of *Betta splendens* have been studied heavily and are well known (e.g., Shapiro & Jensen, 2009). However, the effects of alcohol on these behaviors are less known. We examined the effects of alcohol on aggressive displays prior to and following exposure to a startling stimulus in the form of a marble drop (Arnott & Elwood, 2009). We predicted that aggressive displays would be impacted by the startling stimulus and moderated by alcohol administration. We tested ten experimentally naive male *Betta* fish, which were randomly assigned to a group that received either 0.00% or 0.50% alcohol. The subjects were dosed in their assigned solutions for five minutes daily for 7 days prior to testing. Testing was conducted once daily for 5 consecutive days. On testing days, subjects were dosed immediately before each trial. In each trial, fish were presented with a mirror for 15s, followed by exposure to the startling stimulus, then given 15s to engage with the mirror. Aggressive displays were recorded and coded. Results of a series of 2x2 ANOVAs revealed that post-marble drop, alcohol fish displayed significantly more air gulps than saline treated fish, $F(1,8), = 14.440$, $p = .005$. Further, post hoc analyses revealed that alcohol treated fish showed significantly more air gulps post-marble drop than pre-marble drop ($p < .05$). Results also revealed gill extension occurred significantly more post-marble drop than pre-marble drop ($F(1,8) = 16$, $p = .004$) and was not impacted by alcohol administration. Enhanced gill extension post-marble drop appears to be a true startle response regardless of alcohol administration. Our results offer promising findings that contribute to our general knowledge of factors that influence aggressive displays in *Betta* fish, specifically how substances of abuse impact aggressive displays.

Poster 79

Assessment of interactive antinociceptive effects of oxycodone combined with kappa opioid agonists of varying intracellular signaling profiles in rats

Zamarripa, C.A.[1]; Pareek, T. [1]; Prisinzano, T.E.[2]; Blough, B.E.[3]; and Freeman, K.B.[1]

[1] Program in Neuroscience, Department of Psychiatry and Human Behavior, The University of Mississippi Medical Center, Jackson, MS; [2]University of Kentucky, Lexington, KY; [3]RTI, NC

Aim: Kappa-opioid receptor (KOR) agonists, when combined with mu-opioid receptor (MOR) agonists, have been shown to reduce the reinforcing effects and enhance the antinociceptive effects of MOR agonists. Recently, chemists have developed KOR agonists that exhibit atypical signaling profiles (e.g., "bias" for G-protein signaling) and reduced KOR-typical side effects. Here, we tested a series of KOR agonists reported to vary in terms of signaling bias in combination with oxycodone in a test of thermal antinociception. Methods: Using the hot plate approach, male Sprague-Dawley rats (n=6) received injections of intravenous oxycodone (0.32-5.6 mg/kg), U50,488h (1.0-18.0 mg/kg), nalfurafine (0.01-1.0 mg/kg), or triazole 1.1 (3.2-32.0 mg/kg) in separate, counterbalanced tests, and response latencies were measured. ED_{50} values and 95% confidence intervals were calculated using linear regression and used to identify and test 3:1, 1:1, and 1:3 effect-ratio combinations of oxycodone and each KOR agonist. Dose-addition analysis was used to compare predicted ED_{50} values (Zadd) with experimentally determined ED_{50} values (Zmix) for each combination. Results: All drugs were equi-effective but varied in potency, yielding a potency order of: Nalfurafine > Oxycodone > U50,488h = Triazole 1.1. All combinations were found to produce full thermal antinociception, and dose-addition analysis revealed synergistic effects at the 1:1 and 1:3 ratios of oxycodone combined with nalfurafine and triazole 1.1, respectively. No interactive effects were observed with combinations of oxycodone and U50,488h. Conclusion: This study demonstrates that biased KOR agonists may enhance the antinociceptive effects of MOR agonists to a greater degree than unbiased KOR agonists.

Poster 80

Rethinking sensation seeking: Indirect effects predicting marijuana use through externalizing/internalizing behavior, moderated by impulsivity

Wasserman, Alexander M.; Shaw-Meadows, K.; Mathias, Charles W.; Hill-Kapturczak, Nathalie; Karns-Wright, Tara; and Dougherty, Donald M.

The University of Texas Health Science Center at San Antonio

The dual systems model posits that the relatively earlier development of sensation seeking compared to the more protracted development of impulse control is the impetus for the rise in adolescent risk taking. While there is strong support that high levels of sensation seeking are related to risk behavior, it remains untested whether low levels of sensation seeking are also problematic. In this study, we examined the possibility that both high and low levels of sensation relate to substance use, albeit through different mechanisms. Overall, the goal of the present study was to present mechanisms (through externalizing and internalizing behavior) by which sensation seeking relates to marijuana use.

The study sampled 342 adolescents and measures used include impulsivity and sensation seeking at age 13, externalizing and internalizing behavior ages 13–16, and time-to-event for marijuana use initiation ages 13–16. Growth curve models were estimated for the time-varying assessments of externalizing and internalizing behavior and a survival analysis was estimated for the marijuana use initiation.

For the externalizing behavior model, the interaction between impulsiveness and sensation seeking (SS) was significant such that higher levels of SS predicted the externalizing behavior intercept factor, but only at high levels of impulsiveness. SS also directly predicted earlier marijuana use initiation and indirectly through the externalizing behavior intercept factor. For the internalizing behavior model, the interaction between impulsivity and SS was significant such that lower levels of SS predicted higher internalizing behavior, but only at low levels of impulsiveness. *Higher* SS also directly predicted earlier marijuana use initiation and *lower* SS indirectly predicted earlier marijuana use initiation through higher levels of internalizing.

Poster 81

Opioid Epidemic and MAT program efficacy in a community-based psychiatric clinic

Agrawal, Shireen[1]; Pradeep, Kumar[2]; Suresh, Kumar[3]; Shalin, Shah S. Shalin[4]; Gupta, Ritika[5]; and Yunus, Farhodov Muhammad[6]

Young Scientists of America, Plano Behavioral Health Clinic, Headache TBI and Memory Clinic

The opioid epidemic and challenges to combat addiction still remain a national crisis even after the medicated-assisted treatment program (MAT) has been identified as the FDA-approved delivery system for ideal rehabilitation. This study was conducted to observe the true efficacy of the MAT program while also taking into account comorbidity in patients affected by mood disorders such as general anxiety disorder and major depressive disorder.
Past data shows that opioid dependence and mood disorders may be associated. Hence, the presence of the mood disorders observed would manipulate the efficacy of the MAT program. Additionally, the efficacy of the MAT program per patient would decrease with lower number of visits and any lack of adherence to prescriptions. This retrospective study, which spans nine years, consists of 148 patients diagnosed with opioid-dependence (code F11.20) that were prescribed a combination opioid partial agonist (buprenorphine) and antagonist (naloxone) medication while simultaneously receiving counseling sessions per visit in a community-based psychiatry clinic. The measure of efficacy was defined by the number of relapses per patient as well as drug test results.
Results: ANOVA studies showed MDD patient population had a higher relapse rate compared to no significant difference in GAD patient population. The frequency or adherence to clinic visit patient population showed less relapse compared to the non-compliant patients. Linear regression analysis showed that every clinic visit decreased the relapse rate by 0.67%.
The MAT program in out-patient care is effective in facilitating patients, even those subject to comorbidity due to simultaneous presence of mood disorders and opioid use disorder, to fully reverse the effects of opioids.

Poster 82

Discriminative stimulus effects of mu opioid receptor agonists in rats discriminating fentanyl: differential antagonism by naltrexone

Flynn, Shawn[1]; and France, Charles P.[1,2]

[1]Department of Pharmacology, UT Health San Antonio; [2]Addiction Research, Treatment & Training Center of Excellence

The opioid crisis continues despite the availability of medications that are effective in some patients. A significant number of deaths caused by opioids involve fentanyl and/or one of its very potent analogues (e.g., carfentanil). Many fentanyl analogs have not been studied extensively in vivo. The current study compared the discriminative stimulus effects of fentanyl and carfentanil and their antagonism by naltrexone. Seven male Sprague-Dawley rats were trained to discriminate a 0.01 mg/kg fentanyl from saline while responding under a fixed-ratio 10 schedule of food presentation. Dose effect curves were determined for the opioid receptor agonists alone: fentanyl (0.001-0.1 mg/kg) and carfentanil (0.0001-0.0032 mg/kg). Dose effect curves for fentanyl and carfentanil were then redetermined following a 15-minute pretreatment with 0.1 mg/kg naltrexone. All drugs were delivered intraperitoneally. Fentanyl and carfentanil dose-dependently increased responding on the fentanyl-associated lever and at larger doses decreased the rate of lever pressing. Carfentanil was approximately 10-fold more potent than fentanyl at eliciting >90% responding on the fentanyl-associated lever. Pretreatment with 0.1 mg/kg naltrexone shifted the fentanyl dose-effect curve 10-fold rightward whereas the same dose of naltrexone shifted the carfentanil curve only 3-fold rightward. Differences in the effectiveness of naltrexone to attenuate the discriminative stimulus effects of fentanyl and carfentanil suggests that there may be differences in how fentanyl and carfentanil exert their discriminative stimulus effects. Further evaluation of potential pharmacological and behavioral differences between fentanyl and carfentanil is needed and might provide important insights regarding the apparently increased toxicity of carfentanil, compared with other opioids, in humans.

Poster 83

Potential G-Protein biased ligands with nitrogen-containing substituents at C9 in the 5-(3-hydroxyphenyl)morphan class of opioids

Roth, Hudson G.[1]; Sulima, Agnieszka[1]; Bow, Eric W.[1]; Jacobson, Arthur E.[1]; and Rice, Kenner C.[1]

[1]Drug Design and Synthesis Section, Molecular Targets and Medications Discovery Branch, Intramural Research Program, National Institute on Drug Abuse and the National institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Department of Health and Human Services, 9800 Medical Center Drive, Bethesda, MD 20892-3372, United States

Medicinal chemists have long sought to develop opioids that are capable of inducing analgesia without harmful side effects such as dependence or respiratory depression. The opioid crisis facing the United States today emphasizes the importance of this endeavor. One theory for how this could be achieved is by designing opioids that behave as agonists toward the μ-opioid receptor (MOR) without recruiting the regulatory protein β-arrestin-2, as the latter is proposed to play a role in the manifestation of the negative side effects associated with opioids. Our group has shown that derivatives of the 5-(3-hydroxyphenyl)morphan class of opioids containing an *N*-phenethyl moiety can display such bioactivity. In order to further develop a library of such compounds and assess their potential, we have synthesized a variety of 5-(3-hydroxyphenyl)-*N*-phenethylmorphan derivatives containing nitrogen-bearing substituents at the C9-position for pharmacological evaluation. As there is currently no way to accurately predict what compounds will behave as G-protein biased ligands, each variation at the C9-position requires the synthesis of four distinct diastereomers due to the presence of three centers of asymmetry in this simple class of molecules, two of which are set based on the 5-(3-hydroxyphenyl)morphan employed as the precursor.

Poster 84

Evaluation of schedule-controlled responding in mice with chemotherapy induced peripheral neuropathy

Bilbrey, Joshua A.[1]; Felix, Jasmine S.[1]; Luque-Sanchez, Kevin S.[1]; McMahon, Lance R.[1]; and Wilkerson, Jenny L.[1]

[1]Department of Pharmacodynamics, University of Florida, Gainesville, FL USA.

Due to the continued severity of the opioid abuse epidemic, the need for better pathological pain treatments with diminished abuse liability is more urgent than ever. Unfortunately, the current methods used for examining preclinical pain are fraught with pitfalls, such as false positive results, and must evolve. To elucidate the relationship between neuropathic pain and behaviors aside from sensitivity to light touch, we utilized schedule-control responding in mice. Male C57bl/6 mice were trained on a scheduled-response regimen under a fixed-ratio of 5 and maintained at 90% of their initial body weight. Once stable response rates (i.e., ± 20% of the three-day average) were achieved in 3 consecutive sessions a 4 dose course of paclitaxel was administered and response rates were examined. Elevated response rates were observed initially in the paclitaxel subjects compared to those receiving vehicle. Another relationship examined was between food restriction and mechanical allodynia. The von Frey assay was used to compare the resultant mechanical allodynia of food restricted mice to a matched group of non-food restricted mice receiving paclitaxel or vehicle. The non-food restricted mice receiving paclitaxel developed mechanical allodynia compared to those receiving vehicle. Trends toward decreased sensitivity to mechanical stimuli were observed in food restricted paclitaxel mice compared to non-food restricted paclitaxel mice. These experiments show interesting relationships between newly onset neuropathic pain, schedule-controlled behavior, and mechanical allodynia. Specifically, here we show that immediately following a course of chemotherapy, mice respond at higher rates for food reinforcement. These findings may have important ramifications in the evaluation of novel treatments for neuropathic pain that possess diminished abuse liability.

2020 Behavior, Biology, and Chemistry: Translational Research in Addiction Attendees

Megan Abbott
UT Health San Antonio
abbottm@livemail.uthscsa.edu

Ross Armant
University of Texas at Arlington
ross.armant@mavs.uta.edu

Madeline Beasley
American University
mb3258a@student.american.edu

Kelly Berg
UT Health San Antonio
berg@uthscsa.edu

Bruce Blough
RTI International
beb@rti.org

Kathleen Borgmann
University of North Texas Health Science Center
kathleen.borgmann@unthsc.edu

Harley Buechler
Rowan University
buechlerh3@rowan.edu

Theresa Carbonaro
Drug Enforcement Administration
theresa.m.carbonaro@usdoj.gov

Gabriel Castaneda
UT Health San Antonio
gabrielcastaneda02@hotmail.com

Gregory Collins
UT Health San Antonio
collinsg@uthscsa.edu

Andrew Coop
University of Maryland, Baltimore
acoop@rx.umaryland.edu

Morgan Crowley
University of Florida
morgancrowley@ufl.edu

Kristina Dandy
Georgia College & State University
kristina.dandy@gcsu.edu

Fernando de Moura
Harvard Medical School/McLean Hospital
fmoura@mclean.harvard.edu

Cindal Dominguez
UT Health San Antonio
dominguezc3@uthscsa.edu

Shireen Agrawal
Plano Behavioral Health, PLLC
hellopkumar@yahoo.com

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

Jasmin Beaver
Kent State University
jbeave18@kent.edu

Sanaya Bharadia
University of Michigan
bharadia@umich.edu

Comfort Boateng
High Point University
cboateng@highpoint.edu

Adam Brandner
National Institute on Drug Abuse
abrandner13@gmail.com

Cara Bussell
Norton Sound Health Corporation
Cabussell@nshcorp.org

Astrid Cardona-Acosta
Texas A&M University
astrid@tamu.edu

Samuel Castillo
University of Texas at El Paso
sacastillo7@miners.utep.edu

Catherine Conway
Western Michigan University
catherine.n.conway@wmich.edu

Pierpaolo Cordone
Hunter College, CUNY
pcordone29@gmail.com

Bryan Cruz
University of Texas at El Paso
bcruz2@miners.utep.edu

Monica Dawes
Harvard Medical School/McLean Hospital
mdawes@mclean.harvard.edu

Matthew Deande
UT Health San Antonio
deandehaney@uthscsa.edu

Juan Dominguez
University of Texas at Austin
dominguez@utexas.edu

Dalal Alkhelb
Northeastern University
alkhelb.d@husky.neu.edu

Francisco Battiti
National Institute on Drug Abuse
francisco.battiti@nih.gov

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

Joshua Bilbrey
University of Florida
joshuabilbrey@ufl.edu

Carlos Bolanos
Texas A&M University
bolanos@tamu.edu

Daniel Bryant
Community Health Center, Inc.
bryantd@chc1.com

Jennifer Campbell
UT Health Science Center Tyler
jennifer.campbell@uthct.edu

Erika Carlson
National Institute on Drug Abuse
erika.carlson@nih.gov

Bill Clarke
UT Health San Antonio
clarkew@uthscsa.edu

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

Rebecca Craft
Washington State University
craft@wsu.edu

Paul Czoty
Wake Forest University
pczoty@wakehealth.edu

Lynette Daws
UT Health San Antonio
daws@uthscsa.edu

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

Alison Domzalski
CUNY Hunter College
adomzalski@gradcenter.cuny.edu

2020 Behavior, Biology, and Chemistry: Translational Research in Addiction Attendees

Marie Doyle
Michigan State University
doylema8@msu.edu

Michelle Doyle
UT Health San Antonio
doylemr@livemail.uthscsa.edu

Emma Driver
Georgia College & State University
emma.driver@bobcats.gcsu.edu

Madeline Elsey
University of Texas at El Paso
elseymadeline@gmail.com

Sophie Elvig
National Institute on Drug Abuse
sophie.elvig@nih.gov

Veronika Espinoza
University of Texas at El Paso
vespinoza12@miners.utep.edu

Suzette Evans
Columbia University
se18@cumc.columbia.edu

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

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

Troy D Fort
Kansas State University
tfort1346@ksu.edu

Charles France
UT Health San Antonio
france@uthscsa.edu

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

Ewa Galaj
National Institute on Drug Abuse
ewa.galaj@nih.gov

Lindsey Galbo
Wake Forest University
lgalbo@wakehealth.edu

Kayla Galindo
University of Texas at El Paso
kihinson@miners.utep.edu

Anghelo Gangano
Concordia University Wisconsin
anghelo.gangano@cuw.edu

Brenda Gannon
Mercer University College of Pharmacy
gannon_bm@mercer.edu

Israel Garcia-Carachure
University of Texas at El Paso
igarciacar@miners.utep.edu

Michael Gatch
University of North Texas Health Science Center
michael.gatch@unthsc.edu

Lisa Gerak
UT Health San Antonio
gerak@uthscsa.edu

Saba Ghodrati
UT Health San Antonio
sabaghodratiii@gmail.com

Lee Gilman
Kent State University
tgilman@kent.edu

Priscilla Giner
University of Texas at El Paso
pginer@miners.utep.edu

Brett Ginsburg
UT Health San Antonio
ginsburg@uthscsa.edu

Cassandra Gipson-Reichardt
Arizona State University
cgipsonr@asu.edu

Rajan Giri
The Graduate Center, CUNY
rgiri@gradcenter.cuny.edu

Emma Gogarnoiu
National Institute on Drug Abuse
emma.gogarnoiu@nih.gov

Georgianna Gould
UT Health San Antonio
gouldg@uthscsa.edu

Adriana Gregory Flores
National Institute on Drug Abuse
adriana.gregory-flores@nih.gov

Roland Griffiths
Johns Hopkins University
rgriff@jhmi.edu

Ghali Haddad
University of Mississippi Medical Center
ghaddad@umc.edu

Emily Hilz
University of Texas at Austin
ehilz@utexas.edu

Takato Hiranita
University of Florida
takatohiranita@cop.ufl.edu

Adam Hoch
University of North Texas Health Science Center
adam.hoch@unthsc.edu

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

Victor Jimenez Jr
UT Health San Antonio
jimenezv1@uthscsa.edu

Bernard Johnson
Wake Forest University
berjohns@wakehealth.edu

Chad Johnson
University of Maryland, Baltimore
cjohn167@umaryland.edu

Yuanyuan Kang
University of Houston
kangy@uhd.edu

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

David Kearns
American University
kearns@american.edu

Thomas Keck
Rowan University
keckt@rowan.edu

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

Wouter Koek
UT Health San Antonio
olsonl@uthscsa.edu

Saurabh Kokane
University of Texas at Arlington
saurabh.kokane@mavs.uta.edu

Therese Kosten
University of Houston
takosten@uh.edu

Thomas Kosten
Baylor College of Medicine
kosten@bcm.edu

Anjali Kumari
North Carolina Agricultural and Technical State University
akumari@aggies.ncat.edu

Asimina Lazaridou
Brigham and Women's Hospital
alazaridou@bwh.harvard.edu

Kendyl Lewis
Georgia College & State University
kendyl.lewis@bobcats.gcsu.edu

Jingfei Li
University of Chicago
jingfei@uchicago.edu

Jianfeng Liu
Texas A&M University
jianfengliu@tamu.edu

Oanh Luc
Harvard Medical School/McLean Hospital
oanhtluc@gmail.com

Steve Mabry
University of North Texas Health Science Center
smabry14@gmail.com

Charlotte Magee
University of Utah
charlotte.magee@utah.edu

David Maguire
UT Health San Antonio
maguired@uthscsa.edu

Mariia Makarova
National Institute on Drug Abuse
makarovam2@nih.gov

Hayley Manke
American University
hm2522a@student.american.edu

Peter Manza
National Institute on Alcohol Abuse and Alcoholism
peter.manza@nih.gov

Renata Marchette
National Institute on Drug Abuse
renata.marchette@nih.gov

Michelle Martínez
University of Texas at El Paso
mmartinez77@miners.utep.edu

Julia Martz
University of Texas at Austin
jmartz440@gmail.com

Briana Mason
UT Health San Antonio
briana_mason@live.com

Liliana Maynez-Anchondo
University of Texas at El Paso
lmaynezanc@miners.utep.edu

Erin McClure
Medical University of South Carolina
mccluree@musc.edu

Lance McMahon
University of Florida
lance.mcmahon@cop.ufl.edu

Ashleigh Morgan
UT Health San Antonio
morgana1@livemail.uthscsa.edu

Rithi Mulgaonker
University of Texas Dell at Austin
rithi.mulgaonker@utexas.edu

Michael Nader
Wake Forest University
mnader@wakehealth.edu

Katharine Nelson
American University
kn9165a@student.american.edu

Christina Norman
Wake Forest University
nlnorman@wakehealth.edu

Samuel Obeng
University of Florida
obengs@cop.ufl.edu

Samantha Ortiz Vanderhoof
Kent State University
sortiz2@kent.edu

Myrella Paschali
Brigham and Women's Hospital
mpaschali@bwh.harvard.edu

Avi Patel
University of Florida
apatel98@ufl.edu

Tilak Patel
University of Mississippi Medical Center
patelrtilak@gmail.com

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

Nishita Pondugula
University of Texas at Austin
nishita.pondugula@gmail.com

Jennifer Potter
UT Health San Antonio
potterjs@uthscsa.edu

Cana Quave
UT Health Houston
cana.quave@uth.tmc.edu

Atiqur Rahman
Rowan University
rahmanm2@rowan.edu

Morgan Reeves
University of Florida
morgan.reeves@cop.ufl.edu

Harmony Risca
Western Michigan University
harmony.i.risca@wmich.edu

John Roache
UT Health San Antonio
olsonl@uthscsa.edu

Andrea Rodriguez-Crespo
University of Texas at El Paso
arodricres98@gmail.com

Hudson Roth
National Institute on Drug Abuse
hudson.roth@nih.gov

Lauren Russell
University of Arkansas for Medical Sciences
lnrussell@uams.edu

Lauren Rysztak
University of Michigan
lrysztak@umich.edu

Oscar Sandoval
University of Texas at El Paso
osandoval4@miners.utep.edu

Karl Schmidt
Davidson College
kaschmidt@davidson.edu

2020 Behavior, Biology, and Chemistry: Translational Research in Addiction Attendees

Robert Seaman Jr
UT Health San Antonio
seamanr3@livemail.uthscsa.edu

Jessica Sharp
Davidson College
Jesharp@davidson.edu

Ali Stark
Michigan State University
starkal4@msu.edu

Anapaula Themann
University of Texas at El Paso
athemann@miners.utep.edu

Drew Townsend
Virginia Commonwealth University
s52drew@gmail.com

Andres Vasquez
Rice University
av52@rice.edu

Alexander Wasserman
UT Health San Antonio
wassermana@uthscsa.edu

Ruyan Wu
SUNY At Buffalo
ruyanwu@buffalo.edu

Austin Zamarripa
University of Mississippi Medical Center
czamarippa@umc.edu

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

Omar Sial
Texas A&M University
omarsial@tamu.edu

Justin Strickland
Johns Hopkins University
jstric14@jhmi.edu

Julia Tobacyk
University of Arkansas for Medical Sciences
julia.tobacyk@gmail.com

Aaron Tryhus
Wake Forest University
atryhus@wakehealth.edu

George Ward
National Institute on Drug Abuse
george.ward@nih.gov

Cora Lee Wetherington
National Institute on Drug Abuse, Retired
coraleewetherington@gmail.com

Qiying Ye
University of California Irvine
yeeyingyip@gmail.com

Julio Zuarth Gonzalez
University of Florida
jzuarthgonzalez@ufl.edu

Mark Shapiro
UT Health San Antonio
shapirom@uthscsa.edu

Mark Smith
Davidson College
masmith@davidson.edu

Mousumi Sumi
Rowan University
sumimo73@students.rowan.edu

Andrew Tourigny
University of North Texas Health Science Center
Andrew.Tourigny@unthsc.edu

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

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

Kristen Woodhouse
University at Buffalo
kwoodhou@buffalo.edu

John Yi
University of Mississippi Medical Center
jyi@umc.edu

Notes

Notes

Notes

Available Positions

Research Assistant Positions – Behavioral Biology
Harvard Medical School/McLean Hospital

Research assistant positions are available in the Behavioral Biology Program at McLean Hospital/Harvard Medical School. Ongoing research includes behavioral pharmacology, cognition biology, and multimodal neuroimaging (fMRI, MRS, DWI) projects involving integrated behavior/imaging using animal models of drug abuse and other psychiatric disorders. Project examples include:

1) evaluating role of drug history in behavioral and neural responses to abused drugs
2) identifying neural signatures associated with the behavioral effects of abused drugs
3) determining drug effects on neural, physiological, and cognitive endpoints
4) characterizing functional and anatomical circuits related to drug- and food-motivated behavior
5) in vivo evaluation of novel candidate medications for drug addiction and other psychiatric disorders

RESPONSIBILITIES

- Coordinate, schedule, and conduct daily experiments in laboratory animals to understand behavioral and neural correlates of drug action
- Transcribe, organize, and analyze data and prepare reports (with potential for authorship on research reports and conference presentations)
- Work co-operatively within in vivo lab setting, with ability to perform a range of routine tests
- Work safely (after training) within a magnetic resonance environment
- Identify potential technical problems in daily experiments and troubleshoot solutions

QUALIFICATIONS

- BS or BA related to life sciences/medicine (e.g., psychology, neuroscience, pharmacology, biology).
- Ability to prioritize duties and work in a relatively independent manner under the guidance of senior staff
- Good organizational skills and detail oriented

Please send inquiries with resume to:

Stephen J. Kohut, Ph.D.
McLean Hospital/Harvard Medical School
115 Mill Street,
Belmont, MA 02478
Email: skohut@mclean.harvard.edu

McLean Hospital, an affiliate of Harvard Medical School, is an Equal Opportunity Employer. It is the policy of McLean Hospital to affirmatively provide equal opportunity to all qualified applicants for employment and existing employees without regard to their race, religion, color, national origin, sex, age, ancestry, protected veteran status, disability, sexual orientation, gender identity or expression, or any other basis that would be in violation of any applicable law or regulation.

NIDA T32 Training Program
Postdoctoral Training in Drug Abuse Research: Behavior & Neurobiology
***** Postdoctoral Fellowship in Addiction Research*****

The University of Texas Health Science Center at San Antonio is seeking qualified, highly motivated applicants for a NIDA T32 Postdoctoral Training Program. Postdoctoral fellows receive interdisciplinary training across various laboratories and areas of expertise, taking advantage of the research diversity of participating faculty mentors, including molecular pharmacology, electrophysiology, neurochemistry, biochemistry, neuropharmacology, behavioral pharmacology, clinical trials, and human laboratory studies.

Program Benefits:

- Initial 1-year appointment, renewable for up to 3 years
- Research training with outstanding, well-funded investigators
- Career development opportunities including "Getting a Job Boot Camp"
- Fringe benefits including health care
- Large trainee community and support from the UT Health Office of Postdoctoral Affairs

Additional activities include:

- Seminars
- Journal clubs
- Opportunities to present at local (BBC) and national meetings
- Grant writing/reviewing workshops
- Career development workshops
- Community outreach activities

Eligibility: Applicants must possess a doctoral degree or equivalent and be a US Citizen, non-citizen national, or permanent resident of the US.

Application: Send curriculum vitae, letter of intent, and two letters of recommendation to drugabusetraining@uthscsa.edu (Charles P France, PhD, Program Director, Department of Pharmacology, University of Texas Health Science Center, 7703 Floyd Curl Drive, Mail Code 7764, San Antonio, TX 78229). For more information, please visit the NIDA T32 Training Program Website (http://uthscsa.edu/ARTT/T32/index.asp).

The University of Texas Health Science Center at San Antonio is an Equal Opportunity/Affirmative Action Employer, including protected veterans and persons with disabilities. All Postdoctoral appointments are designated as security sensitive positions. The project described is supported by Award Number T32DA031115 from the National Institute on Drug Abuse. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health.

Poster Index

Maharaj ("Raj") Ticku, PhD

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

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

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

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

Maharaj Ticku Memorial Travel Fellowship for New Investigators

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

See you at BBC 2021!

ARTT
Addiction Research, Treatment & Training
CENTER OF EXCELLENCE

UT Health
San Antonio