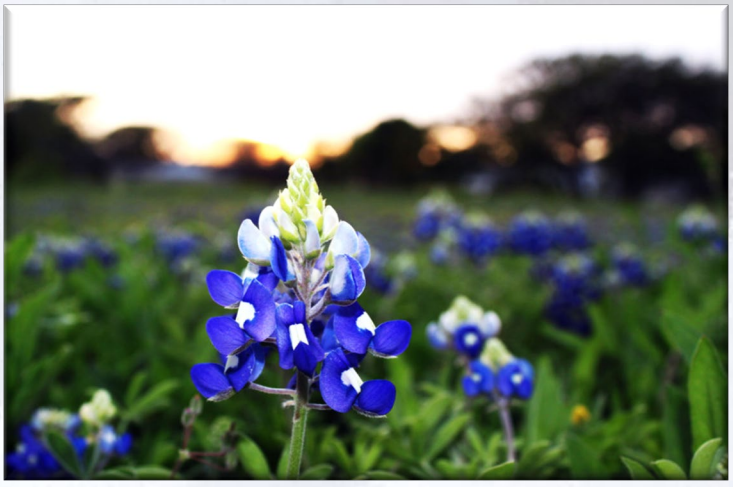
13TH ANNUAL BEHAVIOR, BIOLOGY, and CHEMISTRY:

Translational Research in Addiction

Virtual Event | Hopin | 5-7 March 2021



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BBC Publications

BBC 2011

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

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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

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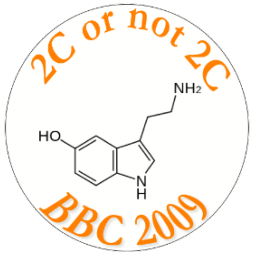
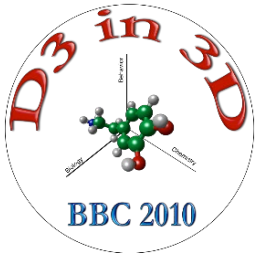
Bachtell RK, Jones JD, Heinzerling KG, Beardsley PM, Comer SD (2017) **Glial and neuroinflammatory targets for treating substance use disorders.** *Drug and Alcohol Dependence* 180, 156-70. PMC5790191





Acknowledgements

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Program Overview

FRIDAY 5 MARCH 2021

11:00 AM – 11:05 AM	**Welcome & Opening Remarks** – Charles France, Gregory Collins
11:05 AM – 11:35 AM	**Keynote Lecture:** Carlos Blanco (Chair: Juan Dominguez) *Interactions between substance use disorders and COVID-19: implications for research*
11:35 AM – 11:40 AM	Break
11:40 AM – 12:30 PM	**Featured Topics Presentations** (Chair: Vanessa Minervini) **Stephanie Strong** |Graduate Student | University of Southern Mississippi *Increased mood disorder symptoms, perceived stress, and alcohol use among college students during the COVID-19 pandemic* **Rodell Barrientos** | Postdoctoral Fellow | Henry M Jackson Foundation *Hapten design dictates molecular recognition of vaccine-induced antibodies to drugs of abuse* **Oanh Luc** | Other | McLean Hospital *Effects of ketamine on reward sensitivity in healthy and chronically-stressed rats* **Kimberly Holter** | Graduate Student | Wake Forest School of Medicine *Sex differences in sleep architecture and brain function observed following administration of NMDAR antagonist MK-801* **Nikki Clauss** | Postdoctoral Fellow | UT Health San Antonio *Role of organic cation transporter 3 in the rewarding properties and locomotor sensitizing effects of amphetamine in male and female mice* **Emily Hilz** | Graduate Student | University of Texas at Austin *Modulation of the estrous cycle by hormonal contraceptives influences amphetamine preference and dopamine activity in female rats*
12:30 PM – 1:55 PM	**Interactive Q&A – Video Presentations Viewing**
1:55 PM – 2:00 PM	Break
2:00 PM – 3:00 PM	**Pathways to Career in Science Workshop**

SATURDAY 6 MARCH 2021

11:00 AM – 11:05 AM	**Welcome & Introduction of Speakers** – Gregory Collins
11:05 AM – 11:35 AM	**Keynote Lecture:** Patricia Janak (Chair: Annette Fleckenstein) *Subcortical brain circuits gate motivation: implications for addiction*
11:35 AM – 11:40 AM	Break
11:40 AM – 12:30 PM	**Featured Topics Presentations** (Chair: Alison Wakeford) **Justin Strickland** | Postdoctoral Fellow | Johns Hopkins University School of Medicine *Quit discounting: sensitivity to health messages and substance cessation prediction* **Kathleen McNealy** | Graduate Student | University of Nebraska-Lincoln *Sex differences and effects of drug exposure order on the reward-enhancing effects of co-administered nicotine and d-amphetamine* **Jessica Proulx** | Graduate Student | University of North Texas Health Science Center *ER-associated regulation of astrocyte mitochondrial function during (METH)amphetamine exposure* **Faiyaz Omerjee** | Graduate Student | California State University, Long Beach *Adolescent Sprague Dawley rats exhibit context-dependent sensitization to low doses of METH while preweanling rats do not in a one-trial paradigm* **Hayley Manke** | Graduate Student | American University *Effects of a novel tamoxifen-analogue (6C) on methamphetamine-induced neurotoxicity*
12:30 PM – 1:55 PM	**Interactive Q&A – Video Presentations Viewing**
1:55 PM – 2:00 PM	Break
2:00 PM – 3:00 PM	**Pathways to Career in Science Workshop**

SUNDAY 7 MARCH 2021

11:00 AM – 11:05 AM **Welcome & Introduction of Speakers** – Gregory Collins

11:05 AM – 11:35 AM **Keynote Lecture:** Jean Bidlack (Chair: Comfort Boateng)
Pharmacological properties of the combination of samidorphan and buprenorphine

11:35 AM – 11:40 AM Break

11:40 AM – 12:30 PM **Featured Topics Presentations** (Chair: Lee Gilman)

Jory Crull | Graduate Student | Medical University of South Carolina
Patient-level perspectives on the use of novel psychotherapeutics for the treatment of substance use disorders

Hannah Alton | Undergraduate Student | McLean Hospital/Harvard Medical School
Serotonin 2A- or 2C-like discriminative stimulus effects of serotonin agonists in nonhuman primates

Hudson Roth | Postdoctoral Fellow | NIH/NIDA
Potential G-protein biased ligands with nitrogen-containing substituents at C9 in the 5-(3-Hydroxyphenyl)morphan class of opioids

Shawn Flynn | Graduate Student | UT Health San Antonio
Discriminative stimulus effects of mu opioid receptor agonist mixtures

Indu Mithra Madhurathakam | Graduate Student | Rowan University
Synergistic antihyperalgesic and antinociceptive effects of morphine and MP-III-024, a positive allosteric modulator at α2GABAA and α3GABAA receptors

Chad Johnson | Faculty | University of Maryland, Baltimore
Novel muscarinic antidepressants that lack cognitive deficits: some insights into key structural features of muscarinic agonists and antagonists

12:30 PM – 2:00 PM **Interactive Q&A – Video Presentations Viewing**

2:00 PM – 2:10 PM **Closing Remarks & Awards** – Brett Ginsburg, Charles France
*Award winners must be present to accept prize

See you at BBC 2022!

Featured Presentations

Featured Presentation 1-1

Hapten design dictates molecular recognition of vaccine-induced antibodies to drugs of abuse

Barrientos, Rodell C.[1,3]; Gutman, Eugene S.[2]; Irvin, Thomas C.[2]; Morgan, J. Brian[2]; Antoline, Joshua G.[2]; Li, Fuying[2]; Torres, Oscar B.[1,3]; Sulima, Agnieszka[2]; Whalen, Connor[1]; Oertel, Therese[1]; Komla, Essie[1,3]; Beck, Zoltan[1,2]; Jacobson, Arthur E.[2]; Rice, Kenner C.[2]; and Matyas, Gary R.[1]

[1]Laboratory of Adjuvant and Antigen Research, US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA; [2]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, USA; [3]Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA.

Active immunization is being explored as a potential therapeutic to combat opioid use disorders. Affinity and selectivity of antibodies are key to an efficacious vaccine. In 2014, the facial recognition hypothesis has been proposed by Matyas et al. to account for the cross-reactivity of antibodies to opioids and found that changing the linker attachment site in the hapten resulted in distinct selectivity. Herein, we tested this theory by exploring haptens with varying linker attachment site, C-1 and C-14, of the morphinan ring, to uncover the determinants of antibody recognition. Haptens were conjugated to tetanus toxoid and mixed with Army Liposome Formulation (ALF) adjuvant with or without aluminum salt. Sera were collected from immunized Balb/c mice and measured cross-reactivity to opioids and cognate therapeutic drugs using equilibrium dialysis. Results revealed that the face of the hapten distal from the linker site served as epitopes recognized by the antibodies. These findings reinforced the facial recognition hypothesis that varying the linker attachment site can be used as a strategy to tune the selectivity of antibodies to drugs of abuse.

Featured Presentation 1-2

Role of organic cation transporter 3 in the rewarding properties and locomotor sensitizing effects of amphetamine in male and female mice

Clauss, Nikki J.[1]; Koek, Wouter[2,3] and Daws, Lynette C.[1,3]

[1]Departments of Cellular and Integrative Physiology; [2]Psychiatry and Behavioral Sciences; and [3]Pharmacology, University of Texas Health Sciences Center at San Antonio, San Antonio, TX USA.

Strategies targeting the dopamine transporter have yielded little benefit in treating addiction to amphetamine or amphetamine-like psychostimulants, possibly due to significant action of these stimulants elsewhere to modulate dopaminergic transmission. Our recent studies support organic cation transporter 3 (OCT3) as a previously unsuspected player in the actions of amphetamine. Here we extend these findings. We used pharmacological (decynium-22 (D22; 0.1 mg/kg), a blocker of OCT3) and genetic (constitutive OCT3 knockout (-/-) mice) approaches to examine the role of OCT3 in mediating amphetamine (1 mg/kg)-induced conditioned place preference (CPP) and sensitization to its locomotor stimulant effects, in males and females. D22 attenuated amphetamine CPP in male and female OCT3+/+ mice; and in female OCT3-/- mice. OCT3-/- male mice did not develop CPP for amphetamine. Sensitization to the locomotor stimulant effects of amphetamine occurred in females regardless of pretreatment or genotype. Male mice did not develop statistically significant sensitization, regardless of pretreatment or genotype. Saline pretreated female OCT3+/+, but not OCT3-/-, mice given an acute injection of amphetamine showed a robust increase in locomotion, whereas male OCT3+/+ and OCT3-/- mice displayed only a modest increase in locomotor activity. D22 pretreatment did not affect the locomotor response to an acute injection of amphetamine in either sex or genotype. These data support OCT3 as a novel mechanism contributing to sex-dependent variation in the rewarding and locomotor stimulant effects of amphetamine-like drugs and have important implications for uptake-2 transporters as targets for therapeutic intervention in the treatment of amphetamine addiction.

Featured Presentation 1-3

Modulation of the estrous cycle by hormonal contraceptives influences amphetamine preference and dopamine activity in female rats.

Hilz, Emily N[1,2]; Olvera, Marcelle E[1] and Lee, Hongjoo J[1]

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

The use of hormonal contraceptives (HCs) is ever-increasing among women in the United States. HCs work in part by altering the rate and manner of ovarian hormone release; however, few studies have sought to characterize the auxiliary influence HCs have on the female brain and behavior. Females are at increased risk of substance abuse, and ovarian hormones such as estradiol and progesterone have been implicated as contributors to this predilection. The purpose of the following experiment was to characterize differences in amphetamine (AMP) preference and subsequent dopamine (DA) activity in naturally cycling or HC-implanted female rats. Rats were conditioned and tested for AMP place preference with either an HC-implant or during estrous cycle stages associated with opposing ovarian hormone levels (i.e., proestrus (high) or metestrus/diestrus (low)). Female rats conditioned and tested in proestrus showed significantly higher AMP place preference compared to metestrus/diestrus or HC-implanted rats and were resistant to extinction of this preference. Additionally, proestrus rats had a significantly higher percentage of active DA cells in the substantia nigra (but not ventral tegmental area) after the final AMP challenge. These results support previous research wherein higher ovarian hormones are associated with increases in drug-addictive behavior and DA activity, while also providing novel insight into how hormone-altering contraceptives may reduce drug- and DA-responsivity in females in a manner similar to what is seen when endogenous ovarian hormone levels are low.

Featured Presentation 1-4

Sex differences in sleep architecture and brain function observed following administration of NMDAR antagonist MK-801

Holter, Kimberly M; Lekander, Alex D; Pierce, Bethany E; and Gould, Robert W

Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, NC USA

Accumulating evidence suggests glutamatergic hypofunction is one underlying factor in the pathology of schizophrenia. Administration of MK-801, an NMDAR antagonist, has emerged as a method to induce schizophrenia-like symptoms in animals. However, there are vast sex differences in human symptomology that are underrepresented in animal models. Evidence suggests that prevalence and severity of negative and cognitive symptoms may be greater in males. Furthermore, sex differences in schizophrenia-induced sleep disturbances have also been reported. Present studies used polysomnography and quantitative electroencephalography (qEEG) measures as a translational biomarker approach to determine if NMDAR antagonists can reveal similar sex differences on sleep and brain function in animals. EEG surface electrodes and wireless transmitters were implanted in male (n=8) and female (n=9) Sprague-Dawley rats. 24h homecage EEG recordings were obtained with MK-801 (0.03-0.3 mg/kg, sc) administered 2h into the light cycle. Activity counts were simultaneously observed. ANOVAs followed by Dunnett's multiple comparisons test were used to examine sex differences and dose-dependent differences compared to vehicle. Consistent with previous literature, MK-801 induced hyperlocomotion and decreased NREM and REM sleep. Females were more sensitive, showing a longer duration and magnitude of effects. However, MK-801 induced profound, dose-dependent increases on awake gamma power only in male rats with no comparable increases found in female rats. Gamma power is highly sensitive to glutamate function, and abnormalities have been associated with cognitive impairment and psychotic symptoms in patients with schizophrenia. This is the first report of a blunted response to MK-801's effects in female rats compared to males, and these sex-related differences may correspond with prevalence/severity of symptom subtypes in humans.

Featured Presentation 1-5

Effects of Ketamine on Reward Sensitivity in Healthy and Chronically-Stressed Rats

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

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

Patients with depression who report high levels of anhedonia (i.e., the loss of pleasure in previously rewarding activities) are more likely to be treatment-resistant and have higher suicide risk. Currently available treatments, such as selective serotonin reuptake inhibitors, are ineffective at treating anhedonia, though the recently-introduced N-methyl-D-aspartate (NMDA) antagonist, ketamine appears to offer rapid and sustained anti-depressant and pro-hedonic effects. The Probabilistic Reward Task (PRT) is a quantitative approach to evaluating hedonia in laboratory subjects, providing behavioral endpoints corresponding to aspects of anhedonia in psychiatric conditions. This task permits the concurrent measurement of response bias, or sensitivity to reward, and discriminability, or task difficulty. A reverse-translated PRT for laboratory animals has been validated in mice, rats, and marmosets, yielding results highly similar to those obtained in humans. The present study was conducted to extend those data by comparing effects of ketamine (2- and 24-hr after injection) on PRT performance in healthy and chronically-stressed rats using an ecologically-relevant stressor (inescapable cold-water [14°C]). Ketamine increased response bias in healthy rats without degrading discriminability. Blunted response biases in stressed rats also could be rescued with ketamine 2- and 24-hr post-injection without altering discriminability—consistent with reports of pro-hedonic efficacy 24-hr post-injection in humans. This study validates this platform as a valuable approach to examine candidate therapeutics for anhedonia.

Featured Presentation 1-6

Increased mood disorder symptoms, perceived stress, and alcohol use among college students during the COVID-19 pandemic

Strong, Stephanie J.[1], Charles, Nora E.[1], Burns, Lauren C.[1], Bullerjahn, Margaret R.[1], & Serafine, Katherine M.[2]

[1] School of Psychology, The University of Southern Mississippi, Hattiesburg, MS USA; [2] Department of Psychology, The University of Texas at El Paso, El Paso, TX USA

The COVID-19 pandemic caused significant disruption during the spring of 2020. Many college students were told to leave campus at spring break and to complete the semester remotely. This study evaluates effects of this disruption on student well-being. A sample of 148 students (86.5% female, 49.3% White) completed measures of psychological symptoms, perceived stress, and alcohol use during the spring 2020 semester at a university in the southeastern U.S. Their results were compared to those of 240 students (87.9% female, 64.2% White) who completed the same measures in the fall 2019 semester. Participants in spring 2020 reported more mood disorder symptoms, perceived stress, and alcohol use than did pre-pandemic participants. Worry about COVID-19 was negatively associated with well-being in multiple domains. Additionally, White students reported a greater effect of the pandemic on well-being than did African American students. Young adults appear to be less vulnerable to the most serious medical complications associated with COVID-19 but nonetheless experience psychological effects from the pandemic. Universities and practitioners who work with college students can help young adults manage their symptoms and avoid behaviors like risky alcohol use when confronted with stressors such as the COVID-19 pandemic.

Featured Presentation 2-1

Effects of a novel tamoxifen-analogue (6C) on methamphetamine-induced neurotoxicity

Manke, Hayley N[1]; Rafi, Harmain[1]; Kuhn, Donald M[2]; Zestos, Alexander G[1] and Riley, Anthony L[1]

[1]Department of Neuroscience, American University, Washington, DC USA; [2] Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI USA.

Amphetamine and methamphetamine have been reported to exert their neurotoxic effects via the activation of the β-isoform of protein kinase C (PKC) which phosphorylates the dopamine transporter (DAT) at N-terminal serines and threonines to increase extracellular dopamine (DA) via reverse transport. Although amphetamine and methamphetamine-induced neurotoxicity is well characterized, no treatment exists for these effects. In this context, the CNS permeant, tamoxifen-analogue PKC inhibitor (6C) has been shown to attenuate amphetamine-induced monoamine release, locomotion and self-administration. Given the mediation of psychostimulant-induced DA release by PKC activity and the role of excess DA to neurotoxicity, the preset study assessed if PKC inhibition by 6C impacts psychostimulant-induced neurotoxicity. In this study, adult female mice were administered a single injection of vehicle or 6 mg/kg of 6C, subcutaneously, 2 h prior to a binge-like regimen of 5 mg/kg of methamphetamine or saline during which they were injected with 5 mg/kg of methamphetamine or saline (IP) every 2 h for a total of four injections. Two days following injections, mice were sacrificed, brains were removed and the striatum was bilaterally dissected to undergo western/immunoblot and HPLC analyses. 6C significantly reduced methamphetamine-induced neurotoxicity when probing for DAT, tyrosine hydroxylase (TH) and DA levels. These results suggest that 6C may be a potential treatment in psychostimulant neurotoxicity. To assess the generalizability of these effects to other psychostimulants, future work should run similar analyses with other amphetamine-related compounds including the new class of beta ketone analogues of amphetamine, the synthetic cathinones, whose effects are mediated by similar and different neurochemical mechanisms.

Featured Presentation 2-2

Sex differences and effects of drug exposure order on the reward-enhancing effects of co-administered nicotine and d-amphetamine.

McNealy, Kathleen R[1]; Houser, Sydney D[1]; Barrett, Scott T[1] and Bevins, Rick A[1]

[1]Department of Psychology, University of Nebraska-Lincoln, Lincoln, NE USA.

Nicotine enhances the value of environmental stimuli and rewards, and reward-enhancement maintains nicotine consumption. d-Amphetamine and other psychostimulants are misused more by women and highly co-used with nicotine. Nicotine, but not cocaine, exposure can potentiate the interactive effects of nicotine and cocaine. We know of no studies examining drug exposure order effects in reward-enhancement, nor examining d-amphetamine. Thus, we examined the effect of exposure order on reward-enhancement by co-administered nicotine and d-amphetamine. We used 20 male and 20 female Sprague-Dawley rats. Twenty rats (10 M, 10 F) completed 33 days of nicotine exposure before 33 days of d-amphetamine exposure (NIC First rats), and 20 rats (10 M, 10 F) received d-amphetamine before nicotine (AMP First rats). We then assessed enhancement within-subjects by examining responding for a visual stimulus following two pre-session injections: one of d-amphetamine (AMP; Sal, 0.1, 0.3, or 0.6 mg/kg) and one of nicotine (NIC; Sal, 0.03, 0.06, 0.1, and 0.3 mg/kg). Data were analyzed with a 4-way ANOVA (Sex x Exposure Order x AMP Dose x NIC Dose). We found a four-way interaction. NIC First females responded more than AMP First females in 0.3 AMP + 0.03 NIC, 0.6 AMP + 0.03 NIC, 0.3 AMP + 0.06 NIC and 0.3 AMP + 0.06 NIC conditions. However, AMP First males responded more than NIC First males in 0.3 AMP + 0.03, 0.6 AMP + 0.03 NIC, 0.1 AMP + 0.06 NIC, 0.3 AMP + 0.06 NIC, and 0.6 AMP + 0.06 NIC, 0.3 + 0.1 NIC conditions. For females, receiving nicotine first heightened interactive effects of low dose nicotine with high dose amphetamine. In contrast, males receiving amphetamine first showed these same heightened interactive effects. Given the role of reward-enhancement in nicotine use, considering prior and current amphetamine use when treating nicotine dependency is warranted.

Featured Presentation 2-3

Adolescent Sprague Dawley rats exhibit context-dependent sensitization to low doses of METH while preweanling rats do not in a one-trial paradigm.

Omerjee, Faiyaz, Sortman, Bo, and Zavala, Arturo R.

Department of Psychology, California State University, Long Beach, Long Beach, CA USA

Methamphetamine (METH) behavioral sensitization is a phenomenon in which repeated administration of METH elicits an augmented behavioral response. Research has found that even one previous pairing is enough to elicit sensitization. Preweanling rats (postnatal day [PD] 24 or younger) exhibit context-independent METH sensitization, a heightened response regardless of what environment the METH was previously paired. Interestingly, adolescent rats (PD 25-50), do not exhibit any sensitized response to METH. Prior studies have examined a wide range of doses of METH (1-6 mg/kg) on the challenge day, but doses lower than 1 mg/kg METH have not been used. Hence, the present study examined one-trial sensitization in preweanling and adolescent rats using 0.1 and 0.3 mg/kg of METH. PD 18, 28, and 38 male and female Sprague Dawley rats were pretreated with saline or 3 mg/kg METH and placed in a novel activity chamber. They were then taken to their home cage, and 45 minutes later, were given the opposite treatment in their home cage. Specifically, those that received METH were injected with saline, and those that were given saline were give 3 mg/kg METH and placed back into their home cage. During the challenge test (24 hours later), the rats were injected with saline or METH (0.1 or 0.3 mg/kg) before being placed in the activity chamber. Additionally, a separate group of rats were given saline all throughout pretreatment. In contrast to prior studies, we found that PD 29 and 39 adolescent male and female rats, but not PD 19 rats, exhibited context-dependent METH sensitization. Interestingly, sex-related differences were observed as PD 29 and 39 male rats exhibited behavioral sensitization only when challenged with 0.1 mg/kg METH, while female rats exhibited behavioral sensitization to both doses of METH. These findings highlight age and sex-dependent effects of METH-induced sensitization using low doses.

Featured Presentation 2-4

"ER-associated Regulation of Astrocyte Mitochondrial Function during (METH)amphetamine Exposure"

Jessica Proulx & Kathleen Borgmann

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

Astrocytes are key regulators of central nervous system (CNS) health and neuronal function. However, astrocyte mitochondrial dysfunction, such as induced by (METH)amphetamine, threatens the ability of astrocytes to provide the essential metabolic and antioxidant support to neurons. This study examined the endoplasmic reticulum (ER)-mitochondrial interface in response to METH exposure to characterize changes in mitochondrial function, the unfolded protein response (UPR), Ca2+ signaling, and the regulation of mitochondria associated membranes (MAMs). We hypothesized that the ER regulates astrocyte mitochondrial function via Ca2+ and UPR/MAM signaling during METH exposure. The effects of METH on astrocytes were examined under both acute and chronic paradigms in primary human astrocytes. Mitochondrial bioenergetics was assessed using Seahorse extracellular flux analyzer while expression of UPR/MAM mediators were determined using protein expression assays. Ca2+ signaling was measured by confocal microscopy using a genetically encoded calcium sensor. Finally, pharmacological inhibition of the UPR pathways were used to delineate the regulatory mechanisms mediating the changes on mitochondrial function. Our results show both acute and chronic METH exposure increased Ca2+ flux and upregulated the expression of UPR/MAM mediators. Astrocyte metabolic capacity was increased following chronic METH exposure which corresponded to an augmented Ca2+ flux and dysregulated UPR induction. Moreover, pharmacological inhibition of IRE1α impaired astrocyte mitochondrial activity. These findings illustrate the importance of ER-mitochondria communication in regulating astrocyte mitochondrial function and identify a novel possible mechanism to manipulate astrocyte mitochondrial function during neurodegenerative pathologies

Featured Presentation 2-5

Quit discounting: Sensitivity to health messages and substance cessation prediction.

Strickland, Justin C[1]; Reed, Derek D[2], Dayton, Lauren[3]; Latkin, Carl[3]; Johnson, Matthew W[1]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD USA; [2]Department of Applied Behavioral Science, University of Kansas, Lawrence, KS USA; [3]Department of Health, Behavior and Society, Johns Hopkins University, Baltimore, MD USA

Recent work shows that commodity-specific outcomes may improve the clinical utility of discounting measures. This study evaluates how the likelihood of alcohol or cigarette use cessation decreases with probability of health benefit upon cessation (i.e., "quit discounting"). We examine how quit discounting: 1) varies by magnitude of health benefit, 2) is sensitive to public health messaging, and 3) predicts reductions in substance use. Participants (N=485) were recruited using crowdsourcing. Two quit discounting tasks were evaluated for hypothetical illnesses varying in severity (mild/severe; within-subject). Participants were randomized to tasks with a matching mild/severe label or tasks without labels (between-subject). Measures were completed for cigarettes and alcohol and for sandwiches as a control commodity. Participants also completed a 3-month follow-up to assess changes in real-world substance use. We observed systematic reductions in quit likelihood with reduced probabilities of health benefit. We also observed smaller reductions in quit intentions with changes in health benefit for the severe than mild task, and larger magnitude differences between the mild and severe tasks in the health label condition. Smaller reductions in quit intentions were predictive of prospective decreases in cigarette and alcohol use. These relationships remained after controlling for "sandwich" discounting, demonstrating pharmacological specificity. These findings show that intentions to quit are systematically discounted by the probability of health benefit upon abstinence and that this discounting is sensitive to the severity of negative health outcome avoided and public health message framing that severity. The prediction of reductions in real-world substance use signifies an individual difference variable that should be evaluated in clinical settings. Supported by: T32DA07209; R01DA042527

Featured Presentation 3-1

Serotonin 2A- or 2C-like discriminative stimulus effects of serotonin agonists in nonhuman primates

Alton, Hannah[1,2]; de Moura, Fernando B. [2,3]; Blough, Bruce E[4]; and Kohut, Stephen J[2,3]

[1]Harvard College, Boston, MA; [2]Behavioral Neuroimaging Laboratory, McLean Hospital; [3]Department of Psychiatry, Harvard Medical School, Boston, MA; [4]Research Triangle Institute, Research Triangle Park, NC.

Drugs that selectively target the serotonin (5HT) 2A or 2C receptor subtypes have been suggested as candidate medications for several psychiatric disorders, including addiction. Drug discrimination procedures have utility in characterizing the in vivo pharmacology of novel drugs by comparing them to an established training drug. Separate groups of adult male squirrel monkeys (n=4/group) were trained to discriminate either the 2A agonist R-DOI (0.06 mg/kg) or the 2C agonist WAY163,909 (0.56 mg/kg) from saline under a fixed ratio schedule of stimulus shock termination. Substitution tests were conducted with serotonin agonists varying in their selectivity for 5-HT2A and 2C receptors, and antagonism studies were conducted with the selective 5-HT2A and 5-HT2C antagonists MDL100,907 and SB242,084, respectively. Both training drugs produced dose-dependent effects in their respective discriminations. R-DOI did not elicit drug-like responding in the WAY163,909-trained group, and WAY163,909 did not produce drug-like responding in the R-DOI-trained group. Drugs with preferential 5-HT2A agonist activity—DOM, 2C-B, 25C-NBOMe, TCB-2, LSD, and psilocin—substituted only in the DOI-trained group. Drugs with preferential 5-HT2C agonist activity—mCPP, Ro 60-0175, and lorcaserin—substituted only in the WAY163,909-trained group. MDL100,907 antagonized DOI only, while SB242,084 antagonized WAY163,909 only. These findings suggest that the two training conditions reported here elicit discriminative stimulus effects selective for 5-HT2A (R-DOI-trained) and 5-HT2C (WAY163,909-trained) agonist activity, which may provide a useful baseline for screening novel compounds acting at serotonin receptors.

Featured Presentation 3-2

Patient-level perspectives on the use of novel psychotherapeutics for the treatment of substance use disorders

Crull, Jory[1]; Jones, Jennifer[2]

[1]Department of Neuroscience, Medical University of South Carolina, Charleston, SC USA; [2]Department of Psychiatry & Behavioral Sciences, Medical University of South Carolina, Charleston, SC

Substance use disorders (SUDs) present a rapidly evolving public health crisis for which the current standard of care is insufficient. Prior research has demonstrated compounds with unique psychoactive properties may improve ability to maintain abstinence across a variety of SUDs; examples of such compounds include psilocybin, ketamine, and 3,4-Methylenedioxymethamphetamine (MDMA). However, target population support for mental health treatment using these medications is unknown. In this study, a cross-sectional survey (n=919) was administered to analyze patient-level perspectives on the use of these novel psychotherapeutics for the treatment of SUDs. We hypothesized that individuals with SUDs would demonstrate differential acceptance of these treatment modalities as a function of prior awareness of these medications. The results showed that the majority of survey participants supported medical trials being conducted with psilocybin (72.1%), ketamine (71.6%), and MDMA (68.1%) in the future. Ketamine support scores, where a higher number demonstrates greater support, were significantly different between participants with versus participants without prior awareness (3.96 vs 3.79; p= .005), but there was no statistically significant difference in support for future research into psilocybin or MDMA based on prior awareness of these potential treatment modalities. These results can be used to direct future research recruitment efforts and provide insight into clinical considerations that should be made when using these treatments.

Featured Presentation 3-3

Discriminative stimulus effects of mu opioid receptor agonist mixtures.

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

[1]Department of Pharmacology; [2]Addiction Research, Treatment and Training (ARTT) Center of Excellence; Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX USA

Two-thirds of the 47,000 opioid overdose deaths in the US in 2018 involved a synthetic opioid such as fentanyl or one of its many derivatives, e.g. carfentanil, which is reportedly 100-fold more potent than fentanyl. Clinical reports suggest that larger doses of the opioid antagonist naloxone are required to reverse opioid overdoses involving carfentanil, compared with other opioid receptor agonists. Highly potent synthetic opioids such as fentanyl and carfentanil are most frequently encountered as adulterants of another drug such as heroin, suggesting that drug interactions might underlie the reported difficulty in reversing overdoses. This study evaluated the discriminative stimulus effects of opioid mixtures to assess interactions between mu opioid receptor agonists. Eight male Sprague Dawley rats were trained to discriminate 0.01 mg/kg fentanyl under a fixed-ratio 10 schedule of food presentation. Dose-effect curves were determined for fentanyl, heroin, and carfentanil alone, and as binary mixtures at fixed-dose ratios of 3:1. 1:1, and 1:3 relative to the ED50 for occasioning fentanyl-appropriate responding for each drug when given alone. Fentanyl, heroin, and carfentanil dose-dependently increased responding on the fentanyl-associated lever and reduced rate of responding. Dose-addition analyses were used to determine the nature of drug interactions (additive, supra-additive, subadditive) for each mixture. Some mixtures of mu opioid receptor agonists, particularly those containing carfentanil, had supra-additive discriminative stimulus effects relative to predictions based on the effects of each drug alone. These results suggest that not only the increased potency of synthetic opioids, but also interactions with other opioid receptor agonists could play a role in the reported increased lethality of these mixtures in humans.
Funding: Welch Foundation AQ-0039, NIH 5R25GM095480

Featured Presentation 3-4

Novel Muscarinic Antidepressants that Lack Cognitive Deficits: Some Insights into Key Structural Features of Muscarinic Agonists and Antagonists.

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. 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. The 3-exo-1-azabicyclo[2.2.1]heptane, 1-azabicyclo[2.2.2]octane, and N-methyltetrahydropyidine 3-substituted-1,2,4-oxadiazoles have proven to be excellent chemical scaffolds for the generation of potent muscarinic agonists/antagonists. Interestingly, addition of a methyl group to the 3-position of the 1,2,4-oxadiazole yields some of the most potent muscarinic agonists currently known. Yet, addition of a cyclopropyl group appears to reduce efficacy and confer antagonist action at muscarinic sites. Herein we show the pharmacological profiles of multiple pairs of methyl/cyclopropyl analogues we have designed in the anticipation of separating antidepressant-like activity from cognitive impairment. (Supported by NIMH Grant 107499).

Featured Presentation 3-5

Synergistic antihyperalgesic and antinociceptive effects of morphine and MP-III-024, a positive allosteric modulator at α2GABAA and α3GABAA receptors

Madhurathakam, Indu Mithra[1]; Uribe, Sarah[1]; Rahman, Mohammad A[1]; Poe, Michael M[2]; Sharmin, Dishary[2]; Cook, James M.[2]; Fischer, Bradford D;[3] Keck, Thomas M[1]

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Opioid and GABAA receptors are both located in central nociceptive pathways and compounds that activate these receptors have pain-relieving properties. To date, the interactive effects of concurrent administration of these compounds in preclinical models of pain-like behaviors have not been assessed. The purpose of this study was to examine the interactive effects of the μ-opioid agonist morphine and the α2GABAA and α3GABAA receptor positive allosteric modulator MP-III-024 in preclinical models of mechanical hyperalgesia and thermal nociception. The antihyperalgesic and antinociceptive effects of morphine and MP-III-024 administered alone were assessed initially, followed by fixed-ratio mixtures of MP-III-024/morphine combinations. Drug interactions were analyzed using isobolographic and dose-addition analyses. In mechanical hyperalgesia assays, each compound produced dose-dependent antihyperalgesic effects, whereas only morphine was effective on thermal nociception. Fixed-ratio mixtures of MP-III-024/morphine were dose-dependently effective in both procedures but produced supra-additive (synergistic) effects in both assays, depending on their relative proportions. Follow-up studies suggest MP-III-024 attenuates morphine-induced locomotor activation. These results demonstrate important interactions between α2GABAA and α3GABAA receptor- and μ-opioid receptor-mediated signals, and suggest that combination therapy may be useful for the treatment of pain-related disorders.

Featured Presentation 3-6

Potential G-Protein Biased Ligands with Nitrogen-Containing Substituents at C9 in the 5-(3-Hydroxyphenyl)morphan Class of Opioids

Roth, Hudson G.[1]; Bow, Eric W.[1]; Kaska, Sophia[2]; Prisinzano, Thomas E.[2]; Sulima, Agnieszka[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
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Medicinal chemists have long sought to develop opioids 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 -opioid receptor (MOR) without recruiting the regulatory protein -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 develop a library of these compounds and assess their pharmacological potential, we have synthesized a variety of derivatives containing amino groups at the C9-position. As there is no way to model what downstream signaling a molecule will activate upon binding to the MOR, each variation at the C-9 position requires the synthesis of four diastereomers due to the presence of three centers of asymmetry in this class of molecules. Two of these centers are set based on the 5-(3-hydroxphenyl)morphan employed as the precursor, while the third is determined by the nature of the reductant in the reductive amination procedure that introduces the amino group at the C9-position.

Video Poster Presentations

Poster 1

Serotonin 2A- or 2C-like discriminative stimulus effects of serotonin agonists in nonhuman primates

Alton, Hannah[1,2]; de Moura, Fernando B. [2,3]; Blough, Bruce E[4]; and Kohut, Stephen J[2,3]

[1]Harvard College, Boston, MA; [2]Behavioral Neuroimaging Laboratory, McLean Hospital; [3]Department of Psychiatry, Harvard Medical School, Boston, MA; [4]Research Triangle Institute, Research Triangle Park, NC.

Drugs that selectively target the serotonin (5HT) 2A or 2C receptor subtypes have been suggested as candidate medications for several psychiatric disorders, including addiction. Drug discrimination procedures have utility in characterizing the in vivo pharmacology of novel drugs by comparing them to an established training drug. Separate groups of adult male squirrel monkeys (n=4/group) were trained to discriminate either the 2A agonist R-DOI (0.06 mg/kg) or the 2C agonist WAY163,909 (0.56 mg/kg) from saline under a fixed ratio schedule of stimulus shock termination. Substitution tests were conducted with serotonin agonists varying in their selectivity for 5-HT2A and 2C receptors, and antagonism studies were conducted with the selective 5-HT2A and 5-HT2C antagonists MDL100,907 and SB242,084, respectively. Both training drugs produced dose-dependent effects in their respective discriminations. R-DOI did not elicit drug-like responding in the WAY163,909-trained group, and WAY163,909 did not produce drug-like responding in the R-DOI-trained group. Drugs with preferential 5-HT2A agonist activity—DOM, 2C-B, 25C-NBOMe, TCB-2, LSD, and psilocin—substituted only in the DOI-trained group. Drugs with preferential 5-HT2C agonist activity—mCPP, Ro 60-0175, and lorcaserin—substituted only in the WAY163,909-trained group. MDL100,907 antagonized DOI only, while SB242,084 antagonized WAY163,909 only. These findings suggest that the two training conditions reported here elicit discriminative stimulus effects selective for 5-HT2A (R-DOI-trained) and 5-HT2C (WAY163,909-trained) agonist activity, which may provide a useful baseline for screening novel compounds acting at serotonin receptors.

Poster 2

Hapten design dictates molecular recognition of vaccine-induced antibodies to drugs of abuse

Barrientos, Rodell C.[1,3]; Gutman, Eugene S.[2]; Irvin, Thomas C.[2]; Morgan, J. Brian[2]; Antoline, Joshua G.[2]; Li, Fuying[2]; Torres, Oscar B.[1,3]; Sulima, Agnieszka[2]; Whalen, Connor[1]; Oertel, Therese[1]; Komla, Essie[1,3]; Beck, Zoltan[1,2]; Jacobson, Arthur E.[2]; Rice, Kenner C.[2]; and Matyas, Gary R.[1]

[1]Laboratory of Adjuvant and Antigen Research, US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA; [2]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, USA; [3]Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA.

Active immunization is being explored as a potential therapeutic to combat opioid use disorders. Affinity and selectivity of antibodies are key to an efficacious vaccine. In 2014, the facial recognition hypothesis has been proposed by Matyas et al. to account for the cross-reactivity of antibodies to opioids and found that changing the linker attachment site in the hapten resulted in distinct selectivity. Herein, we tested this theory by exploring haptens with varying linker attachment site, C-1 and C-14, of the morphinan ring, to uncover the determinants of antibody recognition. Haptens were conjugated to tetanus toxoid and mixed with Army Liposome Formulation (ALF) adjuvant with or without aluminum salt. Sera were collected from immunized Balb/c mice and measured cross-reactivity to opioids and cognate therapeutic drugs using equilibrium dialysis. Results revealed that the face of the hapten distal from the linker site served as epitopes recognized by the antibodies. These findings reinforced the facial recognition hypothesis that varying the linker attachment site can be used as a strategy to tune the selectivity of antibodies to drugs of abuse.

Poster 3

PMAT Deficiency Sex-Selectively Contributes to Amphetamine-Induced Locomotor Sensitization

Beaver, JN[1,2], Ford, MT[1], Gilman, TL[1,2].

[1]Department of Psychological Sciences & [2]Brain Health Research Institute, Kent State University, Kent, OH USA

The plasma membrane monoamine transporter (PMAT) is a polyspecific cation transporter that, in the brain, predominantly takes up monoamines such as dopamine and serotonin. We hypothesize the functional contribution of PMAT emerges when impairment of higher affinity transporters, including dopamine transporter (DAT) or serotonin transporter (SERT), occurs. An example would be in the presence of psychostimulants like D-amphetamine, which reverses transport of dopamine by DAT. No studies have evaluated the contribution of PMAT to psychostimulant responses. Mice constitutively deficient in PMAT were utilized for the present experiments, because no selective inhibitor of PMAT currently exists. We hypothesized that relative to wildtype controls, mice with reduced or diminished PMAT function would exhibit augmented D-amphetamine sensitization. To analyze the effects of amphetamine in PMAT-deficient mice, males and females (N=3-7 per sex and genotype) underwent a D-amphetamine-induced locomotor sensitization paradigm. Each day, after a baseline test (30 min) of locomotor activity in an open field arena, injections of saline (vehicle) then D-amphetamine were administered. Subsequent locomotor responses to each injection were recorded in 10-minute intervals. The total (cumulative) doses used for D-amphetamine were 0.1-4.62 mg/kg, given every 3 days for a total of 5 injection days. Preliminary data indicate a decreased sensitization to D-amphetamine in female PMAT-deficient mice relative to same-sex wildtypes. However, male heterozygotes exhibited augmented D-amphetamine sensitization relative to male knockouts. These results indicate PMAT contributes to D-amphetamine-induced dopamine efflux. PMAT may sex-specifically influence psychostimulant sensitization processes. Future examinations will determine how PMAT function influences additional neurobehavioral dimensions related to psychostimulant use and abuse.

Poster 4

Rational drug design strategy for novel dopamine D4 receptor (D4R) subtype antagonist

Boateng, Comfort A.[1]; Tewolde, Milka[1]; Bourn, Lindsay A.[1]; Korankyi, Ivana V.[1]; Keck, Thomas M.[2]; Free, Benjamin R.[3] Wu, Chun[2] and Stewart, Kent D.[1]

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

D4R-selective ligands have promise in medication development for neuropsychiatric conditions, including substance use disorders (SUD). D4R ligands have been shown to alter cognition and behavior in animal models of drug addiction. A better understanding of D4R-mediated signaling is essential to understanding and treating D4R-associated disorders, including SUD. Despite its clinical implications, there are currently few compounds that selectively modulate the D4R receptor. Herein, we describe a rational drug design strategy leading to the design, synthesis, in silico and in vitro analyses of novel D4R antagonist compounds using computational modelling approach based on the parental scaffold 2-(3-(4-(pyrimidin-2-yl)piperazin-1-yl)propyl)benzo[d] thiazole ligand. Their in vitro binding affinities were determined using [3H]N-methylspiperone radioligand binding in HEK293 cells expressing dopamine D2-like receptors (D2R, D3R, D4R). These binding studies were coupled with functional studies using radioligand binding β-arrestin recruitment and cAMP inhibition displacement assays. We identified several novel antagonists D4R-selective (Ki ≤ 100 nM and >100-fold vs. other D2-like receptors) compounds. Selected compounds were predicted to be brain penetrant, with calculated central nervous system multiparameter optimization of chemical features scores of ranging 4.5-5.8 for representative compounds (6-point score, with scores > 4 indicating brain penetration). Further selected compound tested in Caco-2 membrane permeability tests displayed apical-to-basolateral (A-B) permeability of 27 × 10-6 cm/s.

Poster 5

Substance use in at-risk adolescents: The roles of self-control and religiosity

Burns, Lauren C.[1]; Charles, Nora E.[1], Barry, Chris[2]

[1] The University of South Mississippi, [2] Washington State University

The present study sought to explore the nuanced relationship between religiosity and self-control as predictors of at-risk adolescent substance use. The adolescent period is often characterized by experimentation with drug and alcohol use. Although this behavior is not uncommon, it can nonetheless result in significant negative outcomes. Understanding the nuances of adolescent substance use may assist in earlier identification, prevention, and treatment of substance use disorders (SUDs). Previous research has explored the potential roles of religiosity and self-control in the development and maintenance of adolescent substance use. Generally speaking, individuals with low self-control are more likely to engage in maladaptive behaviors, such as substance use (Sweeten, Buhway, & Paternoster, 2009). Additionally, poor self-control has been shown to predict initiation and frequency of substance use (Wills & Cleary, 1999). Further, religiosity has been linked to decreased problem behavior by means of the promotion of self-control (McCullough & Willoughby, 2009; Salas-Wright, Lombe, Nebbitt, Saltzman, & Tirmazi, 2018). The present study hypothesized that higher self-control and religiosity would be associated with less substance use. Further, self-control was hypothesized to mediate the relationship between religiosity and adolescent substance use. The study included 105 male and female adolescents, ages 16-19. Participants completed self-report measures of substance use and religiosity. Analyses included correlations and PROCESS mediations. Results indicated that religiosity was not significantly associated with substance use, while self-control significantly predicted engagement in alcohol and cocaine use. Additionally, self-control only mediated the relationship between religiosity and alcohol consumption. The present study provides useful information concerning the development of adolescent substance use prevention and intervention resources.

Poster 6

Assessing the physiological and pharmacological mechanisms by which synthetic cathinones ("Bath salts") cause Drug-induced Parkinsonism (DIP)

Chitre Neha M.[1], Gannon Brenda M.[2], Blough Bruce E.[3], and Murnane Kevin S.[4]

[1]Mercer University College of Pharmacy, Atlanta, GA; [2]University of Arkansas for Medical Sciences, Little Rock, AR; [3]Center for Drug Discovery, Research Triangle Institute, NC;[4]School of Medicine, Louisiana State University Health Sciences Center, Shreveport, LA.

Drug-induced Parkinsonism (DIP) is the second most common cause of parkinsonism. DIP is characterized by dysregulation of the brain dopaminergic system. Stimulants like methamphetamine (METH) cause dopaminergic neurotoxicity, increasing predisposition to DIP. Synthetic cathinones (SC) are β-ketone structural analogs of amphetamine. In this study, we evaluate the acute and persistent behavioral and neurochemical effects of exposure to METH, and its prototypical β-ketone analogs, Methcathinone (MC) and α-Pyrrolidinopropiophenone (α-PPP).Swiss-Webster, male mice (7-8 per group) were treated with either METH (5 mg/kg), MC (80 mg/kg) or α-PPP (80 mg/kg), using a "binge"-like dosing regimen (QID, q2h). Physiological effects of stimulants on body weight and rectal temperature were assessed. Motor function was studied using Open-Field Testing (OFT). Cognitive impairments were assessed by Passive Avoidance (PA). Dopamine neurochemistry was evaluated in the striatum using UHPLC-ECD. Data were analyzed by one-way analysis of variance (ANOVA) with post-hoc comparisons by Dunnett's test. METH dosing produced hyperthermic effects. Exposure to METH and α-PPP caused a significant decrease in OFT activity on Day 3. All three drugs caused severe impairments in PA testing, suggesting METH, MC, and α-PPP, each engender strong cognitive dysfunction. Exposure to METH, and MC resulted in significant dopamine depletions in the striatum. These studies demonstrate that METH, MC, and α-PPP cause significant cognitive dysfunction, with mild motor impairments. These results may indicate onset of early-stage parkinsonism. Finally, these results highlight the potential of novel SC to cause DIP, warranting further research.

Poster 7

Role of organic cation transporter 3 in the rewarding properties and locomotor sensitizing effects of amphetamine in male and female mice

Clauss, Nikki J.[1]; Koek, Wouter[2,3] and Daws, Lynette C.[1,3]

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Strategies targeting the dopamine transporter have yielded little benefit in treating addiction to amphetamine or amphetamine-like psychostimulants, possibly due to significant action of these stimulants elsewhere to modulate dopaminergic transmission. Our recent studies support organic cation transporter 3 (OCT3) as a previously unsuspected player in the actions of amphetamine. Here we extend these findings. We used pharmacological (decynium-22 (D22; 0.1 mg/kg), a blocker of OCT3) and genetic (constitutive OCT3 knockout (-/-) mice) approaches to examine the role of OCT3 in mediating amphetamine (1 mg/kg)-induced conditioned place preference (CPP) and sensitization to its locomotor stimulant effects, in males and females. D22 attenuated amphetamine CPP in male and female OCT3+/+ mice; and in female OCT3-/- mice. OCT3-/- male mice did not develop CPP for amphetamine. Sensitization to the locomotor stimulant effects of amphetamine occurred in females regardless of pretreatment or genotype. Male mice did not develop statistically significant sensitization, regardless of pretreatment or genotype. Saline pretreated female OCT3+/+, but not OCT3-/-, mice given an acute injection of amphetamine showed a robust increase in locomotion, whereas male OCT3+/+ and OCT3-/- mice displayed only a modest increase in locomotor activity. D22 pretreatment did not affect the locomotor response to an acute injection of amphetamine in either sex or genotype. These data support OCT3 as a novel mechanism contributing to sex-dependent variation in the rewarding and locomotor stimulant effects of amphetamine-like drugs and have important implications for uptake-2 transporters as targets for therapeutic intervention in the treatment of amphetamine addiction.

Poster 8

Patient-level perspectives on the use of novel psychotherapeutics for the treatment of substance use disorders

Crull, Jory[1]; Jones, Jennifer[2]

[1]Department of Neuroscience, Medical University of South Carolina, Charleston, SC USA; [2]Department of Psychiatry & Behavioral Sciences, Medical University of South Carolina, Charleston, SC

Substance use disorders (SUDs) present a rapidly evolving public health crisis for which the current standard of care is insufficient. Prior research has demonstrated compounds with unique psychoactive properties may improve ability to maintain abstinence across a variety of SUDs; examples of such compounds include psilocybin, ketamine, and 3,4-Methylenedioxymethamphetamine (MDMA). However, target population support for mental health treatment using these medications is unknown. In this study, a cross-sectional survey (n=919) was administered to analyze patient-level perspectives on the use of these novel psychotherapeutics for the treatment of SUDs. We hypothesized that individuals with SUDs would demonstrate differential acceptance of these treatment modalities as a function of prior awareness of these medications. The results showed that the majority of survey participants supported medical trials being conducted with psilocybin (72.1%), ketamine (71.6%), and MDMA (68.1%) in the future. Ketamine support scores, where a higher number demonstrates greater support, were significantly different between participants with versus participants without prior awareness (3.96 vs 3.79; p= .005), but there was no statistically significant difference in support for future research into psilocybin or MDMA based on prior awareness of these potential treatment modalities. These results can be used to direct future research recruitment efforts and provide insight into clinical considerations that should be made when using these treatments.

Poster 9

The CB1 Negative Allosteric Modulator PSNCBAM-1 Reduces Ethanol Self-Administration via a Nonspecific Hypophagic Effect

Donegan, Christa;[1] Uribe, Sarah;[1] Sumi, Mousumi;[1] Buechler, Harley M;[1] Madhurathakam, Indu Mithra[1]; DiGiorgio, Jr., Frank;[1] Rahman, Mohammad A;[1] Sorbello, Alison;[1] Acosta, Alisha A;[1] Fischer, Bradford D;[2] Keck, Thomas M[1]

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

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) has been a target of interest for the development of medications for substance use disorder and other compulsive disorders, but CB1 antagonists/inverse agonists (e.g., rimonabant) have severe side effects that limit their clinical utility, including anxiety, depression, and suicide. 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 did not affect place preference for 2 g/kg ethanol. 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 can reduce ethanol-taking behavior via a nonspecific hypophagic effect.

Poster 10

MDPV and cocaine self-administration under short- and intermittent-access conditions

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When rats self-administer cocaine under short-access conditions, patterns of drug intake tend to be well-regulated. However, these patterns of drug-taking may not mimic patterns of stimulant use in humans, which tends to occur in binges, and do not adequately model stimulant use disorders (SUD), which are characterized, in part, by high levels of compulsive drug-taking. Intermittent-access self-administration paradigms were developed to occasion repeated, binge-like patterns of drug-taking, which result in neurobiological and behavioral changes thought to be related to SUD in humans. Unlike cocaine, when rats are allowed to self-administer the synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV) under short-access conditions, a subset rapidly develop persistently high rates of self-administration that appear similar to the "binge-like" patterns of use reported in humans. These studies aimed to compare the patterns of cocaine (0.32 mg/kg/inf) or MDPV (0.032 mg/kg/inf) self-administration under short (60-min)- and intermittent-access (12, 5-min bins separated by 25-min) in male and female rats. We found that a subset of rats with short-access to MDPV developed high rates of responding and binge-like patterns of self-administration, similar to patterns developed by rats that responded for either cocaine or MDPV under an intermittent-access procedure. However, the changes in response pattern induced by intermittent-access schedule were short-lived, suggesting the "binge-like" patterns of responding were schedule-dependent, and not due to the development of a persistent SUD-like phenotype. In contrast, the high rates of MDPV that emerged under short-access conditions tended to persistent across the 9 weeks of the study, suggesting that MDPV self-administration might provide a novel model of the compulsive drug-taking typical in humans with an SUD.

Poster 11

Effects of sympathomimetics and sympatholytics on the respiratory effects of opioids.

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Rationale: Naloxone is unsatisfactory for reversing the effects of some abused opioids owing to its inadequate potency, lipophilicity, and duration of action, and in dependent subjects, its precipitation of withdrawal. A need exists for therapeutics capable of augmenting the life-saving benefits of naloxone other than through opioid receptor antagonism. Hypothesis: Pharmacological manipulation of monoamines or activity at their receptors will modulate the reversal of opioid-induced respiratory depression provided by naloxone. Methods: Adult male Swiss-Webster mice (n = 8 per condition) were tested using whole-body plethysmography (WBP) to record breath frequency (Freq) and tidal volume (TVb) and to calculate their product, minute volume (MVb). Tests consisted of three consecutive recording periods: a 20-min baseline period, 20-min post-agonist period, and a 1-h reversal period. Oxycodone and fentanyl were tested as representative opioid agonists. Multiple doses of the agonists were initially tested in combination with multiple doses of naloxone, characterizing its reversal of respiratory depression. Prazosin, clonidine, d-amphetamine, and methamphetamine were tested as representative sympatholytics and sympathomimetics alone and in combination with the agonists. Statistical analyses were performed using 2-Way ANOVAs followed by Holm-Sidak tests comparing effects within 5-min test bins. Results: Dose-dependent respiratory depression was observed following the administration of oxycodone and fentanyl that was dose-dependently reversed by naloxone. The sympatholytic compounds prazosin and clonidine both significantly ($p<0.05$) depressed respiration when administered to vehicle-treated mice, while prazosin also augmented fentanyl's respiratory depressant effects. D-amphetamine and methamphetamine depressed respiration at low doses and significantly stimulated respiration at the high doses both in vehicle and opioid-treated mice. Conclusions: Sympathomimetics showed more promise than sympatholytics for facilitating the reversal of agonist-induced respiratory depression.

Poster 12

Discriminative stimulus effects of mu opioid receptor agonist mixtures.

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Two-thirds of the 47,000 opioid overdose deaths in the US in 2018 involved a synthetic opioid such as fentanyl or one of its many derivatives, e.g. carfentanil, which is reportedly 100-fold more potent than fentanyl. Clinical reports suggest that larger doses of the opioid antagonist naloxone are required to reverse opioid overdoses involving carfentanil, compared with other opioid receptor agonists. Highly potent synthetic opioids such as fentanyl and carfentanil are most frequently encountered as adulterants of another drug such as heroin, suggesting that drug interactions might underlie the reported difficulty in reversing overdoses. This study evaluated the discriminative stimulus effects of opioid mixtures to assess interactions between mu opioid receptor agonists. Eight male Sprague Dawley rats were trained to discriminate 0.01 mg/kg fentanyl under a fixed-ratio 10 schedule of food presentation. Dose-effect curves were determined for fentanyl, heroin, and carfentanil alone, and as binary mixtures at fixed-dose ratios of 3:1. 1:1, and 1:3 relative to the ED50 for occasioning fentanyl-appropriate responding for each drug when given alone. Fentanyl, heroin, and carfentanil dose-dependently increased responding on the fentanyl-associated lever and reduced rate of responding. Dose-addition analyses were used to determine the nature of drug interactions (additive, supra-additive, subadditive) for each mixture. Some mixtures of mu opioid receptor agonists, particularly those containing carfentanil, had supra-additive discriminative stimulus effects relative to predictions based on the effects of each drug alone. These results suggest that not only the increased potency of synthetic opioids, but also interactions with other opioid receptor agonists could play a role in the reported increased lethality of these mixtures in humans.

Funding: Welch Foundation AQ-0039, NIH 5R25GM095480

Poster 13

Cocaine-Induced Locomotor Sensitization in PMAT-Deficient Mice

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The plasma membrane monoamine transporter (PMAT) is an uptake2 transporter which we hypothesize removes monoamines during the impairment of uptake1 dopamine transporters (DAT) and serotonin transporters (SERT), such as inhibition during use of psychostimulants (e.g., cocaine). Currently, no previous studies have explored whether PMAT's presence affects cocaine sensitization. Our hypothesis was that cocaine response and sensitization would be increased in mice with reduced (+/−) or ablated (−/−) PMAT function relative to wildtypes (+/+). We hypothesized this due to the attenuated ability of PMAT to compensate for dopamine uptake while DAT, along with other uptake1 transporters such as norepinephrine transporters and SERT, are inhibited. PMAT-deficient and wildtype mice (N=5-12 per sex and genotype) underwent a cocaine-induced locomotor sensitization assay. Each day for 5 consecutive days, following a 30 minute baseline, locomotor activity in an open arena was measured in response to injections of saline followed by injections of cocaine at 10-minute intervals (cumulative doses of 5, 10, 20, and 40 mg/kg). ANY-maze software recorded distance traveled after each injection. Drug dose-responses were converted to area under the curve (AUC), and sensitization was determined by normalization to the first injection day's AUC for each genotype. Two-way repeated measures ANOVAs with Tukey's post-hocs were used to analyze data. The data show that male PMAT +/− mice had significantly less locomotor sensitization on the fourth and fifth day of injections in comparison to wildtype mice. No effects of genotype were detected in female mice, revealing a sex-specific effect of PMAT. The data show that PMAT deficiency limits cocaine sensitization in male but not female mice, thus indicating PMAT contributes to cocaine sensitization in males. Future research will further investigate underlying processes behind this sex-specific difference.

Poster 14

Beta-caryophyllene attenuates cocaine-related behaviors by activation of PPARα and PPARγ receptors: Repurposing a FDA-approved food additive for cocaine use disorder

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National Institute on Drug Abuse Intramural Research Program, Molecular Targets and M

In the last decade, there has been a growing interest in beta-caryophyllene (BCP), a FDA-approved food additive that produces promising therapeutic effects for multiple neuropsychiatric disorders. In this report, we explored the potential utility of BCP for the treatment of cocaine use disorder (CUD) and the underlying mechanisms of action. We found that BCP dose-dependently attenuated cocaine self-administration, drug-primed reinstatement of cocaine seeking and cocaine conditioned place preference, indicative of its preventative effects against relapse and abuse. BCP was previously reported to be a selective CB2 receptor agonist. Unexpectedly, pharmacological blockade or genetic deletion of CB1, CB2, or GPR55 receptors in gene-knockout mice failed to alter BCP's action against cocaine, suggesting the involvement of non-CB1, non-CB2, and non-GPR55 receptor mechanisms. Furthermore, pharmacological blockade of μ opioid receptor or Toll-like receptors complex failed to alter, while blockade of peroxisome proliferator-activated receptors (PPARα, PPARγ) reversed BCP-induced reduction in cocaine self-administration, suggesting the involvement of PPARα and PPARγ in BCP's action. Finally, we used electrical and optogenetic intracranial self-stimulation (eICSS, oICSS) paradigms to study the underlying neural substrate mechanisms. We found that BCP is more effective in attenuation of cocaine-enhanced oICSS than eICSS, the former driven by optical activation of midbrain dopamine neurons in DAT-cre mice. These findings indicate that BCP may be useful for the treatment of CUD, likely by stimulation of PPARα and PPARγ in the mesolimbic system.

Poster 15

Effects of chronic alcohol consumption on brain microtubules: PET imaging studies in nonhuman primates

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Healthy brain function depends on the integrity of the neuronal cytoskeleton provided by microtubules. Repeated exposure to alcohol alters cytoskeletal tubulin units in neurons which can induce morphological and functional changes. Direct in vivo imaging of microtubules in highly translational animal models of alcohol use disorder (AUD) would provide critical information on real-time cytoskeletal changes during the progression of AUD. In the present studies we characterized a novel radiotracer for microtubules, [11C]MPC-6827, and used it to characterize the effects of chronic alcohol consumption in nonhuman primates using positron emission tomography (PET). Two [11C]MPC-6827 PET scans were performed in each of four adult male cynomolgus monkeys one week apart to assess test-retest variability and to serve as a baseline. Next, monkeys were trained to drink ethanol via an operant panel located in their home cage using schedule induction. A third [11C]MPC-6827 scan was performed after three months of ethanol drinking, at which time monkeys had consumed an average of 101.2 (±22.7) g/kg of EtOH. [11C]MPC-6827 showed excellent brain uptake with good pharmacokinetics in the nonhuman primate brain, with a significant correlation between the test and retest scan data ($r = 0.77$, $p = 0.023$). Whole-brain radioactive uptake was ~32 (±3)% lower after alcohol self-administration compared to corresponding baseline scans. These results demonstrate the ability of [11C]MPC-6827 to track alcohol-induced changes in brain microtubules and demonstrate its potential as a in vivo biomarker for microtubule alterations in monkey models of neurological and psychiatric diseases.

Poster 16

Investigating the serotonin transporter and organic cation transporter 3 in serotonin clearance in basal lateral amygdala: Implications for stress-related disorders

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Disruption of serotonergic neurotransmission in the basolateral amygdala (BLA) is associated with a wide variety of stress-related psychiatric disorders, including post-traumatic stress disorder (PTSD), which is highly comorbid with drug abuse. It is well known that the high-affinity serotonin (5-HT) transporter (SERT) is a prime driver of 5-HT clearance from extracellular fluid, and therefore a key regulator of 5-HT tone in brain. However, our lab has shown that in hippocampus, the corticosterone-sensitive organic cation transporter 3 (OCT3), a low-affinity, high-capacity transporter for 5-HT, is also an important player in 5-HT clearance. The amygdala is one of the richest OCT3 expressing regions in brain, raising the possibility that it is a major regulator of 5-HT tone in BLA, and therefore, could be a potential novel target for therapeutic intervention in stress-related disorders. If and how OCT3 is involved in 5-HT clearance in BLA remains unexplored. Using in vivo chronoamperometry to record 5-HT clearance in BLA, our preliminary data show that blocking OCT3 with decynium 22 (D22) augments the ability of the SERT blocker, fluvoxamine, to do so. Since D22 also blocks other OCT subtypes (OCT1 and 2) and the plasma membrane monoamine transporter, we used corticosterone, a more selective blocker of OCT3, in efforts to pinpoint the dependence of this finding to OCT3. Similar to D22, corticosterone potentiated the ability of fluvoxamine to inhibit 5-HT clearance, in a manner that appears to be independent of corticosterone's actions at glucocorticoid or mineralocorticoid receptors. Taken together these data suggest dual inhibition of SERT and OCT3 enhances 5-HT actions in the BLA. Continuing studies are utilizing viral and optogenetic approaches to dissect neural circuitry involvement in the role of SERT and OCT3 in 5-HT clearance in BLA, and in associated stress-relevant behaviors.

Poster 17

Sex and dose-dependent antinociceptive effects of the JNK inhibitor SU 3327 are mediated by CB2 receptors in female, and CB1/CB2 receptors in male mice in an inflammatory pain model

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Activation of c-Jun N-terminal kinases (JNKs) has been implicated in the development and maintenance of chronic pain, as well as development of tolerance to antinociceptive agents in the opioid and cannabinoid class of compounds. In this study, we evaluated the antinociceptive effects of the JNK inhibitor SU 3327 (0.3 to 30 mg/kg) in the formalin pain model with an emphasis on the sex-specific actions of this compound. In wild-type C57BL6J mice, SU 3327 produced strong antinociceptive effects in the formalin pain model which were mediated by CB2 receptors in females, and both CB1 and CB2 receptors in males. SU 3327 at a dose of 10 mg/kg produced antinociception, hypothermia, catalepsy, and hypolocomotion to a similar extent in both males and females. The antinociceptive effects of SU 3327 were more potent in males at lower doses (1 and 3 mg/kg), however hypothermia, catalepsy and hypolocomotion were absent in both sexes at this lower dose range. Analysis of spinal cords using qPCR following SU 3327 administration in the formalin test revealed changes in cannabinoid and inflammatory markers in females only, and only in the high (10-30 mg/kg) dose conditions. Indeed, females shown increase in CB2 mRNA levels, tolerance (β-arrestin 1) and inflammatory (TNF-α, IL-1β and IL-6) -associated markers. The differences between males and females in this study support sex as an important dose-dependent factor in nociception and antinociceptive response as mediated by JNK and the endocannabinoid system.

Poster 18

Evaluation of the functional roles of PPARα and PPARγ in Δ9-THC's CNS Effects

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Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear receptors that regulate gene expression via ligand activated transcription factors. PPARs includes three isoforms: PPARα, PPARγ, and PPARβ/δ. Early studies suggest that Δ9-tetrahydrocannabinol (THC) is a PPAR agonist and the endocannabinoids (AEA, 2-AG, OEA, PEA) may be natural activators of PPAR and PPAR. Accordingly, these receptors have been considered putative cannabinoid receptors, but no studies have investigated whether they are involved in the classical CNS effects of cannabinoids. To address this question, we explored the role of PPAR and PPAR in THC's cannabinoid-like effects using the tetrad and its subjective effects in an optical intracranial self-stimulation (oICSS) design. We found that 1) pretreatment with GW6471 (a selective PPAR antagonist, 3 and 5 mg/kg) or GW9662 (a PPAR antagonist, 2 and 5 mg/kg) failed to alter THC's effects in the tetrad (analgesia, hypothermia, catalepsy, and immobility) at high doses (10, 30 mg/kg, i.p.). 2) oICSS maintained by optical stimulation of midbrain dopamine neurons in DAT-cre mice was inhibited by THC (3 mg/kg, i.p.), shifting the stimulation frequency-response curve downward and this effect was blocked by pretreatment with GW6471 (3 mg/kg), but not GW 9662 (3 mg/kg). Finally, 3) RNAscope in situ hybridization assays indicated that the PPARα isoform is detected on midbrain GABA neurons in the ventral tegmental area (VTA). These findings suggest that a GABAergic PPAR mechanism may be involved in the expression of THC's aversive effects.

Poster 19

Modulation of the estrous cycle by hormonal contraceptives influences amphetamine preference and dopamine activity in female rats.

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The use of hormonal contraceptives (HCs) is ever-increasing among women in the United States. HCs work in part by altering the rate and manner of ovarian hormone release; however, few studies have sought to characterize the auxiliary influence HCs have on the female brain and behavior. Females are at increased risk of substance abuse, and ovarian hormones such as estradiol and progesterone have been implicated as contributors to this predilection. The purpose of the following experiment was to characterize differences in amphetamine (AMP) preference and subsequent dopamine (DA) activity in naturally cycling or HC-implanted female rats. Rats were conditioned and tested for AMP place preference with either an HC-implant or during estrous cycle stages associated with opposing ovarian hormone levels (i.e., proestrus (high) or metestrus/diestrus (low)). Female rats conditioned and tested in proestrus showed significantly higher AMP place preference compared to metestrus/diestrus or HC-implanted rats and were resistant to extinction of this preference. Additionally, proestrus rats had a significantly higher percentage of active DA cells in the substantia nigra (but not ventral tegmental area) after the final AMP challenge. These results support previous research wherein higher ovarian hormones are associated with increases in drug-addictive behavior and DA activity, while also providing novel insight into how hormone-altering contraceptives may reduce drug- and DA-responsivity in females in a manner similar to what is seen when endogenous ovarian hormone levels are low.

Poster 20

Sex differences in sleep architecture and brain function observed following administration of NMDAR antagonist MK-801

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Accumulating evidence suggests glutamatergic hypofunction is one underlying factor in the pathology of schizophrenia. Administration of MK-801, an NMDAR antagonist, has emerged as a method to induce schizophrenia-like symptoms in animals. However, there are vast sex differences in human symptomology that are underrepresented in animal models. Evidence suggests that prevalence and severity of negative and cognitive symptoms may be greater in males. Furthermore, sex differences in schizophrenia-induced sleep disturbances have also been reported. Present studies used polysomnography and quantitative electroencephalography (qEEG) measures as a translational biomarker approach to determine if NMDAR antagonists can reveal similar sex differences on sleep and brain function in animals. EEG surface electrodes and wireless transmitters were implanted in male (n=8) and female (n=9) Sprague-Dawley rats. 24h homecage EEG recordings were obtained with MK-801 (0.03-0.3 mg/kg, sc) administered 2h into the light cycle. Activity counts were simultaneously observed. ANOVAs followed by Dunnett's multiple comparisons test were used to examine sex differences and dose-dependent differences compared to vehicle. Consistent with previous literature, MK-801 induced hyperlocomotion and decreased NREM and REM sleep. Females were more sensitive, showing a longer duration and magnitude of effects. However, MK-801 induced profound, dose-dependent increases on awake gamma power only in male rats with no comparable increases found in female rats. Gamma power is highly sensitive to glutamate function, and abnormalities have been associated with cognitive impairment and psychotic symptoms in patients with schizophrenia. This is the first report of a blunted response to MK-801's effects in female rats compared to males, and these sex-related differences may correspond with prevalence/severity of symptom subtypes in humans.

Poster 21

Enhancement of compulsive-like opioid-directed behaviors in adulthood following adolescent nicotine exposure.

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The neurobehavioral effects of nicotine exposure during development has emerged as a pertinent societal concern following the rise in popularity of electronic nicotine delivery systems (ENDS) among adolescents in recent years. Nicotine use during adolescence is associated with long-term enhancement of liability for the development of subsequent substance abuse disorders (SUDs) in adulthood; however, the etiology of enhanced SUD liability following adolescent nicotine exposure has yet to be fully elucidated. Previously, our lab has demonstrated that both systemic and intra-insular cortex (IC) delivery of nicotine acutely in adulthood modulates the formation of contextual opioid conditioning and enhances opioid self-administration. In the present study we assessed the effects of chronic nicotine exposure in adolescent rats on context learning and opioid self-administration in adulthood. We demonstrate that, relative to controls, adolescent nicotine treatment (0.4 mg/kg 2x day, PND 34-43) engenders deficits in contextual opioid conditioning that closely resembles the behavioral effects of intra-insular nicotine administration in adulthood. Specifically, nicotine-treated rats were less sensitive to development of morphine conditioned taste avoidance (10 mg/kg) and more sensitive to morphine conditioned place preference (10 mg/kg). Finally, nicotine rats were impacted in the ability to learn an association between environmental contexts and punished drug-taking. Specifically, these rats demonstrated enhanced motivation, relative to controls, to self-administer remifentanil on a progressive ratio schedule in a context that had previously been paired with foot-shock punished remifentanil taking. Given our previous findings, and the role of the IC in contextual drug conditioning, we are currently examining markers of neuronal plasticity in the IC. In summary, we demonstrate that adolescent nicotine exposure engenders compulsive-like opioid seeking in adulthood that is less impacted by the negative consequences of drug taking.

Poster 22

Early Adolescent Ethanol Exposure: Influence of Sex on Ethanol Consumption in Emerging Adulthood in C57BL/6J Mice

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Alcohol is one of the most commonly abused drugs among human adolescents. This pattern of consumption is concerning because it can induce damage to the developing brain in a sex-dependent manner. The purpose of the present study was to determine sex-based differences in ethanol consumption and depressive-like behavior in emerging adulthood following early adolescent intermittent binge alcohol exposure. Forty-eight male and female early adolescent C57BL/6J mice were exposed to air and ethanol vapor between postnatal day (PND) 21-36 in an intermittent fashion, with four 2-day cycles. Three weeks following adolescent exposure, mice were tested for 24 hr intermittent voluntary ethanol consumption from PND 61-77 and subsequent depressive-like behavior (PND 79) using the tail suspension test. Preliminary results show there were no robust changes in ethanol consumption in male and female mice. However, there were long-term reductions in body weight in the male ethanol-exposed mice and transient reductions in food consumption during adolescent ethanol exposure in both male and female mice. For the tail suspension test, there was a trend for a sex-dependent interaction for latency to immobility and boli with females showing a phenotype of greater 'depressive-like' behavior. Currently, data collection for duration for immobility in the tail suspension test and estrous cycle effects on ethanol consumption are in progress. The present work suggests that early adolescent binge ethanol exposure does not readily alter ethanol consumption, but may affect depressive-like behavior in female mice.

Poster 23

Novel Muscarinic Antidepressants that Lack Cognitive Deficits: Some Insights into Key Structural Features of Muscarinic Agonists and Antagonists.

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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. 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. The 3-exo-1-azabicyclo[2.2.1]heptane, 1-azabicyclo[2.2.2]octane, and N-methyltetrahydropyidine 3-substituted-1,2,4-oxadiazoles have proven to be excellent chemical scaffolds for the generation of potent muscarinic agonists/antagonists. Interestingly, addition of a methyl group to the 3-position of the 1,2,4-oxadiazole yields some of the most potent muscarinic agonists currently known. Yet, addition of a cyclopropyl group appears to reduce efficacy and confer antagonist action at muscarinic sites. Herein we show the pharmacological profiles of multiple pairs of methyl/cyclopropyl analogues we have designed in the anticipation of separating antidepressant-like activity from cognitive impairment. (Supported by NIMH Grant 107499).

Poster 24

Effects of e-cigarette aerosols containing nicotine on vesicular glutamate and GABA transporters as well as neurobehaviors in C57/J6 mice.

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Neurobehavioral changes have been observed in animal models exposed to nicotine. These changes are associated with altered neurotransmitters levels such as glutamate and gamma-aminobutyric acid (GABA). It is noteworthy that these two neurotransmitters are transported and released from pre-synaptic neurons into the synaptic cleft. These process are regulated in part by vesicular glutamate transporter (VGLUT1) and vesicular GABA transporter (VGAT). Prior studies have reported that impairments in the expression levels of the glutamate and GABA receptors in preclinical models exposed to nicotine for chronic period of time. However, the modulatory role electronic (e) cigarette vapors-containing nicotine on pre-synaptic proteins such as VGLUT1 and VGAT are not fully investigated. Our study delivered e-liquids-vapors-containing (25 mg/ml nicotine, 30% vegetable glycerin and 70% propylene glycol) into C57/J6 mice (n=10, for each group) for 4 weeks through inhalation. Open field was used to measure the memory recognition using novel-object zone. The expression levels of VGAT and VGLUT1 in the frontal cortex (FC) were determined in our study. Cotinine, a major metabolite of nicotine, and nicotine concentrations were detected in the serum at the end of the study using ultra-performance liquid chromatography-tandem mass spectrometer (UPLC-MS-MS). One way ANOVA followed by Tukey's test was used for statistical analysis. Our work found that e-cigarette vapors-containing nicotine induced changes in memory recognition using novel-object assay in the last week of treatment. Chronic exposure to e-cigarette was also able to modulate VGLUT1 and VGAT expression in the FC. Finally, UPLC-MS-MS assay reported cotinine and nicotine in the serum of mice exposed to e-cigarette for 4 weeks. Our data shows possible link between neurobehaviors alterations and changes in the expression of VGLUT1 and VGAT in mice exposed to e-cigarette aerosols-containing nicotine for 4 weeks. Future studies are needed to investigate the effects of targeting VGLUT1 and VGAT on neurobehaviors in animals chronically exposed to e-cigarette vapors-containing nicotine.

Poster 25

Optogenetic stimulation of the NAc-VTA GABAergic pathway is rewarding and potentiates heroin-related behaviors in mice

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Abuse liability of opioids is driven by drug rewarding effects that are mediated primarily by disinhibition of midbrain dopamine (DA) neurons. DA neurons in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) are controlled by local GABA interneurons and GABA inputs from multiple brain regions including the nucleus accumbens (NAc). We have recently reported that GABA inputs to DA neurons from the substantia nigra pars reticulata (SNr) play a role that is more important than VTA GABA interneurons in opioid reward. However, little is known about the functional role of GABA input from the NAc to VTA in opioid reward. Here we show that: 1.) GABA input from the NAc to the VTA is originated from D1 receptor-expressing medium-spiny neurons (D1-MSNs), as assessed by neural tracing; 2.) RNAscope assays show that mu opioid receptors are highly expressed in D1-MSNs, not D2-MSNs; 3.) contingent optogenetic stimulation of D1-MSN terminals in the VTA produced increases in heroin self-administration and cue-induced reinstatement of heroin seeking; 4.) optical stimulation of D1-MSN terminals in the VTA is rewarding (as assessed by optical intracranial self-stimulation and real-time place preference) and co-releases GABA and substance P (as assessed by electrophysiological assays); 5.) the latter effects can be blocked by pretreatment with D1, D2, or NK1 receptor antagonists. Together, all these findings suggest that: 1.) the NAc-VTA D1-MSN projection pathway plays an important role in opioid reward and relapse; 2.) the rewarding effects caused by stimulation of the NAc-VTA pathway involve DA and substance P signaling; and 3.) the cellular and molecular mechanisms underlying enhanced heroin taking and seeking remain to be determined.

Poster 26

Effects of Ketamine on Reward Sensitivity in Healthy and Chronically-Stressed Rats

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Patients with depression who report high levels of anhedonia (i.e., the loss of pleasure in previously rewarding activities) are more likely to be treatment-resistant and have higher suicide risk. Currently available treatments, such as selective serotonin reuptake inhibitors, are ineffective at treating anhedonia, though the recently-introduced N-methyl-D-aspartate (NMDA) antagonist, ketamine appears to offer rapid and sustained anti-depressant and pro-hedonic effects. The Probabilistic Reward Task (PRT) is a quantitative approach to evaluating hedonia in laboratory subjects, providing behavioral endpoints corresponding to aspects of anhedonia in psychiatric conditions. This task permits the concurrent measurement of response bias, or sensitivity to reward, and discriminability, or task difficulty. A reverse-translated PRT for laboratory animals has been validated in mice, rats, and marmosets, yielding results highly similar to those obtained in humans. The present study was conducted to extend those data by comparing effects of ketamine (2- and 24-hr after injection) on PRT performance in healthy and chronically-stressed rats using an ecologically-relevant stressor (inescapable cold-water [14°C]). Ketamine increased response bias in healthy rats without degrading discriminability. Blunted response biases in stressed rats also could be rescued with ketamine 2- and 24-hr post-injection without altering discriminability—consistent with reports of pro-hedonic efficacy 24-hr post-injection in humans. This study validates this platform as a valuable approach to examine candidate therapeutics for anhedonia.

Poster 27

Synergistic antihyperalgesic and antinociceptive effects of morphine and MP-III-024, a positive allosteric modulator at α2GABAA and α3GABAA receptors

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Opioid and GABAA receptors are both located in central nociceptive pathways and compounds that activate these receptors have pain-relieving properties. To date, the interactive effects of concurrent administration of these compounds in preclinical models of pain-like behaviors have not been assessed. The purpose of this study was to examine the interactive effects of the μ-opioid agonist morphine and the α2GABAA and α3GABAA receptor positive allosteric modulator MP-III-024 in preclinical models of mechanical hyperalgesia and thermal nociception. The antihyperalgesic and antinociceptive effects of morphine and MP-III-024 administered alone were assessed initially, followed by fixed-ratio mixtures of MP-III-024/morphine combinations. Drug interactions were analyzed using isobolographic and dose-addition analyses. In mechanical hyperalgesia assays, each compound produced dose-dependent antihyperalgesic effects, whereas only morphine was effective on thermal nociception. Fixed-ratio mixtures of MP-III-024/morphine were dose-dependently effective in both procedures but produced supra-additive (synergistic) effects in both assays, depending on their relative proportions. Follow-up studies suggest MP-III-024 attenuates morphine-induced locomotor activation. These results demonstrate important interactions between α2GABAA and α3GABAA receptor- and μ-opioid receptor-mediated signals, and suggest that combination therapy may be useful for the treatment of pain-related disorders.

Poster 28

Defining Characteristics of Patients at a Student-Sun Free Clinic Who Use Tobacco in Relation to Sociodemographics.

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Introduction: Many tobacco users are motivated to quit, but lack the resources to do so. Previous studies have found significant sociodemographic differences among these patients. However, there is little to no research on the differences among tobacco users at a student-run free clinic (SRFC), most of whom are uninsured. Methods: Through a comprehensive chart review, sociodemographic data (age, sex, race/ethnicity, and education level) were collected from patients' intake forms. Tobacco users were compared against non-users using chi-square tests to determine significant differences between these groups. Results: About 27.8% of the sample (n=3,767) reported tobacco use. Most users were male (54% vs. 46%, p≈0.00). Compared to other races, there was a higher rate of tobacco use among White (36%, p≈0.00) and Black patients (32%, p≈0.00). Higher educational attainment (Associate degree and above) was associated with lower tobacco use (14% vs. 33%, p≈0.00). Discussion: The prevalence of tobacco use in the sample was above the national average of 14%. Furthermore, the sample also had a higher prevalence when compared to insured populations (18%). These differences may be associated with the patients' lower socioeconomic status (SES). These patients tend to have lower success rates of quitting, despite being just as likely to attempt cessation compared to higher SES populations. This disparity in success rates can be aided through direct intervention methods (e.g. counseling, free nicotine replacement therapy) targeting low-SES populations. Conclusion: Overall, Black and White male patients with lower education may be at higher risk for tobacco dependence. However, other variables may also affect tobacco usage (e.g., transportation constraints). The results could lead to future interventions and new strategies for SRFCs to target at specific patient groups. Future research should look at a broader set of metrics and ascertain reasons for sociodemographic differences observed.

Poster 29

Effects of a novel tamoxifen-analogue (6C) on methamphetamine-induced neurotoxicity

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Amphetamine and methamphetamine have been reported to exert their neurotoxic effects via the activation of the β-isoform of protein kinase C (PKC) which phosphorylates the dopamine transporter (DAT) at N-terminal serines and threonines to increase extracellular dopamine (DA) via reverse transport. Although amphetamine and methamphetamine-induced neurotoxicity is well characterized, no treatment exists for these effects. In this context, the CNS permeant, tamoxifen-analogue PKC inhibitor (6C) has been shown to attenuate amphetamine-induced monoamine release, locomotion and self-administration. Given the mediation of psychostimulant-induced DA release by PKC activity and the role of excess DA to neurotoxicity, the preset study assessed if PKC inhibition by 6C impacts psychostimulant-induced neurotoxicity. In this study, adult female mice were administered a single injection of vehicle or 6 mg/kg of 6C, subcutaneously, 2 h prior to a binge-like regimen of 5 mg/kg of methamphetamine or saline during which they were injected with 5 mg/kg of methamphetamine or saline (IP) every 2 h for a total of four injections. Two days following injections, mice were sacrificed, brains were removed and the striatum was bilaterally dissected to undergo western/immunoblot and HPLC analyses. 6C significantly reduced methamphetamine-induced neurotoxicity when probing for DAT, tyrosine hydroxylase (TH) and DA levels. These results suggest that 6C may be a potential treatment in psychostimulant neurotoxicity. To assess the generalizability of these effects to other psychostimulants, future work should run similar analyses with other amphetamine-related compounds including the new class of beta ketone analogues of amphetamine, the synthetic cathinones, whose effects are mediated by similar and different neurochemical mechanisms.

Poster 30

The CCR5 antagonist Maraviroc reduces the reinforcing effects of fentanyl under a food versus drug choice procedure.

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Opioid use disorders (OUDs) in the general public have posed a significant problem to public health, businesses, and interpersonal relationships. While the abuse-related effects of opioids are primarily mediated by μ-opioid receptors, activation of μ-opioid receptors can also enhance the expression of the proinflammatory chemokines and chemokine receptors, such as CC Chemokine Receptor 5 (CCR5). Additionally, CCR5 activation is hypothesized to positively influence the rewarding properties of opioids. To address the growing need for novel, OUD-targeted pharmacotherapies, we utilized a food versus drug choice procedure to evaluate the outcome of pretreatment with Maraviroc, a CCR5 antagonist, on the relative reinforcing effects of fentanyl. Adult male Sprague Dawley rats (n=5) were trained to respond on a fixed ratio 5 schedule of reinforcement for food (grain pellets) on one lever and fentanyl on the other. Food was available during all five, 20-min components, with escalating doses of fentanyl (0.0032-0.1 mg/kg/inf) available during components 2-4; components were separated by a 2-min intercomponent interval. Pretreatment with naloxone (1 and 3.2 mg/kg, intraperitoneal [IP]) reduced fentanyl choice and simultaneously increased the number of trials completed, whereas pretreatment with the dopamine D2-like receptor antagonist haloperidol (0.1-1.0 mg/kg, IP) reduced both drug choice as well as number of trials completed. Pretreatment with Maraviroc (1-10 mg/kg, IP) attenuated fentanyl-taking, effectively reallocating of responding away from drug and towards food. These findings suggest that CCR5 antagonists such as Maraviroc may be useful for the treatment of OUD.

Poster 31

Sex differences and effects of drug exposure order on the reward-enhancing effects of co-administered nicotine and d-amphetamine.

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Nicotine enhances the value of environmental stimuli and rewards, and reward-enhancement maintains nicotine consumption. d-Amphetamine and other psychostimulants are misused more by women and highly co-used with nicotine. Nicotine, but not cocaine, exposure can potentiate the interactive effects of nicotine and cocaine. We know of no studies examining drug exposure order effects in reward-enhancement, nor examining d-amphetamine. Thus, we examined the effect of exposure order on reward-enhancement by co-administered nicotine and d-amphetamine. We used 20 male and 20 female Sprague-Dawley rats. Twenty rats (10 M, 10 F) completed 33 days of nicotine exposure before 33 days of d-amphetamine exposure (NIC First rats), and 20 rats (10 M, 10 F) received d-amphetamine before nicotine (AMP First rats). We then assessed enhancement within-subjects by examining responding for a visual stimulus following two pre-session injections: one of d-amphetamine (AMP; Sal, 0.1, 0.3, or 0.6 mg/kg) and one of nicotine (NIC; Sal, 0.03, 0.06, 0.1, and 0.3 mg/kg). Data were analyzed with a 4-way ANOVA (Sex x Exposure Order x AMP Dose x NIC Dose). We found a four-way interaction. NIC First females responded more than AMP First females in 0.3 AMP + 0.03 NIC, 0.6 AMP + 0.03 NIC, 0.3 AMP + 0.06 NIC and 0.3 AMP + 0.06 NIC conditions. However, AMP First males responded more than NIC First males in 0.3 AMP + 0.03, 0.6 AMP + 0.03 NIC, 0.1 AMP + 0.06 NIC, 0.3 AMP + 0.06 NIC, and 0.6 AMP + 0.06 NIC, 0.3 + 0.1 NIC conditions. For females, receiving nicotine first heightened interactive effects of low dose nicotine with high dose amphetamine. In contrast, males receiving amphetamine first showed these same heightened interactive effects. Given the role of reward-enhancement in nicotine use, considering prior and current amphetamine use when treating nicotine dependency is warranted.

Poster 32

Understanding Barriers and Facilitators to Obtaining a DEA X-Waiver and Prescribing Buprenorphine Post Waiver Training.

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Opioid use disorder (OUD) is a complex public health challenge. Despite widespread initiatives to increase access to evidence-based treatment for OUD, opioid related morbidity and mortality remain high. Understanding of key barriers and facilitators to office-based OUD treatment is limited. To address this crisis, we rapidly designed and implemented a statewide DEA X-waiver training initiative expanding office-based OUD treatment in Texas. This presentation discusses a research project based on a follow-up survey to all providers who attended a GetWaiveredTX training between March 2019 and February 2020. Participants were asked directed and open-ended questions about barriers and facilitators they experienced in two key milestones of OUD treatment: 1) obtaining the waiver and 2) prescribing Buprenorphine. Analysis testing for differences between waivered and non-waivered groups and between prescribers and non-prescribers. Overall response rate was 20%, 126 responses. Barriers to waivering included complexity of the DEA X-waiver process, perceived lack of professional support and referral network, belief that the waiver is not applicable to provider work, difficulty getting started (pharmacy, staff education, practice management), and belief that waiver training time is too long. Barriers to prescribing were betting started (pharmacy, staff education, practice management) and accessing reimbursement for treatment. Most prevalent facilitators were education and support after training, structural changes to the training process, waiver curriculum changes, increase provider support and shortened waiver training time. Improvements are needed in the waiver process, in facilitating connections in provider networks for mentorship, and in practice/organizational level support for OUD treatment.

Poster 33

Adolescent Sprague Dawley rats exhibit context-dependent sensitization to low doses of METH while preweanling rats do not in a one-trial paradigm.

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Methamphetamine (METH) behavioral sensitization is a phenomenon in which repeated administration of METH elicits an augmented behavioral response. Research has found that even one previous pairing is enough to elicit sensitization. Preweanling rats (postnatal day [PD] 24 or younger) exhibit context-independent METH sensitization, a heightened response regardless of what environment the METH was previously paired. Interestingly, adolescent rats (PD 25-50), do not exhibit any sensitized response to METH. Prior studies have examined a wide range of doses of METH (1-6 mg/kg) on the challenge day, but doses lower than 1 mg/kg METH have not been used. Hence, the present study examined one-trial sensitization in preweanling and adolescent rats using 0.1 and 0.3 mg/kg of METH. PD 18, 28, and 38 male and female Sprague Dawley rats were pretreated with saline or 3 mg/kg METH and placed in a novel activity chamber. They were then taken to their home cage, and 45 minutes later, were given the opposite treatment in their home cage. Specifically, those that received METH were injected with saline, and those that were given saline were give 3 mg/kg METH and placed back into their home cage. During the challenge test (24 hours later), the rats were injected with saline or METH (0.1 or 0.3 mg/kg) before being placed in the activity chamber. Additionally, a separate group of rats were given saline all throughout pretreatment. In contrast to prior studies, we found that PD 29 and 39 adolescent male and female rats, but not PD 19 rats, exhibited context-dependent METH sensitization. Interestingly, sex-related differences were observed as PD 29 and 39 male rats exhibited behavioral sensitization only when challenged with 0.1 mg/kg METH, while female rats exhibited behavioral sensitization to both doses of METH. These findings highlight age and sex-dependent effects of METH-induced sensitization using low doses.

Poster 34

"ER-associated Regulation of Astrocyte Mitochondrial Function during (METH)amphetamine Exposure"

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Astrocytes are key regulators of central nervous system (CNS) health and neuronal function. However, astrocyte mitochondrial dysfunction, such as induced by (METH)amphetamine, threatens the ability of astrocytes to provide the essential metabolic and antioxidant support to neurons. This study examined the endoplasmic reticulum (ER)-mitochondrial interface in response to METH exposure to characterize changes in mitochondrial function, the unfolded protein response (UPR), Ca2+ signaling, and the regulation of mitochondria associated membranes (MAMs). We hypothesized that the ER regulates astrocyte mitochondrial function via Ca2+ and UPR/MAM signaling during METH exposure. The effects of METH on astrocytes were examined under both acute and chronic paradigms in primary human astrocytes. Mitochondrial bioenergetics was assessed using Seahorse extracellular flux analyzer while expression of UPR/MAM mediators were determined using protein expression assays. Ca2+ signaling was measured by confocal microscopy using a genetically encoded calcium sensor. Finally, pharmacological inhibition of the UPR pathways were used to delineate the regulatory mechanisms mediating the changes on mitochondrial function. Our results show both acute and chronic METH exposure increased Ca2+ flux and upregulated the expression of UPR/MAM mediators. Astrocyte metabolic capacity was increased following chronic METH exposure which corresponded to an augmented Ca2+ flux and dysregulated UPR induction. Moreover, pharmacological inhibition of IRE1α impaired astrocyte mitochondrial activity. These findings illustrate the importance of ER-mitochondria communication in regulating astrocyte mitochondrial function and identify a novel possible mechanism to manipulate astrocyte mitochondrial function during neurodegenerative pathologies.

Poster 35

Potential G-Protein Biased Ligands with Nitrogen-Containing Substituents at C9 in the 5-(3-Hydroxyphenyl)morphan Class of Opioids

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Medicinal chemists have long sought to develop opioids 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 -opioid receptor (MOR) without recruiting the regulatory protein -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 develop a library of these compounds and assess their pharmacological potential, we have synthesized a variety of derivatives containing amino groups at the C9-position. As there is no way to model what downstream signaling a molecule will activate upon binding to the MOR, each variation at the C-9 position requires the synthesis of four diastereomers due to the presence of three centers of asymmetry in this class of molecules. Two of these centers are set based on the 5-(3-hydroxphenyl)morphan employed as the precursor, while the third is determined by the nature of the reductant in the reductive amination procedure that introduces the amino group at the C9-position.

Poster 36

Low-dose 6b-naltrexol prevents opioid dependence without blocking antinociception in mice and guinea pigs by a novel inter action with the opioid receptor (MOR).

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Opioid analgesics are effective pain medications but cause addiction and other adverse effects, significantly reducing their therapeutic value. Attempts to lower addiction liability have met with only partial success thus far. Molecular studies have demonstrated that G protein coupled receptors including the opioid receptor (MOR) – the main target of opioid analgesics – can exist in multiple conformations with distinct signaling pathways. Biased opioid agonists have promise to selectively cause analgesia, but addiction liability is not fully resolved. We have developed 6-naltrexol (6BN) as a neutral opioid antagonist with moderate peripheral selectivity, to treat peripheral adverse opioid effects (e.g., constipation), and to reduced addiction liability when combined with opioid analgesics. 6BN has relatively low potency as an opioid antagonist, compared to naltrexone. However, at low doses (<0.05 mg/kg), 6BN potently prevents the formation of opioid dependence in guinea pigs and mice (Oberdick, JPET 350:22 (2016) and Safa, bioRxiv, 2020 mdpi https://doi.org/10.1101/2020.07.25.221192. We have developed a novel MOR model to account for these results (Sadee, Molecules 25, 4163; doi:10.3390/molecules25184163 (2020)). The current study is designed to determine the pharmacokinetics of low-dose 6BN in guinea pigs (0.02 mg/kg s.c.), including high affinity binding in brain. The results show that low-dose 6BN results in relative accumulation of 6BN in the brain at high affinity sites (characterization ongoing). Combining low-dose 6BN with opioid analgesics could yield safer pain therapy and facilitate weaning from opioid use.

Poster 37

A scale-up synthesis of benzylideneoxymorphone hydrochloride.

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According to the 2019 National Survey on Drug Use and Health (NSDUH), over 14 million Americans suffer from alcohol use disorder (AUD). Antagonists of the mu opioid receptor (MOR) block endorphin-mediated reinforcing effects of ethanol; however, presently available MOR antagonists like naltrexone (Vivitrol®) are not effective in all patients, triggering the need to investigate medications that have unique pharmacodynamic profiles. Our efforts to develop bifunctional opioid ligands resulted in 7-E-benzylideneoxymorphone hydrochloride (BOM.HCl), a low-efficacy MOR partial agonist/delta opioid receptor (DOR) antagonist. We required 15g of material to evaluate the therapeutic potential of BOM.HCl for reduction of alcohol drinking in large nonhuman primates. The cross-aldol condensation to generate 7-E-alkylidene-4,5-epoxymorphinans on a small (< 1g) scale suffers from low yields (< 50%) and long reaction times (> 1d). In this study, we tested the effect of solvent, reaction time, and workup conditions on the efficiency of converting oxymorphone hydrochloride to BOM.HCl. Our optimized conditions resulted in 59.3% conversion after 24 hours under refluxing methanol. The use of higher-boiling point alcoholic solvents increased the conversion time, yet also increased the production of undesired side products. Future efforts will determine whether other aspects of the cross-aldol condensation can be optimized (e.g., choice of base) and whether these conditions are broadly applicable to other 4,5-epoxymorphinans.

Poster 38

Changes in drug intake following extended-access self-administration of MDPV, methamphetamine, or cocaine in rats.

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Over 18 million people in the United States alone are classified as having a substance use disorder (SUD). The chronic nature of SUDs often facilitates afflicted individuals developing high levels of dysregulated/compulsive drug-taking. While much work has been done characterizing patterns of drug-taking in rats provided access to traditional stimulants (e.g., methamphetamine, cocaine), few studies have investigated these patterns in rats self-administering synthetic cathinones (e.g., MDPV), despite aberrant drug taking patterns reported by users of this class of drugs. The current studies directly compared changes in drug intake over time in rats with short- (90-minute) or extended- (12-hour) access to MDPV (0.032 mg/kg/inf), methamphetamine (0.1 mg/kg/inf), or cocaine (0.32 mg/kg/inf); grain pellets were concurrently available for responding on the alternative lever. Sessions were conducted 5 days per week to allow additional behaviors (e.g., novel object recognition) to be assessed in a drug-free state. Independent of the drug available for self-administration, responding was almost exclusively allocated to the lever associated with drug infusion relative to grain pellets. Changes in the patterns of drug intake under extended-access conditions differed across drugs, with MDPV maintaining the highest level of drug intake, cocaine intake escalating slightly over the 6-week period, and methamphetamine intake becoming erratic and with extended periods of reduced drug taking by the end of the study. These data support the use of extended-access self-administration to recapitulate patterns of drug intake in individuals with SUD. Future studies will evaluate the impact of extended access self-administration on neurobiological changes (e.g., neuroinflammation, neurodegeneration), with the goal of developing pharmacological strategies to mitigate consequences of prolonged stimulant use.

Poster 39

The Effects of Monoamine Reuptake Inhibitors and Releasers on the Positive Reinforcing Effects of Social Contact

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Access to a social partner is reinforcing and has positive incentive value in humans and rodents. Monoamine neurotransmitters play important roles in prosocial behavior, but little research has examined their role in social reinforcement. The purpose of this study was to determine how pharmacological manipulations of dopamine, serotonin, and norepinephrine influence the reinforcing effects of social contact. To this end, male and female Long-Evans rats were pretreated with acute doses of the selective dopamine reuptake inhibitor, WIN35,428, the selective norepinephrine reuptake inhibitor, atomoxetine, the selective serotonin reuptake inhibitor, fluoxetine, the nonselective monoamine reuptake inhibitor, cocaine, and the nonselective monoamine releasers d-amphetamine and (+)-MDMA. Ten minutes later, the positive reinforcing effects of 30-s access to a same-sex social partner was examined on a progressive ratio (PR) schedule of reinforcement. To determine whether the reinforcement-altering effects of these drugs were specific to the social stimulus, the reinforcing effects of a nonsocial stimulus (30-s access to an athletic sock of similar size and coloring as another rat) was determined in control subjects. WIN35,428, d-amphetamine, and cocaine dose-dependently increased breakpoints maintained by a social partner under conditions in which responding maintained by a nonsocial stimulus was not affected. These data indicate that increases in synaptic dopamine, but not synaptic norepinephrine or serotonin, increases the reinforcing effects of social contact in both male and female rats.

Poster 40

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

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Investigating how choices are made may provide insight into preventing harmful choices and encouraging healthy choices. The sequential choice model is explored in this experiment to predict choice in between two simultaneously available options based on the latency to respond for each option when each is presented independently. The hypothesis of this experiment is that what response is made during a choice situation can be predicted by its latency when it is available alone. Food-reinforced behavior in 16 female Lewis rats was observed under three fixed ratio (FRX) high-cost conditions (FR10, FR20, FR40). The low-cost condition was always FR5. Two levers were presented either simultaneously or independently and the cost (number of responses required) of food for each lever was indicated by one of two tones. The latency of the first response on each lever in each trial, as well as the number of fixed-ratios completed on each lever is recorded. Results suggest the probability of shorter response latency when each option is presented independently significantly predicts the pattern of responding during choice trials, when both options are simultaneously available. This relationship was strongest for pellet delivery when the high-cost condition was FR10 or FR20. This suggests that latency to respond for reinforcement in isolation may predict choice when two options are simultaneously available. Demonstrating this relationship could provide an intervention target for a variety of behavioral allocation disorders, by increasing the latency to respond for a problematic outcome or by decreasing the latency to respond for more healthful outcomes, such that latencies for more healthful outcomes are shorter and thus more likely to be chosen when both options are available.

Poster 41

Development of a Nonhuman Primate Model of Punishment of Alcohol Drinking

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Continued alcohol drinking despite negative consequences is a hallmark of alcohol use disorder (AUD). In rodent models of AUD, persistent drinking in the presence of a punishing stimulus such as the bitter tastant quinine may represent an AUD-vulnerable phenotype. Development of such models may aid in the identification of pharmacotherapies to suppress punishment-resistant drinking. In the present study, we extended an established rodent model to nonhuman primates by determining the punishing effects of quinine on ethanol drinking. Five female rhesus monkeys with >5 years of experience drinking ethanol were studied under two conditions. First, the effects of quinine on ethanol consumption were measured when a 4% ethanol solution was presented in an 800-ml bottle in the home cage. Increasing concentrations of quinine (0.03–3.0 g/L) added to the ethanol solution decreased ethanol consumption (measured in g/kg) in all animals. In the second study, we examined quinine-induced punishment using a choice procedure. The same monkeys were given access to two bottles, a 4% ethanol solution and water, for 3 hours per day, and preference was measured as the percentage of ethanol consumed over the total amount of liquid consumed. Once preference was stable (+/- 15% the mean of the previous 3 days), quinine was added to the ethanol for one day. Results show that quinine decreased intake and preference for ethanol and increased preference for water in a manner dependent on quinine concentration. These results establish a novel, translational nonhuman primate model that will be used to characterize the underlying neurobiological mechanisms of punishment-resistant drinking.

Poster 42

Quit discounting: Sensitivity to health messages and substance cessation prediction.

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Recent work shows that commodity-specific outcomes may improve the clinical utility of discounting measures. This study evaluates how the likelihood of alcohol or cigarette use cessation decreases with probability of health benefit upon cessation (i.e., “quit discounting”). We examine how quit discounting: 1) varies by magnitude of health benefit, 2) is sensitive to public health messaging, and 3) predicts reductions in substance use. Participants (N=485) were recruited using crowdsourcing. Two quit discounting tasks were evaluated for hypothetical illnesses varying in severity (mild/severe; within-subject). Participants were randomized to tasks with a matching mild/severe label or tasks without labels (between-subject). Measures were completed for cigarettes and alcohol and for sandwiches as a control commodity. Participants also completed a 3-month follow-up to assess changes in real-world substance use. We observed systematic reductions in quit likelihood with reduced probabilities of health benefit. We also observed smaller reductions in quit intentions with changes in health benefit for the severe than mild task, and larger magnitude differences between the mild and severe tasks in the health label condition. Smaller reductions in quit intentions were predictive of prospective decreases in cigarette and alcohol use. These relationships remained after controlling for “sandwich” discounting, demonstrating pharmacological specificity. These findings show that intentions to quit are systematically discounted by the probability of health benefit upon abstinence and that this discounting is sensitive to the severity of negative health outcome avoided and public health message framing that severity. The prediction of reductions in real-world substance use signifies an individual difference variable that should be evaluated in clinical settings. Supported by: T32DA07209; R01DA042527

Poster 43

Increased mood disorder symptoms, perceived stress, and alcohol use among college students during the COVID-19 pandemic

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The COVID-19 pandemic caused significant disruption during the spring of 2020. Many college students were told to leave campus at spring break and to complete the semester remotely. This study evaluates effects of this disruption on student well-being. A sample of 148 students (86.5% female, 49.3% White) completed measures of psychological symptoms, perceived stress, and alcohol use during the spring 2020 semester at a university in the southeastern U.S. Their results were compared to those of 240 students (87.9% female, 64.2% White) who completed the same measures in the fall 2019 semester. Participants in spring 2020 reported more mood disorder symptoms, perceived stress, and alcohol use than did pre-pandemic participants. Worry about COVID-19 was negatively associated with well-being in multiple domains. Additionally, White students reported a greater effect of the pandemic on well-being than did African American students. Young adults appear to be less vulnerable to the most serious medical complications associated with COVID-19 but nonetheless experience psychological effects from the pandemic. Universities and practitioners who work with college students can help young adults manage their symptoms and avoid behaviors like risky alcohol use when confronted with stressors such as the COVID-19 pandemic.

Poster 44

The Dopamine D4 Receptor Antagonist L-745,870 Does Not Affect Alcohol Reward or Self-Administration in Male Mice

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Current pharmacotherapeutic treatments for alcohol use disorder (AUD) are only modestly effective, necessitating the identification of new targets for pharmacotherapeutic development. The dopamine D4 receptor (D4R) is a target of interest in the development of medications for psychostimulant addiction but has been largely unexplored for AUD. In this study, we investigated the effects of the D4R antagonist L-745,870 in 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 45

Environmental enrichment reduces cue-induced reinstatement of heroin-seeking in male and female rats after prolonged periods of forced abstinence.

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Contemporary long-term treatments for heroin use disorder demonstrate only limited efficacy in promoting long-term abstinence and prevention of relapse. We have previously demonstrated that environmental enrichment (EE), after heroin self-administration, reduces cue-induced heroin reinstatement in male rats. This study is an attempt to extend the "anti-relapse" effects of EE to female rats and to longer periods between self-administration training and EE treatment. This experiment implemented a 3-phase procedure: Intravenous self-administration (IVSA) (phase 1), varying periods of forced-abstinence (phase 2) and extinction/reinstatement (phase 3). In Phase 1, male and female rats were trained to self-administer heroin for 15 days. In Phase 2, no scheduled events occurred for 3 or 15 days. In Phase 3, half of the rats were placed into EE and the other half in non-EE housing. All rats were subsequently tested for drug-seeking in the absence of heroin and drug-cues for 15 days. On the final day, all rats were tested for reinstatement of heroin-seeking by presentation of drug-paired cues. We found that during reinstatement, EE significantly reduced drug-seeking in male and female rats in both 3- and 15-day forced-abstinence groups. These findings indicate that EE is effective in reducing cue-induced heroin seeking in males and females, and when putative incubation of craving has occurred.

Poster 46

Pubertal timing and deviant peer processes predicting marijuana use initiation: The moderating role of impulsivity.

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Pubertal development is a significant change in young people's lives that can increase the liability of substance use. Some youth may experience difficulty during this transitional state, in particular those who may perceive a greater degree of mismatch between their pubertal maturation and chronological age (i.e., perceived pubertal timing [PPT]). Adolescents who perceive themselves to be more physically developed than their same-age, same-sex peers may begin to orient towards older, more deviant peers. We aim to extend prior work by examining if the association is moderated by personality factors that are developing over the course of adolescence, namely impulsivity. In the present study, we hypothesized that PPT would be positively associated with deviant peer affiliation, which in turn would be related to earlier marijuana use initiation. We also hypothesized that the association between PPT and deviant peers would only be significant at high levels of impulsivity. In a longitudinal study, 342 adolescents ages 10–12 (305 with a family history of substance use disorder, 71 without) and their parents were recruited from the community. Participants completed a baseline assessment and follow-up assessments every six months. The measures used include impulsivity and PPT at age 13, deviant peer affiliation ages 13–16, and time-to-event for marijuana use initiation ages 13–16. For girls only, in support of the primary hypothesis, PPT was indirectly related to earlier marijuana use initiation through its positive association with the deviant peer affiliation. This indirect pathway was moderated by impulsivity such that PPT was only related to deviant peer affiliation at high levels of impulsivity. These findings suggest that, for early-maturing girls, reducing impulsive tendencies may prevent affiliation with deviant peers, and in turn marijuana use initiation.

Poster 47

Characterization of the pharmacological properties of buprenorphine at the human mu opioid receptor.

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In 2017 the US government declared a public health emergency to address the national opioid crisis. The number of overdose deaths involving opioids had been steadily growing since the 1990s and had recently spiked to nearly 50,000 American deaths per year. This targeted effort to reduce opioid use disorder had stalled the upsurge of overdose deaths, but recent reports indicate it is on the rise again. Traditional recovery support services such as group therapy have been ineffective for many patients, thus medication assistance has been used to reduce cravings and withdrawal effects to facilitate recovery. One such medication is buprenorphine. Buprenorphine is a long lasting, low efficacy agonist of the mu opioid receptor (MOR) that is sold under the brand Suboxone®, Subutex®, and Zubsolv®. Even though buprenorphine is FDA approved for the treatment of opioid dependance, there are many conflicting reports in the literature about its molecular pharmacology and interactions with multiple opioid receptor subtypes. In ongoing studies, we are rigorously characterizing the pharmacological actions of buprenorphine at the human MOR. Using a genetically encoded biosensor to monitor cAMP levels in real time in HEK293 cells, buprenorphine antagonized the inhibition of forskolin-stimulated cAMP by the opioid peptide DAMGO. Schild regression analysis of this effect suggests that buprenorphine acts non-competitively at the MOR. Buprenorphine antagonism of fentanyl differed from that of DAMGO suggesting a possible allosteric mechanism that is currently being investigated. Understanding the molecular pharmacology of buprenorphine is necessary toward effective treatment of the complex disease of opioid use disorder. This work is supported by the Addiction Research, Treatment & Training (ARTT) Center of Excellence at UT Health San Antonio and a grant from NIH/NIDA (RO1 DA038645).

Poster 48

Avoidance self-efficacy: Personal indicators of risky sex and substance use among at-risk youth

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Adolescent substance use (SU) has been linked to an increased likelihood of engaging in risky sexual behaviors and contracting sexually transmitted infections. The current study examined predictors of SU and risky sexual behaviors among youth enrolled in residential drug treatment. Specifically, this project investigated whether the relationship between race and avoidance self-efficacy was mediated by individual characteristics that are mutable through intervention (risk-taking and assertiveness). To test this hypothesis, 1,580 adolescents were recruited from eight Midwestern residential drug treatment facilities. Two separate parallel mediation models were performed to examine the indirect effect of race predicting risky sex and SU avoidance through the proposed mediating variables (i.e., risk-taking, assertiveness). Results showed the relationships between race and both SU and risky sex avoidance were mediated by risk-taking and assertiveness. These results highlight the importance of targeting these individual characteristics as a means of promoting confidence in avoiding future SU and risky sexual behaviors for at-risk adolescents.

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