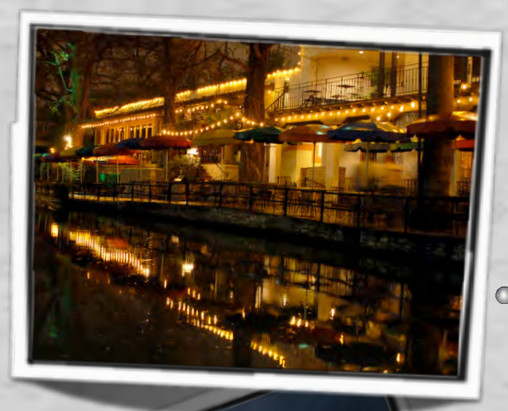
Behavior, Biology, and Chemistry:
Translational Research in Addiction

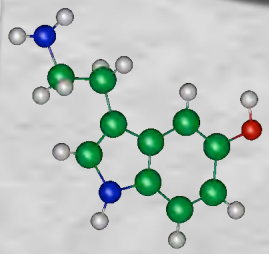
March 14-15, 2015

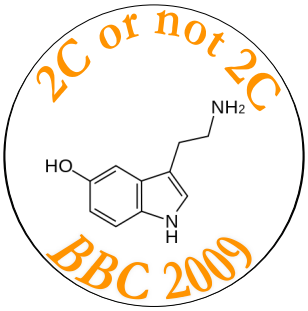
La Quinta Inn & Suites

Medical Center

San Antonio, TX







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Acknowledgements

Sponsors

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Wanda Williams

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Rodolfo Flores	Joseph Pipkin	Alison Wakeford
Brenda Gannon	Christie Pizzimenti	Yafang Zhang
Eric Harvey	Rebecca Pomfrey	
Nathan Holtz	Brittany Priddy	

Program Overview

Friday March 13, 2015

4:00 pm - 6:00 pm	Registration
6:00 pm - 9:00 pm	Opening Reception at Rio Rio on the San Antonio Riverwalk Buses depart from La Quinta at 6:00 pm

Saturday March 14, 2015

7:00 am - 5:00 pm	Registration
8:00 am - 8:05 am	Welcome and Opening Remarks
8:05 am - 10:25 am	Plenary Symposium: "$TAAR_1$: From Chemistry to Behavior and Its Implications in Drug Abuse" Speakers: Gregory Miller, Giuseppe Cecere, David Grandy, Jun-Xu Li (Chairs: Jun-Xu Li and Wouter Koek)
10:25 am - 10:40 am	Coffee Break
10:40 am - 12:00 pm	Open Oral Communications 1 (Chair: Brian Kangas)
12:00 pm - 1:25 pm	**Lunch**
1:25 pm - 2:45 pm	Open Oral Communications 2 (Chair: Paul Romanowich)
2:45 pm - 3:10 pm	Coffee Break
3:10 pm - 4:10 pm	Special Lecture: Amy Newman "Drug design for addiction" (Chair: James Cook)
4:10 pm - 4:30 pm	Poster Set-up
4:30 pm - 7:00 pm	Poster Session
7:00 pm - 9:00 pm	**Dinner** After Dinner Speaker: Robert Balster; "How can you soar like an eagle when reviewers want you to walk like a duck?" (Chair: Ellen Walker)
9:00 pm - 11:00 pm	Hospitality and Entertainment

Sunday March 15, 2015

8:00 am - 9:40 am	Open Oral Communications 3 (Chair: David Maguire)
9:40 am - 9:55 am	Coffee Break
9:55 am - 11:15 am	Open Oral Communications 4 (Chair: William Fantegrossi)
11:15 am - 11:30 am	Coffee Break
11:30 am - 12:30 pm	Special Lecture: George Woody; "Progress in addiction treatment: from one-size fits all to medications and treatment matching" (Chair: Jennifer Potter)
12:30 pm - 12:40 pm	Presentation of travel awards and awards for oral and poster presentations
12:40 pm - 1:30 pm	**Adjournment and Lunch**

See you at BBC 2016!

Program Details

Friday March 13, 2015 (6:00 pm - 9:00 pm)

Opening Reception

Rio Rio on the Riverwalk

6:00 pm	Buses depart from La Quinta
6:30 pm - 9:00 pm	Reception at Rio Rio
9:00 pm	Buses depart for La Quinta

Come and enjoy the beautiful San Antonio Riverwalk. Buses will depart from the La Quinta hotel at 6:00 pm to take you to Rio Rio, a Mexican restaurant on the Riverwalk. Buses will return to La Quinta at 9:00 pm. You will need your badge to board the bus and for dinner. Tickets for spouses and significant others can be purchased in advance or at the registration desk for $40.00.

Saturday March 14, 2015

Welcome and Opening Remarks (8:00 am - 8:05 am)

Plenary Symposium (Chairs: Jun-Xu Li and Wouter Koek)

$TAAR_1$: From Chemistry to Behavior and Its Implications in Drug Abuse

Trace amines refer to a family of minute amount metabolites of aromatic amino acids that include octopamine, tyramine, beta-phenethylamine as well as several other non-catechol amines. Although trace amines were discovered more than 100 years ago, their effects have long been considered non-specific until 2001 when two groups independently cloned a specific trace amine associated receptor (TAAR1). More than a decade has passed since the cloning of TAAR1 and some exciting findings have been emerging in the past several years with the availability of genetically modified mice and the discovery of highly selective TAAR1 ligands. This symposium will discuss the state-of-the-art of TAAR1 research including medicinal chemistry, genetics, pharmacology, and behavior with a special focus on its implications in drug abuse.

8:05 am - 8:40 am	***Gregory Miller***; Northeastern University $TAAR_1$ and drugs of abuse
8:40 am - 9:15 am	***Giuseppe Cecere***; F. Hoffman-La Roche A medicinal chemistry journey toward selective $TAAR_1$ ligands
9:15 am - 9:50 am	***David Grandy***; Oregon Health and Science University The selective $TAAR_1$ antagonist EPPTB reveals two mechanisms of action underlying methamphetamine's stimulant effect in mice
9:50 am - 10:25 am	***Jun-Xu Li***; University at Buffalo Effects of $TAAR_1$ agonists on behavioral indices of drugs of abuse

Coffee Break (10:25 am - 10:40 am)

Saturday March 14, 2015 (continued)

Open Oral Communications 1 (Chair: Brian Kangas)

10:40 am -11:00 am
Brenda Gannon, University of Arkansas for Medical Sciences
In vivo effects of enantiomers of abused "bath salt" constituent 3,4-methylenedioxypyrovalerone (MDPV) in mice: drug discrimination, thermoregulation, and locomotor activity

11:00 am- 11:20 am
Elizabeth Crofton, The University of Texas Medical Branch
Specific knockdown of glycogen synthase kinase 3 beta (GSK3b) in the nucleus accumbens shell decreases neuronal excitability and alters behavior

11:20 am - 11:40 am
Rebecca Pomfrey, American University
The effects of adolescent nicotine exposure on adult cocaine reward, aversion, and self-administration

11:40 am - 12:00 pm
Christina Shin, University of California, Santa Barbara
Incubation of cocaine-craving relates to sensitized glutamate release in the vmPFC in response to cues

Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee
Travel Awardee

Lunch (12:00 pm - 1:25 pm)

Open Oral Communications 2 (Chair: Paul Romanowich)

1:25 pm - 1:45 pm
Raehannah Jamshidi, University of Texas Health Science Center at San Antonio
Structural modifications to the kappa opioid receptor (KOR) agonist, Salvinorin-A, leads to an enhanced antinociceptive profile in peripheral sensory neurons

1:45 pm - 2:05 pm
Fernando Moura, University of Texas Health Science Center at San Antonio
The role of β2 containing subtypes of nicotinic acetylcholine receptors in the discriminative stimulus effects of nicotine, epibatidine, and varenicline in mice

2:05 pm - 2:25 pm
Rachel Slack, NIDA
Using click chemistry toward novel 1,2,3-triazole-linked dopamine D3 receptor ligands

2:25 pm - 2:45 pm
Sherrica Tai, University of Arkansas for Medical Sciences
Convulsant effects of synthetic cannabinoids in mice

Travel Awardee

Coffee Break (2:45 pm - 3:10 pm)

Special Lecture 3:10 pm - 4:10 pm (Chair: James Cook)

Amy Newman, NIDA/NIH: "Drug design for addiction"

Saturday March 14, 2015 (continued)

Poster Set-up (4:10 pm - 4:30 pm)

Poster Session (4:30 pm - 7:00 pm)

Presenters should attend their posters as follows:

4:30 pm - 5:45 pm odd numbered posters

5:45 pm - 7:00 pm even numbered posters

Poster judging (post-doctoral fellows and students) is scheduled for odd- and even-numbered posters as indicated above. Judging begins at the lowest numbered posters and proceeds to higher numbered posters. **There is a 5 minute time limit for presentations**. Three awards will be issued for outstanding poster presentations.

If you do not wish to be included in the poster competition, please notify the registration table.

Dinner (7:00 pm - 9:00 pm)

Tickets for spouses and significant others can be purchased in advance or at the registration desk for $60.00.

After Dinner Lecture (Chair: Ellen Walker)

Robert Balster, Virginia Commonwealth University: "How can you soar like an eagle when reviewers want you to walk like a duck?"

Hospitality and Entertainment (9:00 pm - 11:00 pm)

Come and enjoy the fun in the ballroom!

Sunday March 15, 2015

Open Oral Communications 3 (Chair: David Maguire)

8:00 am - 8:20 am

Comfort Boateng, NIDA
Novel and high affinity D3 receptor-selective ligands as in vivo tools to study addiction

8:20 am - 8:40 am

Nathan Holtz, Rush University Medical Center
The effects of mirtazapine on pramipexole-induced riskiness in a rat model of Parkinson's disease

8:40 am - 9:00 am
Katherine Serafine, University of Texas Health Science Center at San Antonio
Characterization of the behavioral effects of lorcaserin in rat

9:00 am - 9:20 am
Laura Sullivan, University of Texas Health Science Center at San Antonio
Peripheral delta opioid receptor (DOR) function in carrageenan-treated rats is inhibited by lipoxygenase (LOX) metabolites

9:20 am - 9:40 am
Sara Jane Ward, Temple University School of Medicine
Microglial activation and cocaine addiction


Travel Awardee

Coffee Break (9:40 am - 9:55 am)

Open Oral Communications 4 (Chair: William Fantegrossi)

9:55 am - 10:15 am

Brian Kangas, Harvard Medical School
Effects of daily methamphetamine self-administration on learning-to-learn and cognitive flexibility in the nonhuman primate

10:15 am - 10:35 am
Christopher Cunningham, Concordia University
Evidence of biased agonism among diverse cannabinoid CB1 receptor ligands

10:35 am - 10:55 am
Thomas Keck, Rowan University
Neurochemical and behavioral comparison of contingent and non-contingent methamphetamine exposure using binge and long-access yoked self-administration paradigms

10:55 am - 11:15 am
Gregory Collins, University of Texas Health Science Center at San Antonio
Cocaine-caffeine interactions: drug discrimination studies in rats


Maharaj Ticku Memorial Travel Fellowship for New Investigators Awardee

Coffee Break (11:15 am - 11:30 am)

Special Lecture 11:30 am - 12:30 pm (Chair: Jennifer Potter)

George Woody, University of Pennsylvania: "Progress in addiction treatment: from one-size fits all to medications and treatment matching"

12:30 pm - 12:40 pm Presentation of awards for travel, oral, and poster presentations

Adjournment and Lunch (12:40 pm - 1:30 pm)

Abstracts

Oral Communications

1

In vivo effects of enantiomers of abused "bath salt" constituent 3,4-methylenedioxypyrovalerone (MDPV) in mice: drug discrimination, thermoregulation, and locomotor activity

Gannon, Brenda M.[1], Rice, Kenner C.[2], and Fantegrossi, William E.[1]
1–Department of Pharmacology and Toxicology, UAMS, Little Rock, AR 72205
2–Drug Design and Synthesis Section, NIDA and NIAAA, Bethesda, MD 20814

In recent years, synthetic analogues of naturally-occurring cathinone have emerged as psychostimulant-like drugs of abuse in commercial "bath salt" preparations. 3,4-methylenedioxypyrovalerone (MDPV) is a common constituent of these illicit products. As with the more well-known psychostimulant drugs of abuse 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine (METH), MDPV is a chiral molecule; however, the relative contribution of each individual enantiomer to CNS effects has not previously been demonstrated. To examine the behavioral effects of each enantiomer of MDPV, adult male NIH Swiss mice were trained to discriminate 10mg/kg cocaine from saline, and the interoceptive effects of a range of substitution doses of racemic MDPV, S(+)-MDPV, and R(-)-MDPV were then assessed. In separate groups of mice, surgically-implanted radiotelemetry probes simultaneously monitored thermoregulatory and locomotor responses to various doses of S(+)-MDPV and R(-)-MDPV. In these studies, we found that mice reliably discriminated the cocaine training dose from saline, and that doses of 1mg/kg racemic MDPV, 0.3mg/kg S(+)-MDPV, and 10mg/kg R(-)-MDPV all fully substituted for the cocaine training stimulus. Similar to the drug discrimination results, significant potency differences between each MDPV enantiomer and the racemate were observed in biotelemetric assays for motor activity and thermoregulation. These studies suggest that while both the S(+)- and R(-)- enantiomers of MDPV are bioactive, there are significant potency differences between each enantiomer, with the S(+)-MDPV being more potent than R(-)-MDPV. These data contrast with the chiral pyschostimulant METH, where only the S(+)- enantiomer is centrally active, and with MDMA, where both enantiomers are centrally active across a similar range of doses. These studies supported in part by T32 DA022981, UAMS TRI [RR029884], and CTN [RR020146].

2

Specific knockdown of glycogen synthase kinase 3 beta (GSK3β) in the nucleus accumbens shell decreases neuronal excitability and alters behavior.

Crofton, Elizabeth J[1]; Zhang, Yafang[1]; Nenov, Miroslav[1]; Li, Dingge[1]; Laezza, Fernanda[1] and Green, Thomas A[1]

[1]Department of Pharmacology and Toxicology, Center for Addiction Research, Mitchell Center for Neurodegenerative Diseases, The University of Texas Medical Branch, Galveston, TX, USA

Glycogen synthase kinase 3 beta (GSK3β) is implicated to have a critical role in psychiatric disorders including depression and bipolar disorder, but also drug addiction. The often-used mood stabilizer lithium is an inhibitor of GSK3 alpha and beta, although GSK3β is the predominant isoform in the brain. Recent studies found that inhibition of GSK3β in the hippocampus directly effects function of voltage-gated sodium channels and suppresses neuronal excitability. A more thorough understanding of the role of GSK3β in the reward circuitry of the brain could lead to efficacious treatments for drug addiction. In order to explore the role of GSK3β in the nucleus accumbens (NAc), a region critical for reward, we specifically knocked down GSK3β in the NAc shell of rats and examined the electrophysiological and behavioral consequences. We employed a novel adeno-associated (AAV) viral vector using RNA interference to decrease GSK3β. Knocking out GSK3β has previously proven embryonically lethal, but with RNAi we are able to avoid disruption of normal development. We found a significant decrease in spontaneous firing of viral infected NAc shell neurons with loose-patch recordings. Therefore, we examined the behavioral consequences of this reduced neuronal excitability by examining anxiety- and depression-like behavior. We found that decreasing GSK3β in the NAc shell reduces anxiety-like behavior but increases depression-like behavior. Finally, we examined the consequences of decreased GSK3β in the NAc shell on addiction-related behavior. We found that decreased GSK3β increases cocaine-taking and -seeking behavior in the cocaine self-administration paradigm. Further work is exploring the mechanism of the behavioral phenotypes and altered neuronal excitability seen with knock down of GSK3β in the NAc.

3

The Effects of Adolescent Nicotine Exposure on Adult Cocaine Reward, Aversion, and Self-Administration

Pomfrey, Rebecca L.[1]; Bostwick, Tamaara A.[1], Wetzell, B. Bradley[1], and Riley, Anthony L.[1]
[1]Department of Psychology, American University, Washington, DC USA

These studies examined the effects of adolescent nicotine pre-exposure on the rewarding and aversive effects of cocaine and the relationship of these changes to adult cocaine self-administration. In Experiment 1, rats on postnatal day (PND) 28 were divided into two groups and then given daily 0.6 mg/kg injections of nicotine or vehicle (until PND 43). Rats were given baseline and locomotor (every third injection day) tests to examine nicotine-induced locomotor sensitization. They were then allowed to age untreated to adulthood (PND 76), implanted with jugular catheters and allowed to recover for at least five days. On PND 90, they were tested for cocaine self-administration (0.25 or 0.75 mg/kg), progressive ratio (PR) responding, extinction and cue-induced reinstatement. Experiment 2 explored nicotine's potential impact on the balance of cocaine's affective properties. Rats (PND 28- 75) were treated as described above. On PND 76, they were tested for the aversive and rewarding effects of cocaine in a combined conditioned taste avoidance (CTA)/place preference (CPP) procedure. Briefly, rats were given access to a novel saccharin solution, injected with cocaine (5.6, 10 or 18 mg/kg) then placed in CPP chambers. In Experiment 1, the nicotine group showed sensitized locomotor activity over nicotine injections when compared to controls, showing that the nicotine was behaviorally active. All rats in Experiment 1 showed clear, dose dependent responding during cocaine acquisition, PR, extinction and reinstatement, with no nicotine preexposure effect. In Experiment 2, rats showed a significant CTA trial x Drug effect ($p = .012$) with cocaine groups consuming less saccharin over trials with no preexposure or dose group differences. There was no significant CPP (and no interaction with pre-exposure) These studies suggest that adolescent nicotine pre-exposure does not have an impact on adult cocaine self-administration or its affective properties, at least under these specific parametric conditions.

4

Incubation of cocaine-craving relates to sensitized glutamate release in the vmPFC in response to cues

Shin, Christina B., Ruppert-Majer, Micaela A., Serchia, Michela M., Shahin, John R. & Szumlinski,Karen K.
Department of Psychological and Brain Sciences, University of California, Santa Barbara

Relapse to drug-taking is a reoccurring phenomenon impairing addiction recovery that can be triggered by the elicitation of intense drug craving upon re-exposure to drug-paired cues. Cue-elicited drug craving increases in a time-dependent manner during drug abstinence - a phenomenon termed "incubation of craving". The neural substrates of this phenomenon are not fully understood but may involve a sensitization of cue-elicited neurotransmitter release within the ventromedial prefrontal cortex (vmPFC). To test this hypothesis, male Sprague-Dawley rats were trained to lever-press for cocaine (0.25 mg/infusion; 6 h/day), sucrose pellets (45 mg), or for no reinforcer. After 10 consecutive days of self-administration, animals were left undisturbed for either 3 or 30 days where they underwent a 3-h *in vivo* microdialysis session during which they were allowed to respond for presentation of the drug-associated cues, in the absence of reinforcer delivery. As expected, cocaine-trained animals exhibited a time-dependent intensification of cue-reinforced responding that was selective for the lever that previously delivered cocaine while sucrose and control animals did not exhibit a difference in responding across withdrawal. The opportunity to lever-press for cocaine-paired cues elicited a time-dependent sensitization of vmPFC glutamate release during withdrawal, while the capacity of cocaine-cues to elevate extracellular dopamine dissipated with withdrawal. In contrast, the changes in vmPFC glutamate and dopamine elicited by sucrose-paired or neutral cues did not vary with the passage of time during withdrawal. These data provide novel evidence that the glutamate responsiveness of the vmPFC incubates during protracted withdrawal in parallel with the behavioral responsiveness to cocaine-paired cues.

Funded by NIH grant DA024038.

Oral Communications

5

Structural modifications to the Kappa Opioid Receptor (KOR) agonist, Salvinorin-A, leads to an enhanced antinociceptive profile in peripheral sensory neurons.

Jamshidi, Raehannah J[1], Chavera, Teresa A[1], Prisinzano, Thomas E[2], Clarke, William P[1], and Berg, Kelly A[1].
[1]Department of Pharmacology, University of Texas Health Science Center at San Antonio, Texas; [2]Department of Medicinal Chemistry, University of Kansas School of Pharmacy at Lawrence, Kansas.

Functional selectivity, also known as biased agonism, is a term used to describe the ability of drugs to differentially activate signaling cascades coupled to a single receptor subtype. In this study, we compared the agonist activity of the highly selective KOR agonist, Salvinorin-A (Sal-A), to that of its analogue, ethoxymethyl (EOM)-Sal-A. We show here that the addition of an ethoxymethyl group resulted in pronounced differences in KOR-mediated regulation of cellular signaling cascades in peripheral sensory neurons in culture and markedly improved antinociceptive efficacy. In primary cultures of adult rat peripheral sensory neurons, Sal-A inhibited PGE_2-stimulated cAMP accumulation and increased the activity of c-Jun N-terminal kinase (JNK), but not that of extracellular signal-regulated kinase (ERK). In a rodent behavioral model of thermal nociception, intraplantar injection of peripherally-restricted doses of Sal-A into the hindpaw produced robust antinociception. However, the dose response curve (DRC) had an inverted U-shape. The descending limb of the DRC was sensitive to inhibition of JNK activity. Addition of an ethoxymethyl group to Sal-A increased potency (consistent with increased KOR affinity), but not efficacy, of Sal-A to inhibit PGE_2-stimulated cAMP accumulation. Interestingly, unlike Sal-A, EOM-Sal-A increased ERK activation (via a pertussis-toxin insensitive mechanism), but only weakly stimulated JNK activity. When tested in vivo, EOM-Sal-A produced strong antinociception with a similar peak magnitude as that of Sal-A; however, consistent with weak JNK activation, the DRC to EOM-Sal-A was monotonic (not an inverted U-shape). These data strongly support the idea that ligand efficacy for specific signaling pathways can be finely tuned by structural modifications to a ligand, leading to improved therapeutic profiles for the treatment of pain. Supported by: DA024865, GM106035, and TST128233/151325.

6

The role of β2 containing subtypes of nicotinic acetylcholine receptors in the discriminative stimulus effects of nicotine, epibatidine, and varenicline in mice.

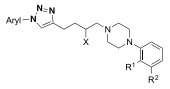
Fernando B. Moura and Lance R. McMahon
Department of Pharmacology, The University of Texas Health Science Center at San Antonio

Tobacco use is due in part to the pharmacological effects of nicotine. Varenicline is a tobacco cessation aid and low efficacy agonist at nicotinic acetylcholine receptors containing β2 subunits (β2* nAChRs). However, it is still unclear which nAChRs mediate the in vivo effects of varenicline and the extent to which low efficacy mediates clinical effectiveness. Drug discrimination was used in the current study to compare the effects of nicotine, varenicline, and the high efficacy nAChR agonist epibatidine. Separate groups of C57BL/6J mice (n=8 per group) were trained to discriminate either varenicline (3.2 mg/kg) or epibatidine (0.0032 mg/kg) from saline under an FR10 schedule of food presentation. Mean number of training sessions for mice to achieve testing criteria were 89±10 and 113±25 for the epibatidine, and varenicline discriminations, respectively, while mean number of training sessions between tests were 6±2 and 9±4 for the respective discriminations. Nicotine and epibatidine produced a maximum of 86-99% drug-appropriate responding among the two discrimination assays. The effects of varenicline were variable within and between mice regardless of the discrimination in which it was tested. The nonselective nAChR antagonist mecamylamine (3.2 mg/kg) antagonized the discriminative stimulus effects of all three drugs, whereas the α7 nAChR antagonist MLA (10 mg/kg) did not. The β2* nAChR antagonist DHβE (3.2 mg/kg) antagonized the effects of nicotine and epibatidine in all of the discrimination assays, whereas DHβE did not significantly antagonize the effects of varenicline in any discrimination assay. The additional training time required to establish and maintain varenicline as a discriminative stimulus, the variable effects of varenicline, and antagonism of nicotine and epibatidine by DHβE in the varenicline discrimination assay are consistent with varenicline having low efficacy. However, the failure of DHβE to antagonize the varenicline discriminative stimulus indicates involvement of multiple receptor subtypes. Supported by USPHS grant DA25267

7

Using Click Chemistry Toward Novel 1,2,3-Triazole-Linked Dopamine D3 Receptor Ligands.

Slack, Rachel D.;[1] Keck, Thomas M.;[1,2] Banala, Ashwini K.;[1,3] Burzynski, Caitlin,[1] Bonifazi, Alessandro;[1] Okunola-Bakare, Oluyomi M.;[1] Moore, Martin;[4] Deschamps, Jeffrey R.;[4] Rais, Rana;[5] Slusher, Barbara S.;[5,6] Newman, Amy H.[1]
[1] NIH/NIDA-IRP/MTMDB/MCS, [2] Rowan [3] GVK Biosciences; [4] NRL; [5]Johns Hopkins University



The dopamine D3 receptor (D3R) is a target of pharmacotherapeutic interest for the treatment of drug addiction. A common molecular template used in the development of D3R-selective ligands incorporates a phenylpiperazine and an extended aryl ring system, connected via a butylamide linker. The amide bond has proven to be synthetically convenient and biologically critical for the high D3R affinity and selectivity of the 4-phenylpiperazine class of ligands; however, when the amide was bioisoterically replaced with a 1,2,3-triazole moiety, the desired D3R-binding functionality of the compounds was maintained. Preparation of the triazole via a copper-catalyzed azide-alkyne click reaction proceeded facilely and allowed for the synthesis of 30 novel compounds. Our studies showed that several of the butyltriazole-linked analogs had binding affinities for D3R in the low nanomolar range and compared favorably to previously evaluated butylamide-linked compounds. Indole-containing 1,2,3-triazole **RDS-02-28**, in particular, had high D3R affinity (K_i = 5.85 nM) and showed high subtype selectivity (165-fold selective for D3R over D2R). Furthermore, when selected compounds were tested for CYP450-mediated phase I metabolism in mouse liver microsomes, **RDS-02-28** and the other 1,2,3-triazole-linked analogs showed modest improvement over the amide-linked analogs. Collectively these studies demonstrate that click chemistry-derived triazoles provide an alternative class of D3R-selective ligands that may have advantages over the traditional benzamides.

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Convulsant effects of synthetic cannabinoids in mice

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Synthetic cannabinoid (SCB) use results in more extreme adverse events than what is typically reported with cannabis exposure. Case reports of seizures and convulsions associated with SCB use have slowly accumulated in the clinical literature, but the mechanism of action for these adverse events is not clear, and reports of convulsions associated with cannabis use are seldom reported. Indeed, much of the impetus behind the medical marijuana movement is its apparent utility in treating epilepsy and seizure disorders. It is thus unclear what properties of SCBs – distinct from those of Δ^9-THC – are responsible for convulsant effects. In these studies, we examined the convulsant effects of acute or chronic SCB exposure, and compared those effects with the classical chemical convulsant pentylenetrtrazole (PTZ) in mice. We found than an acute dose of SCBs JWH-018 or JWH-250 elicited convulsant effects similar to those of PTZ. The convulsant effects of the SCBs were blocked or attenuated by prior administration of the CB1R antagonist / inverse agonist rimonabant, but rimonabant did not alter PTZ-induced convulsions. Pretreatment with the partial agonist Δ^9-THC dose-dependently antagonized JWH-018-induced convulsions, and mice chronically treated with Δ^9-THC or a subthreshold dose of JWH-018 developed tolerance to the convulsant effects of JWH-018. Conversely, mice that received the same chronic cannabinoid regimen were not tolerant to the convulsant effects of PTZ. Finally, PTZ-induced kindling occurred after repeated exposure to a subthreshold dose of PTZ, and subsequent administration of a subthreshold dose of JWH-018 elicited convulsions in these PTZ-kindled mice. Overall, these finding suggest that SCB-induced convulsions occur through a CB1R-dependent pathway, perhaps related to their higher efficacy than Δ^9-THC, and possibility mediated by the same downstream signaling pathways as associated with PTZ-induced convulsions. Supported by RR029884, RR020146 and UAMS Depart. of Pharm. and Tox.

Oral Communications

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Novel and high affinity D3 receptor-selective ligands as in vivo tools to study addiction

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The dopamine D3 receptor (D3R) is involved in brain reward pathways and is a promising therapeutic target for treatment of substance abuse and other neuropsychiatric disorders. Several highly selective and metabolically stable D3R antagonists and partial agonists based on the 4-phenylpiperazine (PP) scaffold have been discovered. One of our most selective and high affinity D3R antagonists, (±)-PG648 (Newman et al. 2009) was selected as a lead for optimization, as well as *in vivo* behavioral evaluation in models of psychostimulant abuse. Although microsomal stability, pharmacokinetic and behavioral data in rats looked promising, (±)-PG648 was not active in nonhuman primates. We hypothesized that, by exploring structural modifications on the (±)-PG648 backbone, novel and metabolically stable ligands with high D3R binding affinity and subtype selectivity would result. In this pursuit, we have prepared analogues in which the 2,3-diCl-phenylpiperazine was replaced with either a 2-OMe,3-Cl-phenyl or a 2,3-naphthyl substituent. In addition, replacement of the indole with a quinoline was also explored. Analogues that were either unsubstituted or had the 3-OH substituted 4-carbon linker between the arylpiperazine and aryl amide were prepared. Previously, the 3-OH substituent has resulted in an increased D3R-selectivity but concomitant metabolic instability. These novel ligands were synthesized and their binding affinities were determined using radioligand binding competition assays in membranes prepared from HEK293 cells expressing human dopamine D2-like receptors. By varying the arylpiperazine substitution, we found several high affinity (K_i=0.1-3.6 nM) compounds with (20-100-fold) selectivity at the D3 versus D2 receptors. Based on binding profiles, a subset of analogues was evaluated in a mitogenesis functional assay in human D2 and D3 transfected CHO cells and was evaluated for off-target activities at 5HT1A, 5HT2A and 5HT2C receptors. Mouse microsomal stability studies supported further development of two analogues in this series: CAB2-015 and BAK4-54. Behavioral studies in WT and D3KO mice that self-administer heroin are underway to determine effectiveness in these models and further define the role of D3R.

10

The effects of mirtazapine on pramipexole-induced riskiness in a rat model of Parkinson's disease

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Riskiness is a common feature of many impulse control disorders (ICDs), such as pathological gambling. It can be measured using probability discounting tasks in which an individual can choose between a small, certain reinforcer, and a larger, uncertain reinforcer. Riskiness is defined as a preference for selecting the large reinforcer when its probability is low. Patients with Parkinson's disease (PD) who are treated with dopamine agonist therapies (e.g., pramipexole; PPX) to alleviate motor deficits are more likely to express the riskiness associated with ICDs than do PD patients prior to PPX therapy or normal controls. The present study used this procedure to assess whether mirtazapine (MIRT), an antagonist at the 5-$HT_{2/3}$ and $\alpha_2$norepinephrine receptors, would reduce PPX-induced riskiness in PD-like rats while still maintaining the therapeutic benefits of PPX. Rats were implanted with a stimulating electrode in the medial forebrain bundle, and lesioned in the dorsolateral striatum with 6-OHDA to induce PD-like motor deficits. They were then assessed in a probability discounting task in which they could choose between small, certain rewarding brain stimulation and a large brain stimulation delivered at various probabilities (i.e., 0.8, 0.5, 0.2, 0.1). Following stability, rats were implanted with subcutaneous osmotic minipumps that infused PPX (1.2 mg/kg/day) for 4 weeks, and behavior was assessed daily. At the start of week 3, rats were implanted with a second minipump that co-infused MIRT (0.5 mg/kg/day) or vehicle with PPX for 2 weeks. PPX increased preference for the larger reinforcer at the 0.2 and 0.1 probabilities compared to baseline, and reversed motor deficits caused by the lesion. MIRT (vs. vehicle) reduced PPX-induced riskiness and did not interfere with the motor enhancing effects of PPX, suggesting that MIRT may be an effective adjunct treatment in PD patients with ICDs. Financial Support: Michael J. Fox Foundation and NIH (USPHSG #NS087559, #DA033121)

11

Characterization of the behavioral effects of lorcaserin in rats

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Lorcaserin is approved by the FDA for treating obesity and its therapeutic effects are thought to be due to agonist activity at serotonin (5-$HT)_{2C}$ receptors. Lorcaserin also binds to other 5-HT receptor subtypes, although its activity at those subtypes is not fully described. The current study used rats to compare the behavioral effects of lorcaserin (0.0032 – 32.0 mg/kg) to those of other 5-HT receptor agonists. The 5-HT_{2C} receptor selective agonist mCPP (0.032 - 1.0 mg/kg) and lorcaserin induced yawning that was attenuated by the selective 5-HT_{2C} receptor antagonist SB 242084 (1.0 mg/kg). The 5-HT_{2A} receptor selective agonist DOM (0.1 – 3.2 mg/kg) induced head twitching that was attenuated by the 5-HT_{2A} receptor selective antagonist MDL 100907 (0.01 mg/kg), lorcaserin (3.2 mg/kg), and mCPP (3.2 mg/kg). Lorcaserin-induced head twitching was revealed only when large doses were combined with the 5-HT_{2C} receptor selective antagonist SB 242084 (1.0 mg/kg). At large doses, lorcaserin also induced forepaw treading that was attenuated by the 5-HT_{1A} receptor selective antagonist WAY 100635 (0.178 mg/kg). While the behavioral effects of lorcaserin in rats are consistent with it having agonist activity at 5-HT_{2C} receptors, these data suggest that, at larger doses, it also has agonist activity at 5-HT_{2A} and 5-HT_{1A} receptors. Lorcaserin is a controlled substance (DEA Schedule IV) and its adverse effects include hallucinations and euphoria, perhaps due to agonist activity at 5-HT_{2A} receptors. Recent evidence suggests that 5-HT_{2C} receptor agonists like lorcaserin might also be effective for treating drug abuse. A better understanding of the activity of lorcaserin at 5-HT receptor subtypes might facilitate the development of new compounds, with fewer adverse effects, for treating obesity as well as drug abuse. This work was supported by USPHS grants T32DA031115and K05DA17918.

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Peripheral delta opioid receptor (DOR) function in carrageenan-treated rats is inhibited by lipoxygenase (LOX) metabolites.

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Opioid receptor systems expressed by peripheral pain-sensing neurons (nociceptors) are under a multi-factorial regulation that appears to be unique to peripheral nociceptors. We have found and reported that opioid receptors (mu, delta and kappa) are functionally inactive under basal conditions. However, pre-treatment with an inflammatory mediator, such as bradykinin (BK) or arachidonic acid (AA), converts opioid receptor systems from an inactive, non-responsive state to a responsive state (i.e., functionally competent). Here we show that functional competence of DOR can also be induced in vivo by brief exposure to carrageenan. Carrageenan produces a state of inflammation that involves the actions of a variety of inflammatory mediators, including BK. When tested 15 min after intraplantar (i.pl) injection of carrageenan (500 µg) into the rat hindpaw, injection of the DOR agonist, DPDPE (20 ug, i.pl.), was effective at blocking the carrageenan induced thermal allodynia. This demonstrates that opioid receptor system functional competence can be induced in response to local inflammation and suggests that peripherally-restricted opioids may be effective at treating pain due to inflammation. However, carrageenan produces a long-term inflammatory state that can last for days. When DPDPE was tested 3 or 24 hrs following injection of carrageenan into the rat hindpaw, it did not block carrageenan-induced thermal allodynia. Interestingly, following injection of the lipoxygenase (LOX) inhibitor, NDGA, into the rat hindpaw 165 min after carrageenan injection, administration of DPDPE 15 min later (i.e., 3 hr following carrageenan) was effective at blocking carrageenan-induced thermal allodynia. These data suggest that, after initial induction of functional competence (15 min), long-term (≥ 3 hr) exposure to carrageenan-mediated inflammatory conditions results in the loss of functional competence of DOR that is mediated by LOX. Further these data underscore the extraordinary regulation of the function of opioid receptors expressed by peripheral sensory neurons. Supported by Owens Medical Research Foundation and NIH grants DA024865, GM106035.

Oral Communications

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Microglial activation and cocaine addiction.

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Recent research illuminates that glia are intimately involved in synaptic plasticity, and that drugs of abuse, in turn, affect glial activity. Specifically, microglia contribute to synaptic plasticity via direct interactions with dendritic spines, synaptic pruning, and regulation of hippocampal neurogenesis. We have combined a series of in vivo, ex vivo, and in vitro experiments to test the hypothesis that cocaine exposure can lead to significant alterations in microglial activation, enhancing cocaine-induced neuroplasticity and contributing to peripheral immune cell invasion, priming the neuroimmune axis for a cycle of neuroinflammation in the context of cocaine addiction. We found that cocaine self-administration increases microglial activation within reward regions of the brain, alongside increases in expression of the transcription factor and synaptic plasticity marker MeCP2. We then determined in vitro that microglia express MeCP2 and that this expression increases significantly following cocaine exposure, suggesting that cocaine's effects on MeCP2 expression may participate in cocaine-induced neuroplasticity. Moreover, we observed that chronic cocaine administration increases cerebrovascular leukocyte rolling and adhesion and subsequent BBB weakening that persists during withdrawal, setting up the likelihood for a persistent dysregulation of neuroimmune signaling that may mirror the cycle of cocaine addiction. This developing narrative identifies novel neuroimmune targets such as activated microglia for treating psychostimulant abuse, for which not a single approved medication exists.

14

Effects of daily methamphetamine self-administration on learning-to-learn and cognitive flexibility in the nonhuman primate.

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Worldwide use of amphetamines exceeds that of heroin and cocaine combined and the illicit use of methamphetamine presents a global health challenge. Chronic exposure to methamphetamine has profound neural impact that may be related to adverse effects on learning. The present study assessed the effects of daily intravenous methamphetamine self-administration on touchscreen-based models of learning in monkeys. Subjects engaged in a repeated acquisition task in which the rate of discrimination learning was assessed over time. Subsequently, the discrimination reversal task was introduced requiring subjects to inhibit a previously reinforced response and respond to the initially ineffective stimulus to obtain reinforcement. Time course between self-administration and touchscreen session was also evaluated. Results indicated that daily methamphetamine self-administration produced markedly deleterious effects on the development of discrimination learning. Importantly, the magnitude of adverse effects was highly correlated with the level of daily methamphetamine intake among individual subjects. Discrimination reversal was largely unaffected. However, when the interval between self-administration and the touchscreen session was reduced, reversal performance was more vulnerable to the direct effects of methamphetamine. These results indicate that methamphetamine can have dramatic deleterious effects on learning and highlights interesting differences between its direct acute effects and the consequences of chronic exposure.

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Evidence of biased agonism among diverse cannabinoid CB1 receptor ligands.

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Biased agonist probes of G protein-coupled receptors (GPCRs) facilitate study of the relationships between GPCR activation of individual intracellular signaling pathways and their influence on behavior. Such ligands also offer great pharmacologic potential, as functionally selective agonists may not produce undesired ancillary effects *in vivo*. The cannabinoid receptor CB1R is an important therapeutic target for reducing pain, stress and anxiety; however, functionally non-selective CB1R activation is associated with tolerance and dependence, learning and memory impairment, and paradoxical anxiogenic behavior. Toward developing functionally selective CB1R ligands, we have begun an investigation into the ability of endogenous and exogenous CB1R ligands to stimulate β-arrestin2 recruitment and inhibit forskolin-induced activation of cyclic AMP (cAMP) *in vitro*. Our results indicate anandamide (AEA) and CP-55,940 are unbiased CB1R agonists when the results of these assays are compared. When the Emax for CP55,940 is used as a comparator, the endocannabinoid, 2-arachidonoylglycerol (2-AG) produced a 3-fold greater recruitment of β-arrestin2 over inhibition of cAMP, whereas phytocannabinoid Δ9-tetrahydrocannabinol (Δ9-THC) produced a 4-fold greater inhibition of cAMP over β-arrestin2 recruitment. The CB1R allosteric modulator, GBR-12909 showed dose-dependent decrease in CP-55,940-induced β-arrestin2 recruitment that was coupled with no modulation of G protein activation ([35S]GTPγS assay) or cAMP inhibition. Our results support the hypotheses that 1) functionally selective CB1R orthosteric agonists can be designed through modification of molecular structure, and 2) that GBR-12909 selectively stabilizes a CB1R active state conformation that prevents β-arrestin recruitment. *This study was supported by R01 DA026996 (CJH) and a New Investigator Award from the American Association of Colleges of Pharmacy (AACP, CWC).*

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Neurochemical and behavioral comparison of contingent and non-contingent methamphetamine exposure using binge and long-access yoked self-administration paradigms.

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Abuse of the highly addictive psychostimulant methamphetamine (METH) can cause long-lasting damage to brain monoaminergic systems. Among the profound physical and mental health problems for individual users, METH abuse is associated with cognitive impairments affecting executive function, working memory, and motor performance. Animal models of METH exposure have been useful in dissecting the molecular effects of the drug on cognitive processes, but most studies to date have utilized acute, non-contingent administrations of METH which do not adequately approximate human METH use. Recent reports suggest long-term, contingent METH exposure via long-access (6-hr; LgA) self-administration paradigms may induce cognitive deficits. In this study, we sought to directly compare the differences in behavioral and neurochemical outcomes of rats following non-contingent "binge" METH administration with rats that received chronic METH via contingent or yoked (non-contingent) LgA METH self-administration in order to better understand the role of contingency and patterns of exposure in METH-induced cognitive impairments. Compared to saline controls, METH reduced striatal dopamine and hippocampal 5-HT levels in binge animals but not LgA animals. Hippocampal BDNF levels were reduced in both binge animals and LgA animals; however, hippocampal TrkB levels were increased only in binge animals. No clear deficits were seen in Y-maze or novel object recognition experiments, but contingent LgA animals had decreased performance in a Morris water maze task of spatial learning and memory. These results show that the pattern of drug exposure and the contingency of administration can differentially affect neurochemical outcomes and behavior in cognitive tasks.

Oral Communications

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Cocaine-caffeine interactions: drug discrimination studies in rats.

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Caffeine is the most widely used psychoactive substance. In addition to high levels of voluntary consumption, caffeine is often used to adulterate illicit drugs (e.g., cocaine, methamphetamine, synthetic cathinones, etc.), in part because it is cheap and legal, but also because its mild stimulant properties are thought to mimic, and possibly enhance, the abuse-related effects of illicit stimulants. In order to test the hypothesis that caffeine enhances abuse-related effects of cocaine, male Sprague-Dawley rats (n=7) were trained to discriminate 10.0 mg/kg cocaine from saline under a multiple-component, two-lever discrimination task using fixed ratio 10 schedule of food presentation. Alone, cocaine and caffeine both dose-dependently increased cocaine-appropriate responding; however, unlike cocaine, caffeine failed to produce exclusive selection of the cocaine-appropriate lever in all rats. Because the nature of drug interactions can vary depending on the proportions at which drugs are combined, dose-response curves for cocaine:caffeine mixtures were generated at three fixed dose ratios (3:1, 1:1, and 1:3). The effectiveness of each cocaine:caffeine mixture to increase cocaine-appropriate responding was then compared to the dose-response curve predicted for a purely additive interaction between cocaine and caffeine. Although a significant main effect was observed for mixtures at the 1:1 and 1:3 ratios, all three of the cocaine:caffeine mixtures were found to be supra-additive at at least one dose level. In addition to demonstrating that caffeine synergistically enhances the discriminative stimulus effects of cocaine, these findings suggests that other abuse-related or toxic effects of cocaine might be similarly enhanced in individuals using both caffeine and cocaine, or when using cocaine that has been adulterated with caffeine.

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Poster Communications

1

Differential Activity of Decynium-22 Analogs: Novel Targets for Probing Low-Affinity/High-Capacity Biogenic Amine Transporters

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We study neurotransmitter clearance by low-affinity, high-capacity uptake-2 transporters. This family includes plasma membrane monoamine transporter (PMAT) and three organic cation transporter isoforms (OCT1-3). We have shown uptake-2 transporters limit the effectiveness of the selective serotonin reuptake inhibitor (SSRI) fluvoxamine. Discerning the transporter type(s) involved is restricted by the unavailability of highly selective ligands. This partnership project examines the pharmacological characteristics of novel uptake-2 compounds. Activity of novel analogs, structurally based on the non-selective inhibitor decynium 22 (D22), were tested in human OCT3-HEK cells. Ligand competitions of [^{3}H]MPP$^+$ uptake were measured in whole, attached cells. Compared to D22, dose-responses of ANSTO compounds shifted 1- or 2 log-rightward, indicating they are less potent inhibitors of OCT3 mediated [^{3}H]MPP$^+$ uptake. ANSTO analogs displayed similar potencies to corticosterone. The IC_{50} values for each compound tested were as follows (in μM): ANSTO 301 (3.9), ANSTO 302 (2.5), ANSTO 303 (0.76), ANSTO 304 (0.71), ANSTO 305 (0.41), ANSTO 306 (0.71), ANSTO 307 (1.2), corticosterone (1.3), decynium 22 (0.072). ANSTO analogs may have higher selectivity at alternate uptake 2 subtypes. Analyses in PMAT over-expressing cells are ongoing. Analogs and SSRI competitions will be measured in brain preparations from OCT3 knockout & PMAT knockout mice for physiological comparisons to cell overexpression systems. These studies will reveal more about the pharmacological profile of these novel compounds for their potential therapeutic application to treat disorders with neurotransmitter dysregulation, such as depression and drug abuse. Supported by NIH MH093320 and NRSA T32DA031115.

2

The evaluation of functionally selective of kappa opioid receptor (KOR) ligands and downstream ERK1/2 phosphorylation

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The modulation of kappa opioid receptors (KOR) is a promising drug discovery target due to KOR involvement in pain, depression, and addiction behaviors. However, the dysphoric effects associated with KOR agonists limit their therapeutic potential and these effects have been suggested to result from KOR interactions with beta-arrestin2 (βarr2). Ligands that induce signaling via the KOR favoring G protein pathways over βarr2 recruitment could provide useful pharmacological tools for elucidating the role that KOR-βarrestin2 mediated signaling plays in the physiological responses to KOR activation. Recently, we published compounds with this desired profile and identified that these analogues induce less ERK 1/2 map kinase activation than the reference agonist, U69,593. Herein, we report additional compounds of the triazole scaffold that display structure activity relationships for the modulation of ERK 1/2 phosphorylation while still maintaining G protein coupling over βarr2 recruitment bias. By developing biased KOR agonists with differentiating downstream profiles it is our hope that these compounds will provide useful pharmacological tools in defining complex KOR signaling and elucidating the significance of KOR-mediated signaling.

This work was supported by NIDA grant 5 R01 DA031927

3

Altered striatal function and sensitivity to the norepinephrine reuptake inhibitor, Desipramine, in selectively bred obesity-prone versus obesity-resistant rats.

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The current obesity epidemic in the US and abroad has heightened the need to understand neural mechanisms that may contribute to over-consumption and obesity. Recent work has highlighted the importance of the mesolimbic reward pathway in abnormal eating behaviors. This neural system is well known to be involved in reward-related decisions and activation of this pathway has been linked to aberrant motivation for both food and potentially addictive drugs. Here we used a selectively bred rat model to examine potential pre-existing differences in mesolimbic function in obesity-prone (OP) versus obesity-resistant rats (OR). Our work shows that OP rats are sensitized to the locomotor activating effects of cocaine compared to OR rats (7.5-30 mg/kg). We then used microdialysis coupled to LC-MS to examine basal and cocaine-evoked (15 mg/kg) levels of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) and their metabolites (3 min sample collection) in the ventral striatum of obesity-prone and obesity-resistant rats. We found no differences in basal concentrations of these transmitters, and a similar cocaine-induced increase in striatal dopamine levels in OP and OR rats, despite enhanced locomotor activity in OP rats. These data suggest locomotor differences are likely due to post-synaptic dopamine-receptor mediated effects. This possibility is currently being explored. In addition, cocaine injection produced an increase in striatal norepinephrine levels only in OP rats. As cocaine is also an effective norepinephrine reuptake inhibitor, we next determined whether OP rats are more sensitive to the eating-suppressant effects of the norepinephrine reuptake inhibitor desipramine (3-10 mg/kg). Preliminary results suggest that OP rats are more sensitive to the appetite suppressant effects of desipramine than OR rats. These data will be discussed in light of the role of mesolimbic systems in reward and motivation.

4

Title: Exploring the relationship between cocaine and food demand elasticity and reinforcer choice: Preliminary results.

Authors: Jung S. Kim, American University; David N. Kearns, American University

Drug addiction has been conceptualized as persistent choice of a drug reinforcer (e.g., cocaine) over non-drug alternatives. Recent studies in rats investigating the choice between cocaine and non-drug reinforcers like food have found considerable individual-subject variability in choice behavior. It is unknown whether rats that prefer cocaine over the non-drug alternative do so because cocaine has especially high value for them or because the non-drug alternative has especially low value. The current study used a behavioral economic measure known as essential value, which scales different reinforcers in terms of a common metric that reflects the reinforcers' demand elasticity, to determine how individual rats' valuations of cocaine vs. a food alternative influenced the choice between them. Male Long-Evans rats were first trained to lever press for cocaine infusions (1.0 mg/kg) and for food (45 mg grain pellet) in separate components of a session. Initially, rats responded for each reinforcer on a fixed-ratio (FR) 1 schedule. Subsequently, the FR requirement was increased in an exponential manner over 3-session blocks up to a maximum FR value of 560 or until rats stopped responding. Resulting demand curves were analyzed and essential values for both reinforcer types were calculated. Upon completion of this phase, rats experienced choice sessions during which they were able to freely choose between cocaine and food, with each available on an FR-1 schedule. Preliminary results indicate that the essential value of cocaine, but not food, was a significant predictor of choice between the two reinforcers. Results suggest that individuals that choose cocaine over the non-drug alternative do so because they have an especially high value for cocaine.

Poster Communications

5

Interactions between the antinociceptive effects of spiradoline and CP55940

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Pain continues to be a significant clinical problem, and there is a need for novel pharmacotherapies that are more effective and have fewer adverse effects relative to currently available drugs (e.g., mu opioid receptor agonists [oxycodone]). Kappa opioid receptor agonists such as spiradoline have marked antinociceptive effects but their use is precluded by adverse effects; nevertheless, their therapeutic potential might be improved if their antinociceptive effects could be selectively enhanced. Cannabinoid receptor agonists such as CP55940 enhance the antinociceptive effects of mu opioid receptor agonists, though it is unclear whether cannabinoids impact the antinociceptive effects of kappa opioid receptor agonists. This study examined the effects of CP55940 and spiradoline administered alone and in combination in rats (n=7) using a warm water tail withdrawal procedure. When administered alone, CP55940 (0.032-1.0 mg/kg, i.p.) and spiradoline (1.0-32.0 mg/kg, i.p.) dose-dependently increased tail withdrawal latency from warm (50 and 55°C) water. Combinations of CP55940 and spiradoline in ratios of 1:3, 1:1, and 3:1 also dose-dependently increased tail withdrawal latency, and the effects of combinations were consistent with an additive interaction. Whether this interaction generalizes to the antinociceptive effects of other kappa opioid/cannabinoid combinations, effects with other pain modalities, or effects other than antinociception is currently unknown. To the extent that cannabinoids enhance some (antinociceptive) but not other (e.g., adverse) effects of kappa opioid receptor agonists, combinations of cannabinoids and kappa opioids might be useful for treating pain. Supported by USPHS grant K05DA017918.

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The effects of prior aversive events on intravenous self-administration and reinstatement in rats

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Even following long periods of abstinence individuals with anxiety disorders have high rates of relapse to drugs of abuse. Although many current models of relapse demonstrate effects of stress, most of these studies examine stressful experiences that occur in close temporal and physical (i.e., within the same context) proximity to the reinstatement test. Little is known about how potentially stressful or fearful experiences in other contexts can cause persistent changes in drug-seeking behavior. In three experiments we examined the effects of fear conditioning on drug-seeking for psychostimulants. In Experiment 1, presentation of a cue previously paired with shock failed to induce reinstatement of cocaine seeking; however, reinstatement was observed following a priming injection of cocaine. In Experiment 2, animals were trained to self-administer intravenous methamphetamine, followed by extinction. They then received either a battery of 15 shocks in a distinct environment or exposure to that context only. Twenty-four hours later animals received a single shock in the self-administration context, and while this failed to produce reinstatement, animals that received a battery of shocks the day before froze significantly more than controls. In Experiment 3 the battery of shocks were administered during acquisition of self-administration. Animals that received shock reinstated significantly more than controls to drug-associated cues and took significantly longer to extinguish lever pressing following drug-cue-induced reinstatement. Taken together, these results suggest that a history of fear conditioning may escalate drug intake during acquisition, as well as induce greater rates of reinstatement to drug-related cues, and confer resistance against extinction following reinstatement. This novel model of fear conditioning and drug intake will allow for the investigation of therapies that might attenuate behaviors that contribute to drug addiction.

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Abuse liability of the novel benzofuran 6-APDB

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Benzofurans, sold online as “benzo-fury,” represent a class of designer drugs that have gained popularity on the ever-expanding market of “legal highs.” Users report that these compounds produce entactogen-like effects similar to MDMA. The current study aims to investigate the behavioral effects and abuse liability of the novel benzofuran 6-APDB. The locomotor effects of 6-APDB were tested in male Swiss-Webster mice over an 8-hour period in an open-field assay of locomotor activity. The discriminative stimulus effects of 6-APDB were tested in separate groups of male Sprague-Dawley rats trained to discriminate cocaine, methamphetamine, or MDMA from vehicle. The rewarding effects of 6-APDB were tested in male Swiss-Webster mice using a conditioned place preference assay. 6-APDB produced locomotor stimulation at 5 and 10 mg/kg starting 30-minutes post-injection and lasting approximately 3 hours. 6-APDB fully substituted for the discriminative stimulus effects of MDMA at 1 mg/kg, but produced low levels of drug-appropriate responding for cocaine- and methamphetamine-trained rats at the same dose. 6-APDB produced conditioned place preference. Our results indicate that 6-APDB produces hyperlocomotion, conditioned place preference, and discriminative stimulus effects similar to MDMA, suggesting that 6-APDB may have potential for abuse. The substitution of 6-APDB for MDMA, but not cocaine or methamphetamine, suggests that this compound may be used as a substitute for MDMA in a club or rave setting, especially as MDMA becomes more difficult to obtain.

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Involvement of CaMKII within the Prefrontal Cortex and the Nucleus Accumbens in the effects of TAAR1 Agonist on Reinstatement of Cocaine Self-administration in Rats

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The trace amine-associated receptor 1 (TAAR1), a novel G protein coupled receptor, has proven to play a crucial role in modulating the dopaminergic system in brain. Our recent study demonstrated that systemic administration of TAAR1 agonist decreased cue- or drug-induced reinstatement of cocaine self-administration in rats. However, the neuronal mechanism underlying the role of TAAR1 in cocaine addiction remains unknown. Here, we examined the effect of selective TAAR1 agonist RO5166017 on cocaine relapse in rats, and investigated the underlying mechanism. Rats were tested drug-induced reinstatement one day after extinction of cocaine self-administration. RO5166017 was administrated 10 min before reinstatement test. Two hours after cocaine reinstatement test, rats were decapitated and tissues of two critical brain regions in drug addiction, the prefrontal cortex (PFC) and the nucleus accumbens (NAc), were harvested for examining the alterations of related molecules. The results showed that RO5166017 (10 mg/ kg, i.p.) reduced cocaine priming-induced reinstatement of cocaine seeking. Cocaine priming elevated the levels of phosphorylated Ca2+/calmodulin-dependent protein kinase II (pCaMKII) and phosphorylated extracellular signal-regulated kinases 1/2 (pERK1/2). Although RO5166017 prevented cocaine priming-induced increase in pCaMKII in both the PFC and the NAc, it did not affect the level of pERK1/2. Furthermore, cocaine priming or RO5166017 did not change the levels of total CaMKII and total ERK1/2 in both brain regions. Altogether, these results suggested that CaMKII-dependent signaling pathway within the PFC and the NAc may mediate the role of TAAR1 in drug-induced reinstatement of cocaine self-administration.

Poster Communications

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Insulin Modulates the Enhanced Rewarding Effects of Nicotine in Diabetic Versus Control Rats

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Rationale: The underlying mechanisms that promote tobacco use in persons with diabetes are not clear. Work in our laboratory has demonstrated that diabetic rats display enhanced rewarding effects of nicotine in conditioned place preference (CPP) and intravenous self-administration (IVSA) procedures. This study examined whether the latter effects are insulin-mediated. **Methods**: Male rats first received administration of streptozotocin (STZ), a drug that destroys insulin-producing cells in the pancreas and produces hyperglycemia. After STZ administration, the rats were either surgically implanted with an insulin pellet or they received a sham surgery. Two-weeks later, the rats were implanted with IV catheters and were tested for nicotine IVSA and others were conditioned with repeated nicotine injections in the presence of distinct environmental stimuli in our CPP apparatus. **Results**: Insulin replacement normalized the rewarding effects of nicotine in diabetic rats to control levels in the IVSA procedure. However, insulin did not alter nicotine reward in the CPP paradigm. **Conclusion**: Our results suggest that insulin modulates the direct reinforcing effects of nicotine, as measured by the IVSA studies. However, insulin may be less critical for modulating the conditioned reinforcing effects of nicotine as assessed in CPP procedures. Future studies are needed to further explore the mechanisms by which insulin modulates the rewarding effects of nicotine in diabetic rats.

10

Discriminative-stimulus effects of tramadol: an individual subjects analysis of mu opioid-receptor mediated effects.

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Drug discrimination procedures use dose-dependent generalization, substitution, and pretreatment with selective agonists and antagonists to evaluate receptor systems mediating interoceptive effects of drugs. Despite the extensive use of these techniques in the nonhuman animal literature, few studies have used human subjects. Specifically, human studies have not routinely used antagonist administration as a pharmacological tool to elucidate the mechanisms mediating the discriminative stimulus effects of drugs. This study evaluated the discriminative-stimulus effects of tramadol, an atypical analgesic with monoamine and mu opioid activity. Three human subjects first learned to discriminate 100 mg tramadol from placebo. A range of tramadol doses (25 to 150 mg) and hydromorphone (4 mg) with and without naltrexone pretreatment (50 mg) were then administered to subjects after acquiring the discrimination. Each subject's drug discrimination, physiological, and subjective effects data were individually examined and analyzed for tramadol drug discrimination, hydromorphone substitution, naltrexone antagonism. Tramadol produced dose-dependent increases in drug-appropriate responding and hydromorphone partially or fully substituted for tramadol in all subjects. These effects were attenuated by naltrexone. Individual subject records indicated a relationship between mu opioid activity (i.e., miosis) and drug discrimination performance. Our findings indicate that mu opioid activity may mediate the discriminative-stimulus effects of tramadol in humans. The correspondence of generalization, substitution, and pretreatment findings with the animal literature supports the neuropharmacological specificity of the drug discrimination procedure.

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A novel mechanism for ethanol reward.

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Addiction to psychoactive substances is detrimental to society, causing myriad public health, economic, and legal issues. There are serious gaps in our knowledge behind the cellular mechanisms of addiction. Using the Allen Brain Atlas to identify genes with selective expression in the ventral tegmental area and substantia nigra we identified retinoic acid as a substrate for addiction. Further, we hypothesized the rewarding effects of ethanol are due primarily to inhibition of retinaldehyde dehydrogenase (RALDH) in this area and that administration disulfiram, a small molecule inhibitor of RALDH, would result in increased locomotor activity, an effect similar to ethanol. We implanted 11 rats with bilateral cannulae inserted into the pVTA. Solutions contained disulfiram suspended in 20% hydroxypropyl beta-cyclodextran with that vehicle as the control. The first experiment involved microinjection via the cannulae of either solution (N=6) or vehicle (N=5) after allowing them to acclimate in the chambers for an hour. Locomotor activity was then recorded after the injection. Our second experiment utilized IP injections to complement the results of the microinjection. Injection of disulfiram directly into the pVTA and systemically each increased locomotor activity. Disulfiram, the RALDH inhibitor, was capable of producing significant locomotor stimulation in our study, thus supporting our hypothesis that RALDH is intimately associated with the reward. Thus, these data support our novel overall hypothesis that ethanol exerts its rewarding effects via a competitive inhibition of retinoic acid synthesis. Ongoing studies are exploring this relationship further by analyzing retinoic acid and retinal levels in the pVTA of rats exposed to ethanol.

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Sex-related differences in the time lag between transdermal alcohol and breath alcohol concentrations.

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The purpose of the present study is to examine the time difference delay, or time lag, in transdermal alcohol concentrations (TAC) and breath alcohol concentrations (BrAC) and to further examine the effects of sex and dose in peak TAC vs. BrAC. Previous research has reported varied and inconsistent time differences in the time to peak TAC vs. peak BrAC. In the current study, participants (32 men, 29 women) were pooled from 3 laboratory studies. In all studies, participants consumed 1, 2, 3, 4, and 5 beers on consecutive study days and wore a transdermal alcohol monitor. Breath alcohol concentrations were measured approximately every 15 minutes for the first 4 hours post-alcohol consumption and every 30 minutes thereafter. There was a dose-related increase in TAC and BrAC, with women tending to have higher peak TAC and peak BrAC than men. Sex differences in both peak TAC and BrAC increased as a function of the number of beers consumed. In addition, the TAC to BrAC ratio came closer to 1 as the number of beers increased. Smooth curves depicting the average time curve of TAC and BrAC for each sex at each beer consumed are also presented. There were no sex- or dose-related differences in the time to peak TAC; however, the time to peak BrAC was longer for women than men. There was no sex difference in the lag time between the time to peak TAC vs. peak BrAC; however, the time lag tended to increase as a function of the number of beers consumed. In conclusion, sex differences are present in the peak of drinking events, as well as the time to the peak; however, no such sex difference exists in the lag time between TAC and BrAC. Future research examining "real world" drinking events and the influence of biological factors such as liver size and skin differences on transdermal alcohol monitoring among light, moderate, and heavy drinkers should be conducted.

Poster Communications

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Attenuation of cue-induced reinstatement of nicotine-seeking behavior by selective blockade of α7 nicotinic acetylcholine receptors in the nucleus accumbens core region of rats

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Our previous studies (Liu et al, 2007, Liu 2014) have showed that neurotransmission via the α7 subtype of nicotinic acetylcholine receptors (nAChRs) plays a role in mediation of conditioned reinforcement by nicotine cues. This study, using a response-reinstatement model of cue-induced relapse in rats, examined neuroanatomical substrates for the suppressant effect of α7 nAChR blockade on the reinstatement of nicotine-seeking responses induced by nicotine cues. Male Sprague-Dawley rats were trained in daily 1-h sessions to intravenously self-administer nicotine (0.03 mg/kg/infusion, free base) on a FR5 schedule. To establish nicotine-conditioned cues, presentations of a neutral sensory stimulus were associated with each nicotine delivery. After lever responding was extinguished by withholding nicotine delivery and its cues, the reinstatement sessions were conducted where the cues were response-contingently re-presented without nicotine availability. Five min prior to the test sessions, rats were subjected to pretreatment with either α7- or α4β2-selective antagonist microinjected into the nucleus accumbens core (NAc) and ventral tegmental area (VTA). Under saline pretreatment condition, re-presenting the cues reinstated responses on the previously active, nicotine-reinforced lever, indicating conditioned incentive properties of nicotine cues. Injection of the α7-selective antagonist methyllycaconitine (MLA) in the NAc but not VTA effectively reduced the magnitude of cue-reinstated lever responses. Similar results were obtained with another α7-selective antagonist α-conotoxin ArIB (ArIB). However, no change was observed after microinjection of dihydro-β-erythroidine (DHβE), a α4β2-selective antagonist. These results indicate that nicotinic neurotransmission via the α7 nAChRs in the NAc region is required for the expression of conditioned reinforcement by nicotine cues, shedding a light on our understanding of the neurobiological mechanisms for smoking relapse triggered by exposure to environmental cues.

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Cholinergic Genetic Variation Moderates Smoking-Induced Striatal Dopamine Release

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Treatment for nicotine dependence, measured by successful smoking cessation, continues to be an enigmatic problem in addiction research. Recent work shows that genetic variation in smoking-induced dopamine (DA) release may be relevant to clinical smoking phenotypes. While we previously reported genetic variants in DA systems (transporter, DRD4 receptor, and catabolic enzyme COMT) that predict inter-individual variation in smoking-induced DA release as measured by positron emission tomography (PET), variation in DA dynamics in smokers remains only partially explained. We hypothesized that more direct moderators of striatal DA signaling would include genetic polymorphisms in the nicotinic acetylcholine receptors (nAChRs), the proximal site of nicotine action. 102 otherwise healthy adult (21-65 years old) tobacco-dependent smokers (15-40 cigarettes per day) were interviewed with standardized questions; completed rating scales related to cigarette usage, mood, and personality; provided DNA; and underwent pre- and post-cigaratte smoking [^{11}C] raclopride PET scans.
Homozygotes for the G-allele at an intron 2 polymorphism in the alpha 7 cholinergic receptor subunit (CHRNA7, rs12915695) showed greater than 3X reduction in radiotracer binding potential, indicating significantly greater smoking-induced DA release, compared to carriers of the A-allele (p=0.001). A complex race by genotype interaction was observed at a variant in the 3' UTR of the alpha 4 subunit (CHRNA4, rs2236196) where significant reduction in radiotracer binding was shown for Caucasian carries of the minor allele, but African American carriers of the major allele (p=0.001). In summary, variants associated with DA release in CHRNA7 and CHRNA4 were associated with smoking endophenotypes. Several SNPs in cholinergic candidates also correlated with measures of craving and dependence. A comprehensive understanding of genetic moderators of nicotine reward and risk for dependence may facilitate the development and individualization of successful treatment strategies.

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The TAAR 1 agonist RO5263397 attenuates behavioral sensitization to nicotine in rats

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Emerging evidence implicates the trace amine-associated receptor (TAAR) 1 as an important modulator of the central dopamine system. Previous research demonstrated the critical modulatory role of the selective TAAR 1 agonist RO5263397 on cocaine-induced behavioral plasticity. This study examined the effects of RO5263397 on nicotine-induced behavioral sensitization, a rodent model of drug-induced behavioral plasticity. Daily treatment with 1 mg/kg nicotine (i.p., 7 days) was sufficient to induce significant locomotor sensitization in rats. The induction of locomotor sensitization by nicotine was significantly attenuated after 7 days of daily RO5263397 treatment (10 mg/kg, i.p.), and notably remained attenuated when rats were retested 7 days after the last drug treatment. In separate groups of rats, a single acute treatment of RO5263397 (3.2-10 mg/kg) was able to dose-dependently attenuate the expression of nicotine locomotor sensitization after a 7 day nicotine withdrawal period. Effects of RO5263397 on two other behavioral indices of nicotine were also examined. RO5263397 attenuated neither nicotine-induced hypothermia nor antinociception. Instead, RO5263397 enhanced nicotine-induced antinociception in the hot water tail-flick test whereas the nicotinic receptor antagonist mecamylamine (1 mg/kg) abolished the antinociceptive effects. Together, these data extend prior evidence that TAAR 1 agonists are important modulators of psychostimulant-induced behavioral plasticity to show that TAAR 1 activation also attenuates certain behavioral effects of nicotine.

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Behavioral Effects of Tobacco Smoke Constituents in Nonhuman Primates.

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Recent preclinical studies in rodents suggest that tobacco constituents other than nicotine (NIC) also exhibit pharmacological properties that may play a role in maintaining tobacco consumption. The present studies were conducted to evaluate, respectively, the NIC-like discriminative-stimulus (S^d) and reinforcing effects of minor tobacco alkaloids [e.g., nornicotine (NOR), anabasine (ANA), anatabine (ANAT), myosmine (MYO), and cotinine (COT)] in nonhuman primates. In drug discrimination (DD) studies, the ability of minor tobacco alkaloids to engender NIC-like S^d effects and, separately, to modify the S^d properties of NIC was determined in squirrel monkeys (n=4) trained to discriminate a highly potent NIC-like agonist [(+)-epibatidine; EPI] from vehicle. In IV self-administration (SA) studies, second-order fixed-interval (SO-FI) schedule procedures in NHP (n=3) were utilized to determine whether selected minor tobacco alkaloids (e.g., ANAT) exhibit NIC-like reinforcing effects. Results from DD studies show that: a) NIC and minor tobacco alkaloids engendered full (NOR, ANA, MYO, ANAT), or no (COT) substitution for EPI; b) the S^d effects of ANAT lasted longer than those of NIC; and c) in interaction studies, combining ED_{50} doses of NIC and ANAT resulted in the full expression of EPI-like S^d properties. Results from our SA studies show that NIC (0.0032–0.032 mg/kg/injection) reliably produced dose-related IV SA behavior under the SO-FI schedule, with peak rates of responding during availability of the unit dose of 0.01 mg/kg/injection. In contrast, ANAT (0.01–0.1 mg/kg/injection) failed to maintain IV SA under the SO-FI schedule; response rates were no greater than for vehicle. Importantly, the highest unit dose of ANAT (0.1 mg/kg/inj) produced observable adverse reactions (e.g., emesis), precluding the study of higher doses. Taken together these findings suggest that non-NIC tobacco constituents may differentially contribute towards maintaining long-term tobacco consumption, and augment NIC's effects. Interestingly, SA studies in monkeys show that the minor tobacco alkaloid ANAT likely does not play a major role in tobacco addiction.

Poster Communications

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Travel Awardee

Effects of norbinaltorphimine pretreatment on THC-induced place and taste avoidance in Sprague-Dawley rats.

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Although Δ^9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, has been shown to have both rewarding and aversive properties that impact cannabinoid abuse potential, little is known about how the aversive effects might vary with specific experiential and subject factors. The aversive effects of THC have been studied in CB57/BL mice using the place conditioning design and appear to be mediated by activity at the kappa opioid receptor (KOR) given that both genetic ablation and pharmacological antagonism of KOR block THC-induced place avoidance. Rats and mice have been shown to differ in behavioral responses to cannabinoids and thus, it is not known if this effect is evident in other species. The present experiment assessed the effects of the KOR antagonist, norbinaltorphimine (norBNI), on THC-induced place and taste avoidance in Sprague-Dawley rats. Specifically, rats were injected with 15 mg/kg of norBNI 24h prior to the pairing of a distinct side of a place conditioning chamber (Experiment 1) or a novel taste (Experiment 2) with one of three doses of THC (0.56, 1.0 and 3.2 mg/kg). Independent of the specific assay, norBNI had no significant effect on the aversive effects of THC. These data suggest that the specific mediation of THC's aversive effects by KOR activity may be species dependent.

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Travel Awardee

Nicotine withdrawal produces an increase in extracellular levels of GABA in the nucleus accumbens that is higher in females versus adult male rats

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Introduction: Women are more vulnerable to tobacco use than men and experience greater symptoms of withdrawal during abstinence from smoking. The neurochemical mechanisms that mediate these sex differences are not understood. Current work in our laboratory on the mechanisms that promote tobacco use in women has focused on the neural circuitry within the nucleus accumbens (NAcc), where dopamine (DA) levels are decreased during nicotine withdrawal. Our mechanistic hypothesis is that females experience greater negative effects during nicotine withdrawal than males. Namely, females display larger decreases in dopamine levels in the NAcc via a greater GABA-mediated inhibition of dopamine in this region. To address this hypothesis we assessed NAcc levels of GABA during nicotine withdrawal in male and female rats. Additionally rats also received yohimbine to compare sex differences in response to a pharmacological stressor. **Methods:** Rats were prepared with an osmotic pump containing a dose of nicotine (3.2 mg/kg; base) that produces equivalent nicotine levels in female and male rats. Fourteen days later, the rats were prepared with dialysis probes aimed at the shell of the NAcc. The following day, samples were collected every 20 min for a 1-hr period following baseline and the nicotine receptor antagonist mecamylamine (1.5 and 3.0 mg/kg, ip) to precipitate withdrawal. Mass Spectrometry techniques were used to asses GABA levels. **Results:** During nicotine withdrawal, females displayed a significantly larger increase in GABA release than males. Similarly, females displayed a larger increase in GABA release in response to yohimbine administration. **Discussion:** These results suggest that females display larger withdrawal-related increases in GABA release than males. This provides evidence for a potential mechanism involving GABA mediated sex differences in nicotine withdrawal.

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Travel Awardee

Serotonin 5-HT$_{2C}$ Receptors in the Ventral Subiculum Regulate Cocaine-Evoked Hyperactivity in Rats

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The ventral subiculum (vSUB) interconnects with limbic-corticostriatal circuit which regulates the behavioral effects of cocaine. Serotonin neurons innervate the vSUB, however, little is known about the 5-HT receptors that are functionally relevant in this region. We investigated the vSUB localization of the 5-HT$_{2C}$ receptor (5-HT$_{2C}$R) and its role in the control of cocaine-evoked hyperactivity. The expression of the 5-HT$_{2C}$R and co-localization with GAD 67 (marker for GABA) in the vSUB were evaluated using immunohistochemical analyses in rats (n=3). We employed virally-mediated genetic knockdown strategy to test the hypothesis that knockdown of the 5-HT$_{2C}$R in the vSUB of rats (n=5) will modulate cocaine-evoked hyperactivity. Motor activity was assessed after saline or cocaine (10-20 mg/kg) in modified open-field chambers. Dense immunoreactivity (IR) for 5-HT$_{2C}$R was observed throughout the vSUB. Only a small proportion of 5-HT$_{2C}$R-IR was co-localized with GAD 67-IR that was restricted to the distal end of the vSUB. Rats with the viral-mediated knockdown of the 5-HT$_{2C}$R in the vSUB exhibited reduced cocaine-evoked hyperactivity compared to control rats ($p<0.05$). No significant differences were observed in the basal locomotor activity between groups. The co-localization of 5-HT$_{2C}$R- and GAD 67-IR was observed in only a small number of vSUB cells and we are currently analyzing co-localization in glutamate neurons. The reduction in cocaine-evoked hyperactivity after knockdown of vSUB 5-HT$_{2C}$R may reflect changes in output of the vSUB to other regions in the limbic-corticostriatal circuit (e.g., nucleus accumbens) known to mediate cocaine-evoked hyperactivity. Future studies will investigate the involvement of 5-HT$_{2C}$R in the vSUB to control cocaine-taking and -seeking behaviors. P50DA033935 (KAC), K05DA022087 (KAC).

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Travel Awardee

CaMKII is involved in antihyperalgesic effects of imidazoline I$_2$ receptor ligands in spinal cord of rats with inflammatory pain

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Systemic injection of imidazoline I$_2$ receptor ligands, 2-BFI and phenyzoline, can significantly attenuate mechanical hyperalgesia induced by complete Freund's adjuvant (CFA) in rats. However, the molecular underpinnings of I$_2$ receptor ligand-induced antinociception remain unknown. The purpose of the present study was to examine the potential involvement of key signaling molecules, the extracellular signal-regulated protein kinase (ERK), PKCε and calcium/calmodulin-dependent protein kinase II (CaMKII), in the antinociceptive effects 2-BFI following intraplantar injection of CFA. 2-BFI and phenyzoline treatment significantly reduced mechanical hyperalgesia in rats. The phosphorylation of ERK and CaMKII in the spinal cord was significantly enhanced after CFA injection compared to normal rats, while there was no significant change in the phosphorylation level of PKCε. Furthermore, the activation of CaMKII was completely prevented by 2-BFI, but no obvious effects were observed on the phosphorylation of ERK and PKCε. Together, these results for the first time suggested that spinal CaMKII signaling might represent an important mechanism underlying I$_2$ receptor ligand-induced antinociception for inflammatory pain.

Poster Communications

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Inhibition of protein phosphatase 1 disrupts the reconsolidation of cocaine reward memory via GSK3 signaling

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Our previous study has demonstrated that glycogen synthase kinase-3 (GSK3) activity is highly induced during memory retrieval, and reconsolidation of cocaine reward memory can be attenuated by inhibition of GSK3. Since protein phosphatase 1 (PP1) is an activator of GSK3β via the dephosphorylation of GSK3β-Ser9, the role of PP1 in the reconsolidation of cocaine associated memories was investigated in this study. Adult male CD-1 mice underwent cocaine conditioned place preference for 8 days. Twenty-four hours after the test for place preference on day 9, mice were confined to the previous cocaine-paired compartment in a drug-free state for 10 minutes to reactivate cocaine-associated memories. Consistent with our previous findings, western blotting indicated that levels of phosphorylated GSK3α*Ser* 21 and GSK3β*Ser*9 were down-regulated in the mouse nucleus accumbens and hippocampus after the reactivation of cocaine cue memories. Interestingly, PP1 inhibition with okadaic acid (OA, 150 ng/3ul, i.c.v) 30 minutes before exposure to the compartment previously paired with cocaine prevented the decrease in the levels of phosphorylated GSK3α/β in both nucleus accumbens and hippocampus. In a further study, administration of OA 30 minutes prior to the reactivation of cocaine cue memories abrogated a previously established place preference when tested 24 hours later, suggesting interference with reconsolidation of cocaine-associated reward memories. These findings suggest that the PP1/GSK3 pathway is critically involved in the reconsolidation of cocaine contextual reward memory.

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Juvenile ketamine exposure enhances the rewarding effects of nicotine in adolescent rats

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Nearly 10% of the pediatric population is diagnosed with major depressive disorder (MDD) and the use of selective serotonin reuptake inhibitors to manage their symptoms is often not effective. Recently, low doses of ketamine, a glutamate NMDA receptor antagonist, has been shown to produce fast-acting antidepressant effects. However, because ketamine is also an abused drug, early exposure to ketamine might increase the abuse potential of other drugs of abuse, such as nicotine. Thus, we examined whether early ketamine exposure increases the rewarding effect of nicotine in adolescent rats using the conditioned place preference (CPP) paradigm. Male and female Sprague-Dawley rats were treated daily with ketamine (0 or 20 mg/kg, OP) from postnatal day (PD) 21-30. Rats were then assessed for nicotine-induced CPP beginning on PD 33 using a 10-day CPP procedure. During days 1 and 10 of the CPP procedure, rats were tested for their preconditioning and postconditioning place preference, respectively, in 15-minute sessions. During days 3-8, rats were conditioned 30-minutes a day with either nicotine (0.0, 0.03, 0.1, 0.3, or 0.6 mg/kg) or saline on alternating days. Days 2 and 9 were rest days. Results demonstrate that early exposure to ketamine modulates the rewarding effects of nicotine in a dose dependent manner. Specifically, male rats pretreated with ketamine continued to show CPP whereas saline pretreated rats showed an aversion to the 0.6 mg/kg nicotine dose. Similarly, female adolescent rats pretreated with ketamine showed a shift toward the nicotine-paired side when injected with the 0.3 mg/kg dose, whereas female adolescent controls failed to exhibit any changes in preference with this dose. Interestingly, at the 0.6 mg/kg dose of nicotine, female adolescent rats pretreated with ketamine exhibited a shift towards the aversive effects of nicotine, whereas controls demonstrated preference for this dose. Results suggest that the use of ketamine early in development may lead to long-term functional changes in the rewarding effects of nicotine.

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Current Challenges in Implementing a Prescription Drug Monitoring Program

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Background: Prescription drug monitoring programs (PDMPs) are surveillance tools designed to monitor and reduce drug diversion and opioid misuse behavior. They are electronic databases maintained by state that capture drug dispensing based on information reported by pharmacies. PDMPs are currently operational in 49 states.

Objective: In support of a study evaluating the feasibility of implementing a PDMP in the Military Health System, we conducted a systematic review of the literature to evaluate PDMP effectiveness. For this review, we defined effectiveness as: changes in physician prescribing patterns and aberrant drug taking behaviors (e.g., doctor shopping and early prescription refills). Changes in drug overdose morbidity and mortality were also examined.

Methods: An electronic search of PubMed and other sources was conducted (January 2000 - December 2014) using the key word 'prescription drug monitoring program'. Abstracts were reviewed by two reviewers to eliminate those unrelated to PDMPs. The remaining papers were reviewed in full to identify those meeting our inclusion criteria.

Results: Our search yielded 181 abstracts that were reviewed for potential inclusion, and 40 papers met our definition of PDMP effectiveness. Of these, 12 examined doctor shopping, 12 examined physician prescribing patterns, 19 examined patient aberrant drug taking behaviors and 2 studies addressed prescription opioid associated mortality and morbidity.

Conclusion: Emerging evidence suggests that PDMPs may be effective tools for opioid risk mitigation. Their effectiveness may be limited by a variety of issues.

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Retinoic acid signaling is a novel mechanism of environmental enrichment.

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Environmental enrichment produces protective addiction phenotype and antidepressant-like effect in rats. Previous studies suggest that rats reared in an enriched condition (EC) showed longer latency in forced swimming test than rats reared in isolated condition (IC).Additionally, EC rats self-administered less cocaine than IC rats. However, the mechanism underlying this protective phenotype is still not fully understood. The goal of this study is to explore novel mechanism of environmental enrichment using high-throughput next generation RNA sequencing. With Ingenuity Pathway Analysis (IPA) and Gene Set Enrichment Analysis (GSEA), the retinoic acid (RA) signaling pathway was detected to be significantly regulated by environmental enrichment. mRNA levels of the genes involved in RA synthesis, transportation and RA target genes are mainly upregulated, while the inhibitors of this pathway are mostly downregulated . CYP26b1 is an enzyme that degrades RA in neurons. Knocking down CYP26b1 in nucleus accumbens (NAc) shell, which causes accumulation of RA, significantly increased cocaine-seeking behavior in rat. In addition, rats with CYP26b1 knock- down showed decreased latency in the forced swim test, suggesting an increase in depression-related behavior. Furthermore, knocking down CYP26b1 in rat reduced sucrose intake in the sucrose neophobia test indicating an anxiogenic-like effect, but also decreased the time spent in the closed arm and junction in the elevated plus maze, indicating an anxiolytic-like effect. This inconsistency will be discussed. In conclusion, the results suggest that retinoic acid signaling in the nucleus accumbens plays an important role in the protective depression phenotype of environmental enrichment.

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Different modulatory effects of the 5-HT$_{1B}$ receptor agonist CP 94,253 on methamphetamine self-administration compared to cocaine self-administration.

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We previously found that the selective 5-HT1B receptor (5-HT$_{1B}$R) agonist, CP 94,253 (CP), shifts the cocaine self-administration (SA) dose-response (DR) curve upward and left during training but produces a downward shift after 3 weeks of forced abstinence. This study examined whether CP has similar effects on methamphetamine (meth) SA. Twenty male Sprague-Dawley rats were trained to self-administer meth (0.1 mg/kg) on a fixed ratio 5 (FR5) schedule of reinforcement. After drug intake stabilized, rats commenced within-session DR training with five doses (0.003, 0.01, 0.03, 0.1, & 0.3 mg/kg). Each dose was available for 30 mins in ascending order with a 5 min time-out between doses. Training continued until drug intake was stable across 3 consecutive sessions. Animals were then treated twice pre- and post-abstinence with CP (5.6 mg/kg, s.c.) or saline (1 mL/kg, s.c.) with order of treatment counterbalanced, to assess CP effects on meth SA. In addition, rats were tested on a progressive ratio (PR) schedule with 0.03 mg/kg meth available to evaluate CP effects on meth incentive motivation. PR testing occurred across two sessions for which rats received pretreatment with 5.6 and 10 mg/kg CP on the first and second sessions, respectively. Pre- and post-abstinence, rats exhibited the typical inverted U-shaped meth SA DR curve with the highest number of infusions obtained at the 0.01 mg/kg dose regardless of pretreatment. Prior to abstinence (n = 10), CP reduced total meth reinforcers obtained for the two highest doses. For post-abstinence (n = 10), CP had similar effects, reducing total reinforcers obtained for the last three highest doses. Paired sample t-tests for breakpoints on PR sessions indicated no significant effect of CP. Unlike the abstinence-dependent modulatory role of 5-HT$_{1B}$Rs on cocaine SA, this study found similar effects of CP pre- and post-abstinence suggesting different mechanisms may regulate meth SA. These findings are important for understanding the clinical efficacy of 5-HT$_{1B}$R agonists as treatments for psychostimulant disorders.

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The effects of low doses of Δ^9-tetrahydrocannabinol (THC) on place and taste conditioning in male and female adolescent rats.

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Many researchers hypothesize that adolescents may be fairly insensitive to the aversive effects of drugs of abuse, and thus particularly vulnerable to insults sustained through adolescent drug use. With marijuana's status as the most widely used illicit drug, it remains unknown if adolescent rodents would show taste avoidance at low doses of THC. Additionally, the majority of reward, aversion and self-administration preclinical work has been performed using male subjects, with many researchers indicating that the affective properties of drugs of abuse may be different in females vs. males (Becker and Hu, 2008; Greenfield et al., 2010). This experiment examined whether low doses of THC, previously reported as both aversive and rewarding in taste and place conditioning procedures respectively, would elicit sexually dimorphic behaviors assessed through a concurrent place and taste conditioning procedure in adolescent male and female Wistar rats. Specifically, male and female rats were treated in adolescence with relatively low/intermediate doses of THC (0.37, 0.75, 1.25 mg/kg) or vehicle. During this testing, all subjects were given access to saccharin followed immediately by an injection of THC and then placed on one side of a place preference chamber. Such a procedure allows an assessment of both THC's aversive and rewarding effects in the same animal. Animals conditioned with THC drank significantly less than controls, with females drinking significantly less than males across the conditioning cycles. THC induced variable effects in the place conditioning design, with no consistent differences between males and females or across dose groups. These results will be discussed in light of THC's rewarding and aversive effects in multiple experimental procedures, as well as future plans to further elucidate the cannabinoid's complicated and innately aversive profile.

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Assessment of psychomotor stimulant mixtures for behavioral sensitization in rodents

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Consumption of illicit methcathinone derivatives is an international public health concern. Recent investigations of mephedrone (MEPH) and methylenedioxypyrovalerone (MDPV) indicate their behavioral and neuropharmacological effects are comparable to those of amphetamines and cocaine. Moreover, case studies and toxicology reports reveal that substance users frequently consume these substances with other drugs, which may pose increased risks for abuse. Despite these reports, there is a paucity of research concerning the combined neurobehavioral effects of these substances with other drugs. The present study consisted of two experiments that investigated the combined effects of MEPH or MDPV with other psychostimulants using the behavioral sensitization assay. Thirty female CD-1 mice received seven injections of saline, AMPH (1.0 mg/kg), MEPH (3.0 mg/kg), or AMPH (1.0 mg/kg) + MEPH (3.0 mg/kg) over an eight day period. Activity was assessed on day 1 and day 8. After a 10 day washout, 1.0 mg/kg AMPH was administered to all animals. Compared to mice treated with AMPH or MEPH, those treated with AMPH + MEPH displayed stronger indices of behavioral sensitization on day 8 and in response to AMPH after the washout period. Experiment 2 utilized similar procedures in 32 male Sprague-Dawley rats (n=8 per group) injected with saline, MEPH (0.5 mg/kg), MDPV (0.5 mg/kg), or MEPH (0.5 mg/kg) + MDPV (0.5 mg/kg) once per day for seven consecutive days. After a 10 day washout, all rats were given 5 mg/kg cocaine. MDPV induced sensitization by day 7 and MEPH appeared to attenuate these effects. However, both MDPV and MEPH + MDPV treatment produced cross-sensitization to cocaine. The results of these experiments suggest methcathinone derivatives can enhance sensitivity to the behavioral effects of *d*-amphetamine and cocaine. Considered together with recent findings that MEPH and MDPV have different sites of action, but may act synergistically on dopaminergic synapses, further research on the abuse liability of these drug mixtures is warranted.

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6' –Guanidinonaltrindole (6'-GNTI) is a delta opioid receptor- kappa opioid receptor (DOR-KOR) heteromer selective agonist in peripheral sensory neurons.

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In peripheral nociceptors, we have found that 6'-GNTI agonist activity for Gi-mediated responses requires expression of both KOR and DOR. In primary cultures of peripheral sensory neurons, 6'-GNTI inhibited adenylyl cyclase (AC) activity by 65%. However, following siRNA knockdown of DOR, 6'-GNTI had no effect on AC activity but antagonized the response to the KOR agonist, U50488. Similarly, when KOR expression was reduced with siRNA treatment, 6'-GNTI had no effect on AC activity, but antagonized the response to the DOR agonist, DPDPE. Thus, 6'-GNTI has affinity, but not efficacy (i.e. acts as an antagonist) when either DOR or KOR expression is reduced. Importantly, these data suggest that 6'-GNTI efficacy requires activation of DOR-KOR heteromers in peripheral nociceptors. We next tested the hypothesis that 6'-GNTI occupancy of the DOR protomer of DOR-KOR heteromers allosterically enhances its own efficacy at KOR. In primary cultures and in a behavioral model of thermal allodynia, we measured 6'-GNTI-mediated responses in the presence of several different selective DOR antagonists. Both 6'-GNTI-mediated inhibition of AC activity as well as antinociception were reduced in the presence of the DOR antagonists naltrindole (2nM, 100x Ki) or 7-Benzlidenealtrexone (1nM, 100x Ki). By contrast, naltriben (NTB, 1nM, 100x Ki), fully substituted for 6'-GNTI occupancy of DOR. The concentration response curves of 6'-GNTI for inhibition of AC activity were superimposable in the absence (DOR occupancy by 6'-GNTI) and presence of NTB (DOR occupancy by NTB). Similarly, in a behavioral model of thermal allodynia, 6'-GNTI produced the same robust antinociceptive response in the presence or absence of NTB. These data are consistent with the hypothesis that 6'-GNTI occupancy of DOR augments its own efficacy at KOR through allosteric interactions between DOR and KOR within the DOR-KOR heteromer.

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A comparison of the antinociceptive effects of UMB 425, a mixed μ-agonist/δ-antagonist, and morphine in rats

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Opioids are a critical class of drugs commonly used to treat chronic pain; however long term use of opioids often leads to tolerance and/or dependence. UMB 425 is a mixed μ-agonist/δ-antagonist that has antinociceptive properties similar to morphine, and has demonstrated reduced tolerance liability after six days of chronic dosing in mice. A warm water tail withdrawal assay was used to compare antinociception and a 5-choice serial reaction time task was used to compare omissions after Sprague-Daley rats were administered morphine or UMB 425. The ED_{80} of both UMB 425 and morphine was calculated for individual rats, and two groups were randomly assigned to receive chronic treatment of either morphine or UMB425. Antinociception and tolerance were measured daily using a single warm water tail withdrawal assay. The group mean ED_{80} of UMB 425 was 4.63mg/kg compared to 11.18mg/kg morphine, and a peak in omissions was observed at lower doses of UMB 425 compared to morphine during the 5-choice serial reaction time task. These data suggest that UMB 425 is more potent than morphine and may have reduced tolerance liability in Sprague-Daley rats, potentially making UMB 425 an alternative to morphine for chronic pain treatment.

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Novel mechanisms for producing nicotine-like effects in monkeys: positive nAChR modulation versus AChE inhibition.

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Galantamine, an acetylcholinesterase (AChE) inhibitor and positive allosteric modulator of nicotinic acetylcholine receptors (nAChRs) that has been approved for use as a cognitive enhancer in humans, has recently demonstrated potential as a smoking cessation aid in pre-clinical assays. One way galantamine might serve as an effective therapy for smoking cessation would be by producing nicotine-like effects. In the current study, a nonhuman primate model of subjective effects was used to examine the extent to which galantamine shares effects with nicotine; moreover, the relative contribution of AChE inhibition and positive allosteric modulation of nAChR to the effects of galantamine was examined. Galantamine was studied in addition to donepezil, another AChE inhibitor which has been approved for attenuation of the cognitive deficits associated with Alzheimer's disease, and PNU-120596, a positive allosteric modulator of nAChRs that produces cognitive enhancement in monkeys. Rhesus monkeys (n=5) discriminating nicotine (1.78 mg/kg calculated as the base weight) responded under a fixed ratio 5 schedule of stimulus-shock termination. Nicotine, galantamine, and donepezil dose-dependently increased nicotine-lever responding; the percentage of nicotine-lever responses was a mean of 98% at 1.78 mg/kg of nicotine, 98% at 1.78 mg/kg of galantamine, and 89% at 0.56 mg/kg of donepezil. The ED_{50} values (95% confidence limits) were 0.41 (0.1-1.74) mg/kg for nicotine, 0.77 (0.46-1.28) mg/kg for galantamine, and 0.20 (0.14-0.29) mg/kg for donepezil. PNU-120596, up to a dose of 10 mg/kg, produced a maximum of 1.25% nicotine-lever responding. Collectively, these results suggest that AChE inhibition and direct nAChR stimulation result in overlapping subjective effects, whereas positive nAChR modulation does not appear to be sufficient to mimic the subjective effects of nicotine. Supported by USPHS Grant DA25267.

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Sex Differences in Alcohol Drinking in Rats

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Although alcohol-related hospitalizations and fatalities are more prevalent among men, women are more vulnerable to alcohol-induced behavioral and physical issues. However, the majority of studies on alcohol drinking and dependence are conducted in male subjects. Importantly, heavy drinking by women has been rising. The neurobiological basis for sex differences is largely unknown and animal models are needed to address this issue. Previous studies have reported that group housed female rats drink more alcohol during diestrous compared with estrous and proestrous phases, but only when the estrous cycle is hormonally synchronized. The present study examined sex differences in alcohol consumption in two rat strains: Long Evans and Wistar. The rats were single housed and given 10% alcohol *vs*. water over a 21-day period in their home cages using a two-bottle choice paradigm followed by twenty-one 30-min daily alcohol *vs*. water operant self-administration sessions. Vaginal smear samples were collected to investigate the effects of the estrous cycle on alcohol consumption. The results indicated that females consumed more alcohol than males in the home-cage two-bottle choice test. Female Long-Evans rats exhibited increased preference for alcohol in the two-bottle choice test compared with female Wistar rats. Under these conditions, the estrous cycle did not affect alcohol intake, in which similar levels of alcohol intake were observed during the proestrous, estrous, and diestrous phases. Under operant conditions, similar levels of alcohol self-administration were observed for males and females. The estrous cycle did not affect alcohol self-administration in the operant condition. Male Long-Evans rats exhibited higher, albeit nonsignificant, alcohol self-administration compared with Wistar rats. In summary, Long-Evans drank more alcohol than Wistar rats. The lack of significant effect of different phases of the estrous cycle on alcohol drinking may encourage more research with female subjects because the estrous cycle is believed to be a confounding factor in behavioral studies. Ongoing studies are investigating sex and hormonal influences on alcohol drinking in a model of intermittent access to alcohol (20%) that is known to produce an escalation of alcohol drinking and model the transition to alcohol dependence.

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Behavioral sensitization following repeated concurrent exposure to methylenedioxypyrovalerone (MDPV) and cocaine in male Sprague-Dawley rats

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Reports of abuse and fatal intoxication associated with synthetic cathinones known as "bath salts" are on the rise nationwide. Methylenedioxypyrovalerone (MDPV), one of the primary constituents of bath salts, is commonly used in combination with other drugs such as cocaine to enhance or prolong stimulant effects. Recent studies have indicated MDPV is a catecholamine transport inhibitor similar to but more potent than cocaine. Co-administration of these substances may therefore result in additive or synergistic effects. The combined behavioral effects of MDPV and cocaine have not yet been thoroughly examined. Behavioral sensitization following repeated psychostimulant exposure is considered an index of neuroadaptive changes in brain dopamine reward pathways. The present study sought to investigate the effects of repeated, concomitant administration of MDPV and cocaine on the development of sensitization and on cross-sensitization to cocaine. Male Sprague-Dawley rats were treated with subcutaneous injections of 0.5 or 1 mg/kg MDPV, 5 mg/kg cocaine, 0.5 or 1 mg/kg MDPV + 5 mg/kg cocaine, or saline. Treatments were conducted once daily for 7 consecutive days with locomotor assessments on the first and last day of treatment. Following a 10-day washout period, all groups were administered a challenge dose of 5 mg/kg cocaine. Behavioral indices evaluated were horizontal activity and stereotypy counts. Repeated exposure to MDPV + cocaine produced a greater increase in the development of behavioral sensitization compared to MDPV or cocaine alone. Increases from Day 1 to Day 7 were more pronounced following exposure to 0.5 mg/kg MDPV compared to 1 mg/kg MDPV when combined with cocaine. Cross-sensitization to cocaine was significantly greater in animals with a history of 0.5 mg/kg MDPV + 5 mg/kg cocaine compared to a history of either drug alone. These results suggest the development of sensitization and cross-sensitization to cocaine may be enhanced by the concurrent administration of MDPV and cocaine. Moreover, these findings warrant further assessment of the enhanced risk or abuse potential of MDPV and cocaine when used in combination.

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Within animal comparison of neuronal activation patterns associated with novelty and cocaine

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Novelty seeking is a personality trait associated with an increased vulnerability for substance abuse. In rodents, novelty seeking has been shown to be a predictor for elevated drug self-administration and compulsive use. While previous studies have shown that both novelty and drugs have actions within the prefrontal cortex (PFC) and nucleus accumbens (NAc), little is known as to whether the same neural ensembles are engaged by these two stimuli. In this project, we wanted to determine if the same neurons were activated during both novelty and cocaine administration. We used the TetTag mouse model to visualize neural activation at two different time points in the same animal. The TetTag mouse model is a dual transgenic reporter line that allows for long lasting temporally controlled tagging of active neurons. Using the TetTag LacZ model, which expresses long lasting beta-galactosidase (beta-gal) in active neurons, we found there were more beta-gal positive neurons in the infralimbic (IL) PFC, prelimbic (PrL) PFC, NAc core, and NAc shell in experimental animals compared to controls. Additionally, in the PrL PFC, NAc core, and NAc shell we found significantly greater co-expression of beta-gal and Fos in the experimental mice. Subsequent analysis indicated that this dual labeling was significantly greater than chance in the NAc core and shell. The data to date suggest that novelty and cocaine activate a similar network of neurons in the NAc, but are inconclusive as to whether or not this occurs in the PFC. Ongoing experiments are investigating if similar trends are observed in other related brain areas, such as the ventral hippocampus. Furthermore, in pilot studies, brain wide silencing of neurons engaged during cocaine self-administration has been found to attenuate not only cocaine self-administration, but also self-administration of an operant sensation seeking task without affecting gross locomotor activity.

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Daily morphine treatment increases premature responding in rats working under a 5-choice serial reaction time task

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Opioid abusers are more impulsive than non-users according to some measures (e.g., delay discounting), but it is unclear whether they are more impulsive according to other measures, such as those reflecting behavioral disinhibition. This study examined the effects of daily morphine treatment on responding under a 5-choice serial reaction time task in rats (n=7). A light was randomly illuminated in one of 5 response holes. Responses in the illuminated target hole (correct) delivered food, whereas responses in the incorrect hole, failure to respond (omission), or responses prior to illumination of the target hole (premature responses) initiated a time-out. Impulsivity was indexed by the number of premature responses, that is, responding before the target stimulus is presented. Morphine administered acutely (0.1-17.8 mg/kg, i.p.) modestly increased premature responding and increased omissions but did not significantly impact response accuracy. Once-daily treatment with 3.2 mg/kg of morphine for 14 days, increased premature responding without significantly impacting trial completion or accuracy. Once-daily treatment with 10.0 mg/kg increased the number of premature responses as well; however, the number of trials omitted remained high throughout treatment, indicating that repeated administration of the larger dose of morphine substantially disrupted performance. Treatment with the mu opioid receptor agonist increases premature responding which supports the notion that repeated opioid administration enhances this form of impulsivity. Taken together with previous research indicating that impulsive individuals are more vulnerable for initiation of drug use, these data suggest that enhanced impulsivity is also a consequence of opioid use. Enhanced impulsivity in the form of behavioral disinhibition might further increase vulnerability for continued abuse and possibly relapse in so far as individuals are more likely to seek out and use drugs without considering the consequences of doing so. Supported by USPHS grant K05DA017918.

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Sweet-fat diet increases the locomotor-stimulatory effects of acute and repeated amphetamine in male DBA mice.

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Diets high in sugar or fat alter the behavioral effects of stimulant drugs of abuse. However, the onset and extent of these alterations are not well known. This study examined the impact of a standard (SD) or high-sugar high-fat (Sweet Fat, SF) diet on locomotor response to acute and repeated amphetamine exposure. Two weeks SF diet increased amphetamine-induced vertical locomotor activity, with no difference in horizontal locomotor activity. Repeated testing revealed locomotor sensitization to amphetamine in both groups, with SF diet mice showing a greater degree of vertical locomotor sensitization than SD mice. These results suggest that a diet high in sugar and fat enhances the effect of amphetamine within two weeks and across multiple amphetamine exposures. Furthermore, this effect is more pronounced in vertical rather than horizontal locomotor activity.

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Towards a model for intravenous self-administration of psychostimulants in mice.

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Previously in our lab, we developed a protocol to train mice to intravenously self-administer methamphetamine without prior food training and using light as a stimulus cue associated with drug infusion (Sharpe et al., 2014, *Int J Neuropsychopharmacol*). Since the daily self-administration sessions were conducted in the dark portion of the light cycle, we sought to develop a protocol that didn't use white light as a stimulus. The goal of the present work was 1) to compare the use of light vs. sound as a paired stimulus to intravenous delivery of methamphetamine and 2) to establish a protocol for cocaine self-administration using a sound signal as a paired stimulus. Male DBA/2J mice were implanted with indwelling catheters in the right jugular vein. A week after surgery, mice were trained to nose-poke under a fixed ratio 3 (FR3) schedule for methamphetamine (0.05 mg/kg/infusion, i.v.) in daily 2 h sessions. One group of animals was trained using a light signal (white light, 15 s) paired to delivery of the drug. In a second group of animals, the light was changed to a sound signal (2 kHz, 2 s). Our preliminary results indicated that mice trained with a light stimulus acquired self-administration faster (3.0 ± 0.2 days) than mice trained with a sound stimulus (5.1 ± 0.4 days). However, the amount self-administered per session was similar between the two experimental conditions (Light: 37.0 ± 2 infusions; Sound: 35.4 ± 2 infusions). A third group of mice was trained to self- administer cocaine (0.5 mg/kg/infusion) under a FR3 schedule using the sound signal as the stimulus cue. On average, these mice reached cocaine self-administration criteria in 6 ± 0.3 days, with an intake of 15.1 ± 0.8 infusions per session. When the FR3 schedule was increased to a FR12 schedule, a slight decrease in the amount self-administered was observed (12.5 ± 0.9 infusions per session). Cocaine dose response curves conducted at both FR3 and FR12 (0.05 - 3.0 mg/kg/infusion) showed decreasing intake as the concentration of cocaine increased. In conclusion, we have developed a protocol using a short sound stimulus cue associated with drug infusion that is effective for training mice to self-administer psychostimulants such as methamphetamine and cocaine.

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The rewarding effects of nicotine in female rats are ovarian-hormone dependent

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Introduction: Previous work in our laboratory has shown that the rewarding effects of nicotine are greater in female versus male rats. It is presently unclear whether ovarian hormones promote the strong rewarding effects of nicotine in females. Moreover, it is unclear whether the ovarian hormone β-estradiol (E2), promotes the rewarding effects of nicotine. To address these issues, the present study examined the rewarding effects of nicotine using intravenous self-administration (IVSA) procedures in intact versus ovariectomized female rats (Study 1). Then, a follow up study examined nicotine IVSA in OVX rats that received either vehicle or E2 supplementation (Study 2). **Methods**: Female rats received ovariectomy (OVX) procedures or had a sham procedure (intact) at post-natal day 45. In study 2, a separate groups rats received OVX procedures and either immediately began an E2 supplementation (OVX+E2) regimen or they received a peanut oil vehicle (OVX+vehicle). The E2 supplementation procedure involved E2 (0.25 mg) administration for 2 consecutive days followed by 2 days of vehicle injection for the remainder of the study. The rats were first trained to operant respond for food and water for 5 days in the operant chambers. Then, they were then implanted with a jugular catheter for IVSA procedures. Following a 4-day recovery period, rats were then given 23-hour access to nicotine IVSA using an escalating dose regimen (0.015, 0.03 and 0.06 mg/kg). Each dose was self-administered for 4 days with 3 intervening days of drug abstinence. **Results**: Our findings from Study 1 revealed that intact females displayed significantly higher levels of nicotine intake as compared to OVX rats across all nicotine doses. The results from Study 2 revealed that the latter effect is likely E2-mediated. Specifically, OVX rats that received E2 supplementation displayed significantly higher levels of nicotine intake as compared to OVX rats that received vehicle. **Conclusion**: Taken together, our data suggest that the rewarding effects of nicotine are enhanced in female rats via the presence of ovarian hormones, such as E2.

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A non-peptide α9α10 nAChR antagonist for pain management: an *in vivo* study

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More than 20% of adults worldwide suffer from pain. Although there are many analgesics on the market (opioids, NSAIDs, etc.), treatment of pain remains a vexing problem. Recent studies have led to the discovery of small molecule antagonists of α9α10 nicotinic acetylcholine receptors (nAChRs) as a novel class of safe and powerful analgesic compounds. However more research is needed to determine the mechanism of action and the types of pain responsive to these compounds. Toward this goal, in this study, a small non-peptide compound ZZ204G (a *tetrakis*-quaternary ammonium analog) was selected and synthesized. The antinociceptive efficacy of ZZ204G was tested in rats using hot water tail flick latency (TFL), hind limb paw withdrawal hot plate threshold (HPT), paw pressure threshold (PPT) and pinprick sensitivity threshold (PST) tests. Results showed that ZZ204G has a long lasting analgesic effect with a quick onset in tests for superficial burning (HPT and TFL) and mechanical pricking pain (PST). The effect of ZZ204G was dose-dependent in three assays (TFL, HPT and PST), with the ED_{50} values of 190.5 ± 18.8 μg/kg (TFL), 25.5 ± 9.1 μg/kg (HPT) and 167.8 ± 79.9 μg/kg (PST), respectively. However, only a weak action was observed in the PPT test, which demonstrates that ZZ204G is less effective for deep tissue (muscle and ligaments) pain. Based on these results and other literature data, the effect of ZZ204G can tentatively be attributed to the modulation of activity of the skin keratinocyte acetylcholinergic system that works in particular to set and maintain excitability thresholds of epidermal nociceptors.

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Assessment of an MDPV+cocaine mixture on conditioned place preference in male Sprague-Dawley rats.

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Recent reports on the abuse of novel synthetic cathinone derivatives (i.e. "bath salts") call attention to serious public health risks of these chemicals. In response to this concern, a growing body of preclinical research has characterized the psychopharmacology and abuse liability of these substances, particularly one of the most common constituents, methylenedioxypyrovalerone (MDPV). MDPV is similar to cocaine in its pharmacological actions and the two drugs administered together may have significant synergistic or additive effects. At present there are no known studies that have utilized the conditioned place preference (CPP) paradigm to assess MDPV and cocaine administered concurrently. The present study used a biased CPP procedure to assess the rewarding and/or aversive effects of an MDPV+cocaine mixture in singly-housed and pair-housed male Sprague-Dawley rats. Thirty-two pair-housed and 32 singly housed rats were injected with MDPV 0.5 mg/kg, cocaine 5 mg/kg, MDPV 0.5 mg/kg + cocaine 5 mg/kg, or saline (n=8 per treatment group) and placed in the non-preferred side of a dual-chambered conditioning apparatus. The following day, each rat received a saline injection and was placed on the opposite side. This conditioning sequence was repeated three additional times for a total of four sequences. On the final day, rats were placed in the testing apparatus and allowed to move freely between both conditioning chambers. Locomotor activity was simultaneously assessed during all trials. Evidence for CPP was assessed by calculating a difference score between time spent in the drug-paired chamber before and after conditioning trials. MDPV, cocaine, and the mixture all significantly increased locomotor activity compared to saline treatment, with greater increases observed following MDPV than cocaine or the MDPV+cocaine mixture. The difference score was also greatest following MDPV treatment in both singly and pair-housed rats. Interestingly, cocaine appeared to attenuate both the locomotor stimulant and place conditioning effects of MDPV.

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The aminopropyl carbazole, P7C3-A20, prevents paclitaxel-induced neuropathic pain.

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Paclitaxel (PTX), a microtubule-targeting anticancer agent, produces a debilitating peripheral neuropathy that is accompanied by neuropathic pain. Patients often experience pain symptoms so severe that it forces dose reduction or complete discontinuation of life-saving chemotherapy to cope with the pain. Currently, only marginally effective therapeutic interventions are available. Recently, a newly identified agent, P7C3-A20, was found to be neuroprotective in several models of neurodegeneration, including Parkinson's disease and traumatic brain injury. Since PTX initiates progressive degeneration of peripheral afferent neurons, this study was performed to evaluate the potential neuroprotective efficacy of P7C3-A20 against PTX-induced peripheral neuropathy. We administered P7C3-A20 (10 mg/kg/day) or vehicle intraperitoneally (i.p.) to adult male Sprague-Dawley rats over a 28-day period. Following two days of treatment with P7C3-A20 or vehicle, rats also received injections of PTX (11.7 mg/kg, i.p.) or vehicle every other day for 5 days. P7C3-A20 did not alter PTX-mediated decreases in body weight or circulating leukocyte counts. Mechanical, cold, and heat nociceptive thresholds were measured multiple times on different days. As expected, we found that PTX increased sensitivity to cold and mechanical stimuli, and decreased sensitivity to heat stimulation in the rats receiving PTX without P7C-A20. Remarkably, rats receiving PTX along with P7C3-A20 exhibited no changes in nociceptive thresholds as compared to the vehicle-treated rats, suggesting that P7C3-A30 completely prevented the development of PTX-induced neurotoxic effects on peripheral sensory neurons. P7C3-A20 may be an exciting new candidate for prevention of peripheral neuropathy in cancer patients receiving chemotherapy.

Poster Communications

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Structure-activity relationships of substituted 1H-indole-2-carboxamides as CB1 receptor allosteric modulators

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Modulation of the CB1 receptor has been targeted in the treatment of a range of disorders such as obesity, drug addiction, pain and inflammation. Recently, several classes of small molecules, including Org27569, have been reported to modulate the CB1 receptor function via the allosteric site(s). These CB1 allosteric modulators have been shown to be allosteric enhancers of agonist binding and affinity and allosteric inhibitors of agonist signaling efficacy in several in vitro functional assays. While it showed limited efficacy in modulating CB1 agonist-induced effects in several animal models in mice, Org27569 dose-dependently attenuated both cue- and drug-induced reinstatement of cocaine- and methamphetamine-seeking behavior in rats. Several structure-activity relationship (SAR) studies on the 1H-indole-2-carboxamide scaffold have been reported since the discovery of Org27569. In an attempt to expand our understanding of the SAR on this scaffold, we have designed and synthesized additional analogs and evaluated their CB1 and CB2 activities in fluorometric imaging plate reader (FLIPR) based calcium mobilization assays. The most potent compound had an IC_{50} value ~ 10 fold more potent than the parent compound Org27569. These compounds dose-dependently reduced the E_{max} of agonist CP55,940, consistent with the negative allosteric modulation mechanism.

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Hypothermic Effects of Δ ^{9}-THC and Nicotine in Kynurenine-3-Monooxygenase (KMO) Knockout Mice

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Kynurenic acid, a metabolic product of the tryptophan-kynurenine synthesis pathway, is both a competitive antagonist at the glycine co-agonist site of NMDA receptors and a negative allosteric modulator at α7 nicotinic acetylcholine receptors (nAChRs). α7 nAChRs are important for mediating the effects of nicotine, but have also recently been implicated in the effects of Δ ^{9}-tetrahydrocannabinol (Δ^{9}-THC), the primary psychoactive component of *Cannabis*. Transgenic mice lacking kynurenine-3-monooxygenase (KMO) exhibit increased levels of kynurenic acid and thus presumably decreased function of α7 nAChRs. The current study examined the extent to which the hypothermic effects of nicotine and Δ ^{9}-THC are modified in KMO knockout mice (n=7) as compared to wild-type C57BL/6J controls (n=7). Δ ^{9}-THC (10 mg/kg) produced a maximum decrease in temperature of 3.0°C at 60 min; hypothermia was no longer evident at 240 min. Nicotine (1.78 mg/kg base) produced a maximum hypothermic effect of 7.2°C at 30 min; this effect was no longer evident at 90 min. The magnitude of effect and the time course of hypothermia produced by Δ ^{9}-THC and nicotine were not significantly different between KMO knockout and wild-type mice. These data suggest that at least some of the in vivo effects of Δ^{9}-THC and nicotine are not affected by differences in endogenous levels of kynurenic acid. Supported by USPHS grant DA25267 and MH090127.

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Intracellular calcium regulates D2 autoreceptor currents in substantia nigra dopamine neurons

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This work investigated the importance of intracellular calcium on dopamine-mediated signaling in the substantia nigra. Dopamine neurons in the substantia nigra are involved in the initiation of voluntary movement and reward-related processes. D2-type autoreceptors on these neurons powerfully inhibit cell firing and have been inversely associated with psychostimulant use. Previous work from our lab suggests that intracellular calcium inhibits maximal autoreceptor-mediated currents in dopamine neurons from mouse brain slices. However, since under physiological conditions only some of the autoreceptors are activated at any given time it is important to determine the effects of calcium on currents induced by lower concentrations of agonist. To address this, we performed patch clamp electrophysiology of dopamine neurons in brain slices from DBA/2J mice, and applied the neurotransmitter dopamine by iontophoresis and bath perfusion. The internal solution of the recording pipette contained either 10 mM BAPTA (high calcium chelation) or 0.025 mM EGTA (control conditions, low calcium chelation). Dopamine iontophoresis was used to determine the maximal D2 receptor mediated current that can be obtained from each cell, and bath perfusion of 3, 10, 30, 100, and 300 μM dopamine was used to investigate the effect of increasing dose on amplitude of currents. The current amplitudes from dopamine bath perfusion were then taken as percent of the pre-perfusion iontophoresis. These experiments show that, at higher concentrations of dopamine bath perfusion, chelating intracellular calcium increases D2 autoreceptor currents. Converging evidence indicates that intracellular calcium levels are important for regulating D2 autoreceptor physiology; however, we do not yet understand the mechanisms behind this regulation. We are beginning to use electrical stimulation to induce endogenous dopamine release, which elicits D2 autoreceptor inhibitory post-synaptic currents, combined with bath perfusion of a protein kinase C inhibitor. By inhibiting parts of the calcium signaling pathway, we will discover which signaling molecules are important for the mechanisms of action of intracellular calcium regulation of D2 autoreceptor-mediated currents.

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Early life methylphenidate treatment does not modulate nicotine-induced behavioral sensitization in adolescent male and female rats.

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Methylphenidate (MPH) is a stimulant used to treat Attention Deficit-Hyperactivity Disorder. The use of MPH is not recommended in children under 6 years of age, yet MPH is prescribed to preschool children as young as two years of age. The long-term functional consequences of this early MPH exposure are not clearly understood. However, preclinical studies have shown that early MPH exposure during postnatal days (PD) 11-20, a period of development similar to preschool children, enhances the abuse potential of drugs of abuse later in life. For example, early MPH exposure enhanced the rewarding and reinforcing effects of nicotine and cocaine, respectively. To date, it is not clear whether this enhancing effect of prior MPH exposure can be generalized to the psychomotor stimulating effects of drugs. Thus, this study sought to determine whether MPH exposure during PD 11-20 modulates nicotine-induced behavioral sensitization during adolescence. Male and female Sprague Dawley rats were treated with MPH (0.0 or 4.0 mg/kg) from PD 11-20. During Nicotine Pretreatment (PD 32-38) rats received daily injections of either saline or nicotine (0.2 mg/kg, or 0.6 mg/kg), and immediately placed into a locomotor activity monitoring chamber for 45 min. On PD 40, all rats received a challenge injection of 0.2 mg/kg nicotine, and were placed into the chamber for 45 min. Male and female rats that were pretreated with nicotine exhibited more locomotor activity across pretreatment days and during the nicotine challenge day compared to controls. However, MPH exposure during PD 11-20 did not affect nicotine-induced locomotor sensitization. The present findings are in contrast with previous findings in which MPH enhanced the rewarding effects of morphine and cocaine. These findings may be due to differential striatal dopamine pathway activation that dictate reward versus locomotor sensitization. It is also possible that the effects of MPH on nicotine are limited to the drug reward and not to the locomotor stimulating effect.

Poster Communications

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Self-administration of the cannabinoid agonist CP 55,940 in Old-World macaques.

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Marijuana is the most commonly abused illicit substance in the United States. Despite this, cannabinoids (CBs) have remained a false negative in self-administration (SA) procedures with the exception of studies using squirrel monkeys. Reasons for this discrepancy may include species differences between New World squirrel monkeys vs. Old-World macaques and rodents, schedules of reinforcement, limited dose ranges tested in previous unsuccessful studies, or even other technical considerations such as vehicle preparation. The purpose of the present study was to attempt to establish intravenous SA of the potent CB_1/CB_2 agonist CP 55,940, using methods deemed successful in squirrel monkeys. Rhesus (n=6) and cynomolgus (n=6) monkeys with a prior stimulant SA history were trained to respond under a fixed-ratio (FR) schedule of food presentation (FR10 in rhesus, FR50 in cynomolgus), with a 60-second timeout after each reinforcer. Once responding was stable, saline was substituted for food pellets for at least 5 consecutive sessions and until responding was extinguished. After re-establishing food-maintained responding, different doses of CP 55,940 (0.005-3.0 µg/kg) were substituted for food pellets, with each dose available for at least 5 sessions and until responding was deemed stable. There was a return to food-maintained responding, for at least 3 sessions, between different CP 55,940 doses. Although still preliminary, at least two doses of CP 55,940 have been tested in all six rhesus monkeys, with evidence of reinforcement in two animals at 0.01 µg/kg/injection. In the two cynomolgus monkeys studied, 0.03 and 0.3 µg/kg CP 55,940 maintained significantly higher responding compared to saline-contingent levels in one monkey. Preliminary results indicate that CP 55,940 demonstrates reinforcing effects in a subset of subjects. However, complete dose-response curves remain to be determined in all subjects. Supported by DA010584.

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Screening, Brief Intervention and Referral to Treatment for driving while intoxicated offenders:impact on treatment initiation and criminal justice violations

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Alcohol use patterns that are risky or harmful for one's health is prevalent among driving while intoxicated (DWI) offenders and is a key predictor of recidivism, however, utilization of alcohol treatment services among DWI offenders is low. Screening, brief intervention, and referral to treatment (SBIRT) is a cost-effective, evidence-based practice used to opportunistically identify problematic alcohol use and reduce its related consequences in high risk individuals. However, there is a limited amount of research on the efficacy of SBIRT delivered in criminal justice settings. To begin to fill this gap, we are currently examining the feasibility and efficacy of delivering SBIRT within a criminal justice setting. The purpose of this presentation is to demonstrate our preliminary findings in this ongoing study. Participants were adults with DWI arrests (n=118) recruited at orientation for pre-trial supervision. Participants were screened for problematic alcohol use using the AUDIT, administered a brief motivational intervention, and if indicated, a referral for treatment was provided. For those referred to treatment, a follow-up telephone call was completed one week later to determine whether they had sought treatment. Records of their pre-trial violations were subsequently obtained from criminal justice records. Our preliminary findings show that the majority of offenders reported alcohol use at levels requiring a referral to treatment (90.6%). Of those referred for treatment and contacted, 26% entered treatment, 48% planned to start, and 26% had no plan to enter treatment. Subsequent alcohol-related violations were significantly lower among those who entered and planned to start treatment compared to those who had no plans to enter treatment. These preliminary results suggest promising outcomes, at least in the short-term, for delivery of SBIRT for alcohol in a criminal justice context.

Preparing Effective Oral Presentation Slides

Adapted from http://www.sfn.org/am2011/index.aspx?pagename=resources_presentation#posters

Clear Purpose - An effective image should have a main point and not be just a collection of available data. Central theme of the image should be readily identified.

Readily Understood - The main point should catch the attention of the audience immediately. Audience is not paying attention to the speaker when trying to figure out the image - minimize this.

Simple Format - With a simple, uncluttered format, the image is easy to design and directs audience attention to the main point.

Free of Nonessential Information - If information doesn't directly support the main point of the image, reserve this content for questions.

Digestible - Excess information can confuse the audience. With an average of seven images in a 10-minute paper, roughly one minute is available per image. Restrict information to what is extemporaneously explainable to the uninitiated in the allowed length of time - reading prepared text quickly is a poor substitute for editing.

Unified - An image is most effective when information is organized around a single central theme and tells a unified story.

Graphic Format – Use graphs to emphasize qualitative relationships "Drug X dose-dependently and markedly increased behavior". Avoid presenting data in Tables.

Designed for the Current Oral Paper – Avoid extraneous information; show evidence and conclusions directly related to the subject of the paper; it is not necessary to communicate how much work was done.

Experimental - In a 15-min presentation, there is not enough time to teach methods. Only mention what is necessary to develop the theme.

Visual Contrast - Contrasts in brightness and tone between illustrations and backgrounds improves legibility. The best color combinations include white letters on black or black on yellow. Never use black letters on a dark background. Many people are red/green color blind - avoid using red and green next to each other.

Integrated with Verbal Text - Images should support the verbal text and not merely display numbers. Conversely, verbal text should lay a proper foundation for each image. As each image is shown, give the audience a brief opportunity to become oriented before proceeding.

Clear Train of Thought - Ideas developed in the paper and supported by the images should flow smoothly in a logical sequence, without wandering to irrelevant asides or bogging down in detail. Everything presented verbally or visually should have a clear role supporting the paper's central thesis.

If using PowerPoint, consider the following:

Use standard fonts, such as Times, Helvetica, or Arial and Symbol. Space is lost and the amount of information per slide is reduced by repeating graphics (including logos), busy backgrounds, and decorative typefaces.

Enhance the legibility of text and diagrams by maintaining color and intensity contrast. Use white or light yellow text and lines on black backgrounds, and/or use black on white or clear backgrounds. Avoid using colors that do not provide enough contrast red or dark green on blue, and avoid yellow on white.

Test your completed presentation on a separate PC-compatible computer to ensure that fonts are standard and components, such as movies, have been included rather than merely linked.

Preparing Effective Posters

An effective poster is self-contained and self-explanatory. Viewers can proceed on their own while leaving the author free to discuss points raised in inquiry.

The poster session offers a more intimate forum for discussion than a slide-based presentation, but discussion becomes difficult if the author must explain the poster to a succession of viewers. Time spent at a poster presentation is not determined by the author, but by the viewer – be prepared for 3 min or less.

An effective poster balances figures and text and is not a page-by-page printout of a journal paper or a slide show. Minimize text! Put yourself in the viewers shoes – how much text are you willing to read?

Layout - Organize illustrations and text using a grid plan. Arrange materials in columns rather than rows. Place the most significant findings at eye level immediately below the title bar; place supporting data and/or text in the lower panels. Use line borders to separate areas. Avoid reflective, plastic-coated paper. Use muted background colors - shades of gray are also effective.

Title - Title, author(s), and affiliation should be at least one-inch high.

Illustrations - design figures for viewing from a distance and use clear, visible graphics and large type. Colors are effective if used sparingly; use dark colors on white or pale backgrounds and light colors on dark backgrounds. Figures should illustrate no more than one or two major points. However, simple figures are unnecessary. Make clear main points. Illustration sequences can be specified with numbers or letters. Omit "Fig." or "Figure" - this is unnecessary and occupies excess space.

Text - Each figure or table should have a heading of one or two lines in very large type stating the "take-home" message. Provide additional essential information in the figure itself set in 16 point or larger type. Minimize narrative. Integrate text that would normally appear in the body (Results and Discussion) of a manuscript in figure legends. Concisely describe not only the content of the figure, but also the derived conclusions. Place brief details of methodology at the end of each legend. Numbered or bulleted lists are effective ways to convey a series of points, even for Introduction and Discussion. Do not set entire paragraphs in uppercase (all capitals) or boldface type.

Place an introduction at the upper left and a conclusion at the lower right, both in large type. The abstract should not be included.

BBC Judge's Evaluation Form

Presentation number/Presenter: _____

Please assign points for each section and an overall score - **(5) Strong** to **(1) Weak**

		STRENGTHS	POINTS	WEAKNESSES
ABSTRACT	**Text:** Logical? Clear? Well-organized? Complete? Sufficiently succinct?			
PRESENATION CONTENT	**Introduction:** Objectives/background clear? Appropriate rationale?			
	Methods and Results: Appropriate design? Appropriate detail? Clearly explained?			
	Conclusions: More than summary? Supported by the data?			
STYLE/ORGANIZATION/VISUALS	**Style:** Clear voice? Volume? Appropriate inflection? Eye contact? Pace? Energy?			
	Organization/Timing: Logical sequence? Appropriate time for different sections?			
	Visuals/Graphs: Visible? Clear? Not cluttered? Used appropriately? See guidelines			

OVERALL SCORE (CIRCLE ONE): **POINT TOTAL**

5 Outstanding	**4 Excellent**	**3 Very good**	**2 Good**	**1 Fair**	

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Maharaj ("Raj") Ticku, PhD

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

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

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

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


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