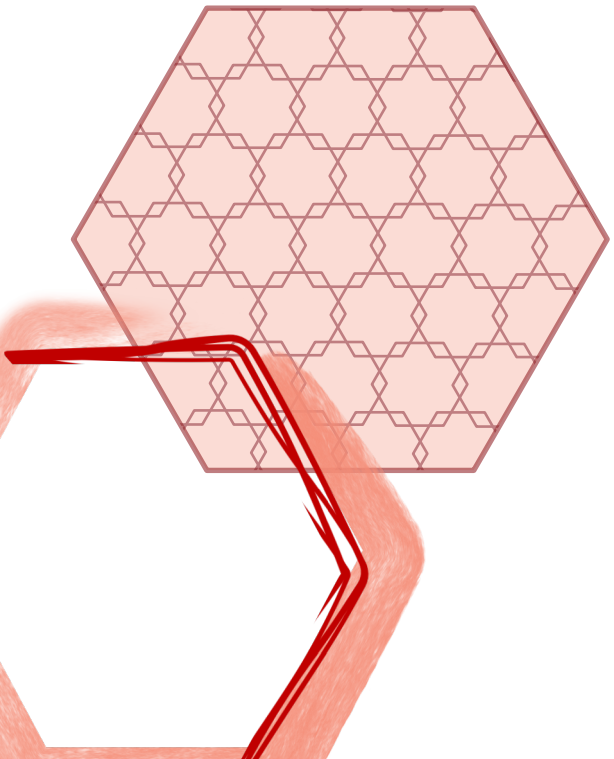
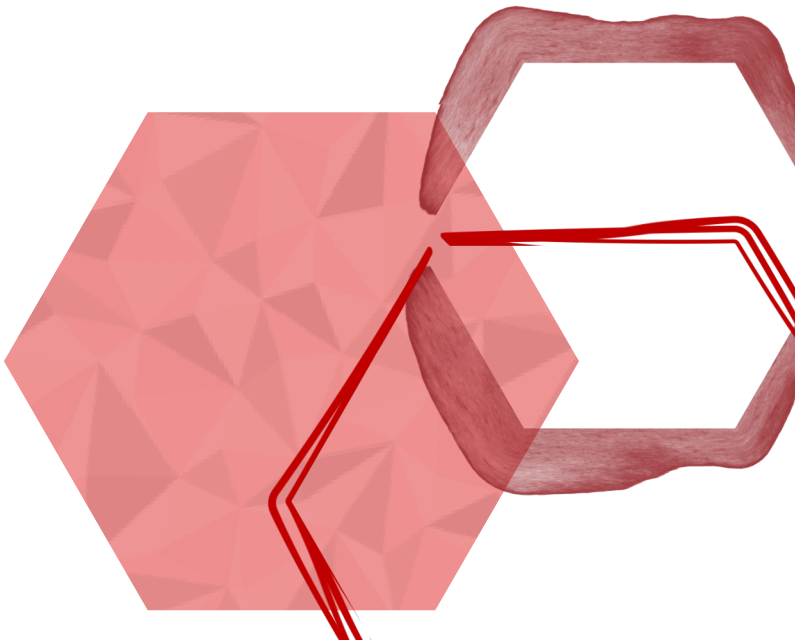
July 9-12, 2023

Atlanta, Georgia USA

Loews Atlanta Midtown

Contents





Welcome to INRC 2023!

Welcome to Atlanta! We hope you will agree that we've created a great scientific program combining diverse expertise, cutting-edge research, and pioneering advances in pre-clinical and clinical opioid research. Take some time to explore Midtown Atlanta and the amazing restaurants, parks, and museums that are within walking distance of Loews. INRC continues to be a society that bridges physiology, pharmacology, genetics, psychiatry, neuroscience, and molecular biology to address critical questions about the central and peripheral actions of opioids. Building a community that strives for excellence through cutting-edge science, a dedication to creating structures that support the identities and voices of our members, and a commitment to promoting diversity in opioid research is what INRC is all about. Our closing reception will celebrate INRC awardees and provide an opportunity to thank the wonderful committees that worked throughout the year to support INRC events and the annual meeting. Enjoy your time at our 54th annual meeting!

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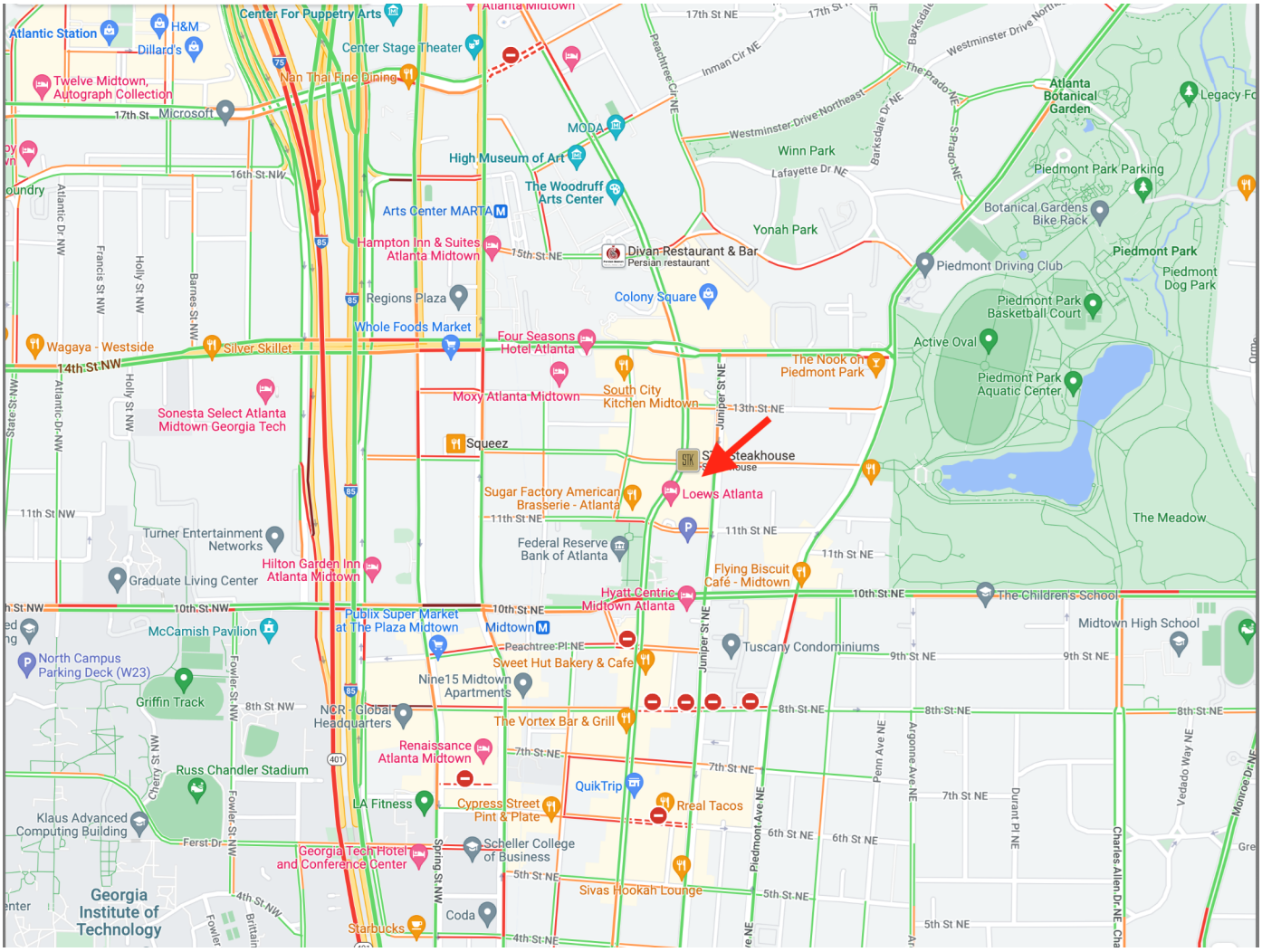
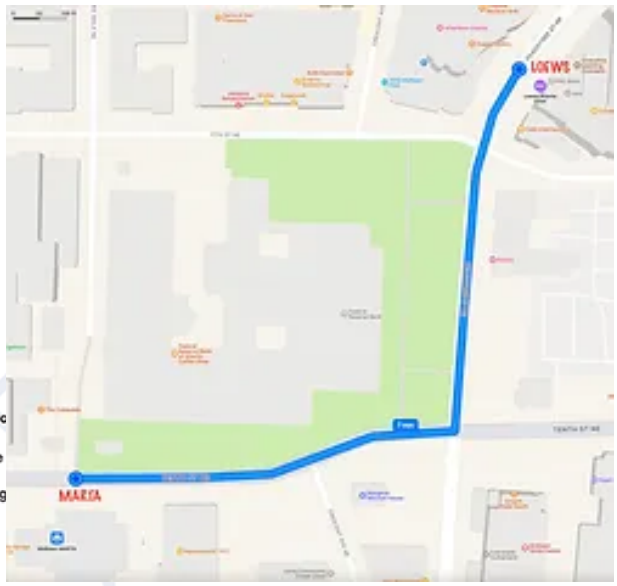


Marta Train System



From Hartsfield Jackson International Airport:

Board either the Red (North Spring) or Gold (Doraville) Line trains and exit the train at Midtown Station (N4).
Exit Midtown station to 10th Street. Walk 1 ½ blocks east toward Peachtree Street. Turn left on Peachtree Street and walk one block north. Loews is located at the corner of Peachtree Street and 11th Street.

Schedule at a Glance

	July 9 Sun	July 10 Mon	July 11 Tues	July 12 Wed
7:00am		Breakfast *Ellington Prefunction*	Breakfast *Ellington Prefunction*	
8:00am		Opening Remarks	Founder's Lecture	Young Investigator's Lecture
9:00am		Plenary Lecture	Plenary Lecture	Hot Topics 4
		Coffee Break	Coffee Break	Coffee Break
10:00am		Symposium 1 and Discussion	Symposium 3 and Discussion	Symposium 6 and Discussion
11:00am		Hot Topics 1	Symposium 4 and Discussion	Hot Topics 5
12:00pm		Lunch - Science Advocacy Workshop	Lunch *On your own*	Lunch *On your own* (Executive Committee lunch - *Inman*)
1:00pm				
2:00pm	Registration *Ellington Ballroom*	Symposium 2 and Discussion	Symposium 5 and Discussion	Symposium 7 and Discussion
3:00pm		Networking Break	Networking Break	Networking Break
		Hot Topics 2	Hot Topics 3	Hot Topics 6
4:00pm		Data Blitz 1	Data Blitz 2	Business Meeting & Closing Remarks
5:00pm	Professional Development *Ellington Ballroom*	Poster Session 1 *Overlook East*	Poster Session 2 *Overlook East*	
6:00pm				Networking Free Time
7:00pm	Opening Reception *Loews Terrace*			Closing Reception *Loews Terrace & Ellington Prefunction*
8:00pm				
9:00pm				Dessert and Dancing *Overlook East*

Plenary Speakers

Dr. Paul Kenny

Director, Drug Discovery Institute, Professor & Chair, Neuroscience, Icahn School of Medicine, Mount Sinai

Paul Kenny is the Ward-Coleman Professor and Chairman of The Nash Department of Neuroscience and Director of the Drug Discovery Institute at the Icahn School of Medicine at Mount Sinai. Dr. Kenny is also co-founder of Eolas Therapeutics Inc., a company focused on developing novel medications for drug addiction. Dr. Kenny graduated from Trinity College Dublin with a degree in Biochemistry. He completed his Ph.D. degree at King's College London, and his postdoctoral training at The Scripps Research Institute in La Jolla, CA. Dr. Kenny has received numerous awards for his research, including the Daniel H. Efron Research Award from the American College of Neuropsychopharmacology (ACNP), the Jacob P. Waletzky Memorial Award from the Society for Neuroscience (SfN), Distinguished Investigator Award from NARSAD, and a MERIT (R35) Award from the National Institute on Drug Abuse (NIDA).

Dr. Yasmin Hurd

Director, Addiction Institute, Professor, Pharmacological Sciences, Neuroscience & Psychiatry, Icahn School of Medicine, Mount Sinai

Yasmin Hurd is the Ward-Coleman Chair of Translational Neuroscience and the Director of the Addiction Institute at Mount Sinai. Hurd holds appointments as faculty of Neuroscience, Psychiatry, Pharmacology and Systems Therapeutics at the Icahn School of Medicine at Mount Sinai in New York City and is globally recognized for her translational research on the underlying neurobiology of substance use disorders and comorbid psychiatric disorders. Hurd's research on the transgenerational effects of early cannabis exposure on the developing brain and behavior and on the therapeutic properties of marijuana has garnered substantial media attention. In 2017, Dr. Hurd was elected to the National Academy of Medicine and, in 2022, Dr. Hurd was elected to the National Academy of Sciences (NAS).

2023 INRC Awardees

Young Investigator's Award

Andrea Bedini, Ph.D.

Associate Professor, Pharmacology, University of Bologna, Italy

Dr. Andrea Bedini is Associate Professor of Pharmacology at the Department of Pharmacy and Biotechnology, University of Bologna (Italy); on March 2023 he obtained the National Habilitation to Full Professor.

Dr Bedini earned both his MSc degree in Medical Biotechnology with honors, and his PhD degree in Cellular and Molecular Biotechnology with outstanding grades at the University of Bologna. He was Visiting Scientist at the Department of Pharmacology and Toxicology, University of Magdeburg (Germany) from August 2006 to February 2007, under the supervision of Prof. Volker Hoellt and Dr. Juergen Kraus, and Visiting Scholar in Prof. Charles Chavkin's research group at the Department of Pharmacology, University of Washington (Seattle, USA) from February 2013 to February 2014.

Dr. Bedini's research has been first focused on the transcriptional modulation of mu-opioid receptor expression in neuronal and immune cells, then on the characterization of innovative mu and kappa opioid ligands with improved pharmacological profiles and on understanding the molecular determinants of such ameliorated profiles. Dr. Bedini's current research focuses on applying molecular and cellular pathway analyses to the development of Quantitative Systems Pharmacology platforms aimed to identify more effective and safer analgesic treatments; within this frame, he recently received a prestigious EU-funded Horizon 2020 grant as team leader of the University of Bologna unit.

Dr. Bedini has attended INRC meetings consistently since 2006 and currently serves on the INRC Executive Committee.

2023 INRC Awardees

Founder's Award

Minoru Narita, Ph.D.

Professor, Pharmacology, Hoshi University School of Pharmacy & Pharmaceutical Sciences, Tokyo, Japan

Dr. Minoru Narita is currently a Professor in the Department of Pharmacology at Hoshi University, Japan. Dr. Narita obtained his Ph.D. in the field of pharmacology, and specifically on opioid research, in Tsutomu Suzuki's laboratory at Hoshi University. After obtaining his Ph.D., he started a postdoctoral fellowship in 1993 in the laboratory of Prof. IK Ho, in the Department of Pharmacology and Toxicology at the University of Mississippi Medical Center. In 1994, Dr. Narita transferred to the Department of Anesthesiology at the Medical College of Wisconsin, in Prof. Leon F Tseng's laboratory, as a Research Associate. He actively worked with Prof. Tseng in the field pain research. Beginning in1996, he served as a Visiting Assistant Professor in the Department of Anesthesiology at the Medical College of Wisconsin. In 1999, he returned to Japan as an Assistant Professor at Hoshi University. In 2011, he became a professor in the Department of Pharmacology at Hoshi University. Dr. Narita also serves as the Chief of the Division of Cancer Pathophysiology at National Cancer Center Research Institute through a joint appointment program. Dr. Narita was twice elected to the INRC Executive Committee and is still a member. He values his connections with many overseas researchers, especially INRC members. A little known fact that Dr. Narita does not have a middle name, but everybody in INRC calls him "Toshi" as a nickname.

This biography and congratulatory address to Dr. Narita were written by Dr. Yasuyuki Nagumo, who is Dr. Narita's apprentice.

Sunday

2:00 pm **Registration at the Loews Hotel**
Ellington Ballroom

4:30 - 6:30 pm **Professional Development**
Ellington Ballroom

- Challenges Starting your Own Lab
  Facilitators: Meaghan Creed & Nicolas Massaly
- Careers in NIH and Grant Writing
  Facilitators: Rita Valentino & David White
- Careers Outside Academia
  Facilitators: Li Fang (DEA) & Ying Qu (Millennium Health)
- What They Don't Tell You About How to Manage a NIH Grant
  Facilitators: Julie Blendy & Brady Atwood
- K Awards – Dos and Don'ts
  Facilitators: Chris Evans & Jakie McGinty
- Pros and Cons of Academic Careers
  Facilitators: Jordan McCall & Andrea Bedini

6:30 - 8:30 pm **Opening Reception**
Loews Hotel Terrace

Monday

7:15 - 8:30 am **Breakfast**

Ellington Prefunction

8:00 - 8:30 am **Opening Remarks**

8:30 - 9:15 am **Plenary Lecture**

Chair: Catherine Cahill (UCLA)

- **A master regulator of opioid withdrawal in prefrontal cortex**

  Dr. Paul Kenny

  Director, Drug Discovery Institute, Professor & Chair, Neuroscience, Icahn School of Medicine, Mount Sinai

9:15 - 9:30 am

Discussion

9:30 - 10:00 am **Coffee Break**

10:00 - 11:00 am **Symposium 1**

New Insights into Opioids and Affect

Chair: Chris Evans (UCLA)

- **10:00-10:15 am**

  Lakshimi Devi (*Icahn School of Medicine at Mount Sinai)*

  Enhancement of endogenous opioid signaling by ketamine

- **10:15-10:30 am**

  Irwin Lucki (*Uniformed Services University)*

  Ketamine's antidepressant effects reduce kappa opioid receptor signaling

- **10:30-10:45 am**

  Elizabeth Perkarskaya (*Columbia University)*

  Investigating the role of mu-opioid receptors in sensory and affective symptoms of neuropathic pain

- **10:45-11:00 am**

  Cecilia Bergeria (*Johns Hopkins University School of Medicine)*

  Examining the role of anxiety and emotional distress in opioid craving using human laboratory models of cue reactivity

11:00 - 11:30 am

Discussion

Monday

11:30 - 12:00 pm **Hot Topics 1**

Chair - Meaghan Creed (*Washington University in St. Louis*)

- Emma Tyner (*Grad Student, University of Pennsylvania*) - Long-lasting effect of chronic social defeat stress on opioid self-administration
- Julia Ferrante (*Grad Student, University of Pennsylvania*) - Investigation of acute and long-term immune changes induced by early-life opioid exposure and withdrawal
- Belle Buzzi (*Grad Student, Virginia Commonwealth University*)- The Classical Psychedelic Psilocybin Mitigates Oxycodone Withdrawal

12:00 - 1:30 pm **Lunch (provided)**

- **Science Advocacy Workshop - Shaping Public Policy**

  Chair - Jim Langford

  Chair of the Substance Abuse Research Alliance (SARA) and Executive Director of the Georgia Prevention Project

This workshop is supported by the Institute of NeuroImmune Pharmacology

1:30 - 2:30 pm **Symposium 2**

Genetic and transcriptome profiling to elucidate novel circuits and signaling using mouse models of opioid misuse disorders

Chairs: Michelle Mazei-Robison (Michigan State University) and Venetia Zachariou (Boston University)

- **01:30 – 01:45 pm**

  Michelle Mazei-Robinson *(Michigan State University)*

  Morphine-induced increase in neuropeptide expression in ventral tegmental area dopaminergic neurons
- **01:45 – 02:00 pm**

  Julie Blendy *(University of Pennsylvania)*

  Influence of Oprm1 A118G SNP in network connectivity in mice
- **02:00 - 02:15 pm**

  Caleb Browne *(Mount Sinai School of Medicine)*

  Transcriptome profiling of the brain's reward circuitry in heroin self-administration identifies a ventral hippocampus gene network related to relapse susceptibility
- **02:15 - 02:30 pm**

  Venetia Zachariou (*Boston University)*

  Oxycodone withdrawal induces HDAC1/2-dependent transcriptional maladaptations in the reward pathway in a mouse model of peripheral nerve injury

2:30 - 3:00 pm

Discussion

Monday

3:00 - 3:30 pm **Networking Break**

3:30 - 4:00 pm **Hot Topics 2**

Chair - M. Imad Damaj (*Virginia Commonwealth University*)

- Chao-Cheng Kuo (*Post Doc, Washington University in St. Louis*) - Multiplexed pharmacological calcium imaging reveals distinct opioid receptor-mediated response profiles of locus coeruleus neurons
- Renata Marchette (*Post Doc, NIDA IRP*) - Ethanol potentiates fentanylinduced apneic events, which is not rescued by naloxone
- Ben Clements (*Post Doc, University of Michigan*) - Combination of Two Positive Allosteric Modulators for the μ-Opioid Receptor

4:00 - 4:30 pm **Data Blitz/Poster Teasers**

4:30 - 6:30 pm **Poster Session 1**

Overlook East

Session Abstracts

Symposium 1: New Insights into Opioids and Affect

This session will explore new developments in our understanding of opioid systems and how they regulate affect. The endogenous opioid system has recently been implicated in mediating the mood-modulating effects of SSRIs and ketamine. New data will be presented by Dr Lakshmi Devi regarding endogenous opioid involvement in ketamine's enduring antidepressant actions. Dr Elizabeth Pekarskaya will discuss the clinical potential of the atypical antidepressant tianeptine, which exhibits unique mu opioid pharmacodynamics, in treating affective symptoms of chronic pain. The session will also address progress in kappa antagonism in modulating affect and Dr. Irwin Lucki will present data that test the hypothesis that ketamine causes a long-lasting desensitization of kappa opioid receptors to mediate its acute and persistent clinical antidepressant effects. Finally, results from laboratory models of opioid cue-induce craving will be presented by Dr Cecilia Bergeria which assess self-report acute craving, anxiety, physiological measures of hypothalamic-pituitary-adrenal axis activation (continuous heart rate and galvanic skin response), cognitive performance, and qualitative descriptions of the effects of cue-induced craving among individuals in treatment for OUD. These studies delineate the role of anxiety in opioid craving and inform ongoing trials evaluating pharmacotherapies (e.g., buspirone, lofexidine) for OUD and craving.

Hot Topics 1

Long-lasting effect of chronic social defeat stress on opioid self-administration

Emma Tyner (*Grad Student, University of Pennsylvania*)

Stress and stressful environments often lead to maladaptive behaviors that can increase vulnerability to substance use disorders (SUDs). While the relationship between stress and SUDs is well documented, the role of individual differences in

stress response and how this may mediate opioid taking is unknown. When presented with a stressor a subset of individuals respond with resilience, while many are susceptible to the detrimental effects of stress. Chronic Social Defeat Stress (CSDS) is a translationally relevant rodent model to investigate molecular mechanisms underlying the development of individual differences in maladaptive behaviors. This paradigm is one of the few tests that reliably distinguishes stress resilient from stress susceptible animals; with approximately 40% showing a resilient phenotype following CSDS. We found that susceptible and resilient phenotypes are stable and persist for at least 2 weeks following CSDS. Furthermore, we found that rodents exposed to CSDS intravenous self-administer more remifentanil than non-stress controls under a continuous reinforcement schedule (fixed ratio 1; FR1). Under a partial schedule (FR2), susceptible mice maintain remifentanil intake while both resilient and non-stress control mice have attenuated intake. Additionally, susceptible mice have a significantly greater progressive ratio breakpoint indicating increased motivation for remifentanil compared to non-stress control mice. Such preclinical models in which variations in response to social stress are observed can be highly informative for understanding the mechanistic the underpinnings driving of these differences. Future studies are aimed at interrogating the mechanisms through which these phenotypes modulate opioid self-administration.

Investigation of acute and long-term immune changes induced by early-life opioid exposure and withdrawal

Julia Ferrante (*Grad Student, University of Pennsylvania*)

Populations affected by the opioid epidemic include pregnant women and their offspring. Infants exposed to opioids in utero are at risk of developing Neonatal Opioid Withdrawal Syndrome (NOWS), a combination of acute somatic withdrawal symptoms. Rodent models of NOWS have recapitulated deficits in development and behavior, but few studies have examined alterations in immune functioning. We developed a mouse model of prenatal opioid exposure that encompasses the developmental equivalent of all three trimesters of human pregnancy in which mice receive morphine throughout gestation and the first two post-natal weeks— a period equivalent to the third trimester of human pregnancy and includes major developmental processes in rodents, including gliogenesis and immune system consolidation. Our model produces significant developmental delays, failure to thrive, and robust withdrawal signs. Further, we observe alterations in several cytokines and interleukins, as well as increased expression of microglia marker Iba1 24 hours following the last morphine injection (withdrawal), though changes in Iba1 expression are not sustained in adulthood. To determine if perinatal morphine exposure alters subsequent immune response, mice received an LPS challenge in adulthood. Mice exposed to morphine in utero show increased Iba1 expression in cortex and decreased levels of cytokines in the spleen following LPS treatment. Further, we observed a sex-specific sickness phenotype, in which morphine-LPS male mice showed significantly greater reductions in body temperature over saline treated-LPS males. These data indicate that early-life opioid exposure and withdrawal may cause acute changes in microglia and differential neuroimmune and peripheral immune response to infection in adulthood.

The Classical Psychedelic Psilocybin Mitigates Oxycodone Withdrawal

Belle Buzzi (Grad Student*, Virginia Commonwealth University*)

Opioid use disorder (OUD) is a major health issue in the United States, with more than 100,000 opioid overdose deaths yearly. Treatments for OUD currently exist, but their efficacy is limited due to misuse potential, undesirable side effects, and low levels of compliance. Cross-sectional studies suggest that lifetime psilocybin use, a classical psychedelic drug, is associated with lower odds of OUD. Therefore, the

current study sought to characterize the effects of psilocybin on different aspects of oxycodone, a widely used prescription opioid drug, withdrawal in mouse models.

We evaluated the effect of psilocybin on oxycodone spontaneous withdrawal in mice. This study used 7-9 week-old C57BL/6J male and female mice who were surgically implanted with osmotic minipumps containing oxycodone (60 mg/kg/day) or saline for 7 days. Each treatment group was further injected with either saline or psilocybin (1 mg/kg ip) 2 hours following removal of minipumps. The next day, mice were evaluated for somatic signs of withdrawal and 7 days later for mechanical hypersensitivity. A separate cohort was also tested to determine the effect of psilocybin on oxycodone antinociceptive properties in the tail-withdrawal test. Oxycodone male but not female mice that received psilocybin showed significantly less somatic signs of withdrawal. However, in both sexes, psilocybin reduced oxycodone withdrawal-induced mechanical hypersensitivity while not altering the antinociceptive effects of oxycodone. Psilocybin shows promising potential for the treatment of opioid withdrawal. Future studies will determine the effect of psilocybin on the reinforcing properties of oxycodone in animals.

Symposium 2: Genetic and transcriptome profiling to elucidate novel circuits and signaling using mouse models of opioid misuse disorders

The panel employs multiple opioids (morphine, heroin, oxycodone) to assess the role of genetic polymorphisms and transcriptional profiles on circuit function and opioid-elicited behavior. This session will discuss the impact of polymorphisms associated with addiction vulnerability on brain connectivity changes under states of morphine physical dependence (Blendy) as well as identification of cell-type specific transcriptional changes (Mazei-Robison), the use of multi-region transcriptomic analysis to identify novel circuits relevant for relapse using a heroin self-administration model (Browne), and the role of pain in opioid-induced transcriptional changes using a novel mouse paradigm for the study of oxycodone physical dependence (Zachariou). The panel is employing cutting-edge approaches to identify novel signaling and circuit mechanisms that contribute to opioid dependence and relapse. Findings from these transcriptomic and circuit studies have the potential to yield innovative therapeutic strategies such as the use of histone deacetylase inhibition to transition to non-opioid medications for the management of chronic pain and prediction of therapeutic efficacy based on brain network connectivity.

Hot Topics 2

Multiplexed pharmacological calcium imaging reveals distinct opioid receptor-mediated response profiles of locus coeruleus neurons

Chao-Cheng Kuo (*Post Doc, Washington University in St. Louis*)

The modular organization of noradrenergic neurons in locus coeruleus (LC) provides functional differentiation during distinct behaviors through the release of norepinephrine (NE). This would suggest that LC modules should act differentially in a behavioral state-dependent manner. The LC is enriched in many G-protein coupled receptors (GPCRs), including the four opioid receptor systems, that are likely endogenously activated during behavior to regulate activity among LC modules. However, the detailed mechanisms remain unclear. Here we perform GCaMP8f calcium imaging of LC-NE neurons in acute brain slices in concert with a large-scale pharmacological scan of multiple GPCR agonists. We use CASCADE, a machine learning-based algorithm, to deconvolute individual LC-NE action potentials from the calcium signals. For firing rates below 4 Hz this approach is nearly 100% accurate and stays at 85% up to 5 Hz. To determine whether anatomical modules are controlled by discrete GPCRs, we inject the retrograde neuronal tracer cholera toxin subunit b conjugated to CF-dye-594 into medial prefrontal cortex (mPFC). Interestingly, the activation of some GPCRs brings a differential effect among distinct

anatomical projections from the LC. For example, the application of DAMGO, a Mu-opioid receptor agonist, causes a stronger inhibition in mPFC-projecting LC neurons compared to non-mPFC projecting cells. Here we introduce a novel, highly efficient method of calcium imaging to investigate pharmacological profile in acute brain slices. Our findings provide evidence that the release of endogenous opioid ligands could be involved in the functional differentiation of modularity of LC-NE system during distinct behaviors.

Ethanol potentiates fentanylinduced apneic events, which is not rescued by naloxone

Renata Marchette (*Post Doc, NIDA IRP*)

Drug overdose deaths involving opioids in the United States top 100,000 individuals annually. Ethanol is estimated to be present in approximately 30% of opioid-related fatalities. This study aims to investigate the potential synergistic effects of ethanol and fentanyl on ventilation.
We used whole-body plethysmography to analyze ventilation parameters on a breath-by-breath basis. Male and female Long Evans rats received two doses of fentanyl (FTN3 and 25 µg/kg, IV) and ethanol (EtOH0.59 and 1.18 g/kg, IV) administered, along with different combinations of both substances.
EtOH1.18 significantly reduced minute ventilation and increased apneic pauses, whereas EtOH0.59 reduced minute ventilation, for 60 minutes. FTN3 exhibited no effect on ventilation, while FTN25 reduced minute ventilation and increased apneic pauses for 15 minutes. When FTN25 was combined with EtOH1.18, a more pronounced reduction in minute ventilation and increase on apneic pauses were observed. The FTN25+EtOH1.18 combination resulted in a 37.5% mortality rate, and the administration of naloxone did not rescue them.
The FTN25+EtOH0.59 combination led to increased apneic pauses compared to either substance alone. To investigate the potential of naloxone in reversing the effects of FTN25+EtOH0.59, naloxone was administered (0.1 mg/kg, IV). Naloxone transiently restored minute ventilation reduction when administered 5 minutes after FTN+EtOH, although it had no effect on apneic pauses.
These results suggest that ethanol exacerbates fentanyl-induced apneic events, possibly contributing to overdose deaths. Additionally, the resistance of these effects to naloxone highlights the need for further research and alternative approaches to address the complexities of combined alcohol and opioid misuse.

Combination of Two Positive Allosteric Modulators for the µ-Opioid Receptor

Ben Clements (*Post Doc, University of Michigan)*

Use of opioid drugs, while effective for analgesia, is limited due to risks of tolerance, abuse, and overdose. Development of adjuvants to increase the analgesic activity of µ-opioids while reducing adverse effects is critical for safer use. Positive allosteric modulators (PAMs) interact with agonist-occupied opioid receptors in a location distinct from the orthosteric site to increase agonist affinity and/or signaling. These compounds have promise as adjuvants, with achievement of enhanced analgesia, potentially without increasing unwanted effects. There are two structurally diverse classes of PAMs that act at the µ-receptor, the thaizolidines (e.g. BMS-986122) and xanthene-diones (e.g. BMS-986187), which suggests different allosteric sites. Initial characterization of PAMs focused on the actions of each structural class. Our objective is to determine the extent to which these structurally different PAMs interact in vitro and in vivo at opioid receptors and the degree of any synergy.
To test behavioral responses, BMS-986187 and BMS-986122 were administered to CD-1 mice (10 mg/kg, i.p.) alongside saline or methadone (10 mg/kg, i.p.). Antinociception was determined using the hot plate assay. Both PAMs with methadone increased latency to respond over methadone alone. In vitro, G protein activation was tested using the GTPγ^{35}S assay. PAMs were tested individually and together with defined concentrations of the µ-agonist DAMGO. Both BMS-986187 and BMS-986122

increased the activity of DAMGO. The combination of both PAMs showed an additive effect, not a synergistic interaction. Future studies will examine how this additive response seen in vitro translates to complex systems in vivo. Supported by R37 DA039997.

Poster Session 1

Please see abstract book for all poster abstracts.

1. CaV3.1 isoform of T-type calcium channels plays an important role in morphine-induced alterations in thalamic excitability and conditioned place preference in mice

Tamara Timic Stamenic[1], Slobodan M. Todorovic [1,2]

[1]Department of Anesthesiology, University of Colorado, Anschutz Medical Campus, Aurora; [2]Neuroscience and Pharmacology Graduate Program, University of Colorado, Anschutz Medical Campus, Aurora

2. Deletion of noradrenergic mu opioid receptors potentiates morphine place preference

Samantha S. Dunn[1], Makenzie R. Norris[1], Jenny R. Kim[1], Chao-Cheng Kuo[1], Gustavo Borges[1], Jordan G. McCall[1]

[1]Department of of Anesthesiology, Washington University in St. Louis, St. Louis, MO, USA; Center for Clinical Pharmacology, University of Health Sciences & Pharmacy in St. Louis and Washington University School of Medicine, St. Louis, MO, USA

3. A novel inhibitory corticostriatal circuit that mediates mu opioid receptor synaptic plasticity

Braulio Munoz[1] and Brady K. Atwood[1,2]

[1]Department of Pharmacology & Toxicology, Indiana University School of Medicine, Indianapolis, IN, 46202, USA; [2]Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN, 46202, USA.

4. Perigestational morphine exposure disrupts postnatal hippocampal development of male and female rats

Meghan E. Vogt[1], Jade Kang[1], Christopher T. Searles[1], Hannah J. Harder[1], Anne Z. Murphy[1]

[1]Neuroscience Institute, Georgia State University, Atlanta, Ga, USA

5. Persistent inflammation selectively activates opioid-sensitive phasic-firing neurons within the vlPAG

Kylie B. McPherson[1,2], Courtney A. Bouchet[1,2], Basile Coutens[1], Susan L. Ingram[1]

[1]Department of Neurological Surgery, Oregon Health & Science University; [2]The Vollum Institute, Oregon Health & Science University

6. Impact of Chronic Pain on Reinforcing Effects of Fentanyl in Male and Female Rats

Gwendolyn E. Burgess[1], Melanie R. Vocelle[1], Emily M. Jutkiewicz[1]

[1]University of Michigan, Pharmacology Department

7. Identification of exogenous and endogenous ligands targeting mu-delta interacting complexes

Ivone Gomes[1], Susruta Majumdar[2], and Lakshmi A. Devi[1]*

[1]Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Department of Pharmacology and Anesthesiology, St. Louis College of Pharmacy, St. Louis, MO, USA.

8. Effects of psychological stress on a mouse model of inflammatory pain

Satoka Kasai[1], Miho Takagi[1], Natsuki Ogawa[1], Junpei Kuroda[1], Yuko Nakatake[1,2], Daisuke Yamada[3], Akinobu Saito[3], Kazumi Yoshizawa[1]

[1]Laboratory of Disease Pharmacology, Faculty of Pharmaceutical Sciences, Tokyo University of Science; [2]Department of Psychopharmacology, National Center of Neurology and Psychiatry; [3]Laboratory of Pharmacology, Faculty of Pharmaceutical Sciences, Tokyo University of Science

9. Glycopeptide Drugs Derived from Oxytocin as Analgesics and for the Treatment of Opioid Use Disorder

Hannah J. Goodman[1], Parthasaradhi Reddy Tanguturi[2], Lajos Z. Szabó[1], Torsten Falk[3], M. Leandro Heien[1], John M. Streicher[2], Robin Polt[1]

[1]Dept. of Chemistry & Biochemistry, BIO5, The University of Arizona; [2]Dept. of Neurology, College of Medicine, The University of Arizona; [3]Dept. of Pharmacology, College of Medicine, The University of Arizona

10. Striatal enkephalin supports conditioned cocaine reward during extinction

Kanako Matsumura[1], In Bae Choi[3], Meera Asokan[4], Nathan N. Le[4], Luis Natividad[2,4], Lauren K. Dobbs[1,2,3,5]

[1]Institute for Neuroscience, University of Texas at Austin; [2]Waggoner Center for Alcohol & Addiction Research, University of Texas at Austin; [3]Department of Neuroscience, University of Texas at Austin; [4]College of Pharmacy, Division of Pharmacy & Toxicology, University of Texas at Austin; [5]Department of Neurology, Dell Medical School, University of Texas at Austin

11. Structure Modifications and In Vitro Evaluation of Mu-opioid Receptor Positive Modulators

Mengchu Li[1], Alex Stanczyk[1], Kun Liu[2], Xinmin Gan[2], Andrew White[2], John Traynor[1]

[1]Department of Pharmacology, University of Michigan; [2]Department of Medicinal Chemistry, University of Michigan

12. Effects of Positive Allosteric Modulation on Mu Opioid-Induced Adverse Effects in vivo

Thomas D. Prince[1], Kelsey E. Kochan[1], John R. Traynor[1]

[1]Department of Pharmacology, University of Michigan

13. Comparison of Morphine and Endomorphin Analog ZH853 for Tolerance and Immunomodulation in Neuropathic Pain

Terrence J. Hunter[3], Zoe M. Videlefsky[3], and James E. Zadina[1,2,3,4]

[1]SE LA Veterans Health Care System, Tulane University; [2]Department of Medicine, Tulane University; [3]Neuroscience Program/Brain Institute, Tulane University; [4]Department of Pharmacology, Tulane University

14. Discovering and validating Oprm1 exon 7-associated variants as novel therapeutic targets for mitigating adverse effects of clinically used mu opioids without altering analgesia in pain management

Shan Liu[1], Jin Xu[1], Raymond Chien[1], Ayma F. Malik[1], Tiffany Zhang[2], Valerie P Le Rouzic[2], Jin Xu[1], Grace Rossi[3], Arlene Martínez-Rivera[4], Anjali Rajadhyaksha[4], Rolen Quadros[5], Channabasavaiah B. Gurumurthy[5], Ying-Xian Pan[1,2]

[1]Department of Anesthesiology, Rutgers New Jersey Medical School, Newark, NJ; [2]Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, NY; [3]Department of Psychology, Long Island University, Post Campus, Brookville, NY; [4]Department of Pediatrics, Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY; [5]Department of Pharmacology and Experimental Neuroscience, University of Nebraska, Omaha, NE

15. Dopamine tone differences in nucleus accumbens subregions during morphine reward and withdrawal

Sarah Warren Gooding[1], Jennifer L. Whistler[1,2]

[1]Center for Neuroscience, University of California - Davis; [2]Department of Physiology and Membrane Biology, UC Davis School of Medicine

16. Navigating the Schedule I Research Registration Process under the Controlled Substances Act

Li Fang[1], Cassandra Prioleau[1], William Heuett[1], and Terrence Boos[1]

[1]Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration, Arlington, VA

17. Identifying the anti-nociceptive mechanism of action for Cannabis sativa terpenes in mouse chemotherapy-induced peripheral neuropathy

Jerry Carr[1], Abigail Schwarz[1], Zhan-Guo Gao[3], Kenneth A. Jacobson[3], and John M. Streicher[1,2]

[1]Department of Pharmacology, College of Medicine; [2]Comprehensive Pain and Addiction Center; University of Arizona, Tucson AZ USA; [3]Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda MD USA

18. Pdyn-iCre Mice: Visualization of KOR and Dynorphin in (Pdyn-iCre x Ai6) x KOR-tdTomato Mice and Anterograde Tracing of PVH pDyn(+) neurons

Chongguang Chen[1], Kathryn Bland[1], Peng Huang[1], Conrad K. Ho[1], Kevin Beier[2], and Lee-Yuan Liu-Chen[1]

[1]Center for Substance Abuse Research and Department of Neural Sciences, Temple University Lewis Katz School of Medicine, Philadelphia, PA; [2]Department of Physiology and Biophysics, School of Medicine, University of California, Irvine, CA

19. Delta opioid receptor agonist KNT-127 regulates neurogenesis and neuroinflammation in the hippocampal dentate gyrus of mice in chronic vicarious social defeat stress model

Akiyoshi Saitoh[1], Toshinori Yoshioka[1], Daisuke Yamada[1], Eri Segi-Nishida[2], Hiroshi Nagase[3]

[1]Laboratory of Pharmacology, Faculty of Pharmaceutical Science, Tokyo University of Science, Noda, Japan; [2]Department of Biological Science and Technology, Faculty of Advanced Engineering, Tokyo University of Science, Katsushika, Japan; [3]University of Tsukuba, Ibaraki, Japan

20. Identifying Novel Orphan G-Protein Coupled Receptors in the Modulation of Opioid-Induced Analgesia in Acute and Chronic Models of Pain

Adrian Pena[1,2], John M. Streicher[1,2]

[1]Department of Pharmacology, University of Arizona College of Medicine; [2]Neuroscience Graduate Interdisciplinary Program

21. Cell-Type Specific Perturbations in the Dorsal Striatum Identified with Single Nucleus RNA-sequencing in a Rat Heroin Self-Administration Model

Jeremy D. Sherman[1,2,3], Yasmin L. Hurd[1,2,3]

[1]Department of Neuroscience, Icahn School of Medicine at Mount Sinai; [2]Department of Psychiatry, Icahn School of Medicine at Mount Sinai; [3]Addiction Institute of Mount Sinai

22. Spinal cord heat shock protein 90 inhibition upregulates protein kinase C-Beta in CGRP neurons to provide enhanced opioid antinociception in acute pain models

Jessica L. Bowden[1,2], John M. Streicher[1,3]

[1]Department of Pharmacology, College of Medicine University of Arizona, Tucson AZ USA; [2]United States Army; [3]Comprehensive Pain and Addiction Center; University of Arizona, Tucson AZ USA

23. Effects of the selective $\alpha 3\beta 4$ Nicotinic Receptors Partial Agonist AT-1001 on Oxycodone Spontaneous Withdrawal and Reinstatement in Rodents

M. Imad Damaj[1], Katherine Contreras[1], Joel E Schlosburg[1], and Nurulain T. Zaveri[2]

[1]Department of Pharmacology & Toxicology, Translational Research Initiative in Pain and Neuropathy, Virginia Commonwealth University, Richmond, VA, 23298; [2]Astraea Therapeutics, LLC, Mountain View, CA 94043

24. The Classical Psychedelic Psilocybin Mitigates Oxycodone Withdrawal

Belle Buzzi[1], Alaina Jaster[2], Eda Koseli[1], Torin Honaker[1], Olivia Ondo[1], Javier Gonzalez-Maeso[2], M Imad Damaj[1]

[1]Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA 23298;

[2]Department of Biophysics and Physiology, Virginia Commonwealth University, Richmond, VA 23298

25. Astrocyte Elevated Gene-1 (AEG-1) Genetic Deletion Prevents Tolerance to Morphine and Reduces its Physical Dependence in Mice

Eda Köseli[1], Bryan Mckiver[1], Shivani Patel[1], Apurva Puli[1], Devanand Sarkar[2], and M. Imad Damaj[1]

[1]Department of Pharmacology and Toxicology, Virginia Commonwealth University; [2]Department of Human and Molecular Genetics, Virginia Commonwealth University

26. Astrocyte Elevated Gene-1 (AEG-1) Deletion Selectively Enhances the Acute Antinociceptive Effects of Opioids

Bryan Mckiver[1], Eda Köseli[1], Shivani Patel[1], Apurva Puli[1], Katherine Contreras[1], Harrison Elder[1], Alyssa White-Presley[1], D Matthew Walentiny[1], Dana E. Selley[1], Devanand Sarkar[2], and M. Imad Damaj[1]

[1]Department of Pharmacology and Toxicology, Virginia Commonwealth University; [2]Department of Human and Molecular Genetics, Virginia Commonwealth University

27. Opioid withdrawal increases excitability and synaptic output of ventral pallidal glutamatergic neurons

Jessica Tooley[1], Meaghan C. Creed[1,2]

[1]Dept. of Anesthesiology, Washington University; [2]Depts. of Psychiatry, Neuroscience, and Biomedical Engineering, Washington University

28. Functional and anatomical characterization of pain-activated associated with chronic pain

Darian Peters[1], Katarzyna Targowska-Duda[2], Jason Marcus[1], Chetan Yarlagadda[1], Gilles Zribi[1], Lawrence Toll[1], Akihiko Ozawa[1]

[1]Florida Atlantic University College of Medicine; [2]Medical University of Lublin Department of Biopharmacy

29. Neural circuits regulating pain behaviors in the anterior cingulate cortex

Katarzyna Targowska-Duda[1,2], Chetan Yarlagadda[1], Darian Peters[1], Marla Minkoff[1], Akanksha Mudgal[1,2], Lawrence Toll[1], Akihiko Ozawa[1]

[1]Department of Biomedical Science, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL; [2]Department of Biopharmacy, Medical University of Lublin, Poland

30. Sex differences in the role of CNIH3 in opioid seeking

Tania Lintz[1], Hannah Frye[1], Elliot Nelson[2], Joe Dougherty[3], Jose Moron[1]

[1]Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO 63110; [2]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110; [3]Department of Genetics, Washington University School of Medicine, St. Louis, MO 63110

31. Opioid Suppression of an Excitatory Pontomedullary Respiratory Circuit by Convergent Mechanisms

Jordan T. Bateman[1], Erica S. Levitt[2]

[1]Department of Pharmacology and Therapeutics, University of Florida; [2]Department of Pharmacology, University of Michigan

32. Analysis of intra-splenic immune cell transformation under chronic dermatitis with pruritus

Naoko Kuzumaki[1,2], Takeru Muta[1], Yuta Sekiguchi[1], Yusuke Hamada[1,2], Yukari Suda[1,2], Michiko Narita[2], Minoru Narita[1,2]

[1]Dept. Pharmacol., Hoshi Univ., Tokyo, Japan; [2]Div. Cancer Pathophysiol., Natl. Cancer Ctr. Res. Inst., Tokyo, Japan

33. Role of peripheral μ-opioid receptors in cancer immunity

Yusuke Hamada[1,2], Michiko Narita[2], Yukari Suda[1,2], Naoko Kuzumaki[1,2], Minoru Narita[1,2]

[1]Dept. Pharmacol., Hoshi Univ., Tokyo, Japan; [2]Div. Cancer Pathophysiol., Natl. Cancer Ctr. Res. Inst., Tokyo, Japan

34. NCP, a dual mu and kappa opioid receptor agonist, is a potent analgesic without reinforcing or aversive properties and blocks stress-induced reinstatement of morphine CPP in mice

Peng Huang[1], Danni Cao[1], Chongguang Chen[1], Saadet Inan[1], Boshi Huang[2], E. Andrew Townsend[3], Matthew Banks[3], Conrad K. Ho, Scott Rawls[1], Yan Zhang[2], Lee-Yuan Liu-Chen[1]

[1]Center for Substance Abuse Research, Temple University Lewis Katz School of Medicine, Philadelphia, PA, USA; [2]Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, VA, USA; [3]Department of Pharmacology and Toxicology, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA

Tuesday

7:15 - 8:30 am **Breakfast**

Ellington Prefunction

8:00 - 8:30 am **Founder's Lecture**

Chair: Susan Ingram (University of Colorado Anschutz Medical Campus)

- **Opioid- and Dopamine-induced Immune Modulation**

  Dr. Minoru Narita

  Professor, Pharmacology, Hoshi University School of Pharmacy & Pharmaceutical Sciences, Tokyo, Japan

8:30 - 9:15 am **Plenary Lecture**

Chair: Anne Murphy (Georgia State University Neuroscience Institute)

- **Translating Opioid Abuse Guides New Targets for Therapeutic Interventions**

  Dr. Yasmin Hurd

  Director, Addiction Institute, Professor, Pharmacological Sciences, Neuroscience & Psychiatry, Icahn School of Medicine, Mount Sinai

9:15 - 9:30 am

Discussion

9:30 - 10:00 am **Coffee Break**

10:00 - 10:40 am **Symposium 3**

Cell- and Projection-specific Circuitry Underlying Heroin Self Administration, Withdrawal, and Relapse

Chair: Jacqueline McGinty (Medical University of South Carolina)

- **10:00-10:10 am**

  Jacqueline McGinty *(Medical University of South Carolina)*

  Protein Kinase A regulates heroin abstinence-induced increase in excitability and synaptic plasticity in Drd1+ and Drd2+ prelimbic neurons that project to nucleus accumbens

- **10:10-10:20 am**

  Jacqueline Paniccia *(Medical University of South Carolina)*

  A thalamo-accumbal 'brake' is disengaged by opioid use in a μ-opioid receptor-dependent manner

- **10:20-10:30 am**

  Jennifer Bossert *(IRP/NIDA/NIH/DHHS)*

  Effect of selective lesions of nucleus accumbens (NAc) MOR-expressing cells on heroin self-administration in male and female rats: a study with novel Oprm1-Cre knock-in rats

Tuesday

- **10:30-10:40 am**
  Giuseppe Giannotti *(Washington State University)*
  Paraventricular thalamic control of withdrawal somatic states following heroin self-administration

10:40 - 11:10 am
Discussion

11:10 - 11:50 am **Symposium 4**

Novel neuronal circuits driving reinforcing behavior and opioid use disorders

Chair: Jose Moron Concepcion (Washington University)

- **11:10-11:25 am**
  Jose Moron Concepcion *(Washington University)*
  Dorsal Hippocampus to Nucleus Accumbens Projections Drive Reinforcement Via Activation of Accumbal Dynorphin Neurons
- **11:25-11:40 am**
  Barbara Juarez *(University of Maryland, Baltimore)*
  Dissecting physiology and function of the parabrachial nucleus during opioid withdrawal
- **11:40-11:55 am**
  Rhiana Simon *(University of Washington)*
  Molecularly-defined cell types within the LS and their role during opioid withdrawal

11:55 – 12:20 pm
Discussion

12:20 - 1:50 pm **Lunch (on your own)**

1:50 - 2:35 pm **Symposium 5**

Mesocorticolimbic plasticity: the crossroad of opioid sensitivity, motivation, and relapse

Chair: Matthew Hearing (Marquette University)

- **01:50 – 02:05 pm**
  James Otis *(Medical University of South Carolina)*
  Noradrenergic regulation of prefrontal neuronal ensembles during relapse to heroin seeking.
- **02:05 – 02:20 pm**
  Emilia Lefevre *(University of Minnesota)*
  Nucleus accumbens fast-spiking interneurons regulate opioid reward and addiction

Tuesday

- **02:20 - 02:35 pm**
  Matthew Hearing *(Marquette University)*
  Sex-specific synaptic plasticity in mesolimbic subcircuits underlying motivational shifts in drug versus non-drug reward

02:35 – 03:00 pm
Discussion

3:00 - 3:30 pm **Networking Break**

3:30 - 4:00 pm **Hot Topics 3**

Chair – Daniel Castro (*Washington University in St. Louis*)

- Braulio Munoz (*Faculty, Indiana University School of Medicine*) - A novel inhibitory corticostriatal circuit that mediates mu opioid receptor synaptic plasticity
- Tamara Stamenic (*Instructor, University of Colorado - Anschutz Medical Campus*) - CaV3.1 isoform of T-type calcium channels plays an important role in morphine-induced alterations in thalamic excitability and conditioned place preference in mice
- Evan O'Brien (*Post doc, Stanford University*) - Allosteric modulation of the μ-opioid receptor

4:00 - 4:30 pm **Data Blitz/Poster Teasers**

4:30 - 6:30 pm **Poster Session 2**

Overlook East

Session Abstracts

Symposium 3: Cell- and Projection-specific Circuitry Underlying Heroin Self Administration, Withdrawal, and Relapse

This session will describe the functional heterogeneity of the circuitry that underlies the transition to addiction using heroin self administration protocols in rodents. **Jacqueline McGinty** will describe cell-type specific adaptations in Drd1- vs. Drd2-expressing prelimbic pyramidal neurons projecting to nucleus accumbens that are bidirectionally regulated during abstinence versus relapse and involve cAMP-dependent PKA activation. Further, disruption of the abstinence-associated adaptations via intra-prelimbic PKA inhibition decreased relapse. **Jacqueline Paniccia** will describe how a thalamo-accumbal 'brake' is disengaged by opioid use in a μ-opioid receptor (μ-OR)-dependent manner. Using two-photon *in vivo* imaging, optogenetic manipulations, and electrophysiological strategies, she will explain how opioid-induced neurobiological adaptations in the paraventricular thalamus (PVT)->NAc system disengage the 'brake' on heroin-seeking behavior through μ-OR-induced weakening of PVT synaptic innervation onto NAc parvalbumin interneurons. **Jennifer Bossert** will introduce a new *Oprm-1*-Cre knockin rat line to study the role of μ-OR$^+$ cells in opioid addiction. She will describe the anatomical and behavioral validation of a new CRISPR-based *Oprm1*-Cre knock-in transgenic rat and will describe functional

studies on sex-dependent involvement of nucleus accumbens μ-OR$^+$ cells in heroin self-administration using a Cre-dependent Casp3 vector to lesion NAc μ-OR$^+$ cells. **Giuseppe Giannotti** will describe how the PVT→NAc pathway mediates heroin-induced wihdrawal signs. By employing chemogenetics to investigate the contribution of the PVT->NAc pathway to heroin withdrawal-induced somatic states following heroin self-administration in rats. They found that the PVT→NAc pathway is necessary for spontaneous withdrawal signs and pain sensitivity after abstinence from self-administered heroin. Moreover, by using withdrawal-related variables to train a regression machine learning model, they were able to accurately predict the individual propensity to relapse. Deepening cell-specific and circuit-based knowledge has the potential to lead to the development of targeted therapeutic strategies to treat opioid use disorder.

Symposium 4: Novel neuronal circuits driving reinforcing behavior and opioid use disorders

This session will provide new insight into the role of novel neuronal circuits involved in reward seeking and opioid use disorders. To date, technical limitations have restricted our ability to dissect the nature of opioid-induced neuroplasticity with any temporal precision. Therefore, by using a combination of cutting-edge technology and behavioral paradigms the goal of this panel is to uncover and dissect the role of novel neuronal circuits in opioid disorders. Dr Moron-Concepcion will show evidence that the dorsal hippocampusnucleus accumbens circuit is critically involved in encoding and maintaining reward-cue associations underlying reinforcement and drug-seeking behavior. Dr Otis will provide evidence for the role ofprefrontal cortical ensemble dynamics from the onset of heroin self-administration to relapse. Dr Juarez will show data involving calcitonin gene-related peptide neurons of the parabrachial nucleus (PBN^{CGRP}) in opioid withdrawal. Finally, Ms Simon will show data suggesting a role for LS Neurotensin-expressing (LS^{NTS}) neurons in opioid withdrawal and nociceptive pain behavior.

Symposium 5: Mesocorticolimbic plasticity: the crossroad of opioid sensitivity, motivation, and relapse

Increasing evidence suggests that the neural circuits and associated opioid-induced adaptations related to withdrawal and drug sensitivity are not necessarily synonymous with those responsible for establishing drug seeking behavior and drug relapse. This session will explore opioid-induced neural adaptations and function of top-down and bottom-up mesocorticolimbic circuits and how they contribute to alterations in motivation for drug, shifts in opioid sensitivity, escalated drug intake, and relapse. Dr. Jim Otis will provide evidence for a sexually dimorphic role of prefrontal cortical ensemble dynamics from the onset of heroin self-administration to relapse. Dr. Emilia Lefevre will present data showing the contribution of nucleus accumbens fast-spiking interneurons to development of fentanyl sensitization and expression of cue-induced reinstatement of drug-seeking. Dr. Matthew Hearing will present data showing a sex-unique shift in motivation for and intake of morphine versus non-drug reward and the underlying role of dopamine subcircuit plasticity within the ventral tegmental area-to-nucleus accumbens shell pathway.

Hot Topics 3

A novel inhibitory corticostriatal circuit that mediates mu opioid receptor synaptic plasticity

Braulio Munoz (*Faculty, Indiana University School of Medicine*)

Corticostriatal circuits are generally characterized by the release of glutamatergic neurotransmitter from the cortex to the striatum. It is well known that this cortical excitatory transmission regulates action selection behavior in the dorsal striatum.

Indeed, we have reported that glutamatergic anterior insular cortical (AIC) inputs to the dorsolateral striatum (DLS) are the solely mediator of mu opioid receptor-mediated long-term depression (MOR-LTD), and the activation of these inputs in the DLS, decrease alcohol binge drinking. However, little is known about the existence, the role and regulation of corticostriatal inhibitory synaptic transmission. Here, using a combination of patch clamp electrophysiology and optogenetics, we characterized a novel corticostriatal inhibitory circuit and its function in expressing mu opioid receptor-mediated inhibitory long-term depression (MOR-iLTD) in the DLS. First, we found that the activation of mu opioid receptor (MOR) by DAMGO produced MOR-iLTD in the DLS and dorsomedial striatum (DMS), this depression in the inhibitory transmission is mediated by presynaptic MORs. Then, we showed that medium spiny neurons from the DLS, received direct inhibitory synapses from the cortex, specifically from the motor cortex and AIC. Using a parvalbumin cre- expressing mice, we identified that this specific cortical neuron-type that sends direct GABAergic projections to the DLS. Moreover, these neurons expressed MOR-iLTD. These data suggest a novel GABAergic corticostriatal circuit that could be involved in the regulation of action selection behaviors, especially for the treatment of opioid and alcohol use disorder.

CaV3.1 isoform of T-type calcium channels plays an important role in morphine-induced alterations in thalamic excitability and conditioned place preference in mice

Tamara Stamenic (*Instructor, University of Colorado - Anschutz Medical Campus*)

The central medial nucleus of thalamus (CeM) has been recognized as a hub through which natural sleep and general anesthesia are initiated but other CeM roles are not well studied. Low-voltage-activated T-type Ca2+ channels (T-channels) are important for neuronal excitability, synaptic plasticity and oscillatory behaviors. The mechanisms underlying the role of T-channels in thalamic excitability and behavioral changes in vivo during morphine exposure are largely unknown.

Here we investigated the effects of acute (10 μM) and repeated (15 mg/kg i.p. 4 days) morphine exposure on CaV3.1 T-channels kinetics and excitability of CeM neurons in an ex vivo slice preparation. We also used mouse genetics to correlate the addictive effects of morphine (conditioned place preference - CPP) with thalamic CaV3.1 T-channels.

Our results showed a reduction of T-channels currents and inhibition of rebound firing in CeM neurons in WT animals during acute morphine application. Morphine stabilizes inactive states of T-channels and shifts inactivation V50 significantly. In current-clamp experiments morphine reduced excitability of CeM neurons after both acute and repeated exposure. The CPP test is commonly used to explore the reinforcing effects of natural and pharmacological stimuli. Our results with suboptimal morphine CPP (6 mg/kg i.p. 3 days), showed that both global deletion (Cav3.1 knock-out animals) and CeM-specific reduction (CeM-selective Cav3.1 knock-down mice) of T-channels resulted in the animals being more sensitive to the rewarding effects of morphine.

We show for the first time the importance of the thalamic CaV3.1 T-channels in both morphine-induced neuronal excitability and morphine-induced CPP in mice.

Allosteric modulation of the μ-opioid receptor

Evan O'Brien (*Post doc, Stanford University)*

The μ-opioid receptor (μOR) is a well-established target for analgesia, yet conventional opioid receptor agonists suffer from serious side effects, namely respiratory depression. Positive allosteric modulators (PAMs) of the μOR have the potential to avoid many off-target effects of orthosteric agonists and enhance natural opioid peptide systems, while negative allosteric modulators (NAMs) may serve as powerful tools in preventing opioid overdose deaths. We screened a large DNA-encoded chemical library against active and inactive μOR to "steer" selections

towards functional allosteric modulators with an 80% hit rate. The most effective μOR PAM enhances the activity of all orthosteric agonists including the native opioid peptide met-enkephalin. Using cryo-electron microscopy, we show that the PAM binds to a site exposed on the active conformation of the intracellular half of the 6th transmembrane helix. The highly enriched NAM compound potently blocks activity of orthosteric agonists and enhances the affinity of the key opioid overdose prevention molecule, naloxone. It accomplishes this by binding to a site on the extracellular vestibule proximal to naloxone, stabilizing a unique, extended inactive conformation of TM7, ECL3 and TM2. The NAM perturbs orthosteric ligand kinetics in therapeutically desirable ways and works cooperatively with naloxone in vivo to inhibit morphine-induced antinociception and side effects while minimizing withdrawal behaviors. Together, the allosteric modulators presented here represent the first detailed structural description of positive and negative allosteric modulatory mechanisms within the μOR, as well as highlight the power of leveraging ensemble selection principles for drug discovery efforts.

Poster Session 2

Please see abstract book for all poster abstracts.

1. Adaptations of the endocannabinoid system after chronic inflammatory pain are driven by corticosterone within the vlPAG

B. Coutens[1], C.A. Bouchet[2], K.B. McPherson[1], B. Boston[1], S.L. Ingram[1]

[1]University of Colorado, Anschutz Medical Campus, Aurora; [2]Colorado State University, Fort Collins

2. Inflammatory pain alters alcohol self-administration in a sex- and dose-dependent manner

Yolanda Campos-Jurado[1], Bilal Zahoor[1], Haziq Latif-Jangda[1], Youssef M. Saad[1], Jose A. Moron[1]

[1]Anesthesiology Department, Washington University in St. Louis

3. NOP Receptor Agonist Attenuates CGRP Induced Acute and Chronic Migraine-Like States

Ariana Perez[1], Bianca Fakhoury[1], George Tarantino[1], Kylie Kealoha[1], Lawrence Toll[1,2], Andrea Cippitelli[1,2]

[1]Department of Biomedical Science, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL; [2]Department of Biomedical Science, Charles E. Schmidt College of Medicine, Stiles-Nicholson Brain Institute, Jupiter, FL

4. Inhibition of Gβγ-PLCβ3 produces antihyperalgesia during ongoing nitroglycerin-induced hypersensitivity

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

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

5. Combination of Two Positive Allosteric Modulators for the μ-Opioid Receptor

Ben M Clements[1], Ram Kandasamy[2], John R. Traynor[1,3]

[1]Edward F. Domino Research Center, Department of Pharmacology, University of Michigan Medical School; [2]Department of Psychology, California State University - East Bay; [3]Department of Medicinal Chemistry, School of Pharmacy, University of Michigan

6. The Therapeutic Potential of PPL-138 as an Agent for Managing Addiction and Chronic Pain

Stefania Volpe[1], Gilles Zribi[1], Andrea Cippitelli[1,2], Lawrence Toll[1,2],

[1]Biomedical Science Department, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL; [2]Biomedical Science Department, Charles E. Schmidt College of Medicine, Stiles-Nicholson Brain Institute, Florida Atlantic University, Jupiter, FL

7. Characterizing a mesolimbic circuit for opioid reward

Rubén A. García-Reyes[1], Hugo E. Córdova Olazábal[1], Daniel C. Castro[1]

[1]Biophotonics Research Center, Washington University School of Medicine in St. Louis

8. Perigestational morphine exposure augments the response to LPS in adult male and female rats

Hannah J. Harder[1], Morgan G. Gomez[1], Christopher T. Searles[1], Meghan E. Vogt[1], Anne Z. Murphy[1]

[1]Neuroscience Institute, Georgia State University

9. Opioids alter the conditioned reinforcing properties of cocaine-paired cues in the New Response Acquisition procedure

Lauren G Rysztak[1,2] and Emily M Jutkiewicz[2]*

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

10. Ethanol potentiates fentanyl-induced apneic events, which is not rescued by naloxone

Renata CN Marchette[1], Lyndsay E. Hastings[1], Emma V. Frye[1], Janaina C.M. Vendruscolo[1], Aidan Hampson[2], Nora Volkow[3], Leandro F. Vendruscolo[4], and George F. Koob[1]

[1]Neurobiology of Addiction Section, INRB, NIDA IRP, NIH; [2]Division of Pharmacotherapeutic Development, NIDA, NIH; [3]Laboratory for Neuroimaging, NIAAA, IRP, NIH; [4]Stress & Addiction Unit, INRB, NIDA and NIAAA IRP, NIH

11. Dissecting the molecular effects of therapeutic pregabalin and morphine concentrations on different neuronal cell models to implement a Quantitative Systems Pharmacology platform

Elisabetta Cuna[1], Monica Baiula[1], Berfin Gülave[2], Elizabeth de Lange[2], Santi Spampinato[1], Andrea Bedini[1]

[1]Department of Pharmacy and Biotechnology - University of Bologna, Bologna, Italy; [2]Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre of Drug Research, Leiden University, Leiden, Netherlands

12. Molecular pathway analysis of morphine and THC coadministration in different neuronal models for the implementation of an innovative quantitative systems pharmacology (QSP) platform to predict combinational analgesic treatments

Monica Baiula[1], Elisabetta Cuna[1], Santi Spampinato[1], Andrea Bedini[1]

[1]Department of Pharmacy and Biotechnology (FaBiT), University of Bologna - Italy

13. Alcohol and Sucrose Consumption in Adolescent Male and Female Rats Perigestationally Exposed to Morphine

Christopher T. Searles[1], Hannah J. Harder[1], Meghan E. Vogt[1], Peter Clements[1], Anne Z. Murphy[1]

[1]Neuroscience Institute, Georgia State University

14. Peripheral Mechanisms of Opioid-Induced Respiratory Depression: Insights and Therapeutic Potential

Brian C. Ruyle[1], Sarah Masud[1], Mubariz Tahirkheli[1], Jose Moron-Concepcion[1]

[1]Department of Anesthesiology, Washington University in St. Louis

15. Investigation of acute and long-term immune changes induced by early-life opioid exposure and withdrawal

Julia R. Ferrante[1], Joseph J. Meissler[2], Khaled Althobaiti[3], Toby K. Eisenstein[2], Michelle E. Ehrlich[3],Julie A. Blendy[1]

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16. Effects of the non-selective opioid ligand, PPL-138, on an animal model of comorbid PTSD-AUD

Kylie Kealoha[1], Ali Idriss[1], Yong Zhang[2], Benjamin Carper[3], Panini Patankar[2], Lawrence Toll[1,4], Kelly Standifer[2], Andrea Cippitelli[1,4]

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17. Long-lasting effect of chronic social defeat stress on opioid self-administration

*Emma Tyner[1], Kyle A. Windisch[1], Seema Bhatnagar[2], and Julie A. Blendy[1]**

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18. Multiplexed pharmacological calcium imaging reveals distinct opioid receptor-mediated response profiles of locus coeruleus neurons

Chao-cheng Kuo[1,2,3,4], Jordan G. McCall[1,2,3,4,5]

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19. Sex-dependent effects of alcohol and oxycodone polysubstance use

Yueyi Chen[1], Salvador Huitron Resendiz[2], Amanda Roberts[2], Adam Kimbrough[1]

[1]Department of Basic Medical Sciences, Purdue University; [2]Animal Models Core, The Scripps Research Institute

20. Regulation of Delta Opioid Receptor Signaling in the Anterior Cingulate Cortex by Agonists and Pain

Marie C Walicki[1,2], Alberto Perez-Medina[2], Hannah Uebele[2], Will Birdsong[1,2]

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

21. Chronic Morphine Induces Facilitation of Morphine Signaling at Thalamo-Striatal Terminals but Tolerance at Thalamo-Cortical Terminals and Thalamic Cell Bodies in a Sex-Specific Manner

Elizabeth R. Jaeckel[1], Erwin R. Arias-Hervert[1], Alberto L. Perez-Medina[1], Yoani N. Herrera[2], Brigitte L. Kieffer[3], William T. Birdsong[1]

[1]Department of Pharmacology, University of Michigan, Ann Arbor, MI; [2]Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI; [3]INSERM U1114, University of Strasbourg, Strasbourg, France

22. Estradiol protects against pain-facilitated fentanyl use via suppression of opioid-evoked dopamine activity

Jessica Higginbotham[1,2,3], Julian Abt[1,2,3], Rachel Teich[1,2,3], Tania Lintz[1,2,3,4], Jose Moron-Concepcion[1,2,3,4,5]

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23. Allosteric modulation of the μ-opioid receptor

Evan S. O'Brien[1], Vipin Ashok Rangari[2], Amal El Daibani[2], Shainnel O. Eans[3], Betsy White[1], Haoqing Wang[1], Yuki Shiimura[1,4], Kaavya Krishna Kumar[1], Kevin Appourchaux[2], Weijiao Huang[1], Chensong Zhang[5], Jesper Mathiesen[6], Tao Che[2], Jay P. McLaughlin[3], Susruta Majumdar[2], Brian K. Kobilka[1]

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24. Implications of NOP receptor system in sociability impairments under migraine condition

Akanksha Mudgal[1,2], Olga Wronikowska-Denysiuk[2], Darian Peters[1], Isabel Snow[1], Madeline Martinez[1], Chetan Yarlagadda[1], Lawrence Toll[1], Akihiko Ozawa[1], Katarzyna Targowska-Duda[1,2]

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25. Influence of pain signals with the facilitation of stress-responsive networks in tumor progression

Yu Okamoto[1], Sara Yoshida[1], Kenichi Tanaka[1], Yusuke Hamada[1,2], Daisuke Sato[1], Michiko Narita[2], Yukari Suda[1,2], Naoko Kuzumaki[1,2], Minoru Narita[1,2]

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26. Mice lacking the endocannabinoid-synthesizing enzyme NAPE-PLD exhibit sex-dependent dysregulations in responsiveness to oxycodone and natural rewards

Taylor Woodward[1,2], Sarah Stockman[2], Fezaan Kazi[2], Hasaan Kazi[2], Ken Mackie[1,2,3], Andrea G. Hohmann[1,2,3]

[1]Program in Neuroscience, Indiana University, Bloomington, IN; [2]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN; [3]Gill Center of Biomolecular Science, Indiana University, Bloomington, IN

27. SRI 22136, A Novel Delta Opioid Receptor (DOR) Antagonist for the Treatment of Alzheimer's Disease

Partha Tanguturi

The University of Arizona

28. Dietary polyphenols drive dose-dependent behavioral and molecular alterations to repeated morphine

Aya Osman[1,2,3], Rebecca S. Hofford[1,3,4], Katherine R. Meckel[3,5], Yesha A. Dave[5], Sharon M. Zeldin[1,3], Ava L. Shipman[1,3], Kelsey E. Lucerne[3,5], Kyle J Trageser[6,7], Tatsunori Oguchi[6,7], Drew D. Kiraly[1,2,3,4,5,8]

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29. Impact of Partial Agonist Opioid Ligands on Methamphetamine Use Disorder in Rodent Models

Gilles Zribi[1], Andrea Cippitelli[1], Lawrence Toll[1]

[1]Florida Atlantic University - Stiles-Nicholson Brain Institute

30. In vitro and in vivo comparison of morphine, fentanyl, and furanylfentanyl

Catherine Demery-Poulos[1], Sierra Moore[1], Kelsey E. Kochan[1], Jessica Whitaker-Fornek[1], Erica S. Levitt[1], Jessica P. Anand[1], and John R. Traynor[1,2]

[1]Department of Pharmacology, University of Michigan Medical School; [2]Department of Medicinal Chemistry, University of Michigan College of Pharmacy

31. Identifying brain regions involved in chronic-pain processing and analgesic treatment

Madeline Martinez[1], Darian Peters[1], Akanksha Mudgal[1,2], Katarzyna Targowska-Duda[1,2], Akihiko Ozawa[1], Lawrence Toll[1]

[1]Stiles-Nicholson Brain Institute, Florida Atlantic University, Jupiter, FL; [2]Department of Biopharmacy, Medical University of Lublin, Lublin, Poland

32. Advances in Drug and Alcohol Research Insights from Covidization and Opioid Epidemic

Emmanuel S. Onaivi[1], Lee-Yuan Liu-Chen[2], Syed F. Ali[3], Michael Kuhar[4], Larry Toll[5], George F. Koob[6]

[1]William Paterson University; [2]Temple University; [3]University of Arkansas; [4]Emory University; [5]Florida Atlantic University; [6]NIAAA-NIH

33. Psilocybin reduces heroin seeking behavior and modulates inflammatory gene expression in the nucleus accumbens and prefrontal cortex of male rats

Gabriele Floris[1,2], Stephanie Sullivan[1,2]

[1]Lewis Katz School of Medicine: Center for Substance Abuse Research, Temple University, Philadelphia, PA USA; [2]Department of Neural Sciences, Temple University, Philadelphia, PA USA

Wednesday

8:00 - 8:30 am **Young Investigator's Lecture**

Chair: Nicolas Massaly (UCLA)

- **Molecular pathway analysis at opioid receptors to develop innovative analgesics: from the characterization of novel ligands to the implementation of Quantitative Systems Pharmacology platforms**

  Dr. Andrea Bedini

  Associate Professor, Pharmacology

  University of Bologna, Italy

8:30 - 8:45 am

Discussion

8:45 - 9:30 am **Hot Topics 4**

Chair – Andrea Bedini (*University of Bologna, Italy*)

- Brian Ruyle (*Post Doc, Washington University in St Louis*) - Peripheral Mechanisms of Opioid-Induced Respiratory Depression: Insights and Therapeutic Potential
- Elisabetta Cuna (*Grad Student, University of Bologna*) - Dissecting the molecular effects of therapeutic pregabalin and morphine concentrations on different neuronal cell models to implement a Quantitative Systems
- Taylor Woodward (*Grad Student, Indiana University*) - Mice lacking the endocannabinoid-synthesizing enzyme NAPE-PLD exhibit sex-dependent dysregulations in responsiveness to oxycodone and natural rewards
- Basile Coutens (*Post Doc, University of Denver Anschutz Medical Campus*) - Adaptations of the endocannabinoid system after chronic inflammatory pain are driven by corticosterone within the vlPAG

9:30 - 10:00 am **Coffee Break**

10:00 - 10:45 am **Symposium 6**

Intersection between pain and opioids (clinical and preclinical)

Chairs: Dominique Massotte/Katia Befort (University of Strasbourg)

- **10:00-10:15 am**

  Yannick Goumon (University of Strasbourg)

  The central metabolism of morphine relies on reactive astrocytes in inflammatory conditions

- **10:15-10:30 am**

  Serge Marchand (University of Sherbrooke)

  Endogenous pain modulation in healthy subjects and patients

Wednesday

- **10:30-10:45 am**

  William Brose (Stanford)

  Opioid prescribing: the evolution of digital therapeutics.

10:45 - 11:15 am

Discussion

11:15 - 11:45 am **Hot Topics 5**

Chair –

- Kylie McPherson (Post Doc, University of Colorado Anschutz Medical Campus) - Persistent inflammation selectively activates opioid-sensitive phasic-firing neurons within the vlPAG
- Jessica Higginbotham (Post Doc, Washington University in St. Louis) - Estradiol protects against pain-facilitated fentanyl use via suppression of opioid-evoked dopamine activity
- Yolanda Campos-Jurado (Post Doc, Washington University in St. Louis) - Inflammatory pain alters alcohol self-administration in a sex- and dose-dependent manner

11:45 - 1:30 pm **Lunch (on your own)**

INRC EXEC Committee Lunch (Inman)

1:30 - 2:30 pm **Symposium 7**

MOR-DOR Interactions: latest findings in neural circuits and important roles as a therapeutic target

Chairs: Wakako Fujita (Nagasaki University, Japan), Lakshmi A Devi (Icahn School of Medicine at Mount Sinai)

- **01:30 – 01:45 pm**

  Dominique Massotte (University of Strasburg)

  Chronic morphine administration or sciatic nerve injury differentially alters mu-delta distribution within neuronal circuits

- **01:45 – 02:00 pm**

  Peng Zhou (Okinawa Institute of Science and Technology Graduate University)

  Modulating metastable homo- and hetero-dimers of opioid receptors for enhancing analgesia

- **02:00 - 02:15 pm**

  Wakako Fujita (Nagasaki University Graduate School of Biomedical Sciences)

  The possible role of RTP4, a chaperone protein of MOPr-DOPr heteromer, in chronic opioid use

Wednesday

- **02:15 - 02:30 pm**
  Ivone Gomes (Icahn School of Medicine at Mount Sinai)
  Identification of exogenous and endogenous ligands targeting mu-delta interacting complexes

02:30 – 03:00 pm
Discussion

3:00 - 3:30 pm **Networking Break**

3:30 - 4:00 pm **Hot Topics 6**
Chair – Barbara Juarez (University of Maryland)

- Mengchu Li (Post Doc, University of Michigan) - Structure Modifications and In Vitro Evaluation of Mu-opioid Receptor Positive Modulators
- Marie Walicki (Grad Student, University of Michigan) - Regulation of Delta Opioid Receptor Signaling in the Anterior Cingulate Cortex by Agonists and Pain
- Eda Koseli (Post Doc, Virginia Commonwealth University) - Astrocyte Elevated Gene-1 (AEG-1) Genetic Deletion Prevents Tolerance to Morphine and Reduces its Physical Dependence in Mice

4:00 - 5:30 pm **Business Meeting & Closing Remarks**

5:30 - 6:30 pm **Networking Free Time**

6:30 - 8:30 pm **Closing Reception**
Terrace and Ellington Prefunction

8:30 - Midnight **Dancing & Dessert**
Overlook East

Session Abstracts

Hot Topics 4

Peripheral Mechanisms of Opioid-Induced Respiratory Depression: Insights and Therapeutic Potential

Brian Ruyle (*Post Doc, Washington University in St Louis*)

Millions of Americans suffer from Opioid Use Disorders (OUD) and face a high risk of accidental overdose, which can cause opioid-induced respiratory depression (OIRD). Synthetic opioid opioid-related overdose deaths continue to rise, thus it is critical to understand the mechanisms by which fentanyl induces respiratory depression. We previously showed that the peripherally-restricted opioid receptor antagonist

naloxone methiodide (NLXM) prevents and reverses OIRD to a similar degree as naloxone. We aim to understand the peripheral contributions underlying OIRD. The vagus nerve expresses mu opioid receptors and terminates in the nucleus of the solitary tract, a critical mediator of basal and reflex-evoked cardiorespiratory function. We used a chemogenetic approach to express Gq-DREADDS in the nodose ganglia and vagal afferent fibers of rats. Fentanyl produced rapid cardiorespiratory depression, characterized by decreased oxygen saturation, heart rate and respiratory rate. Intravenous CNO restored cardiorespiratory parameters faster than saline, suggesting that fentanyl disrupts a vagal-brainstem circuit which contributes to prolonged OIRD. To obtain further insight into the peripheral contributions to OIRD, separate groups of rats underwent three day conditioned place preference (CPP). Fentanyl was administered in home cages, followed by NLXM or naloxone in one side of the CPP box. Rats displayed an aversion to the naloxone-paired side, and this was not observed in NLXM-treated rats. These findings provide insight into peripheral mechanisms that contribute to OIRD and how antagonism of these receptors could be a promising therapeutic strategy for managing OIRD by sparing the CNS-driven acute opioid withdrawal generally observed with the use of naloxone.

Dissecting the molecular effects of therapeutic pregabalin and morphine concentrations on different neuronal cell models to implement a Quantitative Systems

Elisabetta Cuna (*Grad Student, University of Bologna*)

Quantitative systems pharmacology (QSP) approach combines mechanistic models of physiology in health and disease with pharmacokinetics/pharmacodynamics to predict systems-level effects. In the framework of implementing a QSP platform to predict novel, more effective and safer combinations of existing medications to treat chronic pain, we aim to investigate the effects of morphine and pregabalin co-administration at therapeutic concentrations on opioid receptors expression and intracellular signalling in different neuronal cell models.

A comprehensive CNS physiology-based PK model (LeiCNS-PK3.0) was employed to predict morphine and pregabalin minimal, average and maximal concentration at brain extracellular fluid (ECF) following therapeutic regimens. Brain region-specific rat and mouse primary cultures and SH-SY5Y human neuroblastoma cells differentiated into a more mature neuron-like phenotype were employed. Pregabalin effects on morphine-mediated inhibition of adenylyl cyclase, ERK 1/2, p38MAPK phosphorylation, and the expression of seven pain/analgesia-related targets was studied using ELISA assay, Western Blot and qPCR, respectively.

In differentiated SH-SY5Y pregabalin co-treatment increased MOR and CB1 mRNA levels. In this human neuron-like cell model, in rat cortical and striatal primary neurons, pregabalin significantly potentiated morphine ability to inhibit adenylyl cyclase.

After prolonged μ opioid receptor stimulation for 48 hours, morphine ability to activate MOR is dampened. Co-administering pregabalin partially rescued morphine ability to inhibit adenylyl cyclase; moreover, pregabalin co-administration promoted morphine-dependent ERK 1/2 activation.

Our findings showed that morphine-pregabalin combination increased the expression of analgesia-related targets, potentiated morphine-dependent signalling events and partially rescued MOR activation following its desensitization, thus suggesting that pregabalin co-administration may positively impact on morphine pharmacodynamics.
Supported by QSPainRelief (H2020 grant agreement n.848068)

Mice lacking the endocannabinoid-synthesizing enzyme NAPE-PLD exhibit sex-dependent dysregulations in responsiveness to oxycodone and natural rewards

Taylor Woodward (*Grad Student, Indiana University*)

Endogenous opioid and endocannabinoid (eCB) signaling play interconnected regulatory roles in many systems level processes including mood and reward. The eCB system holds promise for treating unwanted side effects of opioids (tolerance, reward, dependence). However, limited understanding of endogenous cannabinoids and their signaling limits the development of potential eCB-based therapeutics. Prior preclinical work suggests that increasing levels of the eCB ligand anandamide (AEA) enhances both natural and drug rewards, whereas genetic deletion or pharmacological inhibition of CB1 receptor (CB1R) signaling attenuates opioid reinforcement. Until recently, there was little consensus regarding the mechanisms of AEA's biosynthesis in vivo. How N-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD), the enzyme responsible for biosynthesis of AEA, directly affects both natural and opioid reinforcement remain unknown. We tested the hypothesis that genetic deletion of NAPE-PLD (and subsequent lowering of AEA levels) would blunt the reinforcing properties of natural rewards and opioid rewards. We examined the performance of wild-type (WT) and NAPE-PLD knockout (KO) mice in a two-bottle choice assay. In this assay, female NAPE-PLD KO mice consumed significantly higher doses of oxycodone compared to female WT mice. Interestingly, NAPE-PLD KO mice consumed higher quantities of quinine and sucrose compared to WT controls. We also found that NAPE-PLD KOs exhibited blunted hyperlocomotion in response to an acute injection of oxycodone, as well as a blunted locomotor sensitization to repeated injections of oxycodone. Genotypic differences between WT and KO males were largely absent. Together, these data suggest that NAPE-PLD regulates behavioral responsivity to both opioid and natural reinforcers.

Symposium 6: Intersection between pain and opioids (clinical and preclinical)

To date, treatments to alleviate chronic pain remain largely ineffective and opiate prescription can lead to drug dependence. This symposium will present recent advances in our understanding of the molecular mechanisms critically involved in chronic pain and morphine metabolism, both at neuronal and glial level and at preclinical and clinical level. It will also address their potential impact in addition to sexual dimorphism on our efforts towards personalized medicine. Y. Goumon will highlight recent findings showing that morphine central metabolism relies on reactive astrocytes in inflammatory conditions. S. Marchand will present important factors to consider for adapted personalized medicine in chronic pain patients including changes in the endogenous opioid system. W.G. Brose will introduce innovative non-drug intervention to improve opiate use safety for clinical management of opiates in chronic pain patient.

Hot Topics 5

Persistent inflammation selectively activates opioid-sensitive phasic-firing neurons within the vlPAG

Kylie McPherson (Post Doc, University of Colorado Anschutz Medical Campus)

The ventrolateral periaqueductal gray (vlPAG) is a key brain area within the descending pain modulatory pathway and an important target for opioid-induced analgesia. The vlPAG contains heterogeneous neurons with respect to neurotransmitter content, receptor and channel expression, and in vivo response to noxious stimuli. This study characterizes intrinsic membrane properties of vlPAG neurons to identify neuron types that respond to inflammation and determine whether the pain-responsive neurons are inhibited by opioids. Surveying 382 neurons identified four neuron types with distinct intrinsic firing patterns: Phasic (48%), Tonic (33%), Onset (10%), and Random (9%). Mu-opioid receptor (MOR) expression was

determined by the ability of a selective MOR agonist (DAMGO) to activate G protein-coupled inwardly rectifying potassium channel (GIRK) currents. Opioid-sensitive neurons were observed within each neuron type. Opioid sensitivity did not correlate with other intrinsic firing features, including low-threshold spiking that has been previously proposed to identify opioid-sensitive GABAergic neurons in the vlPAG of mice. Complete Freund's adjuvant (CFA)-induced acute inflammation (2 hours) had no effect on vlPAG neuron firing patterns. However, persistent inflammation (5–7 days) selectively activated Phasic neurons through a significant reduction in their firing threshold. Opioid-sensitive neurons were strongly activated compared with the opioid-insensitive Phasic neurons. Overall, this study provides a framework to further identify neurons activated by persistent inflammation so that they may be targeted for future pain therapies.

Estradiol protects against pain-facilitated fentanyl use via suppression of opioid-evoked dopamine activity

Jessica Higginbotham (Post Doc, Washington University in St. Louis)

Pain affects over 50% of US adults. Opioids are potent analgesics used to treat pain symptoms but are highly prone to abuse, creating a major dilemma for public health. Evidence suggests that the risk for opioid misuse under conditions of pain may vary based on gender/sex, but the biological basis of this relationship is unclear. Here, we characterize the effects of pain on fentanyl use and decipher its underlying mechanisms within mesolimbic dopamine reward circuitry, providing evidence for regulation by ovarian hormones. Using wireless in vivo fiber photometry, we reveal that pain time-dependently enhances fentanyl use in male rats by enhancing responses from ventral tegmental area (VTA) dopamine (DA) neurons terminating in the nucleus accumbens shell (NAc). Using chemogenetics, we show that high-amplitude, phasic VTA-DA responses to self-administered fentanyl are necessary to drive excessive fentanyl use in males. Ovarian hormones protect females from the pain-induced effects on VTA-DA activity and fentanyl use, but the effects are not attributable to estradiol, per se. Instead, we demonstrate the therapeutic potential of estradiol treatment in males and its ability to reverse the effects of pain on VTA-DA function and fentanyl use. These findings are the first to implicate a role for sex steroid hormones in pain-facilitated opioid use and provide novel therapeutic targets within the mesolimbic DA reward circuitry that may contribute to pain related motivational impairments and risk for opioid abuse.

Inflammatory pain alters alcohol self-administration in a sex- and dose-dependent manner

Yolanda Campos-Jurado (Post Doc, Washington University in St. Louis)

During the last years, multiple clinical and epidemiological studies have revealed that the presence of chronic pain is closely related to Alcohol Use Disorder (AUD). However, there is only a limited number of preclinical studies approaching this problematic and therefore the specific effect of pain on AUD remains not fully discern. In this study we aimed to deeply explore wether the development of an inflammatory pain condition induced by the intraplantar injection of the Complete Freud Adjuvant (CFA) could impact alcohol self-administration (ASA) in animals with a previous history of alcohol exposure. For that, after being exposed to alcohol in their homecages using the drinking in the dark during 2 weeks, male and female rats were trained to self-administer 20% alcohol in a FR3 schedule of reinforcement. Once ASA was stable across days, rats were injected with CFA or saline into their hind-paws. Then, they were subjected to a dose-response test, consited of 3 consecutive sessions for each of the alcohol doses (20%, 30% and 50%), presented in a randomly assigned, ascending or descending manner. Our results show that CFA treated animals increased their total alcohol intake only at lower doses (20% and 30%) in the case of males, and only at a higher dose (50%) in females. These findings may contribute to the better understanding of the intersection between pain

and AUD and to development of more individualized treatments for chronic pain patients with a history of alcohol abuse.

Symposium 7: MOR-DOR Interactions: latest findings in neural circuits and important roles as a therapeutic target

Two decades have passed since the initial identification of multimeric complexes involving opioid receptors. Here we focus on recent advances on MOR and DOR interactions (MOR-DOR) that explore important pathophysiological roles in the development of pain or analgesic tolerance. Also, there has been a focus on investigating the unique pharmacological properties of MOR-DOR for the development of the next generation novel analgesics. In this panel, we discuss and provide examples of exploring MOR-DOR as a therapeutic target. Specifically, Dr. Massotte will describe the distribution of MOR-DOR using double knock-in animals and provide the latest findings in naïve and neuropathic pain models. Dr. Zhou will describe data on MOR-DOR interactions at the plasma membrane using single molecule tracking analysis. Dr. Fujita will describe the latest data exploring a role for RTP4, an endogenous chaperone protein for MOR-DOR, in opioid tolerance. Finally, Dr. Gomes will describe recent findings on the identification of exogenous and endogenous opioid peptide ligands targeting MOR-DOR. In sum, this panel will discuss the important roles and regulation of MOR-DOR and its ligands in treatment of pain and addiction.

Hot Topics 6

Structure Modifications and In Vitro Evaluation of Mu-opioid Receptor Positive Modulators

Mengchu Li (*Post Doc, University of Michigan*)

Mu-opioid receptor agonists are the gold standard for pain treatment. While efficacious for moderate to severe pain, these drugs are associated with serious on-target adverse effects, including abuse liability and respiratory depression. One emerging strategy for potentially safer pain medications is the use of positive allosteric modulators (PAMs) of mu-opioid receptors (mu-PAMs). Preclinically, mu-PAMs enhance antinociception by increasing the efficacy and potency of endogenous opioid neurotransmitters released during pain states. mu-PAMs do not activate MOR directly but require the presence of an orthosteric agonist, such as an opioid peptide. Thus, the activity-promoting effect of the mu-PAMs on endogenous opioids depends on the release pattern of the opioid peptides and so effects are localized and temporal. Consequently, this allosteric strategy has the promise of providing analgesia with fewer side effects. Previous work has identified a molecule, BMS-986122, that enhances the antinociceptive effects of endogenous opioids but does not cause constipation or reward. However, BMS-986122 is not especially potent and does not have ideal properties for a drug. The present study was designed to explore the structure-activity relationships (SAR) of BMS-986122 to identify more potent and drug-like compounds and to study the mechanism of action using in vitro ligand binding and second messenger assays. Stepwise changes to the BMS-986122 molecule give a detailed profile of structural features contributing to activity. This study is supported by DA0039997.

Regulation of Delta Opioid Receptor Signaling in the Anterior Cingulate Cortex by Agonists and Pain

Marie Walicki (*Grad Student, University of Michigan*)

The anterior cingulate cortex (ACC) and its downstream outputs shape pain perception. ACC activity is regulated by endogenous opioids like enkephalins, which can act at both mu and delta opioid receptors. The delta opioid receptor (DOR) is expressed in a majority of inhibitory parvalbumin (PV) interneurons in the ACC, and its activation can disinhibit local circuitry through multiple subcellular effector

pathways. DOR agonists have analgesic and antidepressant-like effects but also display convulsant activity, limiting their clinical utility. DOR signaling is thought to be highly dynamic, but it is unknown how DOR signaling within the cortex adapts to challenges such as repeated drug exposure and pain. Further, it is unknown if DOR signaling is differentially regulated at cellular effector pathways. To address these unknowns, I used patch clamp electrophysiology, optogenetics and pharmacology in brain slices to measure somatic and presynaptic DOR signaling following exposure of mice to inflammatory pain or the selective DOR agonists SNC80 and KNT-127. I also used conditional DOR deletion to determine whether loss of DOR expression on PV interneurons altered opioid-mediated signaling in the ACC and the behavioral effects of SNC80. I have found that only SNC80 treatment induced cross tolerance to the endogenous opioid Met-enkephalin in both effector pathways of PV interneurons, however tolerance at the soma developed more rapidly. Additionally, conditional deletion of DOR on PV interneurons reduces the proconvulsant effects of SNC80. These data suggest that development of cellular tolerance in ACC PV neurons is agonist-specific and is heterogenous based on subcellular receptor location.

Astrocyte Elevated Gene-1 (AEG-1) Genetic Deletion Prevents Tolerance to Morphine and Reduces its Physical Dependence in Mice

Eda Koseli (*Post Doc, Virginia Commonwealth University*)

The prevalence of chronic pain in the US is estimated to be around 20 % in the adult US population. Opioids, such as morphine, are used clinically to treat acute and chronic pain. However, their use is limited due to their side effects such as constipation, tolerance, and addiction. Astrocyte Elevated Gene-1 (AEG-1) is a multifunctional protein that regulates inflammation, myeloid immune cell activity, and lipid metabolism. Recent studies have shown that there is a significant “cross-talk” between the endogenous opioid system and the immune-mediated inflammatory response which could suggest a potential role for AEG-1 in opioid signaling. In our study, we investigated the potential role of AEG-1 in chronic morphine-induced antinociceptive tolerance and physical withdrawal in adult AEG-1 global knockout (KO) and wild-type (WT) male/female mice. To induce tolerance, we injected escalated doses (D1-20, D2/D3-40, and D4-80 mg/kg bid, i.p.) of morphine. On day5, a cumulative morphine dose-response curve was determined using a tail immersion assay to assess antinociceptive tolerance. DRG, Spinal cord, and PAG tissues were collected for gene expression study. In a separate cohort of mice, morphine-precipitated withdrawal by naloxone was assessed. Chronic morphine-treated AEG-1 KO mice displayed a lack of antinociceptive tolerance and a reduction of total somatic signs during precipitated withdrawal compared to WT mice. However, we found no difference in AEG-1 expression in chronic morphine-treated WT mice compared to saline-treated WT mice. Our results suggest that AEG-1 may function as an endogenous modulator on morphine-induced tolerance and withdrawal. This study was supported by R61NS127287.

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