6th

INTERNATIONAL DRUG ABUSE RESEARCH SOCIETY

PROGRAM & ABSTRACTS

Recent Advances in Drug Addiction

September 4 - 8, 2017
Hotel Neptun,
Dubrovnik, Croatia

Conference Organizers:

Syed Ali (USA), Barbara Mason (USA), Jean Zwiller (France),Jesus Angulo (USA), Sulie Chang (USA), Emmanuel Onaivi (USA), Ashraf Virmani(The Netherlands), Emilio Ambrosio (SPAIN), Alicia Brusco (ARGENTINA), Mohan Sopori (USA), Michael Kuhar (USA) and George Koob (USA)

The International Drug Abuse Research Society (IDARS) would like to thank the following organizations for their generous financial support of the meeting:

NIAAA
National Institute on Alcohol Abuse and Alcoholism

NIDA International Program

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NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

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GENERAL INFORMATION ABOUT THE MEETING SITE

DUBROVNIK

Dubrovnik is a stunningly intact walled city on the Adriatic Sea coast of the extreme south of Croatia. Although its population barely exceeds 40,000, it's one of the most prominent tourist resorts of the Mediterranean and listed as a UNESCO World Heritage Site since 1979. Dubrovnik is steeped in stunning architecture and sculptural detail, and boasts spectacular churches, monasteries, museums, and fountains. Dubrovnik is both a seaport and the center of the Dubrovnik-Neretva County. Its population was 42,615 inhabitants according to census data from 2011. Dubrovnik is nicknamed "Pearl of the Adriatic". Tourism is the most important industry in Dubrovnik so according to data from 2012, there were 45 hotels:- twelve S* hotels, nine 4* hotels, twenty two 3* hotels and two 2* hotels.

ARRIVAL by Plane

Dubrovnik airport (IATA: DBV) is located about 20km to the south of the city.

Currency

The official currency of the Republic of Croatia is the Kuna, which has 100 Lipa. (local abbreviation kn, international abbreviation HRK). 1Euro is approx 7, 4 kunas and 1USD approx 6 kunas
All major credit cards
(American Express, Diners, Visa, Eurocard/Mastercard) and Eurocheques (after being changed in banks) are accepted.

Electricity

In Croatia the power sockets are of type C and F. The standard voltage is 230 V and the standard frequency is SO Hz.
Your need for a power plug adapter depends on the power plugs used in your own country.

TAXI SERVICE

- Taxi stand is located next to the Terminal building "B" (Domestic & International Arrivals)
- Taxi service information, as well as taxi fares are published at the Taxi information counter in Terminal building "B" (Domestic & International Arrivals), or taxi phone: 020 640 100
- Taxi driver is obliged to issue the receipt on passenger's request

Airport bus transfers

Croatia Airlines operates buses between the airport and the main bus station in Kantafig (HRK40, 45min), which is 2.Skm northwest of the Old Town. Taxis from the airport to the center will cost HRK350. Going to the airport a bus aims to leave the main bus station 2h before each international flight, and costs HRK40. The airport shuttle schedule is different every day, but there is a shuttle virtually every 30 minutes. Departure times are also displayed in various tourist agencies near Buza Gate or the tourist information office at Pile Gate. The bus passes close to the Old Town en route to the airport and you can board this bus at the bus stop on Petra Kresimira 4 just above the Old Town, by the lower cable car station.

When travelling to the Airport sit on the right hand side (not behind driver) for best views, and vice-versa for the return. On all intercity buses you pay a separate fee of €2 or HRK10 to the driver for luggage. So keep some change ready.

Stay safe

- Dubrovnik is a very safe city, though the usual precautions should be taken to protect yourself from pick-pocketing.

- The streets in the old town can be quite slippery as they've been smoothed down for centuries by people walking over them.

Sightseeing

If you are not staying in Old Town, it's relatively simple get there by bus, as just about every one leads to the Old Town. However, it might be advisable to get a timetable (59] just in case. It costs 12 kn (just over €1) for tickets bought at any kiosk, or 15 kn bought on the bus; ticket valid for 1hr. At selected kiosks (including the international bus station) you can purchase a day pass for 30 kn. This pass is valid for 24 hr of unlimited travel on the city bus network, starting from the first validation. The easiest way to get from the Main Bus Station to the Old Town is by using the (mostly modern and A/C equipped) buses number A, B, C which circulate almost constantly. These buses can be boarded from the bus stop just outside the Main Bus Station. Apart from this, there is another bus service which comes inside the bus station and drops you directly at the Old Town. Schedules are available at the information counter of the Main Bus Station.
The Old Town can be comparatively difficult to navigate on first appearances, as it really is a warren of little streets. There are however signs at the entrances to many of these streets advertising what businesses, shops, restaurants and accommodation are to be found in that direction.

The city is completely pedestrianized and easily small enough to get around on foot, some of the streets are a little steep though.

By bus

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Museums

Some museums offer a discount ticket if you visit more than one museum. For example its 70 kn for the Rectors Palace, Ethnographic museum, Rupe and Maritime museum.

Tourist shops in Dubrovnik

There are many local artisans who specialize in domestic crafts. Popular purchases include: handmade tablecloths, linens, and napkins. Many merchants claim that the necktie was invented in Croatia. Another local specialty is little dolls dressed in local garb.
The Pharmacy, at the Franciscan Monastery creates hand creams and other toiletries based on ancient recipes. The pharmacy is one of the oldest in this part of Europe. It has been operating from the time of its

foundation to the present day.

Drink

The most popular hard alcohol in Croatia is homemade rakija. This is a very strong distilled drink made from a variety of fruits. Examples include sljivovica, made from plums, loza, made from grapes, and orahovica, made with walnuts. All are quite strong.
There are many excellent local wines from both the Peljesac Peninsula and Konavle and it is often less expensive than soft drinks like Coca Cola.
In Dubrovnik internet cafes are plentiful. Rates are generally 25kn/hr.

ATMs: Keep in mind that there are few ATMs outside the Old Town.

Restaurants

There are a wide range of restaurants in the Old Town, mostly offering a very similar menu of local seafood and some meat dishes. The cuisine may not be very imaginative, but it is usually of good quality and very fresh.
Restaurants can be crudely separated into (slightly) cheaper tourist-trap places, and more expensive but first class gastronomic restaurants. There are a few pizzerias, mostly wood-fired and quite acceptable. The Kras chocolate sold at stores is delicious. Remember that Dubrovnik, more so than the rest of Croatia, is well aware of its status as a tourist hot-spot. Rents for restaurant premises are high and consequently the prices on the menus reflect this.

Cafes

There are numerous cafes throughout the Old Town and the entire city with prices varying according to the location (particularly, those located on the Stradun are by far the most expensive but you are paying for the ambiance and people-watching as well). Most cafes serve a wide variety of drinks all day.
If you want to save money, it is definitely worth it to get your breakfast and/or lunch from a supermarket instead of a sit-down cafe, which have high markups. Check out Perno in the Old Town (Antuninska ul. 4). Fresh fruits, drinks, and sandwiches/pastries (cheaper than deli on main street).

Dubrovnik cuisine is characteristically not very spicy and is famous for traditionalism. Many popular meals are characteristic of Dubrovnik such as zelena menestra (it is the name for many sorts of cabbages and other vegetables with meat), pasticada and the famous delicacy dubrovacka rozata. Dubrovnik fish restaurants are popular.

Information on Scientific Sessions

Speaker Instructions

Please bring your presentation on a memory stick/thumb drive to the conference room 30 minutes prior to the beginning of the session on the day you present. Projector, PowerPoint software and a computer (Windows based) will be provided for the presentations.

Poster Presenter Instructions

The poster session will be held adjacent to the meeting room from 4:00-7:00 PM on Tuesday, September 5, 2017 and Wednesday, September 6, 2017. Poster board will be made available beginning at 12:00 noon on Tuesday September 5, 2017.

PLEASE NOTE: The suggested poster size will be 150cm wide x 90 cm tall (5 ft wide and 3 ft tall). Poster presenters are asked to prepare posters which will fit on the board (could be smaller), and should be easily viewed by the audience. Pushpins/tape will be provided for your convenience to display your posters.

The poster numbers are listed on pages 22- 23.

Publication of Proceedings

The proceedings of this satellite meeting will be published in the online IDARS Journal "Journal of Drug of Alcohol Research (JDAR)". All presenters are invited to submit manuscripts for publication in the JDAR. The deadline to submit manuscripts for publication is December 31, 2017. Information for Authors will be available on the IDARS website: www.IDARS.org as well as on www.ashdin.com.

Monday, September 4, 2017

REGISTRATION AND WELCOME

Coral Banquet Hall

4:00 – 8:00 PM

Tuesday, September 5, 2017

7:00 - 9:00AM **Registration: Coral Banquet Hall area**
Breakfast: Neptun Terrace Restaurant from 06:30am until 10:30am

Conference: Coral Banquet Hall

8:30 - 9:00AM **Opening of the Meeting**
Welcome/Travel Award Presentations
George Koob/Syed Ali

SESSION I: NEUROBIOLOGY OF OPIOID ADDICTION: THE GAIN IN THE BRAIN IS IN THE PAIN

Moderators: **George Koob (USA) and Leandro Vendruscolo(USA)**

9:00 -9:20AM **Pain-induced negative affect is mediated via recruitment of the nucleus accumbens kappa opioid system.**
Jose Moron-Concepcion, *Department of Anesthesiology & Neuroscience, Washington University School of Medicine, St. Louis, MO USA*

9:20 -9:40AM **The stress of addiction: Glucocorticoid and CRF receptor mediate negative emotional states and compulsive-like opioid intake.**
Leandro Vendruscolo, *Neurobiology of Addiction Section, Intramural Research Program, National Institute on Drug Abuse, Baltimore, Maryland, USA*

9:40 -10:00AM **Negative emotional learning brain circuits in compulsive-like opioid seeking.**
Stephanie Carmack*, Neurobiology of Addiction Section, Intramural Research Program, National Institute on Drug Abuse, Baltimore, Maryland, USA*

10:00 -10:20AM **Opioid addiction: Hyperkatifeia, and allostasis.**
George Koob, *Neurobiology of Addiction Section, Intramural Research Program, NIDA, NIAAA, Baltimore, Maryland, USA*

10:20 -10:40AM **COFFEE/TEA BREAK**
(Neptun Terrace in front of the meeting room)

SESSION II: ROLE OF BDNF IN ALCOHOL AND DRUG ADDICTION

Moderators: **Howard Becker (USA) and Antonio Noronha (USA)**

11:00 -11:20AM **Increase BDNF in prefrontal cortex reduces dependence-related escalated drinking in mice.**
Howard Becker*, Medical University of South Carolina, Charleston, South Carolina, USA*

11:20 -11:40AM **Epigenetic Programing, synaptic remodeling and psychopathology during alcoholism.**
Subhash Pandey, *University of Chicago, Chicago, Illinois, USA*

11:40 -12:00PM **BDNF enhances activity within extinction circuits to boost cognitive control**
Jamie Peters, *Medical University of South Carolina, Charleston, South Carolina, USA*

12:00 -12:20PM **A new frontier in TMS treatment development: The interaction between BDNF polymorphisms and TMS-associated plasticity.**
Colleen Hanlon, *Medical University of South Carolina, Charleston, South Carolina, USA*

12:20 - 2:00PM **LUNCH – Neptun Terrace Restaurant**

SESSION III: ALCOHOL: TISSUE INJURY AND ADDICTION

Moderators: **Sulie Chang (USA) and Dipak Sarkar (USA)**

2:00 -2:20PM **Binge exposure to high concentration of alcohol induced spleen atrophy differentially.**
Sulie Chang*, Seton Hall University, South Orange, New Jersey, USA*

2:20 - 2:40PM **Alcohol's epigenetic marks transmits for multiple generation.**
Dipak Sarkar, *The State University, New Brunswick, New Jersey, USA*

2:40 - 3:00PM **Morphometric and cerebrovascular effects of alcohol exposure in a baboon model of pregnancy.**
Anna Bukiya, *University of Tennessee Health Science Center, Memphis, Tennessee, USA*

3:00 - 3:20PM **Ethanol, bk channel β1 subunits and cerebral artery reactivity.**
Alex Dopico*, University of Tennessee Health Science Center, Memphis, Tennessee, USA*

3:20 - 3:40PM **Novel potential targets for the treatment of alcoholism and co-morbid conditions.**
Yousef Tizabi, *Department of Pharmacology, Howard University Medical School, Washington DC, USA*

3:40 - 4:00PM **Alcohol-induced cognitive dysfunction during adolescence.**
Ratna Sircar
The City College of New York, New York, New York, USA

4:00 - 5:00PM **COFFEE/TEA BREAK**
(Neptun Terrace in front of the meeting room)

SESSION IV: **POSTER SESSION: 4:00 – 7:00PM**
Moderators: **Ashraf Virmani (The Netherlands) and Ratna Sircar (USA)**

(See Pages 22-23 for a list of Posters)

Wednesday, September 6, 2017

7:00 - 8:00 AM **Registration**
Breakfast: Neptun Terrace Restaurant from 06:30am until 10:30am

SESSION V: COCAINE

Moderators: **Mike Kuhar (USA) and Emilio Ambrosio (SPAIN)**

8:00 - 8:20AM **DA novel cutaneous therapy for drug abuse.**
***Ming Xu**, The University of Chicago, Chicago, Illinois, USA*

8:20 - 8:40AM **Cocaine and Epigenetics – DNA methylation regulates cocaine self-administration by rats.**
***Jean Zwiller**, Université de Strasbourg, Strasbourg, FRANCE*

8:40 - 9:00AM **Combined cocaine and alcohol chronic administration alters plasma amino acids levels in male and female rats.**
***Emilio Ambrosio**, Universidad Nacional de Educacion A Distancia, Madrid, SPAIN*

SESSION VI: METHAMPHETAMINE AND DESIGNER DRUGS (MDMA & BATH SALTS)

Moderators: **Susan Schenk (New Zealand) and Syed Ali (USA)**

9:10 - 9:30AM **Compensatory changes to methamphetamine-induced dopaminergic degeneration and motor impairment in mice.**
***Rosario Moratalla**, Instituto Cajal, Consejo Superior de investigaciones Cientificas, CSIC, Madrid, SPAIN*

9:30 – 9:50 AM **Dynamic control of the dopamine transporter activity by the KAPPA opioid receptors in the dorsal striatum during amphetamine sensitization process.**
***Jose Fuentealba**, Pontificia Universidad Catolica de Chile, Santiago, CHILE*

9:50 - 10:10AM **Reversal effects of sodium benzoate after a binge regimen of methamphetamine in mice.**
***Ming-Haun Chan**, National Chengchi University, Taipai, TAIWAN*

10:10 -10:40AM **COFFEE/TEA BREAK (Neptun Terrace in front of the meeting room)**

10:40 -11:00AM **Chronic voluntary oral methamphetamine induces deficits in spatial learning and hippocampal protein kinase Mzeta (PKMζ) with enhanced astrogliosis and COX-2 levels.**
Peter Serrano, *Department of Psychology, Hunter College, New York, New York, USA.*

11:00 -11:20AM **Methamphetamine neurotoxicity is exacerbated in diabetic animals: Role of neurotrophic factors, oxidative stress and nanomedicine.**
Hari Sharma, *Uppsala University, Uppsala, SWEDEN*

11:20 -11:40AM **Pharmacology of subjective effects of MDMA and MDMA self-administration.**
Susan Schenk, *Victoria University of Wellington, Wellington, NEW ZEALAND*

11:40 -12:00AM **Abuse related effects of "Bath-salts" modeling a mix bag.**
Gregory Collins, *University of Texas Health Science Center, San Antonio, Texas, USA*

12:00 -2:00PM **LUNCH – Neptun Terrace Restaurant**

SESSION VII: HIV-INFECTIONS AND DRUG ABUSE

Moderators: **Mohan Sopori (USA) and Sundaram Ramakrishnan (USA)**

2:00 - 2:20PM **Cocaine-mediated secretion of IP-10 from pericytes: implication for monocyte recruitment into the CNS.**
Shilpa Buch, *University of Nebraska Medical Center, Omaha, Nebraska, USA*

2:20 -2:40PM **Morphine disrupts of gut microbiome and contributes to morphine tolenance: Role of toll like receptor 2.**
Sabita Roy, *Department of Surgery, University of Miami, Miami, FL, USA*

2:40 - 3:00PM **Interaction between HIV and cigarette smoke in the lung diseases.**
Mohan Sopori, *Lovelace Respiratory Research Institute, Albuquerque, New Mexico, USA*

3:00 - 3:20PM **Effects of GPR55 activation on neuronal stem cell proliferation, differentiation, and immune responses to chronic inflammation and HIV infection.**
Yuri Persidsky , *Department of Pathology and Laboratory Medicine, Temple University Health Science Center, Philadelphia, Pennsylvania , USA*

3:20 - 3:40PM **Pathobiology of neural progenitor cells in Methamphetamine abuse and HIV infection: protection by physical activity.**
Michal Toborek , *Department of Biochemistry and Molecular Biology, University of Miami, Miami, Florida, USA*

3:40 - 4:00PM **Potential increased utility of combined Drug Treatments for treating Tobacco Addiction.**
Edward Levin **,** *Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, USA*

4:00 - 4:20PM **COFFEE/TEA BREAK (Neptun Terrace in front of the meeting room)**

4:20-5:00PM **IDARS Business Meeting**

SESSION VIII: POSTER SESSION: 4:00 – 6:00 PM
Moderators: Ratna Sircar (USA) and Ashraf Virmani (The Netherlands)

(See Pages 22-23 for a list of Posters)

Thursday, September 7, 2017

Conference Organizers plan a tour of Dubrovnik

No Scheduled Conference activities

Friday, September 8, 2017

7: 00 - 8:00AM **Breakfast: Neptun Terrace Restaurant from 06:30am until 10:30am**

SESSION IX: MARIJUANA/CANNABINOIDS I

Moderators: **Prakash Nagarkatti (USA) and Emmanuel Onaivi (USA)**

8:00 - 8:20AM **Endocannabinoid in drug dependence: transcriptional and epigenetic adaptations.**
Katia Befort, *Laboratoire de Neurosciences Cognitives et Adaptatives, Université de Strasbourg, Strasbourg, FRANCE*

8:20 - 8:40AM **Epigenetic regulation of immune response by marijuana cannabinoids.**
Prakash Nagarkatti, *USC School of Medicine, University of South Carolina, Columbia, South Carolina, USA*

8:40 - 9:00AM **Behavioral modification following deletion of type 2 cannabinoid receptors in dopamine neurons.**
Emmanuel Onaivi, *Department of Biology, William Patterson University, Wayne, New Jersey, USA*

9:00 - 9:20AM **Is there a cross talk between cannabinoids and microbiota that regulates inflammation?**
Mitzi Nqgarkatti, *USC School of Medicine, University of South Carolina, Columbia, South Carolina, USA*

SESSION X: MARIJUANA/CANNABINOIDS II

Moderators: **Mitzi Nagarkatti (USA) and Alicia Brusco (Argentina)**

9:20 -10:00AM **Social brain, endocannabinoids and alcohol consumption.**
Oscar Prospero-García*, Departamento de Fisiología, Universidad Nacional Autonoma de Mexico, Mexico City, MEXICO*

10:00 -10:20AM **Role of CB1 receptor in vulnerability to morphine dependence in adolescent mice prenatally exposed to a cannabinoids agonist.**
Alicia Brusco, Insituto de Biologia Celular-Fac. Medicina, *Universidad de Buenos Aires, Buenos Aries, ARGENTINA*

10:20 -10:40AM **Zebrafish embryos exposed to THC (delta-9-tetrahydrocannbinol) during gastrulation exhibit alterations in heart rate and synaptic activity at the neuromuscular junction.**
Declan Ali*, Department of Biological Sciences, University of Alberta, Edmonton, Alberta, CANADA*

10:40 -11:00AM **Endocannabinoid stimulation in pregnancy: effects on mother-infant dyad and beyond.**
Anna Brancato, *Department of Sciences of Health Promotion and Mother and Child Care, University of Palermo, Palermo, ITALY*

11:00 -11:20AM **COFFEE/TEA BREAK (Neptun Terrace in front of the meeting room)**

SESSION XI: EMERGING TARGETS FOR MEDICATION DEVELOPMENT IN SUBSTANCE USE DISORDERS

Moderators: **Barbara Mason (USA) and Edith Sullivan (USA)**

11:20 - 11:40AM **Neuroinflammation as a target for medications to treat alcoholism and addiction.**
Fernando Rodriguez de Fonseca, *. Instituto IBIMA, Hospital Regional Universitario de Málaga, Málaga, SPAIN.*

11:40 - 12:00PM **Tackling alcohol use disorder through comprehensive bioinformatics.**
Sean Farris , *The University of Texas at Austin Austin, Texas, USA*

12:00 -12:20PM **Exploring the neural basis of "incubated" alcohol craving by pharmacogenetics and functional gene expression profiling.**
Friedbert Weiss, *Department of Neuroscience, The Scripps Research Institute, La Jolla, California, USA*

12:20 - 12:40PM **Multimodal brain imaging metrics as potential markers for assessing medication development.**
Adolf Pfefferbaum, *Neuroscience Program, SRI International, Menlo Park, California, USA*

12:40 -2:00PM **LUNCH – Neptun Terrace Restaurant**

SESSION XII: DOPAMINE, NMDA RECEPTORS, ALCOHOL AND KETAMINE

Moderators: **Eliot Gardner (USA) and Marco Diana (ITALY)**

2:00 - 2:20PM **Dopamine D3 receptor antagonism decreases PTSD-like behavior in Rats.**
Eliot Gardner, *Intramural Research Program, National Institute on Drug Abuse, U. S. National Institutes of Health, Baltimore, Maryland, USA*

2:20 - 2:40PM **Probing the hypodopaminergic state with TMS in addicts: preliminary observations.**
Marco Diana, *'G. Minardi' Laboratory of Cognitive Neuroscience, University of Sassari, ITALY*

2:40 - 3:00PM **Effects of the NMDA receptor modulating agents on ketamine self-administration.**
Hwei-Hsien Chen, *Center for Neuropsychiatric Research, National Health Research Institutes, Miaoli, TAIWAN*

3:00 - 4:00PM **COFFEE/TEA BREAK (Neptun Terrace in front of the meeting room)**

SESSION XIII: 4:00 PM – 6:00PM
PANEL DISCUSSION AND OPEN FORUM
SUMMARY AND RECOMMENDATIONS

George Koob	**Michael Kuhar**
Howard Becker	**Sulie Chang**
Barbara Mason	**Shilpa Buch**
Emmanuel Onaivi	**Prakash Nagarkatti**
Susan Schenk	**Jean Zwiller**
Eliot Gardner	**Syed Ali**

6:00 PM **CONCLUDING REMARKS/MEETING ADJOURNED**
George Koob/Syed Ali

8:00 - 10:00 PM
FAREWELL DINNER
Lounge Terrace

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21. Chronic voluntary oral methamphetamine induces deficits in spatial learning and hippocampal protein kinase Mzeta (PKMζ) with enhanced astrogliosis and COX-2 levels.
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26. Morphine disrupts gut microbiome and contributes to morphine tolerance: Role of toll like receptor 2.
Sabita Roy **..... 50**

27. Interaction between HIV and cigarette smoke in the lung diseases.
Mohan Sopori **..... 51**

28. Effects of GPR55 activation on neuronal stem cell proliferation, differentiation, and immune responses to chronic inflammation and HIV infection.
Yuri Persidsky **..... 52**

29. Pathobiology of neural progenitor cells in methamphetamine abuse and HIV infection: protection by physical activity.
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33. Behavioral modification following deletion of type 2 cannabinoid receptors in dopamine neurons.
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34. Is there a cross talk between cannabinoids and microbiota that regulates inflammation?
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36. Role of CB1 receptor in vulnerability to morphine dependence in adolescent mice prenatally exposed to a cannabinoids agonist.
***Alicia Brusco* 60**

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***Declan Ali* 61**

38. Endocannabinoid stimulation in pregnancy: effects on mother-infant dyad and beyond.
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40. Tackling alcohol use disorder through comprehensive bioinformatics.
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45. Effects of the NMDA receptor modulating agents on ketamine self-administration.
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***Syed Ali* 70**

47. 3,4-methylenedioxypyrovalerone (MDPV) induces cytotoxic effects on human dopaminergic SH-SY%Y cells.
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50. Effects of exposure to cannabinoid agonist WIN 55, 212-2 on alcohol preference and anxiety in early adolescent CD1 mice.
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ABSTRACTS

1. Pain-induced Negative Affect is Mediated via Recruitment of the Nucleus Accumbens Kappa Opioid System.

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The quality of life for patients suffering from chronic pain is impacted by co-morbidities, such as prolonged negative affective states. The presence of these severe emotional disturbances may contribute to the misuse of drugs of abuse, reported in 25% of pain patients, and lead to involuntary overdose. Thus, uncovering the mechanisms responsible for pain-induced negative affect represents an important step to tackle the opioid epidemic. In the mesolimbic pathway, the nucleus accumbens (NAc) shell plays a central role in the integration of aversive and rewarding stimuli. Prior work has revealed that activation of the dynorphin-Kappa Opioid Receptor (KOR) system decreases reinforcing properties of rewards and induces dysphoria and aversive behaviors. The abundance of dynorphin neurons and KORs in the NAc shell led us to hypothesize a role for this system in pain-induced negative affect. In this study we demonstrate that inflammatory pain, induced by Complete Freund's Adjuvant (CFA) injection in the hindpaw, enhances dynorphin A content and dynorphin neuron excitability in the NAc Shell. PET imaging reveals that CFA-induced inflammation decreases radiotracer binding potential, an indirect measurement of KORs binding pocket occupancy. Overall, our results confirm the recruitment of dynorphin-KORs system in the NAc Shell to drive pain-induced negative affect. This work provides a novel path for future studies aiming to prevent the pain-induced opioid misuse and involuntary overdoses.

2. The Stress of Addiction: Glucocorticoid and CRF Receptors Mediate Negative Emotional States and Compulsive-like Opioid Intake.

Leandro F. Vendruscolo

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Dysfunctional brain reward and stress systems underlie negative emotional states (e.g., increased anxiety and pain) that are thought to drive compulsive opioid intake. We hypothesized that repeated, intense cycles of opioid intoxication and withdrawal excessively activate the hypothalamic-pituitary-adrenal (HPA) axis and elicit glucocorticoid-induced sensitization of extrahypothalamic brain stress systems. More specifically, opioid-induced/glucocorticoid-mediated bidirectional regulation of stress systems leads to HPA axis tolerance that contributes to a hypofunctional reward system, and a concomitant sensitization of stress systems in the extended amygdala. We found that passive heroin administration or intravenously self-administered heroin increased mechanical hypersensitivity (allodynia) and acoustic startle response (a component of anxiety) during acute withdrawal. Both allodynia and anxiety-like behavior were attenuated by the corticotrophin-releasing factor (CRF) 1 receptor antagonist MPZP. CRF1 receptor antagonism also decreased escalated intravenous heroin self-administration that developed in rats allowed extended access (12 h per day) to heroin. Chronic antagonism of glucocorticoid receptors (GR) prevented the development of escalated heroin intake in rats allowed extended access to the drug. Acute mifepristone administration also decreased heroin intake when escalated levels of heroin intake were already established. In conclusion, drugs that normalize, rather than block, a hypofunctional reward system by restoring the function of the HPA axis and desensitize extrahypothalamic stress systems have the potential to selectively and effectively curb compulsive opioid taking and seeking.

3. Negative Emotional Learning Brain Circuits in Compulsive-like Opioid Seeking.

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Environmental stimuli can be classically conditioned to both the pleasurable aspects of opioid intoxication (e.g., high, euphoria), as well as the withdrawal-induced negative emotional states associated with opioid abstinence (e.g., dysphoria, irritability, anxiety, pain). These stimuli are hypothesized to contribute to maintaining opioid seeking and taking via positive and negative reinforcement mechanisms. Here, we tested the hypothesis that neural circuits mediating negative emotional states have a key role in learning that contributes to the maintenance of compulsive opioid seeking. We established an animal model with a well-defined temporal window that allows the association of odor cues with heroin intoxication or naloxone-precipitated heroin withdrawal. We found that when given alone, cues previously paired with withdrawal-induced aversive states can increase operant responding for heroin, promote reinstatement of lever pressing behavior following extinction, and alter sensitivity to painful stimuli in rats given extended (12 h a day), but not limited (1 h a day), access to heroin. Using functional magnetic resonance imaging, we identified several cortical and subcortical brain regions that are activated by presentation of these cues in the absence of heroin, including extended amygdala and hypothalamic stress circuitries. These results point to novel targets for therapeutic intervention, specifically brain circuits of negative emotional learning. We propose that examining fMRI and psychological responses to drug-related cues provides a potentially powerful approach to understanding individual differences underlying factors that lead to compulsive opioid taking and seeking.

4. Opioid Addiction, Hyperkatifeia, and Allostasis.

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Opioids have relieved more human suffering than any other medication, but their misuse has become epidemic-like in the United States. Here, I argue the hypothesis that opioid misuse in the context of recreational use or pain management produces a hypersensitivity to emotional distress, termed hyperkatifeia, and that hyperkatifeia reflects a break in homeostasis of the brain emotional systems, termed allostasis. With excessive opioid use, neural substrates that mediate positive emotional states (brain reward systems) are compromised, and substrates mediating negative emotional states (brain stress systems) are enhanced. A reflection and early marker of such a non-homeostatic state may be the development of opioid-induced hyperkatifeia, defined as the increased intensity of the constellation of negative emotional/motivational symptoms and signs observed during withdrawal from drugs of abuse (derived from the Greek "katifeia" for dejection or negative emotional state) and is most likely to occur in subjects in whom the opioid produces a break with homeostasis and less likely to occur when the opioid is restoring homeostasis, such as in effective acute pain treatment. When the opioid appropriately relieves pain, opponent processes are not engaged. However, if the opioid is administered in excess of need because of overdose, pharmacokinetic variables, or treating an individual without pain, then the body will react to that perturbation by engaging opponent processes in the domains of both pain (hyperalgesia) and negative emotional states (hyperkatifeia). Brain substrates mediating hyperkatifeia are hypothesized to involve the neurocircuitry of the extended amygdala and engagement of neurotransmitter systems such as corticotropin releasing factor, dynorphin, norepinephrine, hypocretin and vasopressin. Repeated engagement of opponent processes without time for the brain's negative emotional systems to reestablish homeostasis will further drive allostatic changes in emotional processes that may produce opioid abuse or addiction, particularly in individuals with genetic or environmental vulnerability.

5. Increased BDNF in Prefrontal Cortex Reduces Dependence-Related Escalated Drinking in Mice.

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We previously demonstrated that repeated cycles of chronic intermittent ethanol (CIE) exposure produces deficits in BDNF mRNA and protein expression in medial prefrontal cortex (mPFC). A series of studies was conducted to examine whether reversing this CIE-induced deficit in BDNF levels attenuates escalated alcohol drinking normally associated with dependence in C57BL/6J mice. In one study, adult male C57BL/6J mice were trained to establish a stable baseline level of voluntary alcohol consumption (15% ethanol vs water; 1-hr/day) and then they received weekly cycles of CIE or control AIR exposure (16 hr/day x 4 days) with intervening weeks of voluntary drinking. As expected, CIE-exposed (dependent) mice showed escalated alcohol drinking over repeated test cycles while AIR-exposed (nondependent) mice evidenced more stable and moderate levels of intake. Bilateral infusion of BDNF (0.5 ug/side) into mPFC blocked CIE-induced escalated drinking but did not alter intake in AIR controls. In another study, mice received bilateral injection of a viral vector containing a BDNF construct or control virus into the mPFC. After at least three weeks, all mice were treated in the CIE-relapse drinking model. Results indicated that viral-mediated BDNF over-expression in mPFC prevented CIE-induced escalation of drinking but did not alter alcohol intake in the AIR nondependent mice. CIE exposure produced the expected elevation in voluntary drinking in mice that received the control virus infusion. Since exercise is known to increase BDNF levels in brain, a third study was conducted to examine whether voluntary wheel-running would attenuate dependence-related escalated drinking. Mice were given access to a running wheel for 2 hr followed 1 hr later by access to alcohol (15% ethanol) for 1-hr each day for 6 weeks. Mice then were treated in the CIE-relapse drinking model, with access to the running wheel continued during drinking test weeks. Separate groups of mice did not have access to a running wheel. Preliminary data indicate that after 6 weeks of exercise (limited access to a running wheel), Bdnf mRNA levels were significantly elevated in the hippocampus (dentate gyrus) and mPFC. Further, CIE-exposed mice with access to the running wheel exhibited an attenuated elevation in drinking. Collectively, these data suggest that reversing the CIE-induced BDNF deficit by infusion of BDNF into the mPFC or preventing the deficit by viral-mediated over-expression of BDNF in the mPFC blocks/prevents escalated drinking associated with alcohol dependence. Also, exercise may attenuate increased drinking in dependent mice via a BDNF mechanism.

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6. Epigenetic programming, synaptic remodeling and psychopathology during alcoholism.

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Alcoholism is a chronic, relapsing disorder often comorbid with anxiety. However, very little is known about the brain mechanisms responsible for the development and maintenance of alcoholism. Epigenetic mechanisms are an emerging area of research modulated both by acute and chronic ethanol exposure. In this presentation, we will highlight the role of histone deacetylases (HDAC) in alcohol-induced psychopathology using various models. We found that condensed chromatin due to increased expression of HDAC2 is responsible for anxiety-like and alcohol-drinking behaviors. Innately higher expression of HDAC2 or adolescent alcohol exposure-induced up regulation of HDAC2 in the central nucleus of amygdala is responsible for condensed chromatin and a reduction in the expression of several genes such as brain-derived neurotrophic factor (BDNF), activity-regulated cytoskeleton-associated protein (Arc), and neuropeptide Y (NPY) which are operative in the regulation of anxiety-like and alcohol drinking behavior. In addition, ethanol withdrawal after chronic exposure in adult rats produced anxiety-like behaviors and, using RNA-sequencing, we found withdrawal after chronic ethanol exposure altered co-expression of several genes that segregate and interact with HDAC2. Interestingly, these genes are involved in the regulation of synaptic plasticity and neuroimmune functions. Knocking down HDAC2, both by siRNA or via pharmacological manipulation with HDAC inhibitor, increased histone acetylation and normalized the deficits in the expression of synaptic plasticity-associated genes. Relaxation of the epigenome in the central nucleus of the amygdala was associated with attenuation of ethanol withdrawal-related anxiety. In addition, we observed that HDAC2 expression is also altered in the post-mortem amygdala brain regions of human alcoholics as compared to age and sex matched control subjects. Taken together, these data demonstrate that relaxing the epigenome within the framework of the amygdala appears to be an attractive pharmacotherapy in treating the comorbidity of alcoholism and anxiety (supported by NIH-NIAAA grants and department of Veterans Affairs career scientist grant to SCP).

7. BDNF enhances activity within extinction circuits to boost cognitive control.

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Numerous studies implicate the infralimbic (IL) prefrontal cortex in extinction memory formation and/or retrieval, for conditioned behaviors as varied as drug seeking and fear. Our previous work demonstrated the striking ability of BDNF to "simulate" extinction memory and reduce conditioned fear, through actions within a hippocampal-prefrontal circuit known to be critical for extinction memory. BDNF is thought to act by enhancing NMDA receptor currents to facilitate neuronal bursting, which can be used to predict successful extinction memory recall. We are actively exploring the therapeutic utility of BDNF to boost extinction memory, along with other strategies for enhancing activity within these known extinction circuits. For example, we have used Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to synthetically activate the IL cortex and enhance extinction memory for cocaine seeking. IL output to the nucleus accumbens shell (NAshell) appears to mediate these inhibitory effects on cocaine seeking (as opposed to IL projections to the amygdala for fear). Unlike BDNF, however, DREADDs were not able to "simulate" extinction, but rather required an existent extinction memory trace to "enhance" extinction memory retrieval. Hippocampal-applied BDNF produced a non-significant trend toward reduced heroin relapse, but suggest other factors contribute to heroin seeking. Collectively these data support the idea that boosting activity in extinction circuits can be an effective therapeutic approach across multiple disorders characterized by deficits in cognitive control. As AAV-mediated gene therapies move closer to the clinic, this DREADD-approach may prove a viable treatment for impulse control disorders like addiction and PTSD.

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8. A new frontier in TMS treatment development: The interaction between BDNF polymorphisms and TMS-associated plasticity.

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Human theta burst stimulation (TBS) has emerged as one of the newest, translationally-derived brain stimulation tools which is being explored as a tool for substance dependence treatment. An FDA-approved treatment for depression, it is widely understood that TBS (a form of rTMS) can induce long term potentiation (LTP) or long term depression (LTD) in a circuit-specific, frequency-dependent manner. That said, some individuals appear to respond to TBS much more than others. This talk will address several variables which likely contribute to the "plasticity potential" of TBS for a given individual. Specific attention will be given to BDNF polymorphisms. Data will be presented indicating that BDNF genotype may be an important modifying factor of theta burst associated cortical plasticity and this, in turn, my influence efficacy of this novel treatment approach for individuals with alcohol and cocaine use disorders.

9. Binge exposure to high concentration of ethanol induced spleen atrophy differentially.

Sulie L. Chang

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Adolescence is an important period for maturation of various physiological functions, including immune responses. Binge alcohol drinking is popular among adolescents and can lead to addictive behaviors and eventually alcoholism in adulthood.
Atrophy of the spleen, a key immune organ, is associated with immune dysfunction. We showed that treatment with 4.8 g/kg/d EtOH for 3 d differentially decreases the size of the spleen in 5 wk old adolescent male F344 rats, but not in adult rats. The spleen size of some of the animals given binge EtOH was comparable to that of the control rats given water, whereas the spleen size in other rats given EtOH had decreased to about 35% of that in the control animals. In the remaining animals, the spleen size was between the two extreme groups. There was also a decrease in the size of the splenic white pulp and a distortion of white pulp structure in Sprague Dawley rats binge treated with EtOH. Immunochemical staining of CD3, a T cell marker, was decreased, as was expression of caspase-3, a key enzyme for cell death, detected by Western blot analysis. These together indicated that binge EtOH-induced spleen atrophy during adolescence may result from a loss of T cells.
DNA methylation is an epigenetic event that operates through post-replication modification of DNA by DNA methyltransferases (DNMTs) to regulate gene expression. We also found that decreased DNMT activity and DNMT1 expression in the spleens of rats treated for 3 d with 4.8 g/kg/d EtOH correlated with a reduction in spleen size. DNA methylation of the T cells may be one of the epigenetic mechanisms underlying the spleen atrophy induced by binge exposure to alcohol during adolescence in a differential manner.

10. Alcohol's epigenetic marks transmits for multiple generation.

Dipak K. Sarkar

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We tested whether alcohol-induced epigenetic modifications of proopiomelanocortin (POMC) gene, that control stress axis, transmit via germline to affect body stress regulation and health of the offspring. We employed two different animal models of alcohol feedings for the germline transmission studies. One model involves preconception alcohol exposure and another involves prenatal alcohol exposure and then studying DNA methylation and histone modifications of POMC genes and impairments related to coping with stress including stress hormone hyper response, anxiety behaviors, immune function and cancer growth in offspring. In both animal models we found maternal alcohol feeding significantly affects POMC gene methylation, gene expression and POMC endophenotypes. Genome-wide analysis identified changes in some key molecular substrates responsible for DNA methylation in the offspring. These data indicate that alcohol induced changes in some of the epigenetic machinery is transmitted across generations via germline. This work is supported by National Institute of Health grants R01 AA11591 and R37AA08757).

11. Morphometric and cerebrovascular effects of fetal alcohol exposure in a baboon model of pregnancy.

Maria Simakova[a] , Ana Tobiasz[b], Olga Seleverstov[a], Shivantika Bisen[a], Jose Duncan[b], J. Scott Jackson[c], Ryan Sullivan [c], J. Pierce Sullivan[c], Steven Davison[c], Zoran Bursac[d], Danielle L. Tate[b], Stacey Barnett[c], Giancarlo Mari[b], Alex M. Dopico[a], **Anna N. Bukiya[a]**

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Binge drinking represents the major form of excessive alcohol (ethanol) consumption in the United States and a well-recognized risk factor for fetal alcohol syndrome (FAS) and fetal alcohol spectrum disorders (FASD). Despite the high prevalence of FAS/FASD, the pathophysiology of fetal damage by alcohol remains poorly understood. One of the major obstacles in studying fetal development in response to alcohol exposure is the inability to standardize timing, amount, and pattern of alcohol consumption, as well as peak blood alcohol levels in pregnant mothers. In the present work, we used baboons (*Papio spp*.) to study alcohol-driven changes in fetal overall growth and cerebral artery function. Pregnant baboons were subjected to alcohol administration via gastric infusion three times during a period equivalent to the second trimester of human pregnancy. During each alcohol-infusion episode, maternal blood alcohol concentrations reached 80 mg/dL within first hour, which is consistent with the current definition of binge drinking. Alcohol level in the amniotic fluid peaked at 63 mg/dL. Control group was infused with orange-flavored drink that was iso-caloric to the alcohol-containing infusion. Fetal morphometric parameters were significantly decreased in alcohol-exposed fetuses at term, but not immediately after alcohol exposure. In contrast, artery Doppler indexes dropped during episodes of alcohol intoxication pointing at the dilation of fetal arteries in presence of alcohol *in vivo*. However, there was no difference in fetal artery function between control and alcohol-exposed fetuses at term.

Fetal cerebral artery function was assessed following artery *in vitro* pressurization at 30 mmHg. Ethanol (63 mg/dL) induced fetal cerebral artery dilation when tested in fetal cerebral arteries harvested from control fetuses at the end of second trimester-equivalent of human pregnancy. Ethanol-induced dilation of fetal arteries was abolished by the mixture of AM251 and AM630, which block cannabinoid receptors (CB) 1 and 2, respectively. In the presence of AM251, the CB receptor agonist anandamide evoked a higher dilation of fetal cerebral arteries. The difference in AEA-induced cerebral artery dilation between control- and alcohol-exposed fetuses vanished in presence of AM630. Thus, alcohol exposure dilated fetal cerebral arteries via cannabinoid receptors and evoked increased CB2 function.

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12. Ethanol, bk channel β1 subunits and cerebral artery reactivity.

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Alcohol intake is well-known to evoke peripheral vasodilation. However, ethanol at concentrations obtained in circulation during moderate-heavy episodic drinking (30-60 mM), has been reported to constrict cerebral arteries in many species, including humans. This ethanol action in independent of ethanol metabolism, endothelial and circulating factors (reviewed in Dopico et al., 2016). Using rodent models, we first demonstrated that ethanol constriction of cerebral arteries was due to a direct interaction between ethanol and large conductance, calcium/voltage-gated potassium channel (BK) subunits and/or their immediate lipid environment, resulting in reduced BK activity in vascular smooth muscle (SM) (Liu et al., 2004). Indeed, recent data indicate that ethanol actions on BK activity and cerebral artery diameter can be counteracted by increased SM cholesterol *in vitro* or driven by a hypercholesterolemic diet. Within a normal cholesterol range in SM, the SM-abundant BK regulatory β1 subunit is needed for ethanol to reduce SM BK activity under physiological conditions of voltage and calcium and, thus, evoke cerebral artery constriction (Bukiya et al. 2009; Kuntamallappanavar & Dopico, 2016). In contrast, the neuron-abundant β4 subunit does not support this ethanol action (Feinberg-Zadek et al., 2008; Martin et al., 2008; Kuntamallappanavar & Dopico, 2016). Thus, we constructed sets of β1/β4 chimeras by swapping different β1/β4 domains and conducted patch-clamp studies to evaluate the ethanol responses of macroscopic currents mediated by the resulting BK complexes. Our data indicate that β1 TM2 is the region that mediates ethanol-induced inhibition of cerebral artery SM BK. We also transfected cerebral arteries from *KCNMB1* K/O mouse with β1/β4 chimeras and found that arteries transfected with the cDNA coding for β_4TM2_1 showed ethanol responses similar to those of β1-containing arteries. Therefore, β1 TM2 is also the BK region that mediates ethanol-induced cerebral artery constriction. Mechanistically, reduction of β1-containing BK activity by ethanol results from drug-induced decoupling of calcium binding and voltage sensor activation, and of calcium-binding and channel opening (Kuntamallappanavar & Dopico, 2016). Current studies aim at addressing whether: a) β1 TM2 contains specific amino acid residues that recognize the ethanol molecule and/or confer cholesterol ability to modulate ethanol action, b) novel agents that target β1 TM2 may counteract ethanol actions on the cerebral circulation, and c) cerebral artery segments that irrigate different brain regions may display differential susceptibility to ethanol-induced constriction and agents that antagonize ethanol action based on differential BK β1 expression across regional cerebral arteries.

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13. Novel Potential Targets for the Treatment of Alcoholism and Co-Morbid Conditions.

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The well known devastating consequences of alcoholism or alcohol use disorder (AUD) on the individual and the society is one of the most pressing medical challenges. Since the current interventions, including pharmacological tools are only of modest efficacy, tremendous effort is being expended in identifying novel targets in combating AUD. Partial obstacle in developing successful medications is lack of full understanding of the circuitries and receptor-transmitter systems in drug addiction in general, and AUD in particular. Moreover, significant co-morbid conditions, e.g. addiction to other substances (e.g. nicotine) and/or mood disorders that occur with AUD, further complicate the challenge at hand. Recent advances, however, offer insight and possible novel targets in AUD and co-morbid conditions. In this presentation two such targets: the ionotropic glutamatergic system as well as the alpha2 adrenergic receptors (Alpha2-AR) will be discussed. Specifically, data on potential exploitation of the NMDA and/or kainate receptors in AUD and nicotine addiction as well as manipulation of the Alpha2-AR in co-morbid AUD and depression will be presented.

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14. Alcohol-induced cognitive dysfunction during adolescence.

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Underage drinking is a global public health concern, and ethanol (EtOH) exposure during adolescence has tremendous societal and personal consequences. EtOH interferes with the ability to form memories, and "blackouts" are relatively common among young drinkers. We and others have reported that in adolescent animals EtOH disrupts the acquisition of hippocampal-based memory. The N-methyl-D-aspartate receptor (NR) is considered to be an important target for EtOH effects. We explored the effects of ethanol-treatment in adolescent rats on the NR receptor-channel complex. Adolescent rats were administered with ethanol and surface-expressed NMDA receptor subunits and NR-associated proteins were measured. Our data suggest that repeated ethanol exposure during adolescence altered NR subunits in a brain region-specific manner. Also, adolescent ethanol effects on NR complex involved alterations in post-translational adaptations (phosphorylation) of distinct NR subunits. Our findings support the hypothesis that adolescent ethanol-induced cognitive deficits are associated with neuroadaptations in the NMDA receptor-mediated glutamatergic neurotransmission. (This research project was supported by grant from NIAAA).

15. A novel cutaneous therapy for drug abuse.

Qingyao Kong[1], Jiping Yue[2], Cynthia Li[2], Xiaoyang Wu[2] and **Ming Xu[1]**

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Cocaine is a commonly abused drug that causes significant morbidity and mortality. There are no FDA-approved medications for treating abuse and relapse in humans. Moreover, there are no interventions for acute cocaine overdose. One promising approach is the use of a genetically modified enzyme butyrylcholinesterase (BChE) that exhibits great catalytic potency and substrate specificity for cocaine hydrolysis to counter the behavioral and toxic effects of cocaine. However, it remains technically challenging to achieve long-term stable delivery of modified *hBChE* in humans. We have made key technical advancement by developing a novel mouse-to-mouse skin transplantation method that allows the stable introduction of engineered epidermal progenitor cells into immunocompetent host mice. Moreover, we have used the CRISPR technology to target the modified *hBChE* into mouse epidermal progenitor cells and transplanted the engineered cells into several mice (GhBChE). GhBChE mice showed very high hBChE levels in plasma, were insensitive to injections of lethal doses of cocaine and did not develop conditioned place preference (CPP) to cocaine yet had normal ethanol-induced CPP. We are determining whether grafting *hBChE*-expressing cells following CPP induction protects GhBChE mice from reinstatement of cocaine-seeking and testing for long-term stable *BChE* expression *in vivo* and protection against cocaine, potential immune responses and approaches to reduce them. We are also expanding this approach into treating alcohol abuse and cocaine and ethanol coabuse. We expect the proposed cutaneous gene therapy to be long-lasting, highly specific and efficient with little individual variation. To be able to stably deliver the modified therapeutic proteins *in vivo* via epidermal progenitor cells has potentials for reducing ongoing drug use and relapse, and protecting against acute drug overdose in users and addicts. This work will lay key groundwork for the development of a highly personalized and long-lasting approach for combating drug abuse.

16. Cocaine and Epigenetics – DNA methylation regulates cocaine self-administration by rats

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DNA methylation is a major epigenetic process which regulates the accessibility of genes to the transcriptional machinery. Here we investigated whether modifying the global DNA methylation pattern in the brain would alter cocaine intake by rats, using the cocaine intravenous self-administration test. Using the fixed-ratio 5 schedule, we found that i.c.v. injection of the DNA methyl-transferase inhibitors, 5-aza-2'-deoxycytidine and zebularine, dose-dependently increased cocaine self-administration. To get some insights about the underlying neurobiological mechanisms, a genome-wide methylation analysis was undertaken in the prefrontal cortex of rats self-administering cocaine and treated or not with 5-aza-2'-deoxycytidine. The study identified near 189,000 differentially methylated regions (DMRs). About half of them were located inside gene bodies, whereas only 9% were found in the promoter regions of genes. It is noteworthy that about 99% of methylation changes occurred outside CpG islands. Gene expression studies confirmed the inverse correlation observed before between increased methylation and transcriptional activation when methylation occurs in the gene promoter. This inverse correlation was not observed when methylation took place inside gene bodies. Using the literature-based Ingenuity pathway analysis IPA, we explored how the differentially methylated genes were related. The analysis revealed that increase in cocaine intake by rats in response to DNA methyltransferase inhibitors underlies plasticity mechanisms which mainly concern axonal growth and synaptogenesis as well as spine remodeling. Together with the Akt/PI3kinase pathway, the Rho-GTPase family was found to be involved in the plasticity underlying the effect of 5-aza-2'-deoxycytidine on the observed behavioral changes.

17. Combined cocaine and alcohol chronic administration alters plasma amino acid levels in male and female rats.

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A high percentage of cocaine users combine cocaine with ethanol intake. When used in a combined way, alcohol consumption increases the plasma levels of cocaine and modifies the biotransformation of cocaine, both in rats and in humans. This is of special concern during early stages of life, since combined exposure to both drugs could induce physiological alterations during later stages of development. In a previous work we studied the effects of combined cocaine and alcohol chronic administration on the metabolic profiles of blood plasma of young-adult Wistar rats (51 days old at the beginning of the experiments) by using a Liquid Chromatography-Mass Spectrometry (LC-MS) untargeted metabolomics strategy. From 120 possible metabolites, eleven metabolites were annotated, where eight were unequivocally identified using standards and three were tentatively identified by matching the MS/MS spectra to libraries. The affected metabolic pathways were mainly those related to the metabolism of different amino acids (Sánchez-López et al. 2017). As an extension of that work, in the present study we have analyzed the blood plasma concentration of several amino-acids, in a targeted metabolomic approach, by using capillary electrophoresis (CE-LIF). As in the previous work, male and female Wistar rats received intravenously one of the following four treatments for 21 days: cocaine (15 mg/kg); alcohol (2 g/kg); cocaine+alcohol (15 mg/kg-2 g/kg); and control (saline). Plasma concentrations of eleven amino acids were identified and quantified: Gly, L-Ala, L-Gln, L-Glu, L-Iso, L-Leu, L-Orn, L-Pro, L-Ser, L-Thr, and Tau. A 2x2x2x2 factorial analysis of variance (cocaine*alcohol*age*sex) was performed. The levels for these four factors were presence of cocaine: yes/no; presence of alcohol: yes/no; sex: female/male; and age: young-adult (51 days) / adult (95 days). Cocaine administration significantly increased L-Iso, L-leu, L-Glu and L-Ser values. The presence of alcohol depleted L-Ala and L-ser and increased L-Gln and L-Orn. Females had higher values than males in five amino acids: L-Iso, L-Leu, Gly, Orn, Gln. Fully adult subjects had higher values of L-Iso, L-Leu and L-Gln compared to young adults. In addition, several interactions were observed: cocaine*alcohol for L-Iso, L-Gln, L-Orn and L-Ser, sex*cocaine for L-Pro and alcohol*sex for L-Gln and L-Iso. These data indicate that cocaine chronic cocaine and alcohol exposure, just alone or combined, modifies plasma amino acid patterns, including essential amino acids, and suggest differential effects depending upon sex and age.

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18. Compensatory changes to methamphetamine-induced dopaminergic degeneration and motor impairment in mice

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Methamphetamine (METH), a psychostimulant with high abuse potential, may double the risk of developing Parkinson's disease. Animal studies have shown that this drug produces persistent dopaminergic neurotoxicity in the nigrostriatal pathway. However, some compensatory changes to dopaminergic damage, as observed with other neurotoxins, may also occur following METH treatment. Our aim here was to confirm such recovery and determine the detailed structural nature as well as possible role of glia.
Three established neurotoxic regimens of METH: single high dose (1x30mg/kg), multiple lower doses (3x5 mg/kg) or (3x10 mg/kg) were administered in mice.
Significant degeneration of striatal dopaminergic fibers as well as motor impairments were observed a day later in all cases. Dopaminergic damage was highest with the 3x10 mg/kg dose followed by 3x5 mg/kg, and 1x30 mg/kg. Regimen-dependent partial recoveries in: tyrosine hydroxylase immunoreactivity, neuronal damage (amino-cupric-silver staining), fiber sprouting (GAP-43 staining), as well as in motor functions assessed by locomotor activity and Rotarod test were detected at 3 day post METH treatment. Additionally, METH treatment resulted in an increase in Iba-1 staining (reflective of microglia activation) after one day that was fully recovered by day 3. However, the increase in GFAP staining (reflective of astroglia activation) that was observed after one day was further increased by day 3.
These results confirm that partial recovery in striatal damage and motor impairment occurs following METH treatment and that astro- and micro-glia may have some role in this compensatory process.

19. Dynamic control of the dopamine transporter activity by the kappa opioid receptors in the dorsal striatum during amphetamine sensitization process

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The habitual intake of psychostimulants drugs has been associated to an increase in stimulated dopamine (DA) release in the dorsolateral striatum (DLS). Dynorphin, the endogenous ligand of kappa opioid receptors, increase significantly its expression in the striatum after both an acute and repeated exposure to amphetamine. The activation of kappa opioid receptors in dopaminergic terminals exerts a complex control on the activity of dopamine transporter (DAT). As the increase in opioid kappa tone modifies DAT activity in DLS in sensitized rats has not yet been studied. The aim of this work is to study the effect of local perfusion of the long-lasting kappa opioid receptor antagonist nor-BNI on the DAT activity in the DLS during the development of amphetamine-induced locomotor sensitization. The rats of sensitized groups were injected once daily during five days with amphetamine (1.0 m/kg, i.p) and the horizontal locomotor activity measured for 50 minutes. The rats of acute group were injected twice with amphetamine on day 1 and day 5. After five days of withdrawal (day 11), rats of sensitized group were injected with amphetamine to assess locomotor expression. Twenty-four hours after the amphetamine expression (day 12), microdialysis no-net flux experiments in the presence of norBNI (250 µM) were carried out to study the extraction fraction (Ed) in the DLS. A significant increase in the DA Ed was observed in the DLS of rats exposed acutely to amphetamine. On the other hand, a significant increase in both basal DA extracellular levels and DA Ed accompanies the expression of locomotor sensitization. Importantly, after the acute exposure to amphetamine the norBNI perfusion causes a decrease in the DA Ed, while an increase in the DA Ed is observed after the expression of amphetamine sensitization. Then, the kappa opioid neurotransmission control dinamically DA homeostasis in DLS, coontributing to increase DAT activity during acute exposure to amphetamine and then attenuating DAT activity during expression of sensitization.

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20. Reversal effects of sodium benzoate after a binge regimen of methamphetamine in mice

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Methamphetamine (METH) abuse has the disruptive health actions leading to prolonged neurological and psychiatric abnormalities. Sodium Benzoate (SB), a food additive and a metabolite of cinnamon, has been reported to reduce microglial and astroglial inflammatory responses and to upregulate the neurotrophic factors including BDNF and NT-3. We have revealed the protective effects of SB on METH-induced behavioral deficits previously. The present study examined the therapeutic effects of SB on the persistent behavioral aberrations after a binge regimen of MA. Male ICR mice received one day drug treatment with four injections of METH (4x 5mg/kg, i.p.) or saline at 2h interval. SB was administered once daily for seven consecutive days after final injection of SB, novel objective recognition test, social interaction and the hallucinogenic 2,5-dimethoxy-4-iodoamphetamine (DOI)-induced Head twitch response were monitored. SB significantly improved the METH-induced cognition deficits, social withdrawal, and hypersensitivity to hallucinogen. Together with our previous findings, SB may not only offer the neuroprotective effects, but also a potential treatment for psychiatric disorders related to METH abuse.

21. **Chronic voluntary oral methamphetamine induces deficits in spatial learning and hippocampal protein kinase Mzeta (PKMζ) with enhanced astrogliosis and COX-2 levels**

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Methamphetamine (MA) research using animal models has focused largely on examining the neurochemical and behavioral deficits induced by injecting relatively high doses of MA [30 mg/kg of body weight (bw)] identifying the upper limits of MA-induced neurotoxicity. Accordingly, we have developed a voluntary oral MA administration (VOMA) model for determining the lower limits necessary to produce neurotoxicity. We show that mice voluntarily consumed on average 1.743 mg/kg bw/hour during 3 hours, and an average of 5.23 mg/kg bw/day over 28 consecutive days. Following 28 days of VOMA, mice exhibited a significant deficit in short-term spatial working memory and spatial reference learning on the radial 8-arm maze (RAM) compared to controls. This was accompanied by a significant decrease in memory markers protein kinase Mzeta (PKMζ), calcium impermeable AMPA receptor subunit GluA2, and the post-synaptic density 95 (PSD-95) protein in the hippocampus. Compared to controls, the VOMA paradigm also induced decreases in levels of dopamine transporter (DAT) and tyrosine hydroxylase (TH), as well as increases in dopamine 1 receptor (D1R), glial fibrillary acidic protein (GFAP) and cyclooxygenase-2 (COX-2), with a decrease in prostaglandins E2 (PGE2) and D2 (PGD2). These results demonstrate that chronic VOMA reaching 146 mg/kg bw/28d induces significant hippocampal neurotoxicity. Future studies will evaluate the progression of this neurotoxic state.

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22. Methamphetamine neurotoxicity is exacerbated in diabetic animals. Role of neurotrophic factors, oxidative stress and nanomedicine

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Methamphetamine (Meth) is the most abused drug and often consumed for pleasure in healthy and/or people suffering from endocrine or cardiovascular diseases. Meth induces severe oxidative stress in the brain leading to brain pathology. Likewise oxidative stress also induces brain damage in diabetics. Whether Meth use in diabetics results in exacerbation of brain damage is still unclear. In this investigation we examined Meth induced brain damage and oxidative stress in diabetes in our rat model.Rats were made diabetic by administration of streptozotocine (75 mg/kg/day for 3 days, i.p.) resulting in blood glucose level to 22 to 26 mM/L within 4 to 6 weeks. In these diabetic rats Meth was administered 10 mg/kg, s.c. and brain pathology, e.g., blood-brain barrier (BBB) breakdown to Evans blue albumin and radioiodine ($^{[131}$-I]), brain edema formation and neuronal, glial and axonal injuries were examined. Immunostaining for Myelin basic protein (MBP) and histological staining of Luxol Fast Blue (LFB) to study axonal degradation, glial fibrillary acidic protein (GFAP) for astrocytic activation and histopathological techniques of Nissl or H&E stain for neuronal injuries were carried out on paraffin sections. Immunohistochemical analyses of enzymes responsible for free radical gas nitric oxide i.e., neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) were examined on paraffin sections. Our observations showed about 3- to 5 fold higher BBB breakdown and 2- to 4-fold greater volume swelling and brain edema formation was seen in diabetic rats after Meth exposure as compared to healthy animals. Interestingly, neuronal, glial cell and axonal injuries were exacerbated by 4- to 6-fold in Meth treated diabetic rats as compared to normal healthy animals. Thus, neuronal damage, astrocytic activation and myelin vesiculation were most prominent in the hippocampus, thalamus, hypothalamus, cerebellum and cerebral cortex. These brain areas also exhibited marked increase in nNOS and iNOS expression. The magnitude and severity of iNOS and nNOS expression was 2- to 3-fold higher in diabetic rats after Meth administration. Furthermore, measurement of brain derived neurotrophic factor (BDNF) using ELISA in Meth treated healthy animals showed significant decrease in hippocampus, cerebral cortex, cerebellum and thalamus. This decrease was further exacerbated in diabetic animals following meth administration. This suggests that exogenous supplement of BDNF could reduce Meth neurotoxicity.These neuropathological changes, NOS expression in diabetic rats were significantly reduced by TiO2-nanowired delivery of Cerebrolysin (a balanced composition of several neurotrophic factors and active peptide fragments) 5 ml/kg, i.p.) 30 min after Meth administration in diabetic rats. On the other hand cerebrolysin treatment enhanced the BDNF levels in brain by 80 to 110 % as compared to untreated group. Whereas higher doses of normal Cerebrolysin (10 mg/kg, i.v.) was needed to induce neuroprotection in Meth treated diabetic animals. These observations are the first to point out that diabetes exacerbates Meth induced neuropathology via oxidative stress and reduction in BDNF and nanodelivery of cerebrolysin is needed for neuroprotection in such situation, a feature that require further investigation.

23. Pharmacology of subjective effects of MDMA and MDMA self-administration

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±3,4-methylenedioxymethamphetamine (MDMA) is a preferential serotonin (5-HT) releasing stimulant and most drug discrimination studies that have employed a training dose of 1.5 mg/kg have attributed the discriminative stimulus effects to serotonergic mechanisms. When a 3 lever discrimination was conducted (amphetamine, MDMA and saline), low doses of MDMA produced almost exclusive responding on the MDMA lever but at doses of 3.0 mg/kg MDMA or higher, responding shifted to the AMPH lever. In order to further investigate the role of 5-HT and DA in the discriminative stimulus effects of low and high doses of MDMA separate groups of rats were trained to discriminate MDMA (1.5 or 3.0 mg/kg) from saline using a two lever, food-reinforced drug discrimination procedure. The SSRIs, fluoxetine (0.3–3 mg/kg), and clomipramine (1–10 mg/kg), and the 5-HT releasing stimulant, mCPP (0.3–2 mg/kg), dose-dependently substituted for the 1.5 mg/kg MDMA stimulus but failed to substitute for 3.0 mg/kg MDMA. The 5-HT_{1A} agonist, 8-OH-DPAT (0.03–0.3 mg/kg), and the 5-$HT_{1B/1A}$ agonist, RU-24969 (0.3–3 mg/kg) substituted for both the low and high dose MDMA stimulus. The generalisation dose-effect curve produced by the 5-HT_{2A} agonist, DOI (0.3–3 mg/kg), was shifted to the right for the 3.0 mg/kg MDMA-trained group. Amphetamine (0.25 and 0.5 mg/kg) and apomorphine (0.125 and 0.25 mg/kg) substituted for the 3.0 mg/kg but not the 1.5 mg/kg MDMA stimulus. MDMA self-administration and drug-seeking following extinction were not altered by 5-HT antagonists. DA antagonists, however, attenuated both of these components of self-administration. The results indicate an important role of DA in MDMA self-administration and in the subjective effects of higher doses of MDMA. Since rats received substantial exposure to MDMA in both procedures prior to the test of the 5-HT and DA ligands, the results support the idea of a shift from 5-HT to DA mechanisms underlies the subjective and reinforcing effects of MDMA.

24. Abuse-related effects of “bath salts”: modeling a mixed bag.

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The recreational use of synthetic cathinones has become a serious public health problem worldwide. In the US, “bath salts” products often contain MDPV (a monoamine transporter inhibitor) or methylone (a monoamine transporter substrate); however, preparations often contain mixtures of multiple synthetic cathinones, or mixtures of a synthetic cathinone and caffeine. In order to determine if the reinforcing effects of mixtures of “bath salts” constituents differed from the reinforcing effects of the cathinones alone, adult male Sprague Dawley rats (n=12 per pair of drugs) were trained to self-administer either 0.032 mg/kg/inf MDPV or 0.32 mg/kg/inf methylone under a progressive ratio (PR) schedule of reinforcement. Drug mixtures were based on the concept of dose equivalence, with each pair of drugs evaluated at three ratios (3:1, 1:1, and 1:3) relative to the mean ED50 for each drug. Dose addition analyses were used to calculate predicted effect levels for an additive interaction for each pair of doses for each combination of drugs using the Emax, ED50, and slope parameters derived from dose-response curves obtained in individual rats. Although high levels of responding were maintained by each of the “bath salts” mixtures, the nature of the interaction varied depending upon the constituent drugs. For combinations containing a cathinone and caffeine (MDPV+caffeine and methylone+caffeine), the interactions were generally additive, however, when mixed at a 3:1 ratio of their ED50s the reinforcing effects of both sets of mixtures were found to be supra-additive. Interestingly, although combining caffeine with MDPV appeared to only increase the potency of the mixture, combining caffeine and methylone resulted in a “bath salts mixture” that appeared to have a significantly greater than additive interaction with regard to reinforcing effectiveness. Unlike with combinations of cathinones and caffeine, when MDPV was combined with methylone from additivity tended to occur in the sub-additive direction, with the onset of toxicity observed with larger dose pairs of the MDPV+methylone mixtures. Together, these studies suggest that the reinforcing effects of binary mixtures containing common bath salts constituents (i.e., MDPV, methylone, and caffeine) are generally additive in nature; however, both supra-additive (MDPV+caffeine and metylone+caffeine) and sub-additive interactions can be observed. Although such interactions could account for the high rates of bath salts abuse, further study will be needed to determine if similar interactions exist between these and other bath salts constituents with regard to other abuse-related and toxic effects.

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25. Cocaine-mediated secretion of IP-10 from pericytes: implications for monocyte recruitment into the CNS

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Cocaine has been known to facilitate the transmigration of inflammatory leukocytes into the brain, which is an important mechanism for HIV entry into the central nervous system (CNS). Pericytes, as important constituents of the blood-brain barrier (BBB), play a key role in maintaining the BBB integrity, yet are poorly studied in the context of CNS inflammation. In the present study, we demonstrate that human brain vascular pericytes (HBVPs) exposed to cocaine manifest increased secretion of IP-10 with a concomitant induction of monocyte transmigration across BBB both *in vitro* and *in vivo*. This effect is mediated by the activation and translocation of sigma-1 receptor (σ-1R) and subsequent interaction of σ-1R with c-Src kinase leading to activation of the Src-PDGFRβ-NF-κB pathway with consequent up-regulation of IP-10 expression. These findings implicate a novel role of IP-10 in the crosstalk of pericytes and monocytes during cocaine-mediated neuroinflammation in the CNS, thereby underscoring the role of pericytes as active constituents of the innate immune responses.

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26. Morphine disrupts gut microbiome and contributes to Morphine tolerance: Role of Toll like receptor 2.

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Opioids are commonly prescribed as pain relievers. In United States, the total number of prescribed opioids has rapidly increased in the past 25 years and the increased incidence of prescription opioid abuse is rapidly becoming a major health problem. Chronic morphine use has been associated with negative consequences such as constipation, immune suppression, and addiction and analgesic tolerance. Our studies show that chronic morphine treatment compromises gut microbial dysbiosis and intestinal epithelial integrity thus leading to intestinal bacterial translocation and systemic immune cells activation. Our hypothesis is that sustained inflammation, originating from gut leakage and dysbiosis, contributes to morphine-induced analgesic tolerance. We observed that the analgesic tolerance was significantly attenuated in both TLR4KO mice and TLR2KO mice. In addition, morphine-induced bacterial translocation into liver and mesenteric lymph nodes was abolished in TLR2KO and TLR4KO mice. Concurrent decrease in pro-inflammatory cytokine levels were observed in morphine-treated TLR4KO and TLR2KO mice compared to morphine-treated wild-type mice. Treatment of morphine treated animals with probiotics, containing bacterial communities that were observed to decrease or to be depleted following morphine treatment, into wild type mice reversed morphine-induced analgesic tolerance and reduced IL-6 and IL-1β levels in the liver. We further show that morphine induced dysbiosis resulted in microglial activation in in the spinal cord of wild type, but was reduced in TLR2KO, TLR4KO mice and in mice treated with probiotics. Our studies demonstrate for the first time that probiotics can prolong the analgesic property of morphine and can be used therapeutically in patients on opioids for pain management.

27. Interaction between HIV and cigarette smoke in lung diseases

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In the era of antiretroviral therapy (ART) both infectious and noninfectious pulmonary disorders such as chronic bronchitis and chronic obstructive pulmonary disease (COPD) are common comorbidities in HIV-positive patients. Chronic bronchitis and COPD are also associated with tobacco smoking and smoking is very common in the HIV-infected population. It has been hypothesized that cigarette smoke and HIV might promote the development lung diseases in a synergistic manner and we have shown that HIVgp120 stimulates mucus formation in normal human bronchial epithelial (NHBE) cells via CXCR4 receptors. Thus, bronchial epithelial cells are potential targets of both cigarette smoke and HIV. To evaluate the interaction between cigarette smoke and HIV, we exposed cynomolgus monkeys to mainstream cigarette smoke and exposed control and cigarette smoke-exposed monkeys to $SHIV_{89.6}$ infection and ART. SHIV infection and/or smoke exposures were continued for 4 additional months. Lung function of the animals was determined by plethysmography using the FlexiVent system and chronic bronchitis by changes in the proximal tracheal rings sizes using ultrasound measurements and immunohistochemical analysis of airway mucus levels. The results indicate that, despite low HIV titers after ART, HIV infection and cigarette smoke synergize to significantly reduce lung function and promote chronic bronchitis. In addition, our results suggest that it is highly likely that HIV infects NHBE cells that are grown on air-liquid-interface. These cells express HIV coreceptors CD4 and CXCR4 and might represent potential HIV reservoirs in the lung. The implication of these results will be discussed with respect to the role of HIV and cigarette smoke in lung diseases.

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28. Effects of GPR55 activation on neural stem cell proliferation, differentiation, and immune responses to chronic inflammation and HIV infection

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New neurons are continuously produced by neural stem cells (NSCs) within the adult hippocampus. Numerous diseases, including major depressive disorder (MDD) and HIV-1 associated neurocognitive disorder (HAND), are associated with decreased rates of adult neurogenesis. A hallmark of these conditions is a chronic release of neuroinflammatory mediators by activated resident glia. Recent studies have shown a neuroprotective role on NSCs of cannabinoid receptor activation. Yet, little is known about the effects of GPR55, a candidate cannabinoid receptor, activation on neurogenesis especially in response to inflammation and HIV-1 infection. In the present study we examined NSCs exposed to HIV-1 and inflammatory cytokines to assess inflammation-caused effects on NSC proliferation and differentiation and the ability of GPR55 agonists to attenuate NSC injury. Protective effects of GPR55 agonists were assessed after treating an *in vitro* low-proliferating phenotype of human NSCs with inflammatory cytokines and HIV-1 related neurotoxic proteins (gp120, tat). NSC proliferation was evaluated via BrdU incorporation. NSC differentiation and neurogenesis was determined via FACS analysis of NSC markers (Nestin, Sox2, DCX, GFAP, βIII Tubulin). Results showed an increase in proliferation rates induced by GPR55 agonist treatment as well as rescued neurogenesis rates after treatment with inflammatory mediators IL-1β, gp120, and tat. Co-treatment of GPR55 agonist with INFγ or TNFα resulted in increased DCX+ cells and a reduction in βIII Tubulin+ cells as compared to untreated, differentiating controls. *In vivo* studies showed reduced numbers of proliferating cells (Ki67) and immature neurons (DCX) in the hippocampal dentate gyrus of $GPR55^{-/-}$ animals as compared to WT. Direct intrahippocampal administration of GPR55 agonist O-1602 (4μg/kg/day) increased NSC proliferation (Ki67, BrdU) and neurogenesis (DCX). Agonist treatment in $GPR55^{-/-}$ animals had no effect. Agonist treatment modulated anxiety-like behaviors while $GPR55^{-/-}$ animals displayed decreased anxiety as compared to WT. These results suggest a neuroprotective role of GPR55 activation on NSCs *in vitro* while *in vivo* studies demonstrate a necessity for GPR55 signaling under homeostatic conditions.

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29. Pathobiology of neural progenitor cells in methamphetamine abuse and HIV infection: protection by physical activity

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HIV-1 infection and methamphetamine (METH) abuse frequently occur simultaneously and may have synergistic pathological effects. Although HIV-positive/active METH users were shown to have higher HIV viral loads and experience more severe neurological complications than non-users, the direct impact of METH on HIV infection and its link to the development of neurocognitive alternations are still poorly understood. In the present study, we hypothesized that METH impacts HIV infection of neural progenitor cells (NPC) by a mechanism encompassing NFκB/SP1-mediated HIV-LTR activation. Mouse and human NPC were infected with EcoHIV and HIV, respectively, in the presence or absence of METH (50 or 100 μM). Pretreatment with METH, but not simultaneous exposure, significantly increased HIV production in both mouse and human NPC. To determine the mechanisms underlying these effects, cells were transfected with different variants of HIV-LTR promoters and then exposed to METH. METH treatment induced transcriptional activity of HIV-LTR promotor, the effect that required both NFκB and SP1 signaling. Pretreatment with METH also decreased neuronal differentiation and proliferation of HIV-infected NPC. Importantly, NPC-derived daughter cells appeared to be latently infected with HIV. This study indicates that METH increases HIV infectivity of NPC, through the NFκB/SP1-dependent activation of HIV LTR, and with the subsequent alterations of NPC neurogenesis. Such events may underlie METH- exacerbated neurocognitive dysfunction in HIV-infected patients.
While no effective therapy is available for the treatment of METH-induced neurotoxicity, exercise is a highly promising approach to improve substance abuse outcomes. Therefore, we employed an animal model to evaluate the impact of METH and exercise on NSC differentiation. The study was based on a chronic exposure to METH (5 days with an escalating doses at 3 h intervals), followed by two weeks of exercise. Control mice expressed strong immunoreactivity for doublecortin (DCX, a marker for immature neurons), which branched to the distal part of the dentate gyrus. In contrast, the processes of the DCX-positive cells were visibly underdeveloped and the number of DCX-positive cells decreased as the result of METH exposure. Importantly, voluntary exercise protected against this effect. Mechanistically, the beneficial impact of exercise was linked to antioxidative and anti-inflammatory effects. These results indicate that exercise can attenuate METH-induced aberrant neurogenesis and suggest that physical activity could also be beneficial to counteract METH- induced progression of HIV-associated neurodegeneration. Supported by DA039576, DA027569, HL126559, MH098891, MH072567 and by the Miami CFAR MH063022. This work was also supported by NSC 2015/17/B/NZ7/02985.

30. Potential Increased Utility of Combined Drug Treatments for Treating Tobacco Addiction

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The brain is an organ of communication, with a variety of neural and glial systems interacting to provide the network bases for behavioral function. Behavioral dysfunction can arise from maladaptive system interactions. As much as it is attempted to reduce the biobehavioral dysfunction to simple causes, there is always a broader network context. Even when a malfunction of a single cell type or a single gene is identified as the primary cause for neurobehavioral dysfunction, the systems to which it is interconnected provide modulatory influences and a context for expression of behavioral impairment. With addiction much has been made of the central involvement of dopaminergic innervation of the nucleus accumbens from the ventral tegmental area (VTA). However, there are close connections of nicotinic acetylcholine systems on the VTA-accumbens pathway with connections from the pedunculo-pontine and dorsolateral tegmental nuclei to dopamine cell bodies in the VTA and interstitial cholinergic neurons on dopamine nerve endings in the nucleus accumbens. Other monoamine systems such as serotonin, norepinepherine and histamine are also involved in the reinforcing effects of drugs as are the primary excitatory and inhibitory neurotransmitter systems glutamate and GABA. We have found with a rat model a variety of drug treatments which decrease nicotine self-administration. These include the dopamine D_1 antagonist SCH 23390, the serotonin $5HT_{2C}$ agonist lorcaserin, and the histamine H1 antagonist pyrilamine as well as chronic administration of nicotine itself. Recently we have been investigating the interactions of these effective treatments to determine if the combinations provide greater efficacy in reducing nicotine self-administration. We have found with young adult Sprague-Dawley rats trained to self-administer IV doses of nicotine (0.03 mg/kg/infusion on an FR1 schedule in one-hour sessions). Chronic nicotine infusions via osmotic minipumps reduced nicotine self-administration. This was augmented by either the D_1 antagonist SCH 23390 or the $5HT_{2C}$ agonist lorcaserin or the H1 antagonist pyrilamine. Combinations of lorcaserin and SCH 23390 did not augment each other's effects. These studies show that chronic nicotine treatment mimicking the nicotine skin patch could be augmented by co-treatments affecting D_1, $5HT_{2c}$ and H1 receptors. These studies provide evidence that certain combined treatments may be useful for increasing the success of smoking cessation. The fact that the brain is an interconnected organ provides access for improved therapy mediated via complementary pathways.

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31. Endocannabinoid in drug dependence: transcriptional and epigenetic adaptations

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Drug abuse often leads to a complex pharmaco-dependent state which is defined by the term addiction. Addiction is a multi-factorial disease with detrimental consequences for individuals and their social environment that implies genetic, neurobiological, psychological and environmental factors. The neurobiological changes underlying the progression to addictive behaviors include transcriptional and epigenetic processes.
The growing consumption of cannabis and its derivatives for recreational use in the population represents a real public health challenge. Cannabis is the most popular illicit substance in Europe and leads to adverse health effects that are demonstrated in preclinical and clinical studies based on the psychotic and addictive properties of this compound. Cannabis interacts with the endogenous cannabinoid system (ECS), which comprises lipid neuromodulators (endocannabinoids), enzymes for their synthesis and their degradation and two transmembrane receptors coupled to G proteins, CB1 and CB2. The CB1 receptor is mainly expressed in the brain and its role in the effect of drugs of abuse has been widely described, whereas the contribution of the CB2 receptors, initially described as a peripheral receptor, has just recently been proposed. The ECS plays a key role in modulation of pain response, with processing of central and peripheral pain signals, learning and memory and emotions. This system is also clearly involved in the modulation of drug reward, not only by cannabinoids, but also by psychostimulants such as cocaine or by opiates, such as morphine. Interestingly, the ECS plays an important role in response to food intake and may be involved in the progression to maladaptive feeding that characterizes obesity and eating disorders. In our studies, we analyze and compare transcriptional adaptations of ECS components in reward-related brain circuits across paradigms of drug intake such as cocaine self-administration or morphine-dependence and paradigms of palatable food consumption. Our main objective is to uncover the impact of epigenetic processes on plasticity mechanisms that lead to dependence. In particular, our approach will bring new insights into maladaptive changes in the brain leading to uncontrolled intake of both drugs of abuse and palatable food and clarify the role of the ECS in these processes.

32. Epigenetic Regulation of immune Response by Marijuana Cannabinoids

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While marijuana is one of the most abused drugs world-wide, it has been used for medicinal purposes as well. Research from our lab has shown that the main psychotropic component in marijuana, Δ(9)-tetrahydrocannabinol (THC), exerts potent anti-inflammatory properties through: 1) Switch from Th1 to Th2, 2) Induction of Tregs, 3) Induction of apoptosis and 4) Promotion of the development of myeloid-derived suppressor cells (MDSCs). We have also shown that these immunological changes are regulated by epigenetic modulation. In order to address this, we used ChIP-Seq to examine the in vivo effect of THC on genome-wide histone modification in immune cells of mice immunized with a superantigen (SEB), including genome-wide repressive histone H3 trimethylation and activating histone H3 acetylation patterns. Our results showed that THC treatment caused histone activation related to Th2 cytokine genes and repressive modification signals to Th1 cytokine genes. These data suggested that such epigenetic pathways may play a crucial role in THC-mediated switch from Th1 to Th2. We also used RNA-Seq to quantify the transcriptome and transcript variants that are differentially regulated by THC and found that the expression of many transcripts was altered by THC. Furthermore, the abundance of many miRNA precursors and long non-coding (lnc) RNAs was significantly altered in THC-treated mice. Our studies demonstrated SEB induced the lncRNA, AW which may correlated with Th1 polarization. We noted down-regulation of the expression of miR-17/92 cluster and miR-374b/421 cluster by THC. On the other hand miR-146a, which has been shown to induce apoptosis, was up-regulated by THC. Lastly, we also noted that the induction of MDSCs by THC was regulated by epigenetic changes including induction of unique microRNA. THC caused hypermethylation at the promoter region of DNMT3a and DNMT3b in MDSCs, which correlated with reduced expression of DNMT3a and DNMT3b. Furthermore, promoter region methylation was decreased at Arg1 and STAT3 in THC-induced MDSCs. THC also suppressed miRNA-17/92 cluster, which targeted Pten, an inhibitor of the PI3K/Akt signaling pathway, thereby inducing T-regulatory cells. Altogether, our study demonstrates that THC may modulate immune response through multiple epigenetic pathways involving histone modifications, DNA methylation as well as microRNA and lncRNA induction (Supported by NIH grants P01AT003961, R01AT006888, R01AI123947, R01AI129788, R01ES019313, R01MH094755, P20GM103641 to PN and MN).

33. Behavioral modifications following deletion of type 2 cannabinoid receptors in dopamine neurons

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Cannabinoid CB2 receptors (CB2Rs) are expressed in mouse brain dopamine (DA) neurons and are functionally involved in several DA-related and other CNS disorders including drug addiction in rodent models. However, the cellular mechanisms underlying this modulation are unclear since the currently available CB2R gene knockout mice are constitutive gene knockout. In addition, both partial N-terminal and C-terminal CB2R-KO mice express truncated CB2R peptides with residual function. Therefore, we generated Cnr2-floxed mice that were crossed with DAT-Cre mice, in which the recombinase expression is under dopamine transporter gene (DAT) promoter control to generate CB2R conditional knockout mice in midbrain DA neurons in DAT-Cre-Cnr2-Lox transgenic mice. By using a novel highly-sensitive RNAscope in situ hybridization method, we detected clear CB2R mRNA expression in VTA DA neurons in wildtype control and DAT-Cnr2 heterozygous mice, but not in the homozygous DAT-Cnr2 cKO mice. We then characterized the DAT-Cnr2 cKO mice in a battery of behavioral test systems. Here we report that the deletion of CB2Rs in dopamine neurons enhances motor activities, modulates anxiety-like and depressogenic-like behaviors and reduces the rewarding properties of alcohol and cocaine. Our data also reveals for the first time that CB2Rs are involved in the tetrad assay induced by cannabinoids which had been largely associated with CB1R agonism. The GWAS secondary analysis indicate that the CNR2 gene is associated with Parkinson's disease and substance use disorders. We conclude that CB2Rs in dopaminergic neurons play an important role in the modulation of psychomotor behaviors, anxiety, depression, and pain sensation and in the rewarding effects of alcohol and cocaine.

34. Is there a cross talk between cannabinoids and microbiota that regulates inflammation?

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There are over 100 trillion microorganisms that live in our gut, lungs, skin and other mucosal surfaces. Such a community includes symbionts (beneficial), commensals (neutral) and pathobionts (detrimental). The homeostasis of these microorganisms is critical for maintaining host health and function. Recent studies have demonstrated that microbiota play a crucial role in the regulation of inflammation. Previous studies from our lab demonstrated that cannabinoids act as potent anti-inflammatory agents. In the current study, we therefore investigated if there is cross-talk between cannabinoids and microbiota, which in turn may regulate inflammation. To that end, we used several models of inflammation. One such model is Staphylococcal Enterotoxin B (SEB) induced acute lung injury (ALI). We observed that THC, a psychoactive ingredient found in *Cannabis sativa*, was able to attenuate ALI by downregulating the pro-inflammatory cytokine storm. A dual-dose of SEB was given to C3H/HeJ mice, which were then treated either with vehicle or THC. SEB-administration caused ALI and 100% mortality while all THC-treated mice survived following suppression of inflammation in the lungs. Furthermore, lung microbiota was collected and 16S rRNA sequencing was performed. The data were analyzed to determine the alpha and beta diversity. There was significant microbial dysbiosis following SEB treatment which was reversed in the presence of THC. The major changes were seen in phylum *Proteobacteria*, class *Alfaproteobacteria,* orders *Caulobacterales* and *Rhizobiales,* and families *Caulobacteriaceae* and *Rhodobacteriaceae* in the lungs of vehicle-treated SEB group. Some of similar changes were also seen in colonic bacterial composition in these groups, which may be due to increased lung permeability following SEB treatment, thereby demonstrating the critical role of gut-lung axis in microbial dysbiosis in this model. Moreover, THC treatment led to elevated Firmicutes phylum due to significant increase in the beneficial genus, *Lactobacillus.* Furthermore, beneficial metabolite levels were significantly higher in the colonic flush of THC-treated SEB mice when compared to vehicle-treated SEB group, specifically butyric, propionic and acetic acids. The role of various cannabinoids in alteration in microbiota was also evident in other models of inflammation. Together, our studies demonstrate that cannabinoids may suppress inflammation, at least in part through regulation of microbiota (Supported by NIH grants P01AT003961, R01AT006888, R01AI123947, R01AI129788, R01MH094755, P20GM103641 to PN and MN).

35. Social brain, endocannabinoids and alcohol consumption.

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Alcohol dependence develops as a multifactorial process. Genetic, epigenetic and social factors count to facilitate it. Several neurotransmission systems are involved, among them, the endocannabinoid system (eCBs). The aim of this study is to support the notion that aversive environmental conditions during infancy and during adolescence, may modify the activity of the eCBs and such changes make the subject vulnerable to develop alcohol dependence. Four groups of rats were manipulated as follows: 1. Rats were separated from their mother (MS) from postnatal day (PND) 1 to PND16 for 3 hours daily. From PND28-42 (adolescence) they were housed as a group of 10 rats (MS+social group, SG). 2. MS rats were housed individually from PND28-42 (MS+social isolation, SI). 3. Rats were maintained with the mother at all times (NMS), but from PND28-42 they were housed as a SG (NMS+SG). 4. NMS rats were housed SI (NMS+SI) from PND28-42. All these rats were maintained in these conditions until PND64. From PND64-74, rats were exposed to voluntary alcohol-intake, i.e. two bottles of liquid, 1 with tap water and the other with a solution of alcohol in water (10% v/v). Alcohol solution was prepared daily and the position of bottles was switched daily. Alcohol intake was estimated as an index of [(g of alcohol/g of body weight)100]. Four other groups of rats subjected to the same manipulation (NMS+SG, NMS+SI, MS+SG and MS+SI) but they did not undergo through the alcohol ingestion period were sacrificed (PND64) and the prefrontal cortex (PFC), the hippocampus (Hipp) and the nucleus accumbens (NAcc) were isolated and prepared to evaluate the expression of CB1R, CB2R and D2R by means of Western blot. NMS+SG consumed about 0.18 of alcohol, NMS+SI and MS+SG ingested about 0.4, and MS+SI ingested about 0.70. Western blot revealed that MS+SG and MS+SI induced an increase in CB1R in the NAcc. No significant changes were observed in the expression of CB2R, but NMS+SI, MS+SG and MS+SI induced a D2R increase in the NAcc. This results indicate that the interference with the maternal bonding (MS) or mate interaction (SI) in early stages of the ontogeny, induces a change in the CB1R and D2R expression in rats that may contribute to facilitate alcohol ingestion in a higher amount than the amount ingested by those rats that grew up under the maternal care and in groups. This study supports the notion that social interactions are playing a crucial role in re-programming the brain in early stages of the ontogeny. Social stressful conditions may re-program the brain in such a way that the brain becomes vulnerable to alcohol high consumption.

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36. Role of CB1 receptor in vulnerability to morphine dependence in adolescent mice prenatally exposed to a cannabinoid agonist

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Cannabinoids and opioids are psychoactive drugs with similar pharmacological effects, as both produce analgesia, catalepsy, hypothermia, motor depression, hypotension and reward effects. CB1 receptor is involved in the motivational properties of opiates and in the development of dependence. The close relationship between cannabinoid and opioid systems is critical during morphine (MOR) withdrawal. CD1 mice deficient in cannabinoid receptor type 1 (CB1 knockout) have a lower intensity of somatic signals to MOR withdrawal induced by naloxone (NAL) as compared to wild-type CD1 mice (WT).
The current work studied: 1) gender differences in the somatic syndrome during MOR withdrawal induced by NAL in CB1 knockout and WT; 2) the effect of prenatal exposure to WIN 55.212-2 (WIN) on the expression of MOR withdrawal in adolescent CB1 knockout and WT. Primiparous pregnant CB1 knockout and WT received WIN or vehicle from gestational day 5; after delivery, dams were replaced by *naive* substitutes. The MOR dependence and withdrawal protocol was implemented in pups at postnatal day 25.
Results: 1) No gender-specific differences were detected between pups; 2) Prenatal exposure to WIN reduced MOR withdrawal expression in WT but not in CB1 knockout, whose MOR withdrawal expression levels showed no significant differences from their vehicle counterparts ($p<0.05$).

37. Zebrafish embryos exposed to THC (delta 9-tatrehydrocannabinol) during gastrulation exhibit alterations in heart rate and synaptic activity at the neuromuscular junction

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Marijuana, one of the most commonly used illicit recreational drugs, is widely used for medicinal purposes, and is rapidly becoming legalized in many jurisdictions. The psychoactive ingredient in marijuana is delta-9-tetrahydrocannabinol (Δ9-THC), which, taken along with alcohol may pose a risk to embryonic development as it freely crosses the placenta. In this study, we exposed zebrafish embryos to Δ9-THC for 5 hours during the brief but critical stage of development known as gastrulation. We then allowed the embryos to develop in normal embryo media until 2 days post fertilization, when we examined them for morphological changes as well as alterations in cells associated with locomotion and in locomotor behaviors. We treated embryos in the gastrulation stage (5.25 hours post fertilization (hpf) to 10.75 hpf) with concentrations of Δ9-THC ranging from 2 mg/L to 10 mg/L. Δ9-THC treated fish had shorter bodies compared with controls and exhibited mild malformations such as blebbing at the tip of the tail. Embryos exposed to higher concentrations of Δ9-THC did not survive past 4-5 days post fertilization and exhibited significant reductions in heart rate. Semi quantitative PCR of whole embryos showed the presence of mRNA for CB1 and CB2 cannabinoid receptors as early as the onset of gastrulation at 5 hpf. Electrophysiological recordings of synaptic activity from white muscle fibers showed a reduction in the frequency of mEPCs but the appearance of a population of high amplitude events following Δ9-THC treatment. Other parameters of synaptic activity at the NMJ were largely normal. Fluorescent labelling of neuromuscular junctions (NMJs) was more intense after Δ9-THC treatment suggesting the presence of greater numbers of nicotinic ACh receptors at the NMJ. Fluorescent labelling of primary and secondary motor neurons were normal, indicating that the morphology and branching patterns of these neurons were unaffected by Δ9-THC treatment. Locomotion studies showed that Δ9-THC treatment resulted in small changes in the C-bend escape response. Together these findings indicate that zebrafish embryos exposed to Δ9-THC during the brief period of gastrulation exhibit alterations in morphology, heart rate and synaptic activity at the NMJ. However, it is also important to note that several of the parameters we examined were largely unaffected.

38. Endocannabinoid stimulation in pregnancy: effects on mother-infant dyad and beyond

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Although cannabis is the most commonly used illicit drug in pregnancy, its impact on development is an underestimated matter. Thus, this study investigates the effects of stimulation of the endocannabinoid system from gestational day 5 to gestational day 20 on maternal behaviour along the postnatal period and on behavioural reactivity, emotional memory and alcohol vulnerability in the offspring. Maternal care was assessed by recording dams' undisturbed spontaneous home-cage behaviour in the presence of their offspring. The progeny was tested from postnatal day 25 onwards for behavioural reactivity in the Open Field and in the Elevated-Plus Maze test; and for fear-associated memory in the emotional-object recognition test. The progeny was also exposed to operant conditioning and binge-like drinking paradigms for assessing vulnerability to alcohol drinking. Our results show that prenatal cannabinoid stimulation induced a de-escalation in maternal behaviour ($p<0.001$) with respect to vehicle over the postnatal period. In particular, cannabinoid-treated dams showed a significant increase in single non-maternal behavioural categories, such as self-grooming ($p<0.001$), dam self-care ($p<0.001$), rearing ($p<0.001$) and general arousal ($p<0.001$), when compared to controls. In the progeny, prenatal stimulation of the endocannabinoid system increased locomotor activity, as shown by a significant increase in total distance travelled ($p<0.01$) and in number of total entries ($p<0.01$) in Open Field and Elevated-Plus Maze, respectively, compared to controls, although it did not modify anxiety-like behaviour. When tested for the emotional memory, the endocannabinoid-stimulated rats showed impaired declarative memory associated to aversive emotional stimuli, since they showed a significant decrease in the Emotional-Object Avoidance Index ($p<0.05$) and in the emotional zone-related Difference Score ON-BSL ($p<0.05$), with respect to controls. In the same rats, a significant reduction in instrumental learning was observed in the operant paradigm, while increased vulnerability to alcohol binge drinking was recorded ($p<0.05$). Indeed, the analysis of binge-drinking pattern indicated increased alcohol-intake and preference ($p<0.001$), when compared to controls. In conclusion, this research highlights that prenatal exposure to cannabinoids for medical or recreational purposes, disrupts the mother-infant dyad and does induce complex disarrangement in the brain progeny that arises during adolescence that involves emotionally salient memories and vulnerability to drug of abuse.

39. Exploring drug-induced neuroinflammation has helped us to identify potential candidates for the development of new therapeutic approaches.

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We will present data concerning three potential targets under study, at different stages of development. The first one is oleoylethanolamide and drugs modeled upon its scaffold. This endogenous lipid has potential use for drug consumption, neuroinflammation and associated depression. The second one will be lysophosphatidic acid 1 receptor (LPA1r) that has been described to modulate alcohol intake and drug-associated memories. The third one is the chemokine Fractalkine receptor (CXCR1) that might be interesting for exploring relapse because of its role on extinction of drug-associated rewarding memories

40. Tackling alcohol use disorder through comprehensive bioinformatics

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The addiction cycle is a downward spiral of events comprising both positive and negative affect. Each stage of the cycle engages a series of molecular processes that further drive continued substance abuse and dependence. Chronic and excessive alcohol consumption, similar to other drugs of abuse, is associated with both genetic and environmental components. Understanding the global architecture of alcohol abuse and dependence necessitates a comprehensive approach. Bioinformatics is capable of aggregating information across multiple independent experiments, model systems, and scientific disciplines. Combining the strengths of bioinformatics with advancements in high-throughput sequencing techniques has demonstrated the widespread actions of acute and chronic substance use on the central nervous system. Our studies have focused on deep RNA-Sseq profiling of postmortem human brain tissue from the superior prefrontal cortex (CTX), nucleus accumbens (NAC), basolateral amygdala (BLA), and central nucleus of amygdala to define molecular systems affected involved in disease. Similar to previously published reports, no singular factor is sufficient for describing disease status. Through a graph-theory based computational approach our analyses demonstrate coordinate expression of molecular networks involving hundreds of genes spanning multiple biological systems and pathways. Layering the human profiles with data collected from model organisms shows conserved and human specific components related to alcohol use disorder. Additionally, the model organisms help refine the diverse phenotypic elements (*e.g.* Withdrawal) involved in the addiction cycle. The tremendous growth in publically available datasets also assists in potential cross-over with novel pharmacotherapies for broadening the spectrum of available medications in human intervention. Bioinformatics continues to scale with the exponential rise in large and complex datasets, facilitating a means to connect the dots among a dense web of molecular responses and discern the underlying elements of substance abuse and dependence. *Supported by the national institute of alcohol abuse and alcoholism (niaaa) grants k99-aa024836 and u01- aa020926.*

41. Exploring the neural basis of "incubated" alcohol craving by pharmacogenetics and functional gene expression profiling

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Drug and ethanol (EtOH) seeking induced by drug-related environmental stimuli is characterized by time-dependent increases. This effect, referred to as the "incubation of craving," may contribute significantly to high relapse risk. Here we examined the neural and molecular basis of this effect. Ample evidence implicates nucleus accumbens (NAc) core neurons in the control of drug and EtOH seeking. These neurons are activated by EtOH-associated environmental stimuli and therefore may represent a neural substrate regulating the incubation of EtOH craving. To test this hypothesis, Wistar rats previously trained to receive response-contingent oral EtOH paired with an environmental cue were tested for cue-induced EtOH seeking following one (Day 1) or 14 (Day 14) days of abstinence. Compared to Day 1, EtOH seeking on Day 14 was significantly increased ("incubated"), paralleled by significantly increased neural activation (Fos expression) in the NAc core and shell. However, baseline (i.e., "non-incubated") EtOH seeking on Day 1 was associated with significant Fos activation only in the NAc core and not shell, consistent with the hypothesis that cue-induced neural activity in the NAc core may drive the development of incubated EtOH seeking. If so, selective disruption of EtOH cue-activated neurons in NAc core should prevent this effect. We therefore injected, Daun02 (a cytotoxic prodrug) into the NAc core of Fos-lacZ transgenic rats immediately following the first EtOH seeking test (Day 1). In Fos-lacZ rats, Daun02 is converted into the cytotoxin daunorubicin following translocation into in Fos+ neurons, thereby inducing apoptosis of activated neurons. This selective "lesion" of EtOH cue-activated neurons on Day 1 spared the expression of non-incubated EtOH seeking (evident on Day 3), but prevented incubation of this behavior evident in Daun02 vehicle controls on Day14. This set of findings confirms that cue-induced neural activity in the NAc core mediates the incubation rather than expression of EtOH seeking and suggests that neuroplasticity developing in distinct EtOH cue-activated neuronal ensembles in the NAc core mediates the time-dependent exacerbation of EtOH seeking. We are currently analyzing transcriptome-wide changes (using RNA-seq) unique to EtOH cue-activated neurons in the NAc core, collected by fluorescence-activated cell sorting (FACS) at various stages of the incubation period. It is expected that the behavioral incubation of EtOH seeking can be traced to distinct changes in the gene expression profile of NAc core neurons. Support: NIH grants AA021549, AA018010 (FW); AA023183 (NS); AA020960, AA021667 (PPS.).

42. Multimodal brain imaging metrics as potential markers for assessing medication development

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Multiple brain imaging modalities using structural (MRI), functional (fMRI), and neurochemical (MR spectroscopy) approaches have been successful in detecting and quantifying differences between individuals with alcohol use disorder (AUD) or substance use disorder (SUD) compared with those free of these disorders. Longitudinal study has identified brain regions, systems, and functions that are at least partially reversible with alcohol abstinence. There is also some brain imaging literature suggesting that among individuals at risk for AUD, those who go on to develop AUD differ in selective brain morphology from those who do not even before initiating alcohol use, consistent with a genetic predisposition for AUD. Considering the versatility of neuroimaging and spectroscopy, these modalities have been readily translated to in vivo animal models of alcohol and substance research. Accordingly, neuroimaging provides unique opportunities for longitudinal tracking of the development of dependence, structural and functional changes that occur with dependence, and the extent that these changes can be reversed or mitigated with abstinence or pharmacological intervention. Study of behaving animals affords the opportunity for a closer translation to the human condition than cross-sectional postmortem study. Finally, animal models focused on the effects of acute and chronic administration of alcohol detectable with brain imaging can shed light on measures that could be of value for screening potential medications for treating alcohol misuse. The presentation will review neuroimaging of acute and chronic alcohol effects in humans and animal models and suggest potential metrics for assessing new medications. Support: AA013521, AA005965, AA017168

43. Dopamine D3 Receptor Antagonism Decreases PTSD-like Behavior in Rats

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Post-traumatic stress disorder (PTSD) is a debilitating anxiety disorder with a high degree of co-morbidity with drug addiction, We have previously shown that highly selective dopamine D3 receptor antagonists are effective in attenuating stress responses related to drug addiction. The objective of the present study was to determine whether these same D3 receptor antagonists attenuate PTSD-like behavior in a laboratory animal model. We used a modified single prolonged stress (SPS) procedure- forced swim for 20 m, followed by restraint for 2 h, followed by inescapable foot shock for 20m. A 2900 Hz tone was paired with the stress-inducing stimuli. Following SPS, each rat was left undisturbed in its home cage for 14 days. Then, the ability of the stress-paired tone to evoke freezing behavior was confirmed. Then, the effects of the DA D3 receptor antagonist YQA14 on tone-evoked PTSD-like freezing behavior was assessed. Then, the effects of the DA D3 receptor antagonist SB277011A on tone-evoked PTSD-like freezing behavior was assessed. We found that: 1) there was a significant increase ($p<0.001$) in stress-paired tone-evoked PTSD-like freezing behavior at 14 days after SPS exposure; 2) YQA14 at both 6.25 mg/kg ($p<0.01$) and 12.5 mg/kg ($p<0.001$) significantly decreased freeze time when the animals were tested post-SPS. The DA D3 antagoinists had no effect on the freeze time in the absence of the SPS-paired tone. We conclude that DA D3 receptor antagonism by SB-277011A or YQA14 prior to re-exposure to a stress-associated environmental cue very markedly attenuates the expression of a PTSD-like fear-conditioned response, similar to the way in which these compounds attenuated the expression of stress-induced reactivation of drug-seeking behavior and stress-induced conditioned fear responses. We suggest that highly selective dopamine D3 receptor antagonists present a novel approach for the treatment and/or prevention of comorbid drug addiction and PTSD.

44. Probing the hypodopaminergic state with TMS in addicts: preliminary observations.

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Repetitive Transcranial Magnetic Stimulation (rTMS) of the dorsolateral prefrontal cortex may affect neuro-adaptations associated with alcohol addiction, potentially influencing drug craving and intake. Previous pre-clinical and clinical evidence suggest a tonically reduced functioning of the mesolimbic dopamine system leading to hypothesize that 'boosting' the hypofunctional system may yield clinical benefits. Here we show that rTMS reduces alcohol and cocaine intake in alcoholics and cocaine addicts. We investigated alcohol intake and dopamine transporter (DAT) availability by Single Photon Emission Computed Tomography (SPECT) in the striatum, in Alcohol Use Disorder (AUD) patients before and after deep rTMS. Fourteen patients underwent baseline clinical and SPECT assessment. Eleven out of 14 patients were randomized into two groups for the REAL or SHAM treatment. Clinical and SPECT evaluations were then carried out after four weeks of rTMS sessions. At baseline, AUD patients showed higher striatal DAT availability than healthy control subjects (HC). Further, patients receiving the REAL stimulation revealed a reduction in DAT availability, whereas SHAM-treated did not. In addition, REAL patients decreased alcohol intake and state anxiety levels. The present results suggest a modulatory effect of deep rTMS on dopaminergic terminals and a potential clinical efficacy in reducing alcohol intake in AUD patients. Similarly, 18 cocaine addicts (DSM-V) were admitted and randomly assigned to the active or sham stimulation protocol in a double-blind experimental design. They received 12 repetitive TMS r(TMS) sessions 3 times a week for 4 weeks at 100% of motor threshold, over bilateral DLPfc. Cocaine intake (ng/mg) was assessed by hair analysis at baseline (before treatment, T0), after one month (end of treatment, T1) and at 3 (T2) and 6 (T3) months later. All subjects received weekly psychological support. Bilateral TMS of the DLPfC produces a lasting reduction of cocaine-intake significantly more in 10 Hz treated patients vs. SHAM. While further studies are required to confirm these preliminary findings, they support the notion that DA can be considered a useful biomarker to be targeted by rTMS in addicts.

45. Effects of the NMDA receptor modulating agents on ketamine self-administration

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Ketamine is frequently used as a "party drug' among young adults and has the potential to lead to addiction. As ketamine is a well-known N-methyl-D-aspartate receptor (NMDAR) blocker, modulation of NMDAR might be an effective strategy to counteract the reinforcing efficacy of ketamine and even to avoid ketamine relapse. The present study evaluated the potential of NMDAR modulators via activation of the glycine binding site for treatment of ketamine addiction using intravenous self-administration (IVSA) procedure in rat. Male Sprague-Dawley rats were trained to IVSA of ketamine under the fixed ration (FR) 1 and 2 schedules. The acute effects of NMDAR modulators on ketamine IVSA under FR2or progressive ratio schedules and cue-, drug-and stress-induced reinstatement of ketamine seeking were examined. Sodium benzoate, a D-amino acid oxidase inhibitor, potentiating NMDAR function through increasing synaptic D-serine concentrations and betaine, acting as a partial agonist of glycine binding site at NMDAR, significantly reduced the ketamine IVSA and reinstatement acutely. Moreover, repeated treatment of these two compounds during forced abstinence decreased the cue-, drug- and foot shock-induced drug seeking behavior. These findings revealed that these NMDAR modulators could reduce the reinforcing efficacy of ketamine and attenuated reinstatement of ketamine-seeking behavior, suggesting modulation of NMDAR activity might provide a strategy to treat ketamine addiction.

46. 3,4-Methylenedioxypyrovalerone (MDPV) induces cytotoxicity and alters tight junctions protein in rat blood-brain barrier endothelial cells

Hector Rosas-Hernandez[1], Elvis Cuevas[1], Susan M. Lantz[1], Syed Z. Imam[1], Kenner C. Rice[2], William E. Fantegrossi[3], Merle G. Paule[1] and **Syed F. Ali[1]**.

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In recent years, the use of synthetic cathinones has grown rapidly as an alternative to classic amphetamine-like drugs. These drugs are usually referred to as "bath salts" with 3,4-methylenedioxypyrovalerone (MDPV) being the most prevalent constituent. Bath salts exert their neurotoxic effects by altering monoamine systems in the brain, in a way similar to methamphetamine (METH) and cocaine. These two drugs of abuse also increase the permeability of capillaries in the blood-brain barrier (BBB). As there is currently no information about the effects of MDPV on brain vasculature, the main aim of this study was to determine if MDPV affects an in vitro BBB model. Using primary cultures of rat brain microvessel endothelial cells (rBMVECs) as the model, we assessed the effects of MDPV (100 µM- 2.5 mM) on cytotoxicity, cellular proliferation, apoptosis, the expression of the tight junction (TJ) proteins occludin and ZO-1 and changes in cellular morphology. MDPV exposure decreased cellular proliferation and increased apoptosis at 1 and 2.5 mM. However, MDPV increased LDH release beginning at 0.25 mM, which correlated with a decrease in the expression of the TJ proteins occludin and ZO-1. The morphological analysis revealed that after MDPV treatment, rBMVECs lost their endothelial morphology and formed a disrupted monolayer. These results suggest that MDPV is cytotoxic to brain endothelial cells via the induction of apoptosis, inhibition of cellular proliferation and decreases in the expression of TJ proteins. Cumulatively, these events may lead to the alteration of membrane integrity and increased BBB permeability, which may in turn contribute to its neurotoxic effects.

47. 3,4-methylenedioxypyrovalerone (MDPV) induces cytotoxic effects on human dopaminergic SH-SY5Y cells

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Background: Synthetic cathinones are a rapidly growing group of psychostimulant drugs usually referred to as “bath salts” and have been used as an alternative to classic amphetamine-like drugs, with 3,4-methylenedioxypyrovalerone (MDPV) being one of the most prevalent constituents. Consistent with the effects of other psychostimulants, MDPV may induce neurotoxicity by altering monoamine systems in the brain or by inducing neuronal apoptosis. Purpose: The aim of this study was to evaluate the effects of MDPV on the human dopaminergic cell line SH-SY5Y. Experimental design: After 24 hour exposure to MDPV (100 μM to 2.5 mM), cytotoxicity, cellular proliferation, and apoptosis were evaluated, whereas reactive oxygen species (ROS) production was evaluated at 2, 4, 6, 22 and 24 hours. Results: MDPV increased ROS production after 1, 4 and 6 hours of exposure in all but the highest concentration; a moderate increase was observed at 22 and 24 hours. Only high concentrations of the drug decreased cellular proliferation, and induced apoptosis and necrosis. Conclusion: MDPV induces dopaminergic toxicity by decreasing cellular proliferation and by increasing apoptosis and necrosis. The production of ROS may play a role in the early response to the drug.

48. Effects of enrıched envıronment and memantıne on naloxone precıpıtated morphıne-abstınence syndrome ın rats.

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Present study was designed to understand more the possible roles of synaptic plasticity and glutamatergic system in development of morphine (MOR) dependence.
Young male Wistar-Albino rats were used in the experiments. While some of the animals were kept for one month in enriched-environment (EE) for the development of synaptic plasticity, some animals were kept in standard-environment (SE). Later, all animals were rendered dependent on MOR by MOR (150 mg) pellets placed under the back skin. Control group received placebo pellets. Seventy-two hours after pellet implantation, the opiate antagonist naloxone (NAL) (1 mg/kg, i.p.) was administered to generate MOR-abstinence syndrome. Saline or memantine (MEM) (10 mg/kg i.p.), the antagonist of N-methyl-D-aspartic acid class of glutamatergic receptor subtype were administered prior to NAL administration. Each animal was immediately taken to the observation cage after NAL injection and the signs of MOR-abstinence were recorded for 15 minutes. Body weights were measured before and after MOR-abstinence syndrome. Immediately after this, animals were decapitated and hippocampi of animals were removed for the analysis of mRNA of tissue plasminogen activator (tPA) which was deemed to be one of the synaptic plasticity indicators. Statistical analysis was made using Mann-Whitney U test and Student's t test whenever appropriate. MEM-group exhibited statistically significant reduction in teeth-chattering, ptosis, diarrhea, weight loss. In the EE-group, jumping, teeth-chattering, locomotor-activity, diarrhea, weight loss were slightly more developed without statistical significance. The levels of hippocampal tPA mRNA expression during MOR-abstinence were found to be close to each other in SE and EE groups while it was significantly lower in MOR-abstinence group than placebo group. Findings suggest that the glutamatergic system may have an important role in MOR-dependence mechanisms, the involvement of glutamatergic system and synaptic plasticity with tPA change in the development of MOR dependence require further investigation.

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49. Role of nitric oxide in prenatal effects of caffeine

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Energy drinks are non-alcoholic beverages that typically contain high levels of caffeine and sugar in combination with other ingredients known to have stimulant properties. Despite the growing energy drinks market and media reports of serious adverse events associated with their consumption, research into their use and effects has been sparse. The number of women who use stimulant drugs during pregnancy, including caffeine also increases from year to year. There are data that the prenatal effect of psychostimulants could lead to delay in development and behavioral disorders in their offspring. It is well known that the neurophysiological effects of caffeine depend on the dose of the drug, as well as the period of its administration. However, mechanisms by which caffeine could influence the brain development are still not well established. Moreover, if the involvement of adenosine brain receptors in the mechanisms of caffeine action has been studied in sufficient details, its possible interaction with other neurotransmitter systems has not been investigated enough. Results of our group and other works have led to the hypothesis that neurophysiological effects of psychostimulant drugs are mediated by free radicals. The purpose of this study was to investigate the role of nitric oxide (NO) in the prenatal effects of caffeine. Experiments were performed using male Wistar rats, originating from pregnant female rats. Pregnant dams received solution of caffeine (1g/L) or water as the sole source of fluid during all their gestation period. In our experiments it was established that NO levels were decreased in the brain of both groups of juvenile male rats (received caffeine or water) on first 4 postnatal days in comparison with that of adult rats. NO generation was lower in the brain of juvenile male rats received caffeine on postnatal day 2 and 3 but not 4, as compared with control animals. No major difference in physiological characteristics of juvenile male rats admitted prenatally by caffeine or water was observed. Long-term consumption of caffeine by female rats during pregnancy led to an increase in locomotor activity as well as to hypoalgesia in their offspring. In the water-maze test major difference in acquisition of the platform location in the water-maze test was observed between juvenile male rats received caffeine during pregnancy and juvenile male rats received water. This fact might indicate that the spatial memory of the experimental group is better developing than in the control group of animals. In summary, we can conclude that the nitrergic system of the brain is involved in prenatal effects of caffeine in rats. The work was supported by RFBR grant 16-04-00722.

50. Effects of exposure to cannabinoid agonist WIN 55,212-2 on alcohol preference and anxiety in early adolescent CD1 mice.

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The endocannabinoid system (eCB) is involved in the modulation of the reward system and participates in the reinforcing effects of different drugs of abuse, including alcohol. The most abundant receptor of the eCB system in the nervous central system is the CB1 receptor (CB1R), which is predominantly expressed in areas involved in drug addiction, such as the nucleus accumbens, the ventral tegmental area (VTA), the substantia nigra and the raphe nucleus. CB1R is expressed in early stages during development and reaches maximum levels during early adolescence. In order to analyze the participation of the eCB system in ethanol (EtOH) preference during adolescent development, adolescent mice were exposed to cannabinoid agonist WIN 55,212-2 for 5 consecutive days. EtOH preference was measured throughout adolescence, and anxiety tests and morphological studies were performed the day after treatment with WIN 55,212-2 finished. Although no statistically significant differences were found in the consumption and preference of EtOH between the groups, mice exposed to WIN exhibited a tendency to higher EtOH preference through the assay. In addition, there was an anxiogenic effect of WIN exposure. Histological analysis through Golgi staining revealed higher dendritic ramifications and fewer dendritic spines in neurons of the subsantia nigra, but no differences in hippocampal neurons. Immunohistochemical analysis of dopaminergic neurons revealed no differences in the expression of tyrosine hydroxylase or the number of dopaminergic neurons in tegmental ventral area and substantia nigra. Nevertheless, analyses of serotonergic neurons in dorsal raphe nucleus show an increase in tryptophan hydroxylase-expressing neurons after WIN exposure during early adolescence.

51. CB1 knock-out mice present changes in neuronal cytoarchitecture which correlate with behavior alterations

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Cannabinoid receptor type 1 (CB1R) is widely distributed in the central nervous system and is involved in processes such as memory, learning, anxiety and mood. Genetic deletion of CB1R causes behavioral alterations similar to those described in animal models of depression but the morphological substrate of this behavior is not fully known. The aim of this work is to analyze cytoskeletal organization in axons and dendrites, ultrastructural synaptic contact and the serotonergic system in CB1R knock-out mice ($CB1R^{-/-}$). $CB1R^{-/-}$ mice showed a decrease in the expression of neuronal cytoskeleton components (Nf-160kDa, Nf-200kDa and MAP-2) and a reduction in the number of primary projections. In addition, results showed a decrease in Synaptophysin expression and an increasing tendency in the number of vesicles in the synaptic terminal in $CB1R^{-/-}$ mice. The number of synapses was not affected but the postsynaptic density thickness was reduced. Tryptophan hydroxylase was increased in the dorsal raphe nucleus, without changes in serotonin expression. Serotonin receptor type 1a expression was increased in CA1 hippocampal area. The absence of CB1R alters neuroal architecture affecting synaptic plasticity and modeling. Such changes might correlate with reported changes in the behavior of $CB1R^{-/-}$ mice. UBACYT 20020130100258BA, UBACYT 20020130300033BA, PIP 2013-2015 0269CO

52. Early changes in microRNA expression following morphine dependence and SIV infection portends chronic inflammatory events

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Opiate abuse and HIV-1 infection are often intertwined and manifest as enhanced neuroinflammation and cognitive deficits. Using the morphine-dependent Simian Immunodeficiency Virus (SIV) macaque model, we previously demonstrated augmented disease progression and neuroinflammation compared to non-dependent SIV controls over a chronic course of infection. As a mechanism of morphine-mediated enhanced disease progression, we sought to examine the rapidly evolving field of microRNA (miR)-mediated regulation of immune activation and disease progression. Herein, we asked the question of whether early changes in microRNA expression profiles in response to acute 3 week SIV infection and 15 weeks of morphine exposure would impact the chronic stage of infection. In particular, we hypothesized that early microRNA changes in the periphery may lead to reciprocal changes in the central nervous system. We performed a comprehensive microarray analysis of miRNAs from both peripheral blood mononuclear cells (PBMCs) and basal ganglia (BG) isolated from all macaques enrolled in this study (saline, morphine, SIV, SIV+morphine). Following assessment by Ingenuity Pathway Analysis (IPA), the most significant functional classes affected pertain to inflammatory, neurological and cardiovascular disease. Lending credence to our hypothesis, there were abundantly more differentially expressed microRNAs (Signal >500; P<=0.01) in PBMCs compared to BG (36 vs 15) alluding to early changes in the periphery leading to future changes in the CNS. Interestingly, miR-29b which we previously found upregulated in PBMCs and BG from our chronic study was also upregulated in PBMCs and BG of morphine and/or acute SIV macaques compared to saline controls. This finding was confirmed by qPCR validation. Mir-29b has been shown to be involved in inflammation and is also upregulated in other neurodegenerative diseases. TargetScan analyses indicated that one target of miR-29b is platelet-derived growth factor (PDGF) which among its many functions, it is critical for neuronal survival. In our chronic study, we revealed that PDGF is downregulated in the BG of morphine-dependent SIV-infected macaques compared to non-dependent, infected animals. In conclusion, herein we show that both morphine dependence and/or SIV infection lead to early changes in microRNA expression profiles in both the periphery and CNS with most occurring in the former, and these changes promote the smoldering inflammation found in the chronic stages of infection and addiction.

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53. Cannabinoid type 2 receptors in brain dopamine neurons modulates anxiety-like and psychostimulant behaviors in floxed DAT-Cnr2 mouse model

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The functional neuronal expression of CB2 cannabinoid receptors has been a subject of controversy and debate and had been referred to as a "sphinx" wrapped in a mystery with "identity crisis". This is because research activities from our lab and those of others have found and reported that CB2Rs are expressed in the mammalian brain and functionally involved in several dopamine (DA)-related and other CNS disorders including drug addiction in rodent models. Therefore, manipulation of CB_2R in mouse models is of critical importance in characterizing the molecular basis of CB_2R neuronal signaling mechanisms. The two available CB2R gene knockout mice contain partial *Cnr2* gene deletion at C- and N- terminal amino acid sequences and residues of CB2R activities might remain. Furthermore, these germline knockout mice in which the CB2R function could be compromised by developmental compensation are not suitable for tissue- and cell-type specific studies at molecular, pharmacological and behavioral levels. Therefore, we have generated *Cnr2*-floxed mice that were crossed with DAT-*Cre* mice, in which the Cre recombinase expression is under DAT (dopamine transporter) gene promoter control, to generate conditional CB2-KO mice in midbrain DA neurons in DAT-*Cre*-*Cnr2*-Lox transgenic mice. By using a novel highly-sensitive RNAscope *in situ* hybridization method, we detected clear CB2R mRNA expression in VTA DA neurons in Dat-heterozygous and wildtype control mice, but not in conditional CB2-KO mice, suggesting neuronal CB2R gene expression in VTA DA neurons. The performance of the conditional DAT-*Cnr2* mutant mice were determined in motor function and emotionality tests in comparison to wild type controls. We report that in the motor function test using the spontaneous wheel running monitors, DAT-*Cre*-*Cnr2* homozygous mice were more responsive to cocaine induced motor activity than heterozygous and wild type mice. In the plus maze test of aversive behavior, DAT-*Cre*-*Cnr2* homozygous mice were less aversive to the open arms of the maze than the heterozygous and the wild type mice. We conclude that CB2R in dopaminergic neurons plays a role in modulating anxiety-like and psychostimulant motor behaviors in mice.

54. Low dose ethanol modulates gene expression in the brain of rats during endotoxin tolerance

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Previous study have shown that following exposure to two low doses (250 ug/kg) of lipopolysaccharide (LPS), rats develop tolerance in elevation of inflammatory cytokines in blood circulation in response to a high dose (32 mg/kg) of LPS. However, the cytokine levels in the brain remain elevated during endotoxin tolerance (ET). Moderate drinking appear to be heath beneficial. In the present study, we examine if treatment with low dose ethanol (EtOH) can modulate gene regulation in the brain of rats during ET. Male F344 rats (7-8 wks) were used and randomly divided into 4 groups, named as Saline+Water, Saline+EtOH, LPS+Water and LPS+EtOH. All rats were treated with LPS (progressively from 250 μg/kg, 500 μg/kg, 1 mg/kg, 2 mg/kg, 4 mg/kg, 8 mg/kg, 16 mg/kg to 32 mg/kg), and/or 16% w/v, 1g/kg/d EtOH for 13 days. Before and after treatment, the locomotor activity (LMA) was recored. At the end of treatment and LMA assessment, three brain regions, including prefrontal contex (PFC), nucleus accumbens (NAc) and striatum (STR), were collected for gene expression analysis. Sixty-eight genes from dopamine (DA) receptors, GABA-A receptors, serotonin receptors (Htr), glutamate receptors (Gr), glutamate receptor ionotropic NMDA (Grin), cholinergic (Ch) receptors, and immune-related genes were examined using real-time PCR Array. The LMA data showed that treatment with LPS decreased total distance and time mobile. Treatment with EtOH did not change these readings in either group given LPS or saline. Gene expression analysis showed that Interleukin 1 alpha (IL-1α), IL-6, IL-11, types 1 and 2 receptors of IL-1 (IL-1r1 and IL-1r2), Cyclin Dependent Kinase (CDK) and Tumor Necrosis Factor (TNF) were significantly upregulated, in contrast, DNA methyltransferase 3b (DNMT3b), Dopamine D4 Receptor gene (DRD4), Solute Carrier family 6 member 2 (SLC6A2) and IL-16 were significantly decreased in LPS group. The expression of IL-1α, IL-1β, IL-1r1, IL-1r2 were upregulated in all three brain areas. Treatment with EtOH partially reversed the LPS effects. However, in NAc, LPS increased IL-1β(29-fold increase) and EtOH further upregulated (40-fold increase). These data demonstrated differential modulation of low dose of EtOH on gene expression in the PFC, NAc and STR of rats during ET.

55. Transcriptional and epigenetic modulations of the endocannabinoid system following cocaine self-administration

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Drug addiction is a complex pathology inducing a long-term neuroplasticity. Although many individuals are exposed to drugs of abuse, only a subset experience the loss of control over drug use and compulsion for drug seeking and taking that defines the addicted state. In 2014, 3.6 million Europeans consumed cocaine which makes this drug the second most consumed drug in Europe. Thus, understanding the neurochemical mechanisms underlying the reinforcing effects of drugs of abuse is critical for reducing the burden of drug addiction in society.
The endogenous cannabinoid system (ECS) comprises lipid modulators (endocannabinoids), enzymes for their synthesis and degradation and two well characterized receptors, CB1 and CB2, which are GPCR coupled to Gi/Go proteins. This system is involved in the modulation of drug reward, in particular in cocaine addiction.
Among the neurobiological mechanisms involved in addictive behaviors, epigenetic processes are emerging as crucial mediators of the long-term adaptations produced by drugs of abuse. In particular, DNA methylation and histone modifications are epigenetic process which regulates the accessibility of genes to the transcriptional machinery. Using a genome-wide methylation analysis in the prefrontal cortex of rats self-administering cocaine, we examined DNA methylation in the Prefrontal Cortex (PfC) in cocaine self-administering rats (Fonteneau et al, 2016) and identified differentially methylated regions in genes of the cannabinoid system. We therefore explored transcriptional regulations induced by cocaine self-administration in brain regions related to reward circuits, including striatum, prefrontal cortex, hippocampus and amygdala. We observed strong gene regulations in the hippocampus. Using a chromatin immunoprecipitation – qPCR approach, we further explored whether these genes could be regulated by the histone modifications H3K4Me3 and H3K27Ac. We also explored functional regulation of CB1 receptor activities in the dorsal striatum, PfC and hippocampus. We will further investigate whether cocaine-induced modifications of the endocannabinoid system involve DNA methylation. Our study will bring new insights on the neuroadaptive processes leading to cocaine dependence and the involvement of the ECS in addiction.

56. Ketamine and NBQX both normalize alcohol-withdrawal induced depressive-like characteristics in rats.

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One of the hallmarks of alcohol use disorder (AUD) is negative affect (dark side) manifested during withdrawal. Recently, the glutamatergic system has been identified as a potential novel target for intervention in AUD. Thus, the current study was designed to evaluate the effects of chronic administration of sub-anesthetic doses of ketamine, an NMDA receptor antagonist, as well as NBQX (2,3-dihydroxy-6-nitro-7-sulfamoylbenzo (f) quinoxaline), an AMPA/kainate receptor antagonist on depressive-like behaviors following withdrawal from chronic intermittent exposure to alcohol vapor. Adult male Wistar rats were exposed to ethanol (EtOH) via inhalation chambers daily (3 h/day) for 7 days, such that a blood alcohol concentration of approximately 150 mg% was achieved during each exposure. This was followed daily by intraperitoneal (IP) injections of either ketamine (2.5mg/kg), NBQX (5mg/kg) or their combination. Approximately 18 h after drug treatment, 5 min open field locomotor activity (OFLA) followed immediately by 5 min forced swim test (FST) was performed. Alcohol withdrawal resulted in an increase in OFLA, but a decrease in swimming in FST, suggesting induction of helplessness in these animals. Ketamine had no effect on OFLA following alcohol withdrawal, but normalized the swimming score in the FST. NBQX attenuated alcohol-withdrawal induced increase in OFLA and like ketamine, normalized the swimming score in FST. The combination of the two drugs, however, not only did not result in any additive effect, but actually had no significant effect on either OFLA or swimming score in FST. These results suggest that both ketamine and NBQX alone, in low doses, may normalize alcohol-withdrawal induced depressive-like characteristics. Thus, glutamatergic receptor manipulation, specifically antagonism of the NMDA or AMPA/kainate receptors may be of therapeutic potential in 'the dark side' of AUD. We are currently investigating possible neurochemical substrates of alcohol-withdrawal induced depressive-like behavior by examining the role of neurotrophic as well inflammatory mediators in discrete brain areas. The findings on the mechanism of action of the drugs will also be presented at the meeting.
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57. Trace amine-associated receptor 1(TAAR) modulates thermal and neurotoxic responses to methamphetamine

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The trace amine-associated receptor 1 (TAAR1) is a G protein-coupled receptor (GPCR) that inhibits dopamine (DA) neuron firing when activated. Methamphetamine (MA) neurotoxicity causes numerous cognitive and physical impairments and is correlated with increased DA neuron firing. Sensitivity to the acute effects of amphetamines is altered when TAAR1 is absent, but the role of TAAR1 on the sustained effects of MA has yet to be elucidated. To investigate the regulatory role of TAAR1 on MA-induced thermoregulation and neurotoxicity, *Taar1* genetic knockout (KO) mice lacking TAAR1 were compared to wildtype (WT) mice. Animals were administered a binge-like dose regimen: 4 i.p. injections, 2 hr apart, of saline or MA (2.5, 5, or 10 mg/kg). Temperature data were recorded *via* radio telemetry and striatal tissue collected 2 or 7 days later for analysis of monoamines and metabolites: DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), serotonin (5HT), 5-hydroxyindoleactic acid (5HIAA), and norepinephrine (NE), as well as tyrosine hydroxylase and glial fibrillary acidic protein (GFAP) expression. MA elicited an acute hypothermic drop in body temperature in *Taar1*-WT mice that was more pronounced at the two lower doses of MA. This hypothermia was significantly attenuated in *Taar1*-KO mice by all MA doses. MA dose-dependently decreased DA and DOPAC levels 2 days following administration and DA levels were lower in *Taar1*-KO compared to -WT mice, regardless of treatment. Seven days later, DA levels were significantly decreased by MA 2.5 and 5 mg/kg in *Taar1*-KO compared to -WT mice, while DOPAC and HVA were lower in *Taar1*-KO compared to -WT mice, regardless of treatment. TH levels were decreased in *Taar1*-KO compared to –WT mice 2 days later, regardless of treatment, though there were no differences between genotype after 7 days. Two and 7 days later, GFAP expression was increased by all doses of MA, and significantly increased by MA 2.5 and 5 mg/kg in *Taar1*-KO compared to -WT mice. There was no effect of genotype on 5HT, 5HIAA, or NE, indicating the regulatory role of TAAR1 on sustained effects of MA is DA-specific. These results demonstrate TAAR1 activation is necessary for MA-induced hypothermia. Additionally, absence of TAAR1 increases sensitivity to MA-induced neurotoxicity, indicating that activation of TAAR1 confers neuroprotection, potentially attributed to TAAR1-mediated acute hypothermia.

David K. Grandy provided *Taar1* transgenic breeders.

58. Epigallocatechin-3-gallate mitigates methamphetamine-induced dopamine terminal damage by preventing oxidative stress and activating glial cells in mouse striatum

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Methamphetamine (METH) is an illicit drug that induces oxidative stress in the brain causing dopamine terminal damage and promoting glial activation. Although mechanisms involved in the METH-induced neuronal damage have been extensively studied in the past two decades, there is still no therapeutic treatment for METH-induced neuronal injury. Previously, our lab has demonstrated that epigallocatechin-3-gallate (EGCG), the polyphenol found in green tea extract, effectively prevented the METH-induced striatal tyrosine hydroxylase reduction and apoptosis. In the present study, we examined the neuroprotective effects of EGCG on METH-induced glial cell activation and oxidative stress in striatal tissue. CD-1 mice received 2 mg/kg of EGCG via intraperitoneal injection (i.p.) 30 minutes prior to METH (30 mg/kg, i.p. injection) and sacrificed at different time points for quantitative analysis. Immunohistochemical staining and Western blots were used to evaluate the changes of microglia and astrocytes in the striatum. Quantitative analysis of reactive microglia revealed that injection of EGCG prior to METH administration significantly potentiated the METH-induced microglial activation in the striatum 24 hours after METH injection. In addition, western blots demonstrated that EGCG also potentiated METH-induced activation of astrocytes, as well as preventing METH-induced tyrosine hydroxylase and glutathione peroxidase reduction. These observations raise the possibility that EGCG mitigates METH-induced dopamine terminal damage by preventing oxidative stress and activating glial cells. (Supported by grant 8 G12 MD007599 from the National Institute on Minority Health and Health Disparities, NIH)

59. **Liquid Chromatography Mass Spectrometry analysis of dialysate samples from rat brain following repeated administration of MDMA**

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Current methods for the measurement and analysis of neurochemical samples collected via *in vivo* microdialysis are inadequate for identifying the myriad of changes in the brain that might be relevant to drug addiction since they require *a priori* hypotheses concerning what neurochemical might be of interest. An analytical procedure that provides a more complete picture of the neuroadaptations that occur as a result of compulsive drug use and provides the means for identifying novel and/or unexpected brain changes would be of great value in regards to the development of new treatments for drug addiction. To achieve this goal, we have been advancing an innovative procedure that utilises *in vivo* microdialysis and Liquid Chromatography Mass Spectrometry (LCMS) with an untargeted metabolomics approach. Microdialysis samples are collected from rats during a behavioural test (sensitisation, drug seeking etc.) following repeated exposure to drugs of abuse. Samples are derivitised and analysed using LCMS. Quantification of several targeted neurotransmitters such as dopamine or serotonin can be carried out simultaneously, whilst untargeted metabolomics analysis allows for the systematic profiling of all neurochemicals within the samples. Neurochemicals that are influenced by repeated drug exposure can be identified and the extent to which these neurochemicals correlate with behaviour (locomotor activity, drug-seeking) can be determined. Preliminary results collected from rats following repeated exposure to MDMA and the methods taken to develop these procedures will be presented.

60. Evidence of opioid dependence via self-administered vaporized fentanyl and analogues in rats

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Opioid dependence is a major public health issue. Inhalation and intravenous injection are the preferred routes of drug administration in experienced opioid users. In preclinical studies, intravenous drug self-administration has been the most commonly used model of opioid dependence, whereas very few studies have used the inhalation route. Here, we present a novel preclinical model of opioid self-administration by inhalation that uses an electronic cigarette technology and does not involve surgeries. Rats trained to nosepoke to obtain 10 s of vaporized fentanyl or sufentanil, two potent synthetic opioids, exhibited a concentration-dependent, μ-opioid receptor-mediated, pattern of drug self-administration. Rats given long access (LgA; 12 h/day), but not short access (ShA; 1 h/day), to vaporized fentanyl or sufentanil escalated their drug intake over time. Compared with ShA rats, LgA rats exhibited somatic signs of opioid withdrawal and withdrawal-induced mechanical hypersensitivity. These findings support the utility of opioid vapor self-administration for investigating the neurobiological basis of opioid addiction.
NIH/NIDA – IRP/INRB

61. Negative Effects of Drugs of Abuse in Male and Female Fertility

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Both men and women should consider limiting or better stopping to smoke, drink or take unnecessary drugs, especially drugs of abuse if they are planning to have babies since these habits will affect not only their chances of achieving pregnancy but also the developmental health of the offspring. This is due to the toxic effects either directly on the sperm and the oocyte but also indirect effects on the endocrine system and other systems involved in successful reproduction, such as libido, erectile function, fallopian tube motility and uterus function. The abuse of anabolic-androgenic steroids, marijuana, cocaine, methamphetamines, and opiotes have been reported to reduce male fertility, possibly through negative effects on the hypothalamic-pituitary-gonadal axis (HPG), sperm function, and testicular structure. (review Fronczak et al 2012). In case of men there is a possibility of recovery after 2 or 3 months of abstinence, especially for sperm quality since new sperm are formed at a high rate and the HPG system may normalize. The situation is different in women since they are born with a fixed number of eggs and these can be directly and irreversibly damaged in the ovaries. The process of ovulation may also be compromised by negative effects on the hypothalamo-pituitary-ovarian (HPO) axis. For example marijuana affects female fertility by inhibiting ovulation by reducing levels of luteinising hormone (LH) needed for ovulation and by slowing movement of the egg through the oviduct and preventing implantation in the uterus. Cocaine use has been shown to cause tubal abnormality. In mice oocyte maturation and fertility rate was negatively affected by ecstacy. Damage to the sperm or oocyte increases the risk of premature babies, low birth weight, and developmental delays and disorders, and even pregnancy loss. This could be due to the damage to the genome and mitochondria in sperm and oocyte as well as other systems of the body, especially the neuroendocrine pathways.

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