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Meeting Abstracts
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Keynote Speakers

"Reward Deficiency Solution System" to Overcome the Opiate/Opioid Epidemic Worldwide

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Abstract

The Brain Reward Cascade (BRC) is a dopamine control interaction between neurotransmitters and genes. Any variations in BRC may cause addictive behaviors. Albeit our Reward Deficiency Syndrome (RDS) bias, we discuss facts and fictions behind molecular genetic testing in RDS and Genetic Addiction Risk Score (GARS), which predicts genetic risk for RDS. Legal opioid iatrogenic induced prescription drug abuse is a global endemic. Understanding pain pathways and dopaminergic tone in pain relief provides therapeutic solutions. In 2011, NIDA reported 8.7% of Americans >12 years have used psychoactive drugs within the past month. The CDC reports 127 Americans die daily from narcotic overdoses. Unfortunately, this has now (2017) translated to a 300% increase in American seeking treatment for opioid dependence since 2000. The overall genetic contribution to the variance of Substance Use Disorder (SUD) is about 50%, whereby the other 50% is epigenetic. However, each candidate gene evaluated by GWAS is relatively small. Research evidence is supportive of the candidate gene approach termed "GARS" which may have important benefits in not only RDS but Posttraumatic Stress Disorder (PTSD) and dissection of "Cultural Diversity". We propose alternative strategies to combat this endemic. Pain control and sensitivity may reside in other neurological loci, particularly the mesolimbic system (reward center), and several genes and polymorphisms may impact pain tolerance and/or sensitivity. We hypothesize pharmacogenetic/pharmacogenomic testing of candidate genes will result in personalized pharmacogenomic solutions. We are hereby proposing "Reward Deficiency Solutions System" [GARS, Comprehensive Analysis of Reported Drugs (CARD), Pro dopamine Regulation (KB220) and mRNA profiling] to overcome the opiate/opioid epidemic in America and across the globe. This novel approach based on "*Neuro-Psychosocial- Genomic [NPSG]*" evidence with required research may lead us to the promised - land.

Management of Epidemic of Opioid Use-HCV Infection in IDUs

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Abstract

Recent epidemic of opiate use and associated viral hepatitis C virus (HCV) infection associated morbidity and mortality has been one of the most devastating events in the US. An estimated 153-300 million people abuse illegal drugs regularly worldwide and globally around 16 million people inject drugs. Of the 20.5 million Americans 12 or older that had a substance use disorder in 2015, 2 million involved prescription pain relievers, and 591,000 involved heroin use. An estimated 23% of heroin users develop opioid addiction. In 2015, there were 52,404 deaths from drug overdose, 20,101 deaths were related to prescription pain relievers, and 12,990 were related to heroin overdose. In addition, an estimated 153 million people are living with viral hepatitis C infection worldwide of which an estimated 4 million are living in the US. Injection drug use is a major

vector in transmission of HCV infection. Up to 60% IDUs may be infected with HCV infection, while up to 90% of IDUs infected with HIV may be co-infected with HCV infection. HCV infection is a serious blood-borne infection that causes liver cirrhosis, liver cancer and death. If untreated, up to 10% of HCV infected people may die from liver cancer each year. In 2007, confirmed in 2014, more people died from HCV-associated complications than from those of HIV/AIDS. In an emerging epidemic of opioid use, recent reports in the US have reported increases in HCV infection among young, 18-25 year-old, non-urban IDUs in most US states. Increases in incident HCV infections among young injectors who've recently transitioned from oral opioid abuse present an important public health challenge requiring a comprehensive, community-based response. This lecture will discuss various aspects of substance abuse and co-occurring infections including clinical management of substance use disorder, the most current medical interventions for HCV infection with directly acting antivirals (DAAs), new research being funded by NIDA/NIH, and funding opportunities available at NIH.

Euphoria and Anhedonia: Dual Disorders in Addiction Medicine, Chicken and/or the Egg

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Abstract

We have worked in addiction medicine, addiction psychiatry and translational addiction research since the 1970s. Though most of Dr. Gold's work has focused on the neurobiology of opioids, cocaine, tobacco, and sugar we have reported on the importance of co-occurring diseases in addiction evaluation, treatment, and outcomes. Gold, in the late 70s reported drug related mood and psychotic illness which persisted far after the offending drug was cleared from the brain and body. More recently, our Group reported on opioids, methamphetamine, and cocaine related neurotoxicity. We also been interested in and reported on host vulnerabilities to addiction. Clinically, addiction medicine experts have argued the causes of low dose vulnerabilities to drugs of abuse, diversity in drug effects and addiction liability. Drugs of abuse may be especially compelling for people who bring to their drug challenge dopamine deficiency or abnormalities associated with RDS. However, it may be more common and likely for drugs of abuse by targeting the brain's reinforcement and pleasure pathways to compromise and undermine them and induce a RDS which becomes evident when drug use is discontinued. Depression causes makes drug use more likely and compelling. But, it commonly can and does occur, post tobacco, alcohol and drug discontinuation. Depression and anhedonia have been ignored as addiction evaluation and treatment has tended to occur in non-psychiatric treatment programs and without Psychiatrists. This may be a backlash to the self – medication hypothesis proposed by the Psychiatrists and vilified by 12 step and other addiction programs who wanted it to be clear that addiction was a primary and progressive disease and that treating the depression and hoping that the addiction would disappear was a dangerous practice. Still, anhedonia, depression, sleep and appetite abnormalities persist post successful detoxification and treatment. Often, they are neither diagnosed nor treated even though failure to treat co-occurring psychiatric disease makes substance use disorder relapse more likely. We discuss the chicken or egg dichotomy in current thinking regarding depression and substance use disorders, evidence for drug induced RDS, role of Psychiatry and Psychiatrists in evaluation and treatment.

Rescue by Naloxone: On the Front Lines of the Opioid Epidemic

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Abstract

The magnitude of the current opioid epidemic is startling: it has been estimated that more than 4% of the adult population (>10 million Americans) currently misuse opioids. Perhaps its' most visible manifestation is the rising number of overdose deaths, estimated at more than 33,000 in 2015. While most overdoses are attributable to prescription opioids, heroin and fentanyl, less expensive and often more available, have now become the focus of national attention. Thus, overdose deaths due to heroin increased by more than 20% between 2014 and 2015, while overdose deaths attributable to synthetics like fentanyl increased by more than 72%.

Parenteral naloxone has been approved to treat opioid overdose for over 45 years. Beginning in the late 1990s, there have been efforts, led principally by the harm reduction community, to distribute improvised intranasal naloxone "kits" and overdose training materials to first responders, including potential bystanders. Many successful rescues have been reported with these

improvised kits, but both the peer reviewed and patent literature suggest that these kits produce plasma concentrations well below those attained using the minimum recommended (0.4 mg) parenteral dose of naloxone. Beginning in 2014, the FDA approved multiple naloxone products to treat opiate overdose, including an auto-injector and an intranasal device that can be used with no prior training. In this presentation, I will describe the pharmacokinetic properties and human use characteristics of an FDA approved intranasal naloxone device developed by the National Institute on Drug Abuse in collaboration with the pharmaceutical sector.

The Neural Correlates of Reward Processing in Behavioral and Drug Addictions

Marc N. Potenza

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Abstract

Behavioral or non-substance addictions have been proposed and given the classification of gambling disorder together with substance-use disorders in DSM-5, this concept has gained significant support. One aspect linking substance and behavioral addictions involves reward processing. From a clinical perspective, individuals with addictions are motivated to pursue behaviors related to the focus of the addiction (drugs in drug-use disorder, gambling in gambling disorder) to the extent of not pursuing other behaviors (occupational, familial) that are typically rewarding for non-addicted individuals. This presentation will focus on neural data supporting abnormalities in reward processing in individuals with gambling disorder. Results from fMRI studies of gambling urges, monetary processing, and gambling-related rewards (during loss chasing and simulated slot-machine gambling) will be presented. Additionally, results from studies of Internet gaming disorder will be presented, particularly given the recognition of Internet gaming disorder in section 3 of the DSM-5 and the possible/likely inclusion of gaming disorder in ICD-11. Findings will be placed into the larger literature of results from other studies investigating reward processing in individuals with addictions.

Whole-Brain Dissection of Cell-Type Specific, Behaviorally-Relevant Brain Circuits

Mike Michaelides

NIDA-IRP, MD, USA

Abstract

Our laboratory implements molecular imaging approaches integrated alongside neuromodulation, molecular, pharmacological, transgenic, and bioinformatic methods for identifying behaviorally-relevant neurobiological mechanisms associated with normal behavior or disease. Special emphasis is placed on reverse-translating findings from clinical research to animals. In addition, clinical relevance of mechanisms studied in animals is determined in humans via bioinformatic, genetic and postmortem tissue examination.

Addiction Prevalence and Co-occurrence: Is there an Addiction "Class"?

Steve Sussman

University of Southern California, CA, USA

Abstract

Dr. Sussman will summarize the results of five studies that explore 11 substance and behavioral addictions (cigarettes/tobacco, alcohol, illicit/other drugs, food, gambling, internet, love, sex, shopping, work, and exercise) on their relative prevalence and co-occurrence. Using an addiction matrix item and latent class analysis, he suggests the existence of an addiction class of subjects and a non-addiction class of subjects. While arguing that addictions are due in part to lifestyle factors that disrupt appetitive motivation processes (e.g., access and stress), which may account for a rather high prevalence in the population, the existence of an addiction class among one-third of teen and emerging adult subjects in the U.S., Spain, and Russia suggests that there may be an underlying vulnerability factor as well (e.g., reward deficiency).

The Impact of Pharmacogenomic Testing on Buprenorphine Dosing for Opioid Use Disorder (OUD) Management in an African-American Population

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Abstract

Buprenorphine, a partial mu-opioid agonist, is considered by many as a safe and effective option for the management of opioid use disorder (OUD). However, dosing limitations imposed by insurance plans can limit the effectiveness of OUD management. For example, Massachusetts imposed a limit of 16 mg of buprenorphine daily. This dosing limitation resulted in (1) marginal savings, (2) questionable diversion reduction, and (3) increased relapse in previously stable patients. These findings may indicate that: (1) the optimal dose for office-based buprenorphine is unknown and (2) buprenorphine daily dosages greater than 16 mg are more effective for some patients. In a collaborative effort between the Howard University National Human Genome Center (NHGC) and the Howard University College of Pharmacy (HUCOP), pharmacogenomic testing was provided to a predominantly African-American patient population receiving buprenorphine for OUD management. Buprenorphine is metabolized by the cytochrome P450 (CYP) enzymes CYP3A4 and CYP3A5. Genotyping 144 patients revealed that 85% of the population carried the CYP3A4*1B allele, which confers an accelerated rate of metabolism compared to the wild type CYP3A4*1 allele. Furthermore, it was found that 43% of the patient population exhibited the CYP3A4*1/*1B phenotype and 42% exhibited CYP3A4*1B/*1B phenotype. The literature indicates that CYP3A4*1B (-392A>G) has an allelic frequency of 2.9% in Caucasians and 35-67% in African–Americans. Due to the accelerated rate of metabolism conferred by the CYP3A4*1B allele, patients carrying this allele metabolize buprenorphine rapidly and are less likely to experience adverse effects from doses of buprenorphine exceeding 16 mg daily. Our data suggests that higher dosing of buprenorphine is necessary to reduce treatment failure in patients exhibiting the CYP3A4*1/*1B and CYP3A4*1B/*1B phenotypes. We are proposing routine pharmacogenomic testing to individualize buprenorphine dosing, reduce opioid recidivism, and improve opioid use disorder management.

Neuroimaging and the Reward Deficiency Syndrome

Rajendra Badgaiyan

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Abstract

Neuroimaging studies have made significant contribution to our understanding of the brain mechanisms that control human cognition and behavior. Using these techniques, several studies have been conducted to understand how the reward system is controlled. Most of these studies have used functional MRI technique to localize the brain areas involved in the processing. Neurotransmitters that process signals in these areas however have not been studied in the human brain, primarily because of the lack of a reliable technique to detect acutely released neurotransmitters in the live brain. Therefore, most of the concepts concerning role of neurotransmitters in reward processing were developed using data obtained in laboratory animals. These data however may not accurately reflect processing mechanisms in the human brain because the executive system has much greater control over cognition and behavior in the human brain than that in the animals. Therefore, to study neurotransmitters involved in the brain processing we developed a technique called single scan dynamic molecular imaging technique which allows detection, mapping, and measurement of neurotransmitters released acutely in the live human brain. Using this method, we studied dopamine release in patients with attention deficit hyperactive disorder (ADHD), which is a form of the reward deficiency syndrome. In these patients, we found a reduction in the amount of dopamine released at rest (tonic release) in the right caudate. We also found compensatory enhancement of the task-induced dopamine release (phasic release) in the same area. These observations suggest that the reward deficiency syndrome is associated with reduced tonic pool of striatal dopamine and clinical symptoms could be due to both, reduced tonic release or increased phasic release. Precise role of the increased phasic release in the expression of symptoms has not yet been fully understood but it has been shown that a high concentration of dopamine interferes with the processing of a variety of executive functions.

Translational Aspects of RDS for Clinicians Treating SUD

David Baron

Keck School of Medicine at USC, CA, USA

Abstract

Historically, translational medicine was described as the "bench to bedside" aspects of understanding and ultimately treating disease. The need to translate advances made in the lab to clinically relevant treatments was the bases of this concept. Research discoveries which did not impact clinical care became viewed by government funding agencies as less important than those which advanced clinical care. A large, well-funded NIH initiative established comprehensive translational programs at leading academic medical centers to promote this type of research (dubbed CTSI's). Expanding this model to include *molecules to main street*, incorporates molecular basic science research, to what it means to the public (not just patients and their families).

Blum and colleagues have conducted extensive research on the role of the reward system in the etiology of SUD's, and developed treatments to correct a core dopamine in balance (lack of homeostasis) resulting in cravings. This presentation will provide an overview of RDS-*molecules to main street*, research and implications for clinicians treating addictive disorders.

Reward Deficiency and Anti-reward Processes in Pathological Gambling

Igor Elman

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Abstract

Uncontrollable gambling is a mounting public health problem associated with devastating outcomes, including suicidality in up to 43% of the patients. However, little is known about the neurobiological mechanisms underlying this disorder while such knowledge may be vital for the development of successful therapeutic interventions. Drug addiction models have heuristic value in this regard as gambling disorder is classified among "Substance-Related and Addictive Disorders" in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Both drug and gambling addictions are characterized by decreased sensitivity to natural reinforcers and stress-like emotional states. In drug addiction, such symptomatology has been attributed to "reward deficiency" and "anti-reward" allostatic neuradaptations, respectively. The purpose of this talk is to highlight potential similarities between a behavioral addiction to gambling and chemical addictions along with reward deficiency- and anti-reward-type phenomena in patients diagnosed with pathological gambling (PG). To that end, I will present clinical data sets pertaining to: 1) reliable and temporally stable markers of neurological compromise, namely neurological soft signs and 2) psychosocial and post-traumatic stress symptomatology along with functional magnetic resonance imaging studies employing: 3) a low dose of infusion of intravenous yohimbine, an α2 receptor antagonist that induces physiological and psychological stress responses; 4) a wheel of fortune-type gambling task and 5) visual processing of rewarding images selected from the International Affective Picture System. Testable hypotheses and further research to unravel the primary versus secondary nature of the observed deficits will be highlighted along with role of the reward-enhancing behavioral and pharmacotherapeutic interventions within the addictions' treatment armamentarium. Because PG is a behavioral addiction wherein neural responses are not confounded by substance-induced neurotoxicity it may provide an ideal model for elucidating the basic neural mechanisms, diagnosis prevention and treatment of addictive disorders at large.

Applied fMRI Studies of Reward Processing in Addiction

Daniel Langleben

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Abstract

Numerous functional neuroimaging studies have shown changes in the salience of visual stimuli signaling reward in addicts. Specifically, stimuli (e.g. "cues") linked to one of more drug of choice generate greater response in the components of the mesocorticolimbic system than stimuli related to naturally rewarding or neutral items. However, several hurdles remain for this phenomenon to acquire clinical utility. They include the specificity of abnormal salience to the drug of choice, the anatomical pattern it invokes and its connection to clinical outcomes. We explored brain and behavioral response to images associated with

normal and abnormal reward in cohorts addicted to heroin, prescription opioids and nicotine. We found that brain response to drug- and other reward-related stimuli in individuals with opioid use disorder has utility in prediction of certain parameters of treatment adherence, is responsive to opioid antagonist treatment and may serve as a measure of social cognition. Albeit preliminary, these observations suggest several paths for translation of the large body of cue-reactivity in addiction to meaningful biomarkers.

Co-morbidity of Alcohol and Methamphetamine Exposure: Neurotoxic Effects on Dopamine in a Rat Model

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Abstract

Alcohol and methamphetamine (Meth) are often co-abused. Individually, both because neurotoxicity evidenced by long-term depletions of dopamine and serotonin but the consequences of their co-abuse are unknown. It was hypothesized that serial exposure to alcohol and Meth enhances the neurotoxicity produced by either drug alone. Male Sprague Dawley rats voluntarily drank 10% ethanol (EtOH) for 24-hr periods, every other day, for 4 weeks and then were exposed Meth. EtOH intake and preference increased over 4 weeks and EtOH drinking increased inflammation, marked by increases in serum and brain lipopolysaccharide (LPS), and brain cyclooxygenase-2 (COX2). Meth alone but not EtOH alone depleted dopamine and serotonin in the striatum. In contrast, serial exposure to EtOH followed by Meth depleted dopamine and serotonin in a manner that was greater than that produced by Meth itself suggesting a synergistic relationship between EtOH and Meth. Moreover, the ability of EtOH to enhance Meth-induced neurotransmitter depletions in the striatum was dependent on the amount of EtOH that was consumed. Administration of the COX inhibitor, ketoprofen during EtOH drinking did not alter EtOH intake but prevented the increases in LPS and COX2 and the subsequent enhancement of dopamine and serotonin depletions in the striatum produced by Meth. The behavioral consequences of the enhanced striatal dopamine depletions were revealed by motor deficits measured by performance in the roto-rod test. These deficits were also prevented by ketoprofen administration during EtOH drinking. Overall, these results support a role for inflammation in mediating the synergistic effects of EtOH and Meth.

Network Analysis Distinguishes Short and Prolonged Functional Changes Caused by Potent 'Bath Salt' Drug MDPV

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Abstract

The abuse of 'bath-salts' continues to be a mental health concern, as chemically-modified variants of these psychoactive drugs appear in worldwide trafficking markets. The bath salt drug 3,4-methylenedioxypyrovalerone (MDPV) produces psychostimulant actions that are at least 10 times more potent than cocaine. Its primary molecular mechanism involves the inhibition of transporter-mediated uptake of dopamine (DA) and norepinephrine. Clinical and toxicological reports indicate that human MDPV users may experience adverse behavioral and cognitive reactions. High doses of MDPV triggers a psychosis-like, excited delirium syndrome involving hyperthermia, cardiovascular agitation, mania, panic, confusion/cognitive impairment and violent behavior. Understanding the neural mechanisms mediating the adverse effects of MDPV may help curb the long-term outcomes of intoxication and shed light on neural mechanisms of drug-induced psychosis. Indeed, MDPV-induced excited delirium shares similarities with psychotic episodes seen in psychiatric conditions (e.g., positive symptoms of schizophrenia) and with use of other psycho-stimulant drugs. We used a functional connectomics-based strategy to assess brain network topology in MDPV-exposed rat brain. We provide the first evidence of the emergence of a Rich club network 24 h after MDPV. The

enhanced Rich club connections at 24 h were distinct from the effects of MDPV 1 h after exposure. Formation of this potently connected sub-network was associated with impaired social interaction and cognitive function and altered DAT protein density and distribution.

Featured Presentations

Ineffective Psychotropic Medications Continue to be Prescribed for Anorexia Nervosa

David M. Garner[1,2*], Michael L. Anderson[1], Christopher D. Keiper[2], Rachel Whynott[3] and Lisa Parker[3]

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Abstract

Treatment recommendations suggest medication should not be the primary treatment for eating disorders (ED) and empirical evidence demonstrates their ineffectiveness in anorexia nervosa (AN). The current presentation will provide data on the frequency of psychotropic prescriptions in a clinical sample of eating disorder (ED) patients indicating their use is very common but inconsistent with evidence-based recommendations. This study adds new evidence regarding diagnostic and age-based comparisons of psychotropic prescription frequency in EDs not examined in earlier studies. The sample consisted of 501 ED patients admitted to an adult partial hospitalization or adolescent residential program. A retrospective chart review was conducted on consecutive first admissions. Patients were divided into two diagnostic groups: anorexia nervosa (AN=287) and bulimia nervosa (BN=214), as well as two age groups: adults (age≥18; N=318) and adolescents (age<18; N=183). Forty-one different psychotropic medications (891 prescriptions in all) were prescribed for 429 patients. Overall, 85.6% of the total sample reported using one or more psychotropic medications. Of 429 patients using any medications, 46.9% were on two or more, 25.3% on three or more, and 11.0% four or more. Antidepressants were most commonly prescribed (89.5% of those on medication) with no significant differences in usage patterns based on diagnosis. However, there was greater medication use among adults (89.6%) compared to adolescents (78.7%). The current presentation extends earlier research indicating the overwhelming evidence for a research-practice gap in the mental health field in general, and how resistance to evidence-based treatment extends to eating disorders treatment.

Food Addiction: Why Some People Can't Stop Eating Unhealthy Food

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Center for Food Addiction Freedom, CA, USA

Abstract

Research has documented that most Americans, including health care providers, believe that it is personal lifestyle choices that impact obesity. Obese people are given education about dietary choices, portion sizes, and energy balance for weight loss, yet even highly motivated individuals fail repeatedly using this outdated weight loss model. As per research, the high failure rate is blamed on the individual who is then perceived by health care providers as being noncompliant, unattractive, lazy, annoying, and a waste of time. Food addiction has surfaced as the possible cause of chronic overeating, binge eating, and obesity in some people. The concept of food addiction has been controversial for many years because this theory lacked scientific evidence, however recent research has strengthened the case for food addiction, now making it relevant in the scientific community.

Food addiction theory suggest that certain foods may trigger an addictive process like alcohol or drug dependence and may help explain why so many people are unable to control their consumption of unhealthy foods making it impossible to lose or sustain weight loss. There continues to be a reliance on outdated theories and assumptions about obesity and treatment that only work for a small percentage of overweight or obese people. This session will introduce and educate participants on the recent theoretical advancements that aim to explain modern obesity, aid them in identifying symptoms of food addiction scientifically, and give them new tools and resources for assessing and treating food addiction.

MeCP2 Regulates Ethanol Sensitivity and Intake

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Abstract

We observed that the methyl-CpG binding protein 2 (MeCP2) was differentially regulated by a history of alcohol dependence. Thus, we investigated sensitivity to ethanol and ethanol drinking in MeCP2308/Y mice, which results in impaired binding of MeCP2 to the NCoR/SMRT transcriptional repressor complex but preserves methylated DNA-binding and a mild Rett-like phenotype. MeCP2308/Y mice were more sensitive to ethanol's stimulatory and sedative effects than wild-type (WT) mice, drank less ethanol in a limited access 2 bottle choice paradigms and did not show increased drinking after induction of dependence with exposure to CIE vapors. Alcohol metabolism did not differ in MeCP2308/Y and WT mice. For confirmation, we also tested sensitivity to ethanol's sedative effects of a second line of mice with a mutation in the methylated DNA-binding domain (MBD) of MeCP2, also resulting in a mild Rett-like phenotype, MeCP2T158A. Similarly, to MeCP2308/Y mice, also MeCP2T158A mice showed longer loss of righting reflex (LORR) not explained by differences in alcohol metabolism. Thus, two independent lines of mice with two separate MeCP2 mutations showed dramatically increased sensitivity to the sedative effects of alcohol, despite their mild Rett-like phenotype. Lastly, using the Gene Set Enrichment Analysis (GSEA) algorithm, we found a significant overlap in the genes regulated by alcohol and by MeCP2 using 2 separate gene expression datasets. Together, these results indicate that MeCP2 contributes to the regulation of ethanol sensitivity and drinking and suggest MeCP2 as a key master regulator of alcohol-sensitive genes.

Addiction: Natural Rewards vs. Drugs of Abuse

Patricia Sue Grigson

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Abstract

Over the last decade or so we have begun to examine how drugs of abuse commandeer natural learning, memory, and motivational systems to take control of behavior. In our first such paper, we reinterpreted 30 years of data, and in so doing, identified a new rodent model for drug-induced devaluation of a natural reward and cue-induced craving (Grigson, 1997). Using drug self-administration, we revealed robust individual differences whereby some out bred rats are more likely than others to avoid a natural reward cue, such as saccharin, in anticipation of the availability of drug. Importantly, greater avoidance of the saccharin cue was found to be associated with greater seeking and taking of cocaine (Grigson & Twining, 2002) and heroin (Imperio & Grigson, 2015). While addiction is a chronic condition, thought to develop over time, our recent work shows that, in fact, individual differences in vulnerability for drug-seeking and taking can emerge immediately, following even a single exposure to drug (Colechio & Grigson, 2014; Colechio et al., 2014). That said, such vulnerabilities and/or resiliencies are not set in stone. Vulnerability for drug taking is increased in adult rats by a history of having binged on fat (Puhl et al., 2011) and by chronic sleep deprivation (Puhl et al., 2013), and it is reduced in adult rats by yoked delivery of drug (Twining et al., 2009), exposure to an enriched environment (Puhl et al., 2012), or transplant of human retinal pigment epithelial cells (Venkiteswaran et al., 2016).

Neuroimaging and Neuromodulation of the Mu-Opioid System in Chronic Pain Patients *In-vivo*

Alexandre F. M. DaSilva

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Abstract

In the U.S. 100 million adults suffer from chronic pain. One of those debilitating pain disorders is migraine, which affects most of the patient's life, from childhood to late adulthood. Moreover, some migraine sufferers can develop a progressive state of this disease with more than 15 attacks per month. This state is referred to as chronic migraine, a disorder whose patients experience significantly greater headache impact on daily life and have a large potential for substance abuse, especially opiates.

Understanding this process *in vivo* is crucial to determine the systems involved in the persistence and relief of chronic pain, especially the μ-opioidergic system, arguably one of the principal endogenous pain modulatory systems in the brain. The goals of this presentation are: First, to exploit the μ-opioidergic receptor mediated mechanisms in chronic pain, including migraine; Second, to discuss the central μ-opioid mechanisms directly associated with non-invasive brain stimulation and placebo in those patients; Third, to investigate the immediate and long-term central effects of non-invasive brain stimulation on the μ-opioid system in chronic pain patients.

Translational Neuroimaging: Reduced Neural Response to Natural Reward Cues is Associated with Treatment Outcome in Prescription Opiate Use Disorder

Scott Bunce[1*], Andrew S. Huhn[1,2], Dean Stankowski[1], Ed Bixler[1] and Roger Meyer[1]

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Abstract

Identifying factors that increase risk of relapse among individuals with substance use disorders (SUD) would allow the opportunity for individualized interventions, facilitating better outcomes. Anhedonia, the inability to feel pleasure, is an important but understudied element of a neuroadaptive model thought to underlie vulnerability to relapse in SUDs. Previous research using fMRI has shown reduced activation to pleasant stimuli in rostral prefrontal cortex among heroin-dependent patients in early recovery. In the current study, a translational neuroimaging technology, functional near-infrared spectroscopy (fNIRs), coupled with a cue reactivity paradigm, was used to evaluate the hypothesis that reduced neural response to natural reward cues would be associated with poorer treatment outcome among a sample of recently withdrawn patients in residential treatment for prescription opiate use disorder (POD). In addition to self-report measures of anhedonia, patients with POD completed a cue reactivity task which included three categories of positive stimuli (highly palatable food, social interactions, and emotional intimacy) while their rostral, dorsolateral prefrontal cortex (dlPFC) and ventrolateral prefrontal cortex (vlPFC) were monitored using fNIRs. Patients were then followedafter discharge to assess 90-day treatment outcomes. In a sample of 35 patients with known treatment outcomes, reduced response to positive stimuli in left vlPFC was associated with relapse within 90 days (n=20 relapsed) t (33) =2.48, p = 0.02. This reduced neural response to positive stimuli appeared to be independent of depressive symptomatology (Hamilton Rating Scale for Depression). Results will be discussed considering implications for potential clinical application.

Neureka! Neurofeedback: A Potential New Approach to Activating Dopaminergic Systems

Jonathan D. Cowan

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Abstract

Brainwave measurements termed Neureka! have been related to positive feelings such as happiness, love, gratitude, satisfaction, anticipating good events, and joy in three experiments. Furthermore, Neureka! measurements used as biofeedback combined with focus biofeedback have significantly elevated happiness and attention in a sample of mixed drug abusers and normal after twelve 25 minute sessions of training, and this has lasted four months.

Neureka! is a specially clarified approach to 40 Hz. rhythm measurement and biofeedback, developed by the author, which appears to isolate the "event binding rhythm", which scans the cortex originating from the center of the thalamus, and returns there with information used to integrate events. It is therefore very important in new learning, as is dopamines, which are both a memory consolidator and a reward system for new learning. Training Neureka! boosts memory.

It is not surprising that my finding is that Neureka! measured over the medial prefrontal cortex, which has the largest concentration of dopaminergic terminals in the cortex, and is an extension of the dopaminergic system in the midbrain, is associated with these rewarding, positive feelings.

I propose that Neureka! neurofeedback can be used to train individuals deficient in dopamine activity to raise these levels on their own, and thereby avoid reward deficiency syndromes. By learning to create and attribute bursts of dopamine and other reward chemicals to their own efforts, they will gradually heal themselves and lead happier lives. Further studies to verify the causal chain are necessary. I am actively seeking collaborators.

Comprehensive Analysis of Reported Drugs (CARD) is Not Only a Drug Urine Screen but a Tool to Improve Clinical Outcomes

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Abstract

America is faced with widespread out of control Substance Use Disorder (SUD) especially opiate/opioid licit and illicit use and abuse. Since 2000 until 2016 there has been a 3000 percent increase in people seeking drug abuse treatment. In response to these great concerns the Comprehensive Analysis of Reported Drugs (CARD) has taken the lead in offering clinics with a means to analyze in one sample both compliance to prescribed medications and abstinence from non-prescribed or illicit drug abuse. Since the inception of the CARD thousands of samples have been processed. To address this concern, we carried out a number of studies that shed light on 1) in a general drug –treatment population (i.e. in-patient, residential etc.) both compliance and abstinence; 2) improvement of clinical outcomes over time with utilization of CARD; 3) compliance and abstinence specific to Buprenorphine /Naloxone (BUP/NAL) utilization in Opioid Substitution Therapy (OST). CARD data was used in this post-hoc retrospective observational study from 10,570 patients, filtered to include a total of 2,919 patients prescribed at least one treatment medication during 2010 and 2011. The first and last urine samples (5,838 specimens) were analyzed. Compliance was significantly higher in residential than in the non-residential treatment facilities. Independent of level of care, 67.2% of the patients (n = 1963; P<0.001) had every treatment medication found in both first and last urine specimens (compliance). In addition, 39.2% of the patients (n = 1143; P<0.001) had no substance of abuse detected in either the first or last urine samples (abstinence). Compared to non-compliant patients, compliant patients were marginally less likely to abuse opioids, cannabinoids, and ethanol during treatment although more likely to abuse benzodiazepines. In a longitudinal study over one year improvement was found whereby, a statistically significant upward trend ($p = 2.353\times10^{-8}$) of abstinence rates as well as a similar but stronger trend for compliance (($p = 2.200\times10^{-16}$) occurred. In another study, CARD was used to determine both compliance and abstinence in a large cohort of BUP/NAL patients attending OST. Buprenorphine/naloxone was present in 93.4% of first samples (n=1282; p<0.0001) and in 92.4% of last samples (n=1268; p<0.0001). Concomitantly, unreported drugs of abuse were present in 47.7% (n=655, p=0.0261) of samples. Patients who were compliant to the BUP/NAL prescription were more likely than non-compliant patients to be abstinent during treatment [p=0.0012; odds ratio=1.69 with 95% confidence interval (1.210, 2.354)]. Longitudinal analysis of all 2011 samples revealed a reduction in opiate abuse and a significant improvement in both compliance ($p<2.2 \times 10^{-16}$) and abstinence ($p< 2.2 \times 10^{-16}$) during treatment. These statistically significant results provide initial evidence that utilization of CARD may assist clinicians in providing a tool that not only provides presence or absence of drugs in the urine but possible longer term impact on improving clinical outcomes requiring more required research.

Addiction: The Essence of Surrender

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Abstract

In this presentation, I will discuss the many core issues that need to be addressed in the individual's life as the disease of addiction, is essentially an obsession with power and control. Addiction causes an individual a fundamental inability to live peacefully and contently and using only induces a temporary state of relief from a deep insistent discomfort in the individual's life. Addicted individuals are perfectly skilled at the art of self-detachment by rising above or below the conscious self. Over time addiction fundamentally becomes a disease of isolation. Addicted individuals suffer from and incompleteness and emptiness that needs to be addressed in treatment. With the concept that all change starts in the mind, to have a breakthrough it requires a shift of awareness and consciousness in the individual, a shift in how they see themselves and deal with their problems. The answers lie in the discovery of our inner freedom, with the freedom of choice and free will the individual will have many reasons to feel optimistic about their life and future. Bringing the mind, body, soul and self together as one to have a breakthrough in recovery. Addicted individuals must heal what is broken; one must start with the inner core of their being. Our answers to many questions of life lie in our soul buried under the wounds of our past and present. One must rise from the unconscious addictive thinking into a conscious thinking, where recovery is given meaning and purpose, thus enhancing the individual's life.

Strategies to Target Methamphetamine Induced Inflammation at the Synapse

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Abstract

Methamphetamine (meth) is a potent stimulant that has significant abuse potential. To further add a layer of complexity is the emerging role of sex differences with females moving more quickly to regular use, greater dependence and higher relapse rates with meth. While studies have described the pharmacodynamics of meth in detail, how inflammation induced by chronic meth at the synapse differs between the sexes has not been examined. Our focus is on understanding of inflammation responses and developing novel and more efficacious targets for treatment. One emerging anti-inflammatory drug of interest is ibudilast, a phosphodiesterase inhibitor that modulates the activity of glial cells such as microglia and astrocytes by suppressing the production of pro-inflammatory cytokines. We recently demonstrated the anti-inflammatory effect of ibudilast in attenuating inflammation at the synapse associated with chronic meth intake in male rats as evidenced by decreased meth seeking (i.e., active lever presses) in extinction. Extending this behavioral correlate at the synaptic level using a proteomics approach, we identified the synaptic signaling protein phosphatidylethanolamine-binding protein 1 (PEBP1) to be down regulated in the synaptosomes of male rats that had self-administered meth and subsequent reversal by ibudilast treatment during extinction. Current ongoing works are focused on assessing the effectiveness of ibudilast in attenuating inflammation varies with between the sexes including elucidating the role of synaptic PEBP1 as a potential pathogenic marker for meth seeking between the sexes.

Neuroanatomical Substrates of Behavioral and Drug Addictions – Relationships with Impulsivity

Sarah W. Yip

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Abstract

Individuals with gambling disorder (GD) and with cocaine-use disorder (CUD) exhibit clinical and neurobiological similarities. However, direct comparison between these two disorders is rare. To further understanding of the neurobiological mechanisms of addictions, we directly compared neural structure between individuals with gambling disorder (n=38), individuals with cocaine-use disorder (n=38) and healthy control individuals (HC; n=38). Analyses of diffusion MRI data indicated similar alterations in white matter microstructure among individuals with GD and CUD, relative to controls, within striatal and parietal tracts (pFWE<0.05). Voxel-based morphometry (VBM) analyses indicated reductions in prefrontal cortical grey matter among individuals with CUD, relative to GD and HC individuals (pFWE<0.05). VBM analyses further indicated a negative association between trait impulsivity and grey matter volumes within the bilateral amygdala and hippocampus across all participants (pFWE<0.05). These data suggest common white-matter features across behavioral and drug addictions, but raise the possibility that prefrontal cortical grey matter reductions may be specific to CUD. They further indicate largely separable effects of impulsivity versus diagnostic groupings on grey matter volumes.

Implementation Findings of an Evidence-Based Strategy to Assess and Manage Risky Substance Use in Oncology Patients

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Abstract

Background: Risky alcohol and drug use during cancer treatments causes significantly worse quality of life outcomes for patients. Screening, brief intervention, and referral to therapy (SBIRT) is an evidence-based intervention that enhances

identification and management of risky substance abuse behaviors. Originally implemented in primary care and emergency medicine, its use in oncology clinics has not been studied.

Methods: This quality improvement project used evidence-based methods to implement a screening and intervention program in the radiation oncology clinic in this NCI-designated Comprehensive Cancer Center. The intervention consisted of three components: 1) Staff training; 2) Development of an electronic documentation infrastructure using validated screening instruments and clinical decision support 3) electronic toolkits with SBIRT resources, including cancer-specific handouts.

Results: The clinic achieved 54% mean screening rate over the initial 9-week implementation period (218 screened/407 patients seen in consult). Of the 218 patients screened, 14.7% screened positive for risky alcohol or drug use and 46.9% of those patients received a brief intervention. Notable disease-specific positive screening rates were seen.

Conclusions: The incorporation of SBIRT screening and management techniques into the workflow of a busy radiation oncology clinic was feasible. Even with suboptimal screening rates, a clinically significant number of patients with signs of risky substance use were identified and managed with early interventions. Given the poor outcomes associated with risky substance use in oncology patients, these tools may be valuable to improving patient care outcomes. Future research should tie patient outcomes to proactive screening and management of risky substance use**.**

Pathway and Cell-Specific Kappa-Opioid Receptor Modulation of Excitatory-Inhibitory Balance Differentially Gates D1 and D2 Accumbens Neuron Activity

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Abstract

Endogenous dynorphin signaling via the kappa-opioid receptor (KOR) in the nucleus accumbens (NAcc) powerfully mediates negative affective states and stress reactivity. NAcc KOR signaling has been implicated in mediating negative affective states during drug withdrawal and stress-induced drug-seeking behavior. Excitatory inputs from the hippocampus and amygdala play a fundamental role in shaping the activity of both NAcc D1 and D2 MSNs, which encode positive and negative motivational valences, respectively. However, a circuit-based mechanism by which KOR modulation of excitation-inhibition balance modifies D1 and D2 MSN activity is lacking. Here, we provide a comprehensive synaptic framework wherein presynaptic KOR inhibition decreases excitatory drive of D1 MSN activity by the amygdala, but not hippocampus. Conversely, presynaptic inhibition by KORs of inhibitory synapses on D2 MSNs enhances integration of excitatory drive by the amygdala and hippocampus. In conclusion, we describe a circuit-based mechanism showing differential gating of afferent control of D1 and D2 MSN activity by KORs in a pathway specific manner. These results provide a potential mechanism by which heightened NAcc KOR signaling could mediate negative reinforcement of drug-seeking behavior.

Effective Advocacy and Case Management of Domestic Sex Trafficking Cases

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Abstract

Victims of Human Trafficking frequently report substance abuse as a coping mechanism to deal with their constant exposure to trauma. Many victims go unidentified due to misrepresentation of victims of this crime and an assumption that victims of trafficking do not disclose this crime happening against them. Some examples of obstacles to victim disclosure: service providers assume it takes numerous visits with victims to develop a rapport, mandated reporting laws keep victims from disclosing, and Law Enforcement often states that victims distrust them because they are in law enforcement. This workshop will focus

on how to increase identification of victims of domestic sex trafficking by focusing on disclosure/interviewing techniques, understanding sex trafficking related trauma and risk factors, cross system collaboration and effective victim engagement in services. In addition, mandated reporting will be introduced as an ally to help victims understand their options including reporting the crime. Building strong and trusting relationships with other agencies in the community and with law enforcement is the key to successfully assist victims and to empower them to be their own agents of change. This workshop will provide example of successful program collaboration between advocates, law enforcement, judicial systems and community agencies all focusing on providing best support for the victims in their journey of healing and empowerment.

Combined Behavioral and Pharmacological Treatments to Prevent Common Mechanisms of Cocaine and Stress to Trigger Relapse to Drug Use

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Abstract

Relapse is a common feature of cocaine addiction. In rodents, it can be elicited by cues, stress or the drug. Restraint stress-induced reinstatement of cocaine-conditioned place preference (CPP) is a useful model to study the mechanisms involved in stress-induced relapse of drug-seeking behavior. There is evidence that the glutamate ionotropic NMDA and metabotropic mGluR2/3 and mGluR5 receptors are critically involved in drug- and cue-induced reinstatement of seeking behavior and drug-CPP responses. The aim of this study was to investigate the contribution of these receptors within nucleus accumbent (NAc) core vs. shell to restraint stress-induced reinstatement of cocaine-CPP. After extinction of cocaine-conditioned preference, animals were administered with the MK 801, MPEP or LY 379268, systemically and/or into intra-core or intra-shell before restraint (30 min) or left undisturbed in their home-cage. Three days later these animals were evaluated in a second stress or drug-induced reinstatement. Since during the second reinstatement the effect mirrored that observed in the first one, another set of experiments explored a possible influence of the pharmacological treatments on the drug memory reconsolidation processes. First, we demonstrated that restraint stress-induced reinstatement of extinguished cocaine-CPP was blocked by MK 801 or MPEP intra-core, but not intra-shell, administration. Second, we showed that all pharmacological treatments administered immediately, but not three hours later, of the first stress-induced reinstatement or the reactivation/evocation session (without stress exposure) suppressed a second stress or drug-induced relapse to cocaine. Pharmacological treatments during the memory reconsolidation window could help to prevent relapse to drug use following stress or drug.

Reward, Mood and Endogenous Opioids

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Abstract

Deficiencies in the reward pathway can alter mood states and produce changes in behavior contributing to psychiatric disorders including depression and addiction. Dopamine and glutamate are two key neurotransmitters in the reward pathway, but it is also highly regulated by opioid systems. Therefore, changes in endogenous opioids and their target receptors may disrupt neurobiological control of mood and reward. My laboratory is interested in the delta-opioid receptor (DOR) system comprised of DORs and their endogenous ligands enkephalins, which are highly expressed within the striatum and frontal cortex. Activation of DORs produces a unique profile of activity, including stimulant-like effects, antidepressant-like effects, and antihyperalgesia; however, these compounds appear to lack primary reinforcing effects, such that they do not maintain self-administration behavior, nor alter thresholds in intracranial self-stimulation procedures, nor stimulate (to any great extent) dopamine release. Blockade or elimination of DORs has been shown to alter emotion-related behavior and reward learning. Our recent data suggests that DORs may play an important role in the conditioned stimuli associated with drugs of abuse. These studies suggest that the DOR system be involved in the underlying neurobiology mediating reward and may be a novel target for treating reward deficiency-related disorders.

Evidence-Based Holistic Modalities to Overcome Addictions

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Abstract

This workshop demonstrates the integration of the most current evidence-based holistic modalities with the best of the traditional treatment model. Discussion will feature information about Amino Acid and Nutraceutical use for brain repair, Ibogaine 1-day detoxification, Hyperbaric Oxygen Therapy for brain and tissue repair. The session will also cover the utilization of group/individual/family therapy with nutrition, massage, microbiome repair, acupuncture, yoga, vocational/educational assistance, sauna detoxification, colonic therapies, karate, exercise, 12-step program participation and other modalities. The workshop will be conducted in a lecture format with open question and answer.

Opioid Substitution Treatment

Martin Haraldsen

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Abstract

As a general practitioner (GP) in the years when opioid substitution treatment (OST) became common in the western world I read about the good results of the simple treatment with buprenorphine under the auspices of GPs. In France, the drug related deaths (DRD) in 1999 had dropped by 79% during few years. In 1995 some treatment was given with low-dose buprenorphine and methadone, from 1996 mainly with high-dose buprenorphine. With top priority for OST, consultations and buprenorphine became free of charge. Soon patients could take the drug home for one week at a time without supervised dosing. (This differed from methadone which was started in special clinics and followed closely thereafter).

Benzodiazepines were given to taper down from higher doses to prevent use of worse substances, not least alcohol. In other European countries OST took different forms. The European Union (EU) with 28 countries, has for 30 years collected DRD statistics. EU has been more eager to quality assure DRD than to draw conclusions from the vast difference of DRD. This may now change, as there are certain characteristics for optimal OST, which I will show. Besides France, three other countries have chosen the same model. Portugal has taken one step further: In 2001 to decriminalize user dosages of cannabis, amphetamine and heroin and follow up as a health problem. Before they had the worst open drug scenes in Europe, now nearly no DRDs. Now the DRD in the Norwegian capital is much higher than in Portugal.

Co-existing Pain and SUD: Nursing has a Plan

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Abstract

Patients with Substance Use Disorders and Pain have the right to be treated with dignity, respect and the same quality of pain assessment and treatment as all other patients (Oliver, Coggins, Compton, Hagan, Matteliano. et al., 2012). Opiates are a treatment option for severe persistent pain disorders, and have been considered a safe treatment option when benefits exceed risks for persons with substance use disorders (SUD). Despite evidence that addiction occurs in only a small percentage of persons exposed to opioids (Volkow & McLellan, 2016), recent national attention to illicit use has amplified fear of opioids. Fears create strain between providers and the pain patients entrusted to their care. Nurses are concerned about safely prescribing or administering opioids based solely on pain intensity, as well as the limited availability of sanctioned alternatives for pain control. Assessment strategies for reducing risk of addiction or relapse of addictive disease including integrative and relationship- based therapeutic options, SBIRT, and Medication Assisted Therapy.

Modulation of Dopamine-Dependent Behaviors by Cannabinoid Receptor 2 (CB2R) Located in Midbrain Dopamine Neurons Using Cre-Lox Mouse Model

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Abstract

Cannabinoid receptor 2 (CB2R) was previously thought to be a peripheral receptor expressed in immune cells, but not in brain neurons. We found that CB2R is expressed in midbrain dopamine neurons and up-regulated by chronic cocaine self-administration. In addition, activation of CB2R by JWH133 inhibits cocaine self-administration, reduces dopamine release in nucleus accumbens, and suppresses dopamine neuronal firing in rats and mice. These findings are supported by recent studies demonstrating that CB2R is expressed in dopaminergic terminals in the nucleus accumbens where CB2R modulates the action produced by activation of muscarinic receptor 4 (Foster et al. 2016, Neuron), and is expressed in hippocampal pyramidal neurons where CB2R mediates neuronal self-hyperpolarization (Stempel et al. 2016, Neuron). In the present study, we generated Dat-Cnr2 transgenic mice to conditionally knock out CB2R in brain dopamine neurons using Cre-Lox techniques. RNAscope in situ hybridization detected clear CB2R mRNA expression in VTA dopamine neurons in heterozygous and wild type control mice, but not in Dat-Cnr2 homozygous dopamine neuron specific knockout mice. We found that DAT-Cnr2 mice produced an enhanced locomotor response to cocaine, compared to heterozygous and wild type mice, as assessed by spontaneous wheel running test. In the elevated plus maze test, an animal model of anxiety, deletion of CB2R in dopamine neurons significantly increased the time spent in the open arms of the maze, compared to the heterozygous and the wild type mice, suggesting an anxiolytic effect. We conclude that CB2R in dopaminergic neurons modulates cocaine's psychomotor stimulant effects and anxiety-like behaviors.

Underlying Effects of Early Life Stress on Mood, Fear, and Alcohol Drinking: Comparison with a Genetically Alcohol Preferring Model

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Abstract

Adverse, maladaptive experiences during the perinatal period and in childhood permanently impacts brain function to induce vulnerability to mental health disorders and even addiction. When compounded by a genetic risk factor for neuropsychiatric disease, the environmental exposure to stress can trigger, exacerbate or accelerate disease development. Our laboratory has been actively investigating the role of early life stress during the prenatal or neonatal period on the development of anxiety, depression, fear, impulsivity and excessive alcohol drinking. We will discuss behavioral outcomes in adolescent DISC1-/- and DISC1 +/+ transgenic mice previously exposed to prenatal stress. In addition, adult offspring from the early postnatal maternal deprivation stress (MS) rat model exhibited neuroanatomical, biochemical and structural changes in brain loci associated with reward and emotional processing. We propose an underlying mechanistic basis for excessive alcohol drinking and impulsivity that involves regulation of the alpha2 subunit of GABAA inhibitory neurotransmitter receptor, and corticotropin releasing factor (CRF) receptor function, and show that pharmacological compounds acting at those receptors are individually sufficient to rescue the excessive drinking phenotype and impaired reward processing. These findings will be discussed in the context of alcohol-preferring (P) rats which innately drink more alcohol and have disrupted dopamine and GABA receptor regulation and thus may share 'reward deficiency' traits with alcohol-drinking MS rats.

General Practitioners' Prescribing Patterns at Primary Healthcare Centers in National Health Insurance, Gezira, Sudan

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Abstract

Background: The appropriate use of medicines is an essential factor for accomplishing provision of quality health services for patient safety and rational utilization of health resources. In Sudan, general practitioners (GPs) provide 80% of insured patients' health services. Pharmaceutical services cost started increasing since 2010.

Objectives: The study aimed to use the World Health Organization's and International Network for the Rational Use of Drugs prescribing indicator to assess prescription quality among GPs at different types of Primary Health Care Centers (PHCCs) in the National Health Insurance Fund (NHIF), at Gezira State, Sudan.

Method: The study had followed WHO established guidelines. A cross-sectional retrospective study was carried out across six months on 197 general practitioners (GPs) representing 90% of the total study population (220), who has valid prescriptions. For each doctor, systematic random samples of one hundred prescriptions were collected. The 19,700 prescriptions were analyzed by Stata-12.

Results: The mean medication per patient was 2.55±1.32; the percentage of prescriptions prescribed by generic name was 46.34%, and percentage of prescriptions contained antibiotics and injections were 54.71% and 12.84%, respectively. The percentage of medicines prescribed from the NHIF medicine list of GPs was 81.19%. The overall Index of Rational Prescribing Indicator (IRDP) was 3.39, while the average cost per prescription was 40.57 SDG. Apart from antibiotics prescription the prescribing quality of NHIF facilities were further from optimal prescribing practice than State Ministry of Health-owned facilities, and others facilities owned by private, universities, and Non-Governmental Organizations.

Conclusion: The present study collectively provides strong evidence of irrational prescribing practice among general practitioners with significant disparities, particularly, in terms of overuse of antibiotics, underuse of generic names and adherence to GPs medicines list.

Neurobiological Predictors and Mechanism of Treatment Response for Adolescent Substance Use Disorders: Towards a Developmental Model of Recovery

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Abstract

Addictive disorders, most which start during adolescence, represent a significant cost to the individual and society. A fundamental barrier to progress in treatment science has been the lack of understanding about the basic mechanisms of treatment-related behavioral change and the mediators of treatment response. While the short-term effectiveness of substance use treatment in adolescent substance use disorders (SUDs) is promising, there is considerable response variation, and two-thirds of youth relapse within 6 months of treatment. The neurobiological mechanisms underlying individual response to substance use treatment are poorly understood. Furthermore, a unified biologically-based neurodevelopmental model of addiction recovery is lacking. Early studies suggest that circuitry strength within and between cognitive control/self-regulatory, salience/motivational, and negative affect processing brain systems may be central to recovery from drug addiction. In this presentation, Dr. Hammond will present a state of the science update on neurobiological predictors and mechanisms of treatment response in addictive disorders, focusing on adolescent SUDs. His review will seek to bridge treatment-based outcome research with current translational neuroscience approaches towards a neurobiologically-based developmentally-informed model of substance use treatment and addiction recovery. He will examine the scientific literature and discuss neurotransmitter systems, brain regions, and neural circuits that are thought to be relevant to treatment response and recovery from SUDs in context of current theories of addiction. Strengths and limitations of studies will be discussed along with future directions for the field.

Prescribed Drugs – A New Crime Field?

Thomas Schwarzenbrunner

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Abstract

Substitution treatment, a controlled medical prescription of synthetic opioids in the context of oral maintenance therapy, is widely available and has become the most important form of treatment in Austria. In sum, a proportion of 60% of the estimated high-risk opioid users have meanwhile been in opioid substitution treatment. Prominent critics see the success of this form of treatment skeptical. They say that only 5% of patients will be abstinent in the long term and many prescribed drugs will land on the black market. Therefore, the goal must be to get away from the substitution treatment to abstinence-oriented treatment. Is that correct?

Concerning the abstinence rate this is right, only few patients become abstinence in a long term. But the aims of the treatment are to be seen much more differentiated. First of all, the treatment must be seen as harm reduction, as in palliative care. A large part of the patients achieves a health and social stabilization. The housing situation, the life situation and job-related integration are improving significantly. Drug-related crime can also be dramatically reduced. Abstinence-oriented treatment must be a complementary offer for substitution treatment and not as competition. It is also correct that prescribed drugs land on the black market. But in the analysis of the police data, it can be seen that only a very small part of the issued opioid-pharmaceutical (around 0,15%) are confiscate by the police on the black market. On the other hand, the overwhelming majority of patients no longer provide opioids via the black market.

In summary: Treatment pays off!

Reduced Striatal Dopamine Transporter Density Associated with Working Memory Deficits in Opioid-Dependent Male Subjects: A SPECT Study

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Abstract

Research on the effects of repeated opioid use on striatal dopamine transporters has yielded inconsistent results, possibly confounded by a history of methamphetamine or methadone exposure in opioid-dependent individuals. Previous studies have shown that striatal dopamine transporter density is positively correlated with the cognitive performance of healthy volunteers. This study aimed to investigate changes in striatal dopamine transporter density and their functional significance in opioid-dependent individuals. Single-photon emission computed tomography (SPECT) with [99mTc]TRODAT-1 as a ligand was used to measure striatal dopamine transporter levels in 20 opioid-dependent individuals and 20 age- and sex-matched healthy controls. Opioid-dependent individuals had no history of methamphetamine or methadone use. The Wisconsin Card Sorting Test (WCST) was performed to assess neurocognitive function. We found that compared with healthy controls, opioid-dependent individuals showed a significant reduction in striatal dopamine transporter density. They also showed poorer performance on the WCST in terms of the trials administered, total errors, perseverative responses, perseverative errors, and non-perseverative errors. Striatal dopamine transporter levels negatively correlated with non-perseverative errors not only in opioid-dependent individuals but also in healthy controls. These findings suggest that in human, repeated opioid exposure reduces striatal dopamine transporter density, which can be associated with non-perseverative errors. Non-perseverative errors may be one of the more sensitive parameters in WCST to identify working memory deficits associated with striatal dopamine transporter reduction. Moreover, we suggest that whether opioid-associated neurotoxicity is reversible depends on the brain region.

Narcotic Analgesics: Not Only Addiction, but also, Structural Changes (Experimental Research)

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Abstract

Pain ranges make up 90% of all complaints when appealing for primary health care, so the problem of drug therapy and effective pain control is still relevant. However, besides the use of analgesics per medical indication for use, a fact of groundless use of analgesics has been growing dynamically for the recent years. Therefore, the prevalence rate of opioid use at least once a year (Recovery Brands, 2013) is 61.0 in the USA and up to 27.0 in Europe per 1000 adults.

Modeling of long-term effect of narcotic analgesics was performed by using a semi-synthetic opioid analgesic Nalbuphine. The study was carried out on 16 mature white male rats aged 3.0 and 160-180 g in weight. The research material included semi-thin and ultra-thin sections of white rat's eyeball vascular tunic. Specimens were studied and photographed with microscope magnification: ×1000- x 8000.

It has been revealed that the 4-week introduction of Nalbuphine to white rats causes lesions of endothelial and basement membrane of hemomicrocirculatory bloodstream's units, epithelium of ciliary processes, cellular and non-cellular elements of the iris and the choroid. It has been proved that changes of restructuring angioarchitectonics of the eyeball vascular tunic indicate the development of angiopathy, which obviously leads to circulatory disorders of the organ of vision. Thus, a deterioration of visual function in conditions of long-term use of narcotic analgesics is expected.

Reward Genomic Disparity in Opiate/Opioid Dependent African Americans: Embracing "Dopamine Homeostasis" Through Epigenetic Manipulation

Panel Participants

Georgia M. Dunston, Bradford Wilson, Lorelle Bradley, Edwin Chapman, Olivia Finley, Earl Ettienne, Marjorie C. Gondré-Lewis, Kareem Washington and Kenneth Blum

Abstract

In the era of precision medicine, especially as it relates to diagnosis and treatment and even prevention of opiate/opioid addiction, it is the position of the panelists that the term, "race" to define the biology of individuals and human populations is anachronistic and should be dropped in modern lexicon. While there may be variations on the theme, we prefer genome-based terminology to define individuals and /or population ancestry aligned with their country/continent of origin (e.g. African Americans, Euro, Anglo or Caucasian Americans, Mexican Americans etc.). Moreover, science shows that extant human populations reflect a continuum of genome variation (polymorphisms) that cannot be partitioned into so-called "race/racial groups or subgroups. Thus, it is our position that biological/clinical phenotypes should be associated with genome variation underlying biological pathways, processes and/or mechanisms, instead of 'race' as a biological group or subgroup in human genome research. This is particularly critical in the era of precision medicine, when old, outdated definitions of populations as "race(s)" severely compromises the power of the human genome and research on genome variation to reveal the biological underpinnings of clinical phenotypes of interest. The latter is of concern in precision medicine for African Americans, this being a population with the broadest spectrum of genome variation reflective of its African roots in human history and admixture in more recent population history in America (Nature Genetics 2004 supplement). We have chosen the term "ethnic" rather than race in terms of addressing cultural diversity which reflects both genomic and environmental interactions in health disparities of the African-American community here in Washington DC and across the nation, to clearly expose both pharmacogenomic (metabolic) and genetic addiction risk in African Americans. For example, African Americans have a higher frequency of polymorphic alleles affecting the mu opiate receptor as well as the CYP3A4 *1B allele associated with ultra–metabolism of burprenorphine (85%*1B compared to 17% in Caucasians). The greater genome variation in African Americans is 'value-added' in dissecting molecular mechanisms underlying the pathobiology of opiate/opioid addiction, and in designing interventions based on the individual's genotype in this era of precision medicine.

Bariatric Surgery Effects on Alcohol Intake and Molecular Imaging: Preclinical Data

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Abstract

Bariatric surgery remains the most effective treatment for decreasing weight in morbidly obese individuals. Recent data shows that some of these individuals show increased risk for alcohol abuse as well as more generally attributes of Reward Deficiency Syndrome (RDS). Specifically work in our group and others have shown clinical as well as preclinical data that show increased responding for alcohol as well as increased alcohol consumption. We aim to explore the underlying mechanism of this phenomenon by looking at the corresponding role of reward signaling following bariatric surgery compared to weight loss and sham surgery animals. We hypothesize that bariatric surgery in animals alters dopamine signaling and is mediated by several molecules. *In vivo* functional connectivity assessment with microPET is aiming to map out the brain circuit functional changes in response to optogenetic stimulation of the mesolimbic dopamine pathway.

Preclinical Research on Alcohol and Substance Use Following Bariatric Surgery

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Abstract

Roux-en-Y gastric bypass (RYGB) is a very effective and common treatment for morbid obesity and metabolic disorder. Similar to human studies, rodent models of obesity have shown that RYGB produces reduced preference and motivation for sweet and fatty foods and thus may reduce both palatability and rewarding effects of 'junk foods'. In contrast, concerns have been raised by clinical reports of an increased risk for alcohol use following RYGB surgery. This presentation will focus on our recent studies in dietary obese rats that provide evidence that RYGB increases the rewarding effects of alcohol and morphine. As for potential underlying mechanisms, we investigated involvement of altered ghrelin signaling, dopamine D2 receptors, and changes in vagal neuronal functions. We found operant responding for alcohol and morphine was significantly greater in RYGB rats. Furthermore, compared to obese surgical controls, RYGB rats were more sensitive to ghrelin receptor antagonist D-[Lys3]-GHRP-6 (IP) in reducing alcohol reward, and demonstrated greater D2 receptor expression in the striatum. In addition, central vagal neurons demonstrated increased sensitivity to anorexigenic hormones. These findings collectively provide evidence that RYGB surgery may alleviate obesity-related deficits in vagal, ghrelin, and dopamine signaling, which is beneficial to eating behaviors (moving away from rich foods) while also posing a risk for new onset substance use and abuse (substituting drugs for food). Future research is warranted to determine underlying mechanisms and identifying individual risk factors preoperatively.

Bypassing Sweets for Alcohol: Clinical Research on Ingestive Behavior Following Bariatric Surgery

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Abstract

Bariatric surgery procedures provide the most successful long-term treatment for obesity. Currently, the three most popular bariatric surgeries performed worldwide are the Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), and laparoscopy adjustable gastric banding (LAGB). All three procedures decrease gastric volume, but unlike LAGB, in which the stomach/intestine remain intact, both SG and RYGB alter stomach anatomy and RYGB also reroutes the intestine. Despite the numerous health benefits of these procedures, mounting evidence shows an increased risk of alcohol use disorders (AUD) after stomach surgeries in patients who had no history of alcoholism before the procedure. The precise mechanism(s) underlying this association is uncertain, but we hypothesize it is due to gastric resection surgery-induced changes in both: 1) alcohol pharmacokinetics and 2) gut-brain peptides, which modify brain pathways that play a role in food and alcohol reward (e.g., ghrelin, glucagon-like peptide 1). I will review epidemiological findings supporting an increased risk of AUD after gastrectomy surgeries, and will present data of an ongoing study in which we are evaluating the effects of RYGB, SG or LAGB surgery

on the pharmacokinetics and subjective effects of ingesting ~ two standard drinks. Our data, combined with data from others, underscore the need to make patients aware of the alterations in alcohol metabolism that occur after these bariatric surgery procedures to help reduce the risk of potential serious consequences of moderate alcohol consumption.

Reducing Problem Alcohol Use Following Bariatric Surgery: Behavioral Self-Management

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Abstract

Although bariatric surgery is the most effective treatment for severe obesity, there are psychological factors that increase risk for long-term post-operative alcohol misuse and weight regain. It has been established that a significant proportion of bariatric patients have a self-reported history of using food for behavioral/emotional self-regulation. Without explicitly teaching skills that target adaptive coping, there is increased risk for problematic weight regain and alcohol misuse following bariatric surgery. Behavioral and emotional self-regulation can be taught, monitored, and reinforced via personalized self-management. This session will introduce the Bariatric Outcomes: Skills for Sustained Surgical Success (BOSSSS) program and review pilot study outcomes, with special emphasis on alcohol use results. The BOSSSS program incorporates self-determination theory in order to empower patients to select intervention elements tailored specifically to their needs and preferences. The specialized cognitive behavioral therapy within BOSSSS targets impulsive and compulsive behaviors, with a distinct emphasis on finding adaptive, replacement reinforcers. Mobile and wearable health technologies are incorporated in order to maximize ease of self-monitoring and facilitate communication with clinicians and other BOSSSS participants. Preliminary data demonstrate that hazard drinkers, per Alcohol Use Disorders Identification Test (AUDIT-C) baseline results, were especially responsive to the intervention. Weight regain and hazard drinking were significantly reduced in long-term post-operative bariatric surgery patients. Future directions and new BOSSSS intervention elements targeting reinforcement pathology will conclude the session. Ultimately, personalized self-management programming can effectively target self-regulation in order to reduce risk for problematic alcohol use in post-operative bariatric patients.

Cannabinoid Receptor-mediated Synaptic Signaling and Neural Plasticity in Neurons of the Central Nervous System

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Abstract

We study the function of the endogenous cannabinoid (endocannabinoid) system in regulating neural activity at synapses in the olfactory bulb, the first central relay station in the brain for the processing of olfactory information coming from the nose. The endocannabinoid system involves CB1 receptors and endocannabinoids. Olfactory bulb neurons express high levels of CB1R. Endocannabinoids mediate retrograde signaling at synapses in several brain regions through a form of short-term neural plasticity. Endocannabinoids are released from depolarized principal neurons and rapidly diffuse to presynaptic inhibitory interneurons to transiently reduce pre-synaptic firing and neurotransmitter (GABA) release. Output neurons such as mitral cells in the olfactory bulb are computational elements in brain circuits that integrate incoming signals with membrane properties to generate behaviorally relevant synaptic output.

In mouse brain slices, we used whole-cell patch-clamp recordings to study how cannabinoid receptors regulate the activity of mitral cells, key olfactory bulb output neurons. We applied depolarizing voltage steps to mitral cells and measured if cannabinoid-mediated retrograde signaling is present in mitral cells as a change in the amplitude and frequency of spontaneous inhibitory currents. Our data support the notion that retrograde signaling is present in neural circuits involving mitral cells. Mitral cells release endocannabinoids which, through retrograde signaling, inhibit GABA release of presynaptic neurons, the periglomerular cells. This, in turn, allows mitral cells to temporarily regulate their synaptic input and relieve them from synaptic inhibition. Endocannabinoids function as retrograde messengers to mediate plasticity at olfactory bulb synapses. Support: National Science Foundation and Latham Trust Fund.

Blood Sugar Dysregulation & Relapse

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Abstract

The Pre-Frontal Cortex has the job of allowing us to plan, exercise willpower, make appropriate choices, resist impulse, think through consequences and apply skills. These functions are crucial to the on-going sobriety of a recovering addict. But what does the PFC need to optimally do its job, and what impairs it? This presentation will look at the possible role adequate Vs inadequate glucose availability to the PFC plays in preventing cravings slips and relapse in the recovering addict. It will further explore the relationship between the adrenaline response to dropping blood glucose levels, and the effect of adrenaline, or sympathetic arousal, on the optimal functioning of the PFC. It will conclude with suggestions as to how eating protein with complex carbohydrates every four hours, and the use of the amino acid L-Glutamine, can reduce cravings and relapse by ensuring a steady flow of energy to the PFC.

Reward Deficiency Syndrome in Children: Management Using Holistic and Integrative Approaches to Treat Impulsivity in Children

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Abstract

Children can clinically present with signs and symptoms of the Impulsive Behavioral manifestations of Reward Deficiency Syndrome from birth through adolescence. These present as disorders known as Colic, Autism, ADHD and various behavioral problems. This presentation highlights the use a holistic history and physical exam, specified diagnostic studies and holistic and integrative modalities to diagnose and manage impulsive behaviors that manifest in childhood. Attendees will attain the following objectives:

Identify key history taking tools and skills to assess impulsivity in children at all stages of development.

Identify neuro-developmental disruptors including infections, toxin exposures, metabolic and hereditary factors that contribute to impulsivity.

Understand Various Holistic and Integrative Modalities used to manage impulsive symptoms in children.

Apply Appropriate Holistic and Integrative Modalities in the treatment of impulsivity in children.

Neurocognitive and Clinical Psychopharmacological Evidence Showing Anti-reward Deficiency Behaviors with a "Pro-dopamine Regulator" (KB220)

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Abstrac

The concept of Reward Deficiency Syndrome (RDS) is defined as an umbrella term to help explain substance and non-substance related repetitive behaviors leading to aberrant reward seeking behavior linked to genetic and epigenetic infractions of the brain reward circuitry, which results in hypodopaminergia and reward dissatisfaction. Over the last four decades Blum's group has developed a "Pro-dopamine Regulator" (KB220). Both animal and human studies support its potential use in attenuating aberrant reward seeking behavior. However, RDS has been associated with several unwanted neurocognitive, sexual

and traumatic symptomatology. We now report that KB220 administration results in the following anti-RDS behaviors: 1) in a patient with repetitive paraphilia behavior, following a one-week administration of KB220z, the repetitive paraphilia was eliminated 2) two patients with terrifying nightmares, refractive to any medication to attenuate these "bad dreams," reported elimination of lucid nightmares and indicated conversion to happy dreams following administration of KB220z. Other studies from our laboratory extending this seminal work in eight clinical cases with known substance abuse, childhood abuse and diagnosed PTSD/RDS, were administered KB220z. Administration of KB220z™ was associated with the elimination of unpleasant and/or terrifying, lucid dreams in 87.5% of the cases presented, whereas one very heavy cocaine abuser showed a minimal response. In four cases the elimination of nightmares continued for up to 12 months after cessation of taking KB220z. 3) In a case study of a 72-year-old male ADHD, (non-addictive) patient, following KB220z, Low-Resolution Electromagnetic Tomography (LORETA) revealed increased current source density in theta and alpha frequency bands, averaged across Eyes Closed, Eyes Open and Working Memory conditions, in the anterior, dorsal and posterior cingulate regions. We also observed increased theta current source density in the right dorsolateral, prefrontal cortex during the Working Memory task, relative to baseline, which correlated with improved performance in the Working Memory condition. 4) We tested the acute effect of KB220Z, (liquid Nano variant) on long-term memory impairment in a 77-year-old (AC), highly functional male with ADHD utilizing the Semantic Verbal Fluency Test. AC's semantic verbal fluency increased from the 30th percentile (pre-test), to the 76th percentile after the first administration of KB220z, and increased further to the 98th percentile, following a second administration of KB220z, approximately six months later. While more research is required these results suggest attention to pro-dopamine regulation as a treatment option in all RDS behaviors.

Incubation of Drug Craving After Prolonged Voluntary Abstinence

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Abstract

In previous studies, we and others have used a rat model of drug relapse and craving to demonstrate time-dependent increases in cue-induced drug seeking after experimenter-imposed (forced) abstinence from several drugs of abuse (heroin, cocaine, methamphetamine, nicotine), a phenomenon we termed incubation of drug craving (Grimm et al. Nature, 2001; Pickens et al. TINS, 2011). In these studies, the rats were removed from their drug self-administration environment during extended periods of forced abstinence. More recently, we have established a novel rat model in which we observe incubation of drug craving after extended periods of voluntary abstinence in the drug environment. Voluntary abstinence is achieved using a mutually exclusive discrete choice procedure in which food-sated male and female rats with prior extended history of intravenous methamphetamine or heroin self-administaration can choose every day (20 trials per day) between the palatable food and the drug. In this lecture, I will present our initial behavioral, pharmacological, and brain circuit characterization of incubation of drug craving after voluntary abstinence. I will conclude the lecture by discussing the clinical implications of our preclinical results.

Cinnamaldehyde-based Inhibitors of Nicotine Metabolism: Potential for Addiction Treatment

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Abstract

Overcoming nicotine addiction is a tremendous challenge, however, unlike many diseases for which there are numerous treatment options, there are only three pharmacological treatments developed specifically for smoking addiction. An extensive body of evidence indicates that variability in the rate of nicotine metabolism influences smoking behavior and cessation rates. Thus, the primary enzyme responsible for nicotine metabolism, cytochrome P450 2A6 (CYP2A6), is a potential therapeutic target for treating nicotine addiction. This presentation will describe recent results indicating that cinnamaldehyde (trans-cinnamic aldehyde), a natural product present in cinnamon, is a metabolism-dependent inhibitor of CYP2A6. Moreover, a model that predicts changes *in vivo* nicotine clearance, based on metabolism-dependent inhibition data generated from human liver microsomes, showed that the clearance of nicotine could be substantially slowed by low blood concentrations of cinnamonaldehyde: the fold-changes for the area under the curve ranged from 1.3 to 1.6 and 2 to 3.3 at 0.1 μM and 1 μM cinnamaldehdye, respectively. The results also show that inhibition is selective for CYP2A6; the IC50 for CYP2A6

was 10.5-fold lower than the IC50 for CYP2E1. The IC50 values for other major drug metabolizing P450 enzymes (e.g., CYP3A4) were 15.8-fold higher or more than the IC50 value for CYP2A6. Evidence for the mechanism of inhibition and results from experiments aimed at assessing the binding affinity and inhibition potency of compounds structurally-related to cinnamaldehyde will also be described.

Opioid Management in Portugal/France

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Abstract

Parts of USA have 100 times as many drug related deaths per inhabitant (DRD) as Portugal, a country to learn from. 16 years ago, it had a DRD many times above the average of the European Union (EU), now only a fraction of the average after radical introduction in 2001 of: 1) opioid substitution treatment (OST) as low threshold, and 2) the pioneering system decriminalization: Being caught with drugs for own use brings about follow-up by a professional team instead of incarceration.

Opioid addiction is as a shrewd chronic disease together with its often-complicating diseases. Portugal (10 million inhabitants) had a huge heroin problem, with about 1% seriously addicted, about three times the EU average – a high prevalence of HIV infection besides DRD.

The main goal was substantially to improve the accessibility of the patients to the OST throughout the country and to reduce waiting time for first appointment. Methadone, buprenorphine and its combination with naloxone are the medications to choose between. Methadone is restricted to the drug addiction institutional services (SU) which may have agreements with other facilities (Primary care Centers, Therapeutic Communities, Harm reduction Programs, NGO, etc.) is for free. OST by GPs is also offered, but only with the more ideal drug: buprenorphine, like in France. In France, all is for free, but not in Portugal, where it is sold to reduced costs due to its economic crisis.

Physical and Addictive Health Correlates of an Aboriginal Community

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[2]*London South Bank University, School of Health Sciences, London, UK*

Abstract

Introduction: Worldwide, indigenous populations have poorer physical and mental health and greater problems of addiction than non-indigenous peoples. These disparities are cited as a result of colonization that imposed regulations on traditional life leading to economic, social, and structural disadvantage and marginalization including lack of access to health care. Aboriginal Australians have an earlier and higher mortality rate than their non-indigenous counterparts. When they are ill, they are more likely to die due to late presentation, inadequate care, and complicated illnesses related to tobacco, drugs, alcohol and overeating.

Study objective: In 2013, a student-led clinic was developed to address clinical placement shortages while providing free health and social services in a predominantly Aboriginal community in Australia.

Design: Health data was collected at 18 months and again at 3 years from over 3,000 clients enrolled in the clinic to determine health changes and outcomes of student-delivered services.

Methods: Data was entered into a practice management software program and analysed using SPSS.

Results: Population health indicators at 18 months identified some positive changes to health patterns-smoking, drinking, waist size, and body mass index. Data at 3 years suggest these trends continue with additional significant findings of reduced BMI, lessened smoking, and changes in risky drinking. While speculative, these health gains may be related to the ease of access to help in a culturally appropriate non-hierarchical setting that includes targeted health promotion activities that focus on these lifestyle factors.

Opioid Detoxification without Stress – Mission Possible

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Abstract

Stress related to opioid detoxification is characterized as unavoidable and unquestionable response. Quantitative expression of this response indirectly can be evaluated by SOWS and OOWS scales. Routine biochemistry analysis does not reflect stress response, the most appropriate analysis are stress hormones cortisol and adrenocorticotropic hormone investigations. Statistically reliable increase of cortisol concentration always is observed immediately after Naltrexone induction. Stress hormones have been used in few studies as direct markers of stress response during opioid detoxification. Statistically significant increase of both markers has been reported during detoxification under general anesthesia and conscious sedation. Objective of the study is to check the hypothesis that novel Naltrexone induction regime creates lower stress response. We present the results of randomised double-blind study comparing stress response to different opioid antagonist Naltrexone induction regimes during rapid opioid detoxification under conscious sedation. The study was registered in ClinicalTrials.gov (Identifier: NCT02362256). Control group (N-30) received a single 12,5 mg dose, interventional group (N-30) received a gradual increasing dose from 50 μg to a total of 12,5 mg according to a predefined protocol. Serum concentrations of stress hormones were measured before Naltrexone induction and every 1, 5, and 23 hours after the induction and compared in both groups. Following Naltrexone induction, levels of cortisol and adrenocorticotropic hormone increased significantly (p=0,005 for adrenocorticotropic hormone and p<0,001 for cortisol respectively) in control group and decreased in interventional group. Gradual increase of Naltrexone dose instead of single total dose reduces stress response to rapid opioid detoxification procedure under conscious sedation.

Effects of Early Life Stress on Mesolimbic Dopamine Function

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Abstract

Adverse early life experiences such as child neglect and abuse increase the risk of developing addiction and stress-related disorders through alterations in motivational systems including mesolimbic dopamine (DA) pathway. Here we investigated whether a severe early life stress (i.e., maternal deprivation, MD) promotes DA dysregulation through an epigenetic impairment of synaptic plasticity within the ventral tegmental area (VTA) DA neurons. Using a single 24 h episode of MD and whole-cell patch clamp recording in rat midbrain slices, we show that MD selectively induces long-term depression (LTD) and shifts spike timing-dependent plasticity (STDP) toward LTD at GABAergic synapses onto VTA DA neurons through epigenetic modifications of the postsynaptic scaffolding A-kinase anchoring protein 79/150 (AKAP79/150) signaling. Histone deacetylase (HDAC) inhibition rescues GABAergic metaplasticity and normalizes AKAP signaling in MD animals. MD-induced reversible HDAC-mediated GABAergic dysfunction within the VTA may be the mechanistic link for the increased propensity to mental health disorders following MD.

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