MONDAY, SEPTEMBER 10 9:00 AM–9:45 AM
PLENARY LECTURE

001

ALCOHOL POLICY DEVELOPMENT AND RESEARCH: A COMPLEX INTERFACE

V. Poznyak
Department of Mental Health and Substance Abuse, World Health Organisation, Geneva, Switzerland

Psychoactive, toxic and dependence-producing properties of alcohol are well documented, and recent research findings expand the list of health conditions with causal relationship to alcohol consumption. In spite of around 3 million deaths attributable worldwide to alcohol every year and around 250 million people affected by alcohol use disorders, effective alcohol control policies lack strong support in many societies and jurisdictions. The WHO Global strategy to reduce the harmful use of alcohol is the only global non-binding policy framework on alcohol that was negotiated and agreed at the intergovernmental level. The recent global policy developments, including Sustainable Development Goals 2030 with special health target on substance abuse and strategies for prevention and control of Noncommunicable Diseases (NCDs) create new opportunities for effective alcohol control. Research findings on effectiveness and cost-effectiveness of policy options prompted development of "best buy" concept that includes feasible policies and interventions with an average cost-effectiveness ration of ≤1$ 100/DALY. For reducing the harmful use of alcohol these policy options include increase in excise taxes and prices of alcoholic beverages, reduction in physical availability of retailed alcohol and comprehensive restrictions or bans on alcohol advertising. Screening and brief interventions (SBI) for hazardous and harmful drinking have good cost-effectiveness ratio, but their implementation in health systems is limited. The 11th revision of the International Classification of Diseases, released in June 2018, is expected to facilitate implementation of alcohol-focused interventions in health services. The global data on implementation of alcohol policy options indicate that research efforts do not necessarily translate into science-based policy developments, and factors influencing the complex interface between research and alcohol policy development will be discussed in the presentation.

TUESDAY, SEPTEMBER 11 8:15 AM–9:00 AM
PLENARY LECTURE: THE ISBRA TABAKOFF AWARD

301

DEVELOPING NEUROSCIENCE BASED TREATMENTS FOR ALCOHOL ADDICTION – CHALLENGES AND PROSPECTS

M.A. Heilig
Center for Social and Affective Neuroscience, Sweden

Neurobiological research on addictive disorders has grown exponentially in the past two decades. It has also become increasingly sophisticated in its ability to identify neural circuits and molecular mechanisms behind drug seeking and taking. These advances have fueled hopes that novel, neuroscience based treatments would emerge and transform treatment of alcohol addiction. That hope has not yet materialized. Existing medications for alcohol addiction provide proof-of-principle for pharmacological treatment of this disorder, but their discovery precedes the neuroscience revolution, and they have not been adopted broadly enough to transform clinical practice.
This talk will review the ups, downs and new ups over two decades of translational work attempting to identify and target novel mechanisms for treatment of alcohol addiction. The first theme will discuss the limitations of focusing on brain reward mechanisms as therapeutic targets, and review our work on reprogramming of the transcriptome within key brain structures as a mechanism behind long-term neuroadaptations that fundamentally change the incentives behind alcohol seeking. The second theme will discuss the limitations of studying drug seeking in isolation. It will introduce the critical importance of studying alcohol seeking in the context of availability of natural rewards, and of individual vulnerability. Implications for medications development will be discussed.

TUESDAY, SEPTEMBER 11 9:00 AM–9:45 AM
PLENARY LECTURE

002

BURDEN OF DISEASE CAUSED BY ALCOHOL AND ALCOHOL USE DISORDERS – WHAT DO WE KNOW AND WHERE DO WE GO?

J. Rehm
Centre for Addiction and Mental Health, Toronto, Canada

Alcohol use has long been known to be a major risk factor for burden of disease and injury. The newest global and regional estimates of alcohol-attributable burden of disease as measured in deaths, years of life lost and disability adjusted life years will be presented, with emphasis on alcohol-attributable infectious disease, gastrointestinal disease and injuries.
The contribution of heavy drinking occasions and liver disease in the etiology of alcohol-attributable disease burden will be highlighted, as well as the interaction with between alcohol use and socioeconomic status and poverty. As a specific example of the latter, we will highlight the contribution of alcohol to the current stagnation of life expectancy in the USA.

TUESDAY, SEPTEMBER 11 1:50 PM–2:35 PM
PLENARY LECTURE

003

LIVER PARENCHYMAL CELLS AND SINUSOIDAL CELLS: CELL SOCIOLOGY IN ALCOHOLIC LIVER DISEASE

Y. Takei
Department of Gastroenterology, Mie University School of Medicine, Japan

Since the direct hepatotoxicity of ethanol was demonstrated by Charles Lieber almost half a century ago, significant progress has been made in research on the mechanism of alcohol liver disease (ALD). Consequently, the mechanism of ALD is considered to be diverse and multifaceted. In the late 1980s, it was proposed that alcohol is not only the direct toxicant to liver parenchymal cells, but also targets a variety of liver sinusoidal cells including Kupffer cells, stellate cells and sinusoidal endothelial cells (SECs). This hypothesis led to the general theory that alcohol-induced liver damage is a result of multiple, complex parallel processes. Ethanol-induced factors that communicate stress signals between hepatocytes and non-parenchymal cells initiate and perpetuate the pathological processes responsible for liver damage and disease progression to alcoholic hepatitis and cirrhosis. For example, at high concentrations, ethanol evokes endothelin-1 expression in SECs and causes contraction of the hepatic sinusoid leading to disturbed hepatic microcirculation. Moreover, ethanol increases gut-derived endotoxins (pathogen-associated molecular patterns), leading to the activation of Kupffer cells, culminating in the overproduction of toxic mediators such as tumor necrosis factor-α. Thus, interaction and crosstalk between hepatocytes and non-parenchymal cells appear to be crucial to the pathogenesis of ALD.

WEDNESDAY, SEPTEMBER 12 9:00 AM–9:45 AM
PLENARY LECTURE

004

ON THE USE OF COGNITIVE TRAINING IN THE TREATMENT OF ALCOHOL USE DISORDERS
R.W. Wiers[1,2,3]
[1]Department of Developmental Psychopathology, Addiction Development and Psychopathology (ADAPT) Lab, The Netherlands, [2]Department of Developmental Psychology, Faculteitshoogleraar FMG UvA, The Netherlands and [3]Department of Psychology, Universiteit van Amsterdam, The Netherlands

Alcohol Use Disorders (AUDs) are typically treated with psychosocial treatments and/or medication. However, there is a third category of interventions to consider: varieties of Cognitive Training (CT). Two types of CT can be distinguished: those in which general abilities are trained (e.g., working memory training) and those in which initial motivational reactions to alcohol are targeted, so called cognitive biases (Cognitive Bias Modification, CBM). I will review the state of affairs in both. Training of general abilities takes a long time, but does show promise for a subgroup of patients. CBM has shown to increase 1-year abstinence in several large clinical trials, with effect sizes similar to medication for alcohol (NNT = 12). It is also becoming clear for which individuals CBM shows most promise as an add-on treatment (those with a strong cue-reactivity and/or impulsivity), and we are beginning to understand the neurocognitive mechanisms underlying training effects (e.g., reduced cue-reactivity). CT shows modest but reliable effects as add-on to regular psychosocial treatment, but does not appear to work in the absence of psychosocial treatment, nor in the absence of motivation to change (e.g. in proof-of-principle studies in students). Finally, I will sketch ways forward, such as combining training with neurostimulation.

WEDNESDAY, SEPTEMBER 12 1:50 PM–2:35 PM
PLENARY LECTURE

005

ALCOHOL PHARMACODYNAMICS AND NEUROFUNCTIONAL DOMAINS UNDERLYING ALCOHOL USE DISORDER
V.A. Ramchandani
Section on Human Psychopharmacology, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA

Alcohol use disorder has a tremendous negative individual and global impact, and there is an urgent need to understand its etiology as well as to advance treatment for this devastating illness. Research on the clinical pharmacology of alcohol is necessary to explain how variability in alcohol response affects the risk of developing this disorder. Furthermore, an improved understanding of the genetic, environmental, and neurobiological factors that affect alcohol response could lead to the development of novel treatments.
Dr. Ramchandani's presentation will focus on research advances in characterization of the pharmacological effects of alcohol in humans across the neurofunctional domains of incentive salience, negative affect, and executive dysfunction that are critical to the cycle of addiction. He will include examples of his own human laboratory research that utilizes novel intravenous alcohol administration paradigms to provide a platform of highly controlled alcohol exposure, combined with a range of pharmacodynamic measures, in individuals across the spectrum of alcohol consumption and risk. These studies provide important insights into the relationship between alcohol pharmacodynamics and risk of alcohol problems, and facilitate the identification and screening of potential targets for treatment of alcohol use disorder.

SUNDAY, SEPTEMBER 9 1:30 PM–3:00 PM
SYMPOSIUM
ISBRA-APSAAR SYMPOSIUM: ALCOHOL AND THE BEHAVIOURAL ADDICTIONS PART 1: ALCOHOL AND GAMBLING DISORDER
ORGANIZER/CHAIR: SAWITRI ASSANANGKORNCHAI CHAIR: JOHN B. SAUNDERS

006

ALCOHOL AND BEHAVIOURAL ADDICTIONS: AN OVERVIEW
M.W. Abbott
National Institute of Public Health and Mental Health Research, Auckland University of Technology, New Zealand

This presentation provides an overview of alcohol and behavioural addictions, including examination of their common and distinctive features and consequences. Consideration is given to the increasing convergence of on-line gambling and gaming and possible implications for prevention and treatment Particular emphasis is given to problem gambling and gambling disorder, including their definition, assessment and epidemiology. Major risk factors and wider gambling-related morbidities and harm are considered, in part drawing on clinical and large prospective jurisdiction-wide studies conducted by the presenter and colleagues in New Zealand, Sweden and Australia. These studies include the first to apply burden of harm methodologies to gambling.

007

PREVALENCE AND CORRELATES OF THE BEHAVIOURAL ADDICTIONS
H.J. Rumpf
Department of Psychiatry and Psychotherapy, University of Lübeck, Germany

Pathological gambling has been discussed as a disorder with similarities to substance use disorders since many years. It is now included as a behavioural addiction in DSM-5 and is currently suggested for introduction in ICD-11. In addition, gaming disorder is suggested for ICD-11 and it has been introduced as condition for further studies in DSM-5. This presentation reviews prevalence data from non-Asian countries for these disorders and data on the more broader term Internet addiction. Data providing prevalence estimates differ widely which is due to different assessment instruments used and recruitment via non-representative samples as well as other methodological issues. This diversity of findings can be found in all disorders but is even more pronounced in gaming and Internet use disorders compared to gambling. This might be related to the fact that the majority of studies have used convenience samples and only few general population studies have been conducted. Cross-national studies that used the same methodology in different countries are more valid for comparisons. Some data exist and show significant differences between countries for gaming disorder in adolescents. Male gender, unemployment, migration background and psychiatric comorbidities are some of the correlates of these disorders and provide opportunities for prevention approaches.

008

PREVALENCE OF GAMBLING AND GAMING DISORDERS IN ASIAN COUNTRIES

P. Kittirattanapaiboon[1], S. Assanangkornchai[2]
[1]Department of Mental Health, Ministry of Public Health, Thailand and [2]Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Thailand

Gambling and gaming problems have been identified as an emergent public health issue along as the increase in technology and Internet access in the modern world nowadays. The aim of this paper is to present the findings from a nationwide survey of gambling disorders among general population and gaming involvement and gaming disorder among adolescents in Thailand. Based on the National Mental Health Survey in Thailand in 2013, using the Composite International Diagnostic Interview, the estimated lifetime prevalence rates of DSM-IV pathological and problem gambling were 0.90% (95% confidence interval (CI): 0.51–1.29) and 1.14% (95% CI: 0.58–1.70), respectively. These rates are lower than that found in other Asian countries, for example South Korean, Japan, Taiwan and Singapore, which may due to the use of different research instruments and the unavailability of many kinds of gambling in Thailand. Based on the Thai Game Addiction Screening Test, 3.5% and 5.2% of the male and female high-school students in 2016 could be classified as having problematic game playing. These prevalence rates also seem low. Comparisons of the prevalence and characteristics of both conditions with other Asian countries where data are available and some questions for future research will be discussed.

009

DIAGNOSIS AND CLASSIFICATION OF THE BEHAVIOURAL ADDICTIONS IN ICD-11

J.B. Saunders
Centre for Youth Substance Abuse Research, University of Queensland, Australia

New forms of gaming and gambling have emerged in recent years, most notably role-playing and multiplayer online games and on-line betting. Concerns are voiced from members of the community, families, health professionals and gamers and gamblers about adverse impacts arising from excessive involvement with these activities. This presentation focuses on the features of gaming and gambling disorders and their similarities and contrasts with alcohol and other substance use disorders. Some features such as “immersion” in gaming and “chasing” losses appear distinct. Whether physiological features such as tolerance and withdrawal occur in gaming and gambling disorder are matters of continuing research. Both disorders are included in the international diagnostic systems DSM-5 and ICD-11, the latter being scheduled for publication in late-2018. Gaming and gambling disorders in the draft ICD-11 are defined as (i) impaired control over the activity, (ii) increasing priority in life, such as gaming or gambling take precedence over other interests and responsibilities, and (iii) their continuation or escalation despite negative consequences. The diagnosis also requires significant impairment in personal, family, social, educational, occupational or other important areas of functioning. The presentation will review the basis of these criteria and evidence for the addictive nature of these two disorders.

SUNDAY, SEPTEMBER 9 **3:30 PM–5:00 PM**

SYMPOSIUM

ISBRA-APSAAR SYMPOSIUM: ALCOHOL AND THE BEHAVIOURAL ADDICTIONS PART 2: GAMING DISORDER: DIAGNOSIS AND MANAGEMENT

ORGANIZER/CHAIR: SAWITRI ASSANANGKORNCHAI CHAIR: JOHN B. SAUNDERS

010

TECHNIQUES FOR SCREENING AND ASSESSMENT FOR GAMING DISORDER

R. Kalayasiri[1], D. Saingam[2], S. Assanangkornchai[2]
[1]Department of Psychiatry, Chulalongkorn University Faculty of Medicine, Thailand and [2]Epidemiology Unit, Prince of Songkla University Faculty of Medicine, Thailand

Gaming disorders have been considered as a type of behavioral addiction. However techniques for screening and assessment for gaming disorder are still lacking. In Thailand, Pornnoppadol and colleagues developed the Game Addiction Screening Test (GAST) that was used as the main instrument to assess gaming involvement and gaming disorder in a nationwide survey among adolescents in Thailand. The GAST includes versions for gamers and their parents. Each version was designed to assess three major domains of gaming disorder including preoccupation, loss of control, and function impairment. Of 38,186 high school students, 3.5% and 5.2% of male and female had problem gaming in 2016. We will discuss psychometric properties of the GAST from this nationwide data and review screening and assessment tools for gaming disorder from other countries. Related factors and association with other mental health will be presented.

011

ASSESSMENT AND MANAGEMENT OF GAMING AND ONLINE GAMBLING DISORDER IN YOUNG ADULTS IN INDONESIA

K.S. Kurniasanti
Department of Psychiatry, University of Indonesia, Indonesia

Digital technology was growing very rapidly. It lead to risk of mental development problems in youth and young adult, such as gaming and online gambling disorders. The problem was found in many teenagers and young adults around the world, including Indonesia. Previous study showed that 20% students in secondary and high schools in Jakarta suffered from internet addiction. A specific assessment tool to determine internet addiction among adolescents and young adults in Indonesia isn’t yet available in this time. Prior study has been conducted to develop a valid and reliable Indonesian version of Internet Addiction Diagnostic Questionnaire as a screening instrument for internet addiction prevention. Teenagers, young adults, and parents should be involved through assessment to assist in early diagnosis of potential internet (gaming and online gambling disorders). Teenagers and young adults at risk in gaming and online gambling disorders should also be screened for comorbid behavioral problems such as depression, anxiety, attention deficit, and hyperactivity disorder. Initial management of gaming and online gambling disorders was important to avoid any negative impacts. Unfortunately, there was no specific service or national guidelines management for gaming and online gambling disorders. The Indonesian government through the health ministry was developing preventive guidelines of gaming and online gambling disorders for community.

012

MANAGEMENT OF GAMING DISORDER AND INTERNET ADDICTION IN JAPAN
S. Mihara, H. Nakayama, S. Higuchi
National Hospital Organization Kurihama Medical and Addiction Center, Japan

Background: The treatment of gaming disorder (GD) and internet addiction (IA) is in its infancy worldwide. In an attempt to gauge the treatment and counseling capacity in relation to GD and IA in Japan, we conducted a survey of mental health and welfare centers (MHWC), in 2016. These centers are the principal facilities providing consultation services for mental health problems in prefectures and major cities.
Methods: The survey aimed to clarify the centers' functionality in the early identification of GD and IA. It also included questions to identify specialist medical and non-medical facilities providing specialist treatment or counselling services.
Results: All 69 centers responded to our survey. The majority (n = 53, 77%) solely provided non-specialist consultation, with 12 (17%) providing specialist consultation. The number of centers that offered both face-to-face and telephone-based consultations is on the rise but still limited. The number of medical facilities offering specialist treatment was 38, while the number furnishing specialist counseling stood at 3, for the whole of Japan.
Conclusion: Our study suggested that the number of MHWCs and facilities providing specialist treatment and/or counseling were limited. Currently, information on treatment and counseling capacity and demand is being updated and will be presented at the meeting.

013

GOVERNMENT POLICIES AND PROGRAMS TO MINIMIZE THE HARM FROM GAMING DISORDER
S.K. Lee
Psychiatry, Hallym University, Chuncheon Sacred Heart Hospital, Korea

Korea is well known to be one of the most wired, hyper-connected country in the world, where more than 94% of people have high-speed connections in broadband Internet service. The securing of the internet construction has caused the merit and demerit. The most serious thing is the adverse effect of Internet addiction. Especially, as the problems of adolescent Internet addiction became a social issue, the Korean government has been promoting the prevention and minimizing of Internet addiction since the early 2000s.
The policies of the Korean government are as follows: First, school-based screening and promotion of preventive education, second, individual and group counseling, treatment support programs, third, regulations to restrict excessive use of games, fourth, controlling to accessibility for gaming. More than five Korean government agencies have participated and involved in these policies for Internet gaming problems. Nevertheless, there are differences in the basic concept of Internet addiction among government agencies, overlapping with the policies of youth, and the problem of policy dilemma is constantly exposed due to the conflicting value of youth protection and game industry promotion. We will review the effectiveness of the Korean government's diverse various Internet game addiction prevention and resolution policies.

SUNDAY, SEPTEMBER 9 **1:30 PM–3:00 PM**
SYMPOSIUM
DIRECT ALCOHOL MODULATION OF ION CHANNELS: INSIGHTS AND ENIGMAS IN THE POST-STRUCTURE ERA
ORGANIZER/CHAIR: REBECCA J. HOWARD CHAIR: R ADRON HARRIS

014

DETERMINING THE *IN VIVO* IMPORTANCE AND ACTION OF ETHANOL ON THE BK POTASSIUM CHANNEL
J. Pierce
University of Texas at Austin, USA

Alcohol has many *in vivo* molecular targets. Our lab uses unbiased genetic approaches to help determine which molecule represents the most significant target for mediating acute responses to ethanol. Independent forward, reverse and GWAS genetic studies point to the BK potassium channel. Studies have shown that ethanol directly activates the BK channel at pharmacologically relevant concentrations of 20–100 mM. Although direct evidence supports a major role of the BK channel for behavioral responses to alcohol in the nematode *C. elegans*, only indirect evidence, so far, supports a role for the BK channel in ethanol-mediated responses in mammals. We recently discovered a single conserved residue that can be mutated to render the BK channel insensitive to ethanol but unaltered for normal function when assessed *in vitro* and *in vivo*. We will present our latest results on how the BK channel and this conserved residue contribute to different alcohol behaviors in worm and mammal.

015

DUAL ACTIVATION OF NEURONAL G PROTEIN-GATED INWARDLY RECTIFYING POTASSIUM (GIRK) CHANNELS BY CHOLESTEROL AND ALCOHOL
P.A. Slesinger[1], A. Schlessinger[2], Y. Zhao[1], I. Glaaser[1]
[1]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, USA and [2]Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, USA

Activation of G protein-gated inwardly rectifying potassium (GIRK) channels provides an important component of inhibition in the brain. In addition to the canonical G protein-activation pathway, GIRK channels are activated by small molecules but less is known about the underlying gating mechanisms. Here we used a reconstitution strategy with highly purified mammalian GIRK2 channels incorporated into liposomes and demonstrate that cholesterol or intoxicating concentrations of ethanol, i.e., >20 mM, each directly activate GIRK2 channels, in the absence of G proteins. Notably, both activators require the membrane phospholipid PIP_2 but appear to interact independently with different regions of the channel. Elucidating the mechanisms underlying G protein-independent pathways of activating GIRK channels provides a unique strategy for developing new types of neuronal excitability modulators.

016

CLUSTERS OF HYDROPHOBIC AMINO ACIDS IN THE MEMBRANE-ASSOCIATED DOMAINS REGULATE ION CHANNEL GATING AND FORM PUTATIVE SITES OF ALCOHOL ACTION IN THE NMDA RECEPTOR

R.W. Peoples
Department of Biomedical Sciences, Marquette University, USA

The *N*-methyl-D-aspartate glutamate receptor (NMDAR) is a major target of alcohol in the brain. Studies from this and another laboratory have identified individual positions in the NMDAR membrane-associated (M) domains that regulate alcohol sensitivity and ion channel gating. The solved structure of the GluN1/GluN2B NMDAR in the closed state shows close apposition of these alcohol-sensitive positions in M3 and M4 at the intersubunit interfaces. Recent work from this laboratory has provided evidence that clusters of these positions in M3 and M4 of the NMDAR GluN1 and GluN2A-C subunits form putative sites of alcohol action. Positions within the clusters interactively regulate alcohol sensitivity and ion channel gating, and the clusters form pockets with both hydrophobic and hydrogen bonding characteristics that could accommodate alcohol molecules. Although the positions regulate gating, changes in gating due to mutations at these positions do not account for changes in receptor alcohol sensitivity. Selected dual mutations at these positions can essentially eliminate NMDAR alcohol sensitivity. These findings are consistent with the existence of four sites of alcohol action on the NMDA receptor at the M3–M4 domain intersubunit interfaces. These studies were supported by grants R01 AA015203-01A1 and AA015203-06A1 from the NIAAA to R.W.P.

017

ALCOHOL MODULATION VIA ALLOSTERIC TRANSMEMBRANE SITES IN PENTAMERIC LIGAND-GATED ION CHANNELS

R.J. Howard[1], S.A. Heusser[1], Y. Zhuang[2], M. Lycksell[1], G. Klement[3], L. Orellana[1], E. Lindahl[1,3]
[1]Department of Biochemistry & Biophysics, Stockholm University, Sweden, [2]Section of Chemistry, Uppsala University, Sweden and [3]Biophysics Research Unit, KTH Royal Institute of Technology, Sweden

Small-molecule modulators such as alcohol have been shown to bind an intersubunit transmembrane site in pentameric ligand-gated ion channels. However, due in part to limited crystallographic data, the structural basis and mechanistic impact of these interactions remain unclear. Using the structurally accessible model system GLIC, we applied a combination of X-ray crystallography, oocyte electrophysiology, and molecular dynamics simulations to characterize interactions stabilized in particular functional states by alcohol. Mutations at the subunit interface stabilized solvent-mediated interfacial contacts specific to the apparent open state, a mechanism distinct from mutations in the channel pore, leading to nonadditive effects on gating. We also found evidence for both potentiation and inhibition via distinct allosteric sites, depending on the functional state most favorably bound. Our results provide structural and dynamic detail for an allosteric model of ion channel gating and modulation, including a critical role for solvation at subunit interfaces.

SUNDAY, SEPTEMBER 9 3:30 PM–5:00 PM

SYMPOSIUM

GENETIC AND EPIGENETIC SIGNATURES THAT MEDIATE DIFFERENTIAL ALCOHOL DRINKING AND ETHANOL RESPONSES

ORGANIZER: KRISTIN HAMRE CHAIRS: FENG C. ZHOU AND KRISTIN HAMRE

018

GENOMIC SIGNATURE OF ALCOHOL PREFERRING (P) AND NON-PREFERRING (NP) RATS

F.C. Zhou, C.-I. Lo, L. Lumeng, R. Bell, W.M. Muir
Indiana University School of Medicine, USA

Alcohol use disorders (AUD) is prevalent in families. To date, the genetic signature that passes across generations to increase the tendency to drink is not apparent. To address this issue, we sequenced the selectively inbred Alcohol-Preferring (P) rats and non-preferring (NP) rats lines that exhibit many features consistent with alcoholism. Using whole-genome sequencing to identify regions with genetic differences that are associated with alcohol drinking preference and using the population stratification index (Fst), we identified, over 70,000 signatures of selection (SS, excessive differentiation in the genomic architecture between lines) in ~2800 genes associated with alcohol preference at FDR < 0.1%. The distribution of these SS were in the decreasing order of intron > UTR > promoter > Exon >> intergenic regions, suggesting that differences in alcohol preference were primarily due to alterations in intronic and regulatory regions. We found over 500 missense variants in exons. We confirmed among all SS previously identified genes: e.g. *Grm2* (glutamate metabotropic receptor 2), *NPY1r* (neuropeptide-Y receptor Y1) and *Snca* (synuclein); and newly identified genes involved in synaptic memory and reward behavior, e.g. ion channels (*Kcna5 &6, Kcnh1&5, Scn5a*), excitatory receptors (*Grm1, Slc17a6, Grin2b, Gria4*), GABA receptors (*Gabra2&4, Gabrb1*), opioid receptor (*Opcml, Oprk1*), and synapses (*Pdzrn3, Camk2b, Nsmf*).
Funding: P60AA07611 and AA016698.

019

GENETIC POLYMORPHISMS OF ADH1B AND ALDH2 AND THEIR PHENOTYPES IN JAPANESE ALCOHOLIC MEN

A. Yokoyama
National Hospital Organization Kurihama Medical and Addiction Center, Japan

ADH1B (rs1229984) and ALDH2 (rs671) genotypes affect alcoholism susceptibility. We evaluated ADH1B/ALDH2 genotypes in 4109 Japanese alcoholic men during 2004–2017. A increase in inactive ALDH2*1/*2 heterozygotes in Japanese alcoholics had been reported; 3% in 1972 and 13% in 1992 under the sociocultural influence. This tendency has been continuing; 14.8% during 2004–2007, 15.9% during 2008–2012, and 17.3% during 2013–2017. Slow-metabolizing ADH1B*1/*1 is rare (3–7%) in Japan. However, 27.4% of the subjects has ADH1B*1/*1(38.6% in their 30s, 33.3% in 40s, 28.3% in 50s, 25.5% in 60s, and 17.5% in 70s). A simple alcohol flushing questionnaire is reliable in detecting inactive ALDH2. However, among the ALDH2*2 alcoholics, current or former flushing was reported in 48.4% of ADH1B*1/*1 and in 77.3% of ADH1B*2 carriers ($p < 0.0001$). Among the ALDH2*1/*1 alcoholics, it was 6.7% of ADH1B*1/*1 and 10.0% of ADH1B*2 carriers ($p < 0.005$). Among 971 of the subjects the proportion of who have ever been told to be reeking of alcohol more than 12 h after drinking was 52.3% in ADH1B*1/*1, 32.1% in ADH1B*1/*2, and 27.5% in ADH1B*2/*2 carriers ($p < 0.0001$). It was 43.6% in ALDH2*2 and 34.7% in ALDH2*1/*1 carriers ($p < 0.05$). Alcohol flushing and time of alcohol lingering are modulated by the ADH1B/ALDH2 genotypes, determining alcoholism susceptibility.

020

TRANSCRIPTIONAL REGULATION OF LINE-1 RETROTRANSPOSONS IN MODELS OF ALCOHOL USE DISORDER

I. Ponomarev, C.T. Tulisiak, L.B. Ferguson, C. Bridges, E.K. Erickson, R. Dayne Mayfield, R. Adron Harris
Waggoner Center for Alcohol & Addiction Research and the College of Pharmacy, The University of Texas at Austin, USA

Transposable elements (TEs) are genomic repeats that constitute approximately 50% of the mammalian genomes. Some TEs are transcriptionally activated in a number of psychiatric conditions and in cancer, though whether they mechanistically contribute to these diseases is unknown. To evaluate transcriptional regulation of TEs in Alcohol Use Disorder (AUD), we measured expression of Long Interspersed Nuclear Element 1 (LINE-1) retrotransposons in models of AUD using Illumina microarrays. We re-analyzed our published microarray data from postmortem superior frontal cortex (SFC) of human alcoholics and matched control cases and identified one probe that mapped to multiple genomic locations containing Human-Specific LINE-1 (L1HS) sequence. L1HS had higher expression in alcoholics compared to controls and we validated this finding using RT-qPCR in two independent cohorts of subjects. We also observed elevated expression of L1HS in alcoholic SFC at the protein level using commercially available antibody and immunofluorescent histochemistry. We examined LINE-1 expression in mouse brain and showed that several microarray probes representing this TE were differentially expressed in various brain regions and cell types of two mouse models of alcohol binge drinking. We hypothesize that transcriptional regulation of LINE-1 retrotransposons in brain may contribute directly or indirectly to neuroadaptations and neuropathologies associated with AUD.

021

EPIGENETIC DYSREGULATION IN THE MPFC REGULATES ALCOHOL-ASSOCIATED BEHAVIORS

E. Barbier[1], R. Barchiesi[1], E. Domi[1], G. Augier[1], E. Augier[1], C. Wahlestedt[2,3], M. Heilig[1]
[1]Center for Social Affective Neuroscience, IKE, Linkoping University, Sweden, [2]The Center for Therapeutic Innovation, University of Miami Miller School of Medicine, Miami, FL, USA and [3]Department of Psychiatry & Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, USA

Substantial evidence suggests that epigenetics have been implicated in the pathophysiology of alcohol dependence. However, the specific molecular mechanisms mediating dependence-induced neuroadaptations remain largely unknown. We found that a history of alcohol dependence persistently increases DNA methylation in the prelimbic cortex (PL). Infusion of the DNA methyltransferase inhibitor RG108 into the PL of postdependent rats, prevented both escalation of alcohol consumption as well as dependence-induced neuroadaptation of several genes. For instance, decreased level of genes that code for proteins involved in synaptic neurotransmission were restored by a chronic treatment of RG108. Our results are in accordance with prior post-mortem studies, which have shown changes in the expression pattern of genes involved in synaptic neurotransmission in the prefrontal cortex of alcoholics. Moreover, infusion of RG108 also restored the level of the histone methylating enzyme PRDM2. Knockdown of PRDM2 in the PL of non-dependent rats show similar alcohol-associated behaviors than post-dependent rats, suggesting a role of PRDM2 in escalation of alcohol consumption, compulsivity- and relapse-like behaviors. Together, our findings identified a functional role of DNA methylation in alcohol dependence-like behavior phenotypes where DNA methylation-dependent downregulation of *Prdm2* rats may be one of the mechanisms through which DNA hypermethylation induces alcohol-seeking behavior.

SUNDAY, SEPTEMBER 9 **1:30 PM–3:00 PM**

SYMPOSIUM

RISK FACTORS FOR ALCOHOLIC LIVER DISEASE

ORGANIZER/CHAIR: HELMUT K. SEITZ CHAIR: MANUELA G. NEUMAN

022

GENETICS AS RISK FACTORS IN ALCOHOLIC LIVER CIRRHOSIS (ALC)

D. Seth
Royal Prince Alfred Hospital and Centenary Institute, Australia

The weak relationship between the amount of alcohol consumed and development of ALC displays severe liver disease in some with moderate alcohol use and mild injury in others with high alcohol consumption, leading to the obvious question – what factors determine whether or not a heavy drinker develops ALC? The evidence for a genetic basis has been investigated for genes involved in ALC pathogenesis, but remain largely unconfirmed. Genome-wide searches have identified several polymorphisms in PNPLA3, TM6SF2 and MBOAT7 associated with the risk of ALC. These gene variants are also shared with the risk for NAFLD/NASH, indicating non-specificity to alcohol-induced liver disease. Most recently, HSD17B13 (rs72613567) and SAMM50 variants (known in NAFLD) showed variable risk associations with ALC. Intriguingly, all these genes are involved in lipid processing pathways. PNPLA3 rs739409 increases hepatic lipid accumulation, TM6SF2 rs58542926 controls lipid droplet size and number, MBOAT7 (rs641738) acyltransferase remodels phospholipids leading to hepatic inflammation. This suggests that dysfunctional lipid metabolism presenting as steatosis as an initial pathophysiological change, plays an important role in the chronic development of alcoholic- and non-alcoholic liver diseases. Importantly, it also indicates a link between the underlying genetic variation and obesity, another risk factor for both ALC and NAFLD.

023

THE INTERPLAY OF ALCOHOL WITH DRUGS INCLUDES MULTIPLE FACETS

M. Neuman
University of Toronto, Canada

These include the effects of alcohol on the effects of other hepatotoxicants, and on the pharmacological effects of various drugs. Also relevant is the possible role of alcohol on the effects of carcinogenic agents. Less striking, but significant, are the effects of other drugs on the effects of ethanol. More difficult to identify but presumably significant, are the effects of alcohol-drug interplay on the development of alcoholic liver disease. A common denominator of them is the role of metabolism of ethanol and of ethanol-induced P-4502E1 (CYP2EI) in affecting the toxicity of some hepatotoxicants and the effects of some drugs. Less prominent but also relevant is the effect of interplay with alcohol dehydrogenase and aldehyde dehydrogenase in the toxicity of some drugs.

Alcohol had been regarded as toxic for the liver for several centuries, although during this century the recognition was temporarily in abeyance. Held responsible for cirrhosis in the 18th century and labeled a hepatotoxin in the 19th century, alcohol was cleared of hepatotoxicity during the first half the 20th century only to be reinstated as a hepatotoxic agent during the second half. This century has also seen the recognition that alcohol can enhance the toxic effect of other hepatotoxic agents. Most of the attention had focused on the increase, by alcohol intake of acetaminophen toxicity. Ethanol also has been found to enhance the hepatotoxic effects of aflatoxin B_1, allyl alcohol, bromobenzene, cocaine, enflurane, galactosamine, halothane, isoniazid, nitrosamines, thioacetamide, vinyl chloride, and vitamin A. The toxicity of several hepatotoxicants is unaffected, and of at least one, amanitine, is decreased by ethanol. The effect of ethanol on the toxicity of carbon tetrachloride and acetaminophen have been studied most extensively. These studies have demonstrated that the enhancement of toxicity by ethanol does not depend on ethanol-induced hepatic injury but rather on the enhancement of activity of the cytochrome P450 2E1 that convert the respective hepatotoxicants to their active metabolites. Nevertheless, inhibition by ethanol of regenerative response to injury may contribute to enhancement of toxicity by ethanol. The enhancement of toxicity by ethanol may have a bearing on the liver disease of alcoholism as well as on the toxicity and carcinogenicity of individual toxicants.

024

HEPATIC SINUSOIDAL PRESSURE AS PROGRESSION FACTOR FOR ALCOHOLIC LIVER DISEASE: DOES SPLEEN STIFFNESS ALLOW TO ALLOCATE THE HISTOLOGICAL SIDE OF PRESSURE ELEVATION?

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[1]Centre of Alcohol Research University of Heidelberg, Germany and [2]National Liver Institute, Menoufia University, Egypt

Background: Sinusoidal pressure elevation has been proposed as an important progression factor of alcoholic liver disease (ALD).
Aim: Cross sectional analysis of liver and spleen stiffness (LS, SS) in patients with ALD and hepatitis C (HCV) and their response to alcohol withdrawal and HCV treatment.
Methodology: We prospectively assessed LS and SS in 105 patients with ALD and 218 patients with HCV both before and after alcohol withdrawal and HCV treatment using the FibroScan (Echosens, Paris).
Results: Despite lower mean LS in HCV (15.4 vs. 25.3 kPa), SS was significantly higher in HCV as compared to ALD (40.3 vs. 29.3 kPa, $p < 0.0001$). Consequently, the ratio of SS to LS was significantly higher in HCV as in ALD (3.9 vs. 1.6, $p < 0.0001$). LS significantly decreased after treatment in both diseases by comparable scale (-8.5 vs. -4.7 kPa, $p < 0.0001$), so did SS (-4.5 vs. -11.1 kPa, $p < 0.0001$).The average portal vein pressure was lower in ALD.
Conclusion: We here demonstrate that a lobular liver disease such as ALD has three times lower spleen stiffness as portal-pronounced HCV. It needs to be investigated whether patients with ALD would progress faster to liver cirrhosis but show fewer complication of portal hypertension as compared to HCV.

025

CYTOCHROME P450 (CYP2E1) AS A RISK FACTOR FOR ALCOHOLIC LIVER DISEASE (ALD)

H.K. Seitz
Centre of Alcohol Research University of Heidelberg, Germany

One mechanism by which alcoholic liver disease (ALD) progresses is oxidative stress and the generation of reactive oxygen species, among others due to the induction of cytochrome P-4502E1 (CYP2E1). Experimental data underline the key role of CYP2E1. ALD improved in CYP2E1 knockout mice as well as in rats receiving the specific CYP2E1 inhibitor chlormethiazole (CMZ). To study the role of CYP2E1 in the pathogenesis of ALD we determined CYP2E1, 8-hydroxydeoxyguanosine (8-OHdG), as well as 1,N^6-etheno 2′deoxyadenosine (edA) in hepatic biopsies scored for steatosis, inflammation and fibrosis of 97 patients diagnosed with ALD. A significant correlation was found between CYP2E1 and edA ($p < 0.0001$) as well as between CYP2E1 and 8-OHdG ($p = 0.039$). Both CYP2E1 ($p = 0.0094$) and edA ($p < 0.0001$) also correlated significantly with the stage of hepatic fibrosis. To study whether CYP2E1 inhibition improves ALD, we performed a randomized trial to treat patients with ALD for alcohol detoxification with either CMZ or clorazepate (CA) for 7–10 days. An interims analysis showed a significant inhibition of CYP2E1 by CMZ and a significant improvement of serum transaminase activity in the CMZ group as compared to the CA group already after 7 days demonstrating that CYP2E1 may be an important therapeutic target in ALD.

SUNDAY, SEPTEMBER 9 3:30 PM–5:00 PM

SYMPOSIUM

CELLULAR AND EXTRACELLULAR EFFECTS OF ALCOHOL EXPOSURE IN LIVER AND EXTRAHEPATIC ORGANS

ORGANIZER: CAROL A. CASEY CHAIRS: TERRENCE M. DONOHUE AND CAROL A. CASEY

026

ETHANOL ADMINISTRATION INCREASES POLYUBIQUITYLATION OF HEPATIC LIPID DROPLET MEMBRANE PROTEINS

P.G. Thomes[1], M. Strupp[1], J. Kubik[1], T.M. Donohue[1], M. Mcniven[2], C. Casey[1]
[1]University of Nebraska Medical Center, USA and [2]Mayo Clinic College of Medicine, USA

Prior to lipophagy and lipolysis, lipid droplet (LD) membrane proteins are targeted for degradation by the ubiquitin proteasome system (UPS) or by lysosomes. Specific polyubiquitin (polyUB) chain “codes”, including K48 and K63 polyUB chain linkages attached to their target proteins, generally determine whether the targeted protein will be degraded by the UPS (K48) or by lysosomes (K63). Thus, poly UB coding of LD membrane proteins control the turnover rates of LDs. Because ethanol (EtOH) administration promotes LD accumulation by blocking LD degradation, we ascertained whether dysregulation of LD catabolism includes alterations in polyUB coding of LD membrane proteins. After pair-feeding male Wistar rats control and EtOH liquid diets for 5 weeks, we isolated liver LD-enriched fractions and quantified K48 and K63 polyUB proteins by immunoblotting. After normalizing to the LD membrane marker perilipin-2, we found that LD proteins from EtOH-fed rats exhibited 1.6- and 1.4-fold higher levels of both K48 and K63 polyUB chain-linked proteins, respectively, than pair-fed controls, suggesting that an EtOH-induced block in the degradation of LD membrane proteins likely contributed to LD accumulation in livers of EtOH-fed rats.

027

TRANSCRIPTION FACTOR EB (TFEB) AND LIPOPHAGY ARE DISRUPTED BY ETHANOL FEEDING AND NORMALIZED AFTER ETHANOL WITHDRAWAL

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Chronic ethanol administration to rodents disrupts hepatic autophagy, the lysosomal pathway that degrades cellular macromolecules and organelles. Lipophagy is the selective autophagic breakdown of lipid droplets, which accumulate in liver after heavy drinking. Here, we hypothesized that, because chronic ethanol consumption slows autophagy, it likely retards lipophagy, resulting in fatty liver associated with lower (active) nuclear levels of TFEB, the transcription factor that governs autophagy and lysosome biogenesis. To test this, we fed male Wistar rats liquid control (C) and ethanol (E) diets for 5–7 weeks. We then withdrew E diet from randomly-selected E-fed rats, replacing it with C diet for 7 days. All remaining animals were continued on C or E diet. Results showed that liver nuclei from E-fed rats had 4-fold lower levels of TFEB, while their liver triglycerides (TGs) were 3-fold higher than C-fed rats. Hepatocytes from E-fed rats also exhibited slower autophagic flux with significantly fewer lysosomes than C-fed animals. In contrast, liver TGs in 7 day E-withdrawn rats were 60% lower than E-fed rats and their nuclear TFEB level rose 66% beyond that of C-fed rats, suggesting that after ethanol withdrawal, nuclear TFEB activity was rather rapidly restored, thereby accelerating lipophagy.

028

UPREGULATED AUTOPHAGY IN SERTOLI CELLS OF ETHANOL-TREATED RATS: EVIDENCES, MECHANISMS AND IMPLICATIONS

N. Eid[1], Y. Ito[1], A. Horibe[1], H. Hamaoka[1], Y. Tanaka[1], Y. Otsuki[2], Y. Kondo[1]
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A few studies investigated the involvement of prosurvival autophagy in testicular damage by ethanol as compared to studies on other organs such as the liver. We investigated the autophagic response of Sertoli cells (SCs) to acute ethanol toxicity (5 g/kg ethanol) using a rat model and cultured SCs. Compared to the control group (given PBS), we observed enhanced germ cell apoptosis in the ethanol-treated rats (ETRs) in association with upregulation of iNOS and reduced expression of androgen receptor protein levels in SCs, which were resistant to apoptosis. Meanwhile, autophagy was upregulated in ETR SCs compared to the control group, as evidenced by TFEB nuclear translocation, enhanced expression of autophagy proteins LC3, LAMP-2, pan cathepsin and reduced expression of p62. Moreover, excessive accumulation of PINK1 (sensor of damaged mitochondria and mitophagy) was observed in ETR SCs. This upregulation of SC autophagy was confirmed ultrastructurally and by immunofluorescent double labelling of autophagosomal and lysosomal markers. Study of cultured SCs confirmed the enhanced autophagic response to ethanol toxicity, which was cytoprotective based on decreased viability of SCs upon blocking autophagy with 3-MA. Enhanced autophagy in SCs appears to be a prosurvival mechanism, essential for testicular homeostasis and fertility upon exposure to various stressors.

029

ROLE OF SPLICING REGULATOR SLU7 IN ETHANOL-INDUCED INFLAMMATION AND LIVER INJURY

M. You
Department of Pharmaceutical Sciences, Northeast Ohio Medical University, USA

Erroneous precursor mRNA (pre-mRNA) splicing contributes to liver diseases. Splicing regulator Slu7 governs splicing of genes implicated in lipid metabolism, inflammation, development, and progression of fibrosis and cirrhosis in liver. We investigated Slu7 in the development and progression of alcoholic steatohepatitis. Adenovirus-mediated alteration of hepatic Slu7 expression in mice fed with or without (as control) ethanol in diet was utilized. Ethanol administration significantly increased gene and protein expression of Slu7 in the liver and intestine of mice compared to control mice. Ethanol-mediated elevation of Slu7 correlated with development of steatohepatitis. Knockdown of hepatic Slu7 by Ad-Slu7 shRNA treatment ameliorated inflammation and attenuated liver injury in ethanol-fed mice. Mechanistically, reducing liver Slu7 expression increased expression of sirtuin 1 (Sirt1) full-length gene and repressed the splicing of SIRT1 into SIRT1-DeltaExon8 isoform in ethanol-fed mice. Concordance with ameliorated splicing of Sirt1, knockdown of hepatic Slu7 inhibited the activity of nuclear factor kappa B (NF-kappaB), normalized iron homeostasis, reduced oxidative stress, and attenuated liver damage in ethanol-fed mice. Additionally, hepatic Slu7 gene and protein were significantly elevated in patients with alcoholic steatohepatitis. Our study illustrated roles of Slu7 in alcoholic liver injury and suggested that dysregulated Slu7 contributes to the pathogenesis of human alcoholic steatohepatitis.

030

MIF INHIBITION PROTECTS HEPATOCYTES FROM GAO-BINGE-INDUCED INJURY INDEPENDENT OF NEUTROPHIL ACCUMULATION

L. Nagy
Cleveland Clinic, USA

Macrophage migration inhibitory factor (MIF) is increased in circulation of cirrhotic and alcoholic hepatitis (AH) patients and MIF−/− mice are protected from liver inflammation and injury in a chronic model of alcohol-induced steatosis. We therefore hypothesized that MIF might play a contributing role to liver damage in AH and tested this using a genetic deletion of MIF and a novel, small-molecule MIF inhibitor in the Gao-Binge(acute on chronic) model of murine alcoholic hepatitis (mAH). The peak of liver injury and inflammation occurred 6 h after ethanol binge. Both MIF deletion and inhibition protected mice from liver injury as measured by plasma ALT, but did not prevent the robust neutrophil accumulation known to occur in the Gao-Binge feeding model. Instead, the protective effect of MIF deletion or inhibition was associated with decreased development of ER stress following Chronic-Binge model of mAH. Furthermore, MIF inhibition *in vitro* directly protected hepatocytes from ethanol-induced cytotoxicity. Taken together, these results suggested that MIF contributes to ethanol-induced hepatotoxicity in mice through modulation of hepatocyte-specific ER stress, independent of neutrophil accumulation and that pharmacological MIF inhibitors could represent novel therapies for patients with AH.

SUNDAY, SEPTEMBER 9 1:30 PM–3:00 PM

SYMPOSIUM

POSSIBILITIES AND CHALLENGES USING E-HEALTH AND M-HEALTH FOR ADDICTION TREATMENT

ORGANIZER/CHAIR: AYUMI TAKANO CHAIR: TOSHIAKI BABA

031

SMARTPHONE-BASED SELF-MONITORING APPLICATION FOR DRUG USERS: CO-PRODUCTION WITH TARGETED USERS

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Various smartphone-based applications (app) have been developed to promote mental health, however, dissemination of these applications is still challenging. We developed a new smartphone-based application for drug users who do not seek and receive treatment. The program was developed in collaboration with ex-drug users, peer educators, a lawyer, and ICT developers, as well as researchers to determine preferences and to maximize utility. The topics discussed included: a user-friendly application, protection of user privacy and confidentiality, and motivators for drug users to encourage personal responsibility in healthcare. The discussions provided several ideas for functionality, such as: self-monitoring, encouragement messages, and display of related information. The self-monitoring includes a daily record of drug use, emotions, and triggers of drug use that users can customize. The users can check monthly and annual progress. Different encouragement messages are provided by cartoons that are displayed after each login. The related information functionality includes an embedded page with basic information about mental health and support services and an updatable page providing recent information, such as for public events. A pilot study will be conducted to assess the usability and acceptance of this app among active drug users.

032

POLICY IMPLICATIONS OF EHEALTH INTERVENTIONS FOR ADDICTION

T. Baba
Department of Mental Health Policy, National Institute of Mental Health, Japan

There are some attempts to develop evidence-based eHealth interventions for addiction. Similar efforts have already made in depression and they are already incorporated in the national policy e.g. NICE guidelines in England and Wales. In this presentation, the speaker is going to talk about what is expected after evidence-based eHealth interventions are developed in the addiction medicine with special reference to cost-effectiveness and resource implications.

033

HOW EFFECTIVE IS A BRIEF WEBSITE INTERVENTION WITH PERSONALIZED NORMATIVE FEEDBACK AMONG JAPANESE ADULTS WITH RISKY DRINKING? FINDINGS FROM A PILOT RCT

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Screening and brief interventions are one approach for preventing and treating alcohol-related problems. The literature shows that computer-delivered interventions can be an effective method because of several technological advantages such as accessibility and cost-effectiveness. Although effectiveness of computer-delivered interventions is limited for less 6 months according to the literature, interventions with personalized normative feedback and psychoeducation have shown some promising results for risky drinking. Meanwhile, its effectiveness is not known in Japan. In my part of presentation, I will introduce development of a screening brief intervention and tentative results of a randomize controlled trial for reducing risky drinking among Japanese adults with problematic drinking. The speaker and co-authors have developed a website that includes personal normative feedback and psychoeducation. Outcome measures include drinking quantity, drinking frequency, and alcohol-related consequences. Follow-up assessment takes place at 1, 2, and 6 months. Results will be discussed during the presentation. This type of web-based brief intervention has the possibility of being implemented in Japanese school and workplace settings as a prevention tool.

034

M-HEALTH INTERVENTIONS FOR GAMBLING PROBLEMS

R. So[1], T. Baba[2], S. Furuno[3], H. Okada[3], T.A. Furukawa[4], S. Matsushita[3], S. Higuchi[3]
[1]Okayama Psychiatric Medical Center, Japan, [2]School of Integrated Health Sciences, Faculty of Medicine, The University of Tokyo, Japan, [3]National Hospital Organization Kurihama Medical and Addiction Center, Japan and [4]Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Japan

Less than 10% of people with gambling disorder (GD) seek any formal treatment though there are effective psychological interventions such as cognitive behavioral therapy. The reason for this treatment gap might be the lack of specialized therapists and facilities for gambling problems as well as the psychological barriers in gamblers to receive face-to-face treatment.
Interventions delivered by mobile devices (M-health) for GD could reduce the treatment gap. A recent meta-analysis showed the potential effectiveness of M-health interventions for GD, however, their drop-out rate was more than twice that of face-to-face interventions. To solve the high drop-out rate, we have developed a chatbot program to support problem gamblers' recovery delivered by LINE, the most popular messaging app in Japan like WhatsApp and WeChat.
In our presentation, I will show what is known and unknown about M-health interventions for GD by reviewing extant literature. Then, I will introduce the development process of the chatbot and the protocol of our ongoing randomized controlled trial to evaluate the effect of the chatbot for problem gamblers.

SUNDAY, SEPTEMBER 9 3:30 PM–5:00 PM
SYMPOSIUM
PERSPECTIVES OF OCCUPATIONAL THERAPY IN ADDICTION
ORGANIZER: TETSUTARO KOSAGO CHAIR: HITOSHI MAESATO

035

ADDICTION BEHAVIOUR AS AN OCCUPATION

Y. Sato
Okayama Psychiatric Medical Center, Japan

We occupational therapists regard a behaviour as one form of occupation and a client as an occpational being. Addiction is a disorganized behavioral pattern or a disorganized occupational pattern, but it gives us some merits or some meanings. For example they are to be calm downed, to be relaxed and so on. They make difficult for us to realize the pattern is the disease because usually a disease does not give us any merits or meanings. We need to treat addiction with occupational perspectives; the meaning of the occupation, the form of the occupation, the function of the occupation, and the transition of the occupation with clients.

036

OCCUPATION-FOCUSED INTERVENTION FOR RECOVERY FROM ADDICTION
T. Misawa, T. Kosago
National Hospital Organization Kurihama Medical and Addiction Center, Japan

Substance use arises when people engage in an excessive pattern of using alcohol or mood-altering. An individual with a substance abuse problem chooses occupations that inevitably will have a negative impact on their physical, mental and social health.
Occupational Therapists may work with individuals to help identify strengths, values, interests, resources and challenges in order to implement plans for recovery.
Establishing occupational performance patterns that may be meaningful patterns of time use for individual needs and creating opportunities for self-discovery may help replace unhealthy activities with healthy, meaningful activities.
"Occupation" is everyday term so that is likely to accept it is not as important as other treatment programs. But it has been clarified that occupational satisfaction would be the protect factors for the risk of relapsing in mental health problems and violent behaviours. We would like to introduce how Occupational therapist' interventions make one's occupational changes.

037

THE COLLABORATIVE POTENTIAL OF OCCUPATIONAL THERAPY IN SUBSTANCE ADDICTION AND REHABILITATION
M.P. Sy, N. Ohshima
Tokyo Metropolitan University, Japan

Substance addiction and rehabilitation (SAR) is a practice area within mental health that inevitably poses a demand for specialized services, manpower, budget, and efficient hospital-to-community transitioning. Both the Philippines and Japan are faced with similar issues but address them differently in terms of treatment setting, the model of practice, and human resources. Specifically, occupational therapy (OT) has been documented to be involved in SAR since the early 1990s but its roles and contributions have been limited to symptom reduction, detoxification, and skills training. This oral presentation aims to inform the community of addiction care specialists about the collaborative nature of occupational therapists. A portion of the Q-methodology study by Sy and associates (2018) will be used to further describe how the principles of interprofessional collaboration (IPC) can both improve the health outcomes of clients with substance use disorder and promote the therapeutic benefits of meaningful activities as part of their recovery and community re-integration.

038

OCCUPATIONAL THERAPY TO MEET THE NEEDS OF ALCOHOL DEPENDENCE CLIENTS
T. Kosago[1], T. Misawa[1], T. Mizuno[2]
[1]National Hospital Organization Kurihama Medical and Addiction Center, Japan and [2]Showa University Karasuyama Hospital, Japan

Occupational therapy in Japan often uses creative activities and physical activities. This is influenced by historical background. Furthermore, Cognitive Behavioral Therapy is the mainstream of treatment, and many professionals including occupational therapist could have the common perspectives for intervention of CBT. It pleases to have Evidence-Based methods as part of many professionals, however the core roles of occupational therapy seems to be lacking. In many countries, occupational therapy has not taken active role in the treatment team of addiction.
We examined OSA version 2 for our clients, which is one of an evaluation scale of occupational therapy, for clarifying the needs of the clients with alcohol dependence. As the result, our research suggested the importance to assess the clients with alcohol dependence from various perspectives which concerns to the life and the occupation as well as the alcohol problems. We believe that these results contribute to other professionals in alcohol problems.

SUNDAY, SEPTEMBER 9 1:30 PM–3:00 PM
SYMPOSIUM
GAMBLING AND GAMING DISORDER
ORGANIZER/CHAIR: HANNU ALHO CHAIR: SUSUMU HIGUCHI

039

TREATING GAMBLING DISORDER WITH FAST ACTING OPIOID ANTAGONIST – NALOXONE NASAL SPRAY: A NOVEL FEASIBILITY STUDY
H. Alho, S. Castren
Clinicum, University of Helsinki, Helsinki, Finland

The strongest empirical support for medication assisted treatment for Gambling Disorder (GD) is for opioid receptor antagonists naltrexone and nalmefene. However, oral administration of these drugs is associated with slow absorption and adverse events. We have recently shown that intranasal (i.n.) administration of the mu opiate receptor (MOR) antagonist naloxone results in a rapid occupation of brain MORs.
We conducted an open label, pilot study to investigate the feasibility of using an i.n. naloxone spray in GD. Twenty participants received "as needed" naloxone in group A (maximum dose 8 mg/day) or in group B (maximum dose 16 mg/day). During the 8 week treatment period gambling activity, adherence to study drug and adverse events (AE) were monitored. Study completion rate was 90%. Participants' attitude toward using the nasal spray was positive throughout the trial. The high dose group (B) used naloxone nasal spray more than group A ($p < 0.001$). There were no group differences in medication related AEs. All participants reduced gambling activity measured by SOGS. Based on these results and our PET studies with naloxone nasal spray, we recently launched a randomized, placebo controlled study of naloxone nasal spray (ClinTrias.Gov IDs: 2017-001946-93) for the treatment of GD.

040

TEMPERAMENT AND CHARACTER PROFILE IN PATHOLOGICAL GAMBLING: A COMPARISON WITH ALCOHOL DEPENDENCE

C. Han, K. Lee
Department of Psychiatry, Gangnam Eulji Hospital, Eulji University, Seoul, Korea

Background: The purpose of this study was to investigate the differences in temperament and personality characteristics of GD and alcohol dependence (AD) patients.
Methods: A total of 132 (56 GD and 76 AD) patients completed the 140 5-point Likert items on the Temperament and Character Inventory-Revised Short version (TCI-RS). We performed independent sample *t*-test, correlation analysis, and Fisher's transformation to see the differences between groups.
Results: The mean age was 39.5 for GD and 44.8 for AD ($t = 2.482$, $p = 0.014$). There are no differences in temperament dimensions. But, in character dimensions, only GD patients had lower self-transcendence (ST) than AD ($t = 4.6$, $p < 0.001$). In the temperament dimension, Novelty seeking (NS) and age showed a negative correlation in both groups. In the personality dimension, ST and age showed a positive correlation in GD, SD and age in AD. In the group difference of the correlation test, the SD was statistically significant ($z = -3.19$, $p < 0.001$).
Conclusion: In this study, we found that there are differences in personality dimensions between GD and AD. This findings suggest that low ST, and SD may be related to GD in the character dimension.

041

PRESENT SITUATION OF GAMBLING AND PREVALENCE OF GAMBLING DISORDERS IN JAPAN

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[1]National Hospital Organization Kurihama Medical and Addiction Center, Japan and [2]School of Public Health, Graduate School of Medicine, University of Tokyo, Japan

Purpose: The results of the nationwide South Oaks Gambling Screen (SOGS) revealed a higher prevalence of gambling disorder in Japan compared with other countries. The present study aimed to confirm the results of that survey.
Subjects and Methods: We investigated general gambling behaviors among 10,000 randomly-selected Japanese participants aged 20–74 years using semi-structured interviews. The participants also completed the SOGS. The Ethics Committee at Kurihama Medical and Addiction Center approved the study protocol.
Results: The overall response rate was 53.7%. The results indicated that 80.6% of men and 57.2% of women had gambled during their lifetime and 41.9% and 24.4% respectively, had gambled during the previous year. The lifetime SOGS score was ≧5 (95% CI: 3.1–4.2%) for 3.6% of the respondents, compared with 0.8% during the previous 12 months (95% CI: 0.5–1.1%).
Conclusions: The prevalence of lifetime SOGS scores ≧5 was higher in Japan than in other countries, suggesting that periodic gambling surveys are needed to understand the actual situation of gambling disorder in Japan.

042

CLINICAL CHARACTERISTICS OF TREATMENT SEEKING INDIVIDUALS WITH GAMBLING DISORDER IN JAPAN: A SYSTEMATIC COMPARISON OF DIAGNOSTIC CRITERIA IN ICD-11 AND DSM-5

T. Matsuzaki, S. Matsushita, S. Higuchi
National Hospital Organization Kurihama Medical and Addiction Center, Japan

Background: Kurihama Medical and Addiction Center in Japan have started outpatient treatment for gambling disorder in 2013. Due to an increasing demand, we started an inpatient treatment program for gambling disorder in 2017. However, clinically meaningful characteristics of these Japanese patients have not been fully studied.
Objective: The aim of this study is to describe the clinical characteristics of the patients with gambling disorder in Japan. In particular, reported symptoms when using DSM-5 diagnostic criteria will be compared against ICD-11 diagnostic criteria.
Method: The participants were 113 patients who were diagnosed with gambling disorder and received CBT treatment at our hospital from June 2013 to April 2017. Their intake information, including demographic data and reported symptoms, were used for the analyses.
Results and Discussion: Of 113 subjects, 92.0% were male, 56.6% were married, and 69.9% were employed. The mean age at first visit was 39.3. The mean debt at first visit was about $20,000. The most preferred type of gambling was Pachinko/Slot machine (90.3%) and second most preferred type of gambling was horseracing (20.4%). By using participants' reported symptoms, ICD-11 diagnostic criteria were compared against DSM-5. The results of the analyses and clinical implications of these findings will be discussed.

SUNDAY, SEPTEMBER 9 3:30 PM–5:00 PM
SYMPOSIUM
RECENT FINDINGS REGARDING INTERNET ADDICTION AND GAMING DISORDER
ORGANIZER: HIDEKI NAKAYAMA CHAIR: DAI-JIN KIM

043

PRECISION MEDICINE IN BEHAVIOR ADDICTION

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The application of precision medicine, which tailors treatment to an individual based on genetic and lifestyle factors, has the potential to improve prognosis of both substance and behavioral addictions by identifying the best available intervention. Lately, machine learning techniques are enabling personalized and predictive medicine by training algorithms for diagnosis and treatment. The DETOX project has launched to elucidate psychological and neurobiological correlates of Internet gaming disorder (IGD) and smartphone addiction and to develop the Smart Healthcare Platform which provides big data analysis system and risk prediction algorithms which identify individual risk factors and offer personalized treatment. Our researches have proceeded to the application of machine learning techniques to neuroanatomical features extracted from brain imaging data to provide a computation-based classification of IGD that provides better understanding and precise therapeutic intervention.

044

THE ROLE OF MOTIVES IN ADDICTIVE VIDEO GAMING

J. Billieux
University of Luxembourg, Luxembourg

Research on online video games has highlighted that an individual's motivations for playing have a crucial role in the onset of online game involvement and in its continuation. A decade ago, Yee (2006) conducted the first empirical studies aimed at identifying the various motivations of online game players. Three broad types of motivations were identified: those related to achievement, to social activity, and to immersion in a virtual world. Each was subdivided into specific subcomponents (e.g. the social factor comprises distinct types of motives such as playing to create new relationships or seeking to solve problems through teamwork). In the current talk, we will emphasize how considering models such as the one developed by Yee is relevant to explore the uniqueness of video game misuse (e.g., in comparison to other types of Internet-related disorders). Results from recent studies having longitudinally explored the relations between gaming motives and actual in-game behaviours will also be presented. Eventually, we will discuss the relevance of existing models of online game motives in relation to distinct types of video games (e.g., FPS, RTS, MOBA, MMORPG).

045

THE COHORT STUDY ON GAMING DISORDER: THE INTERNET USER COHORT FOR UNBIASED RECOGNITION OF GAMING DISORDER IN EARLY ADOLESCENCE (ICURE) STUDY

S.-j. Jo[1], H.W. Yim[1], H. Jeong[1], H.J. Son[1], H. Han[1], S.-y. Lee[2], Y.-s. Kweon[2], H.-k. Lee[2], S.-y. Bhang[3], J.-s. Choi[4]
[1]Department of Preventive Medicine, College of Medicine, The Catholic University of Korea, Korea, [2]Department of Psychiatry, Uijeongbu St. Marys Hospital, College of Medicine, The Catholic University of Korea, Korea, [3]Department of Psychiatry, Eulji Hospital, College of Medicine, Eulji University, Korea and [4]Department of Psychiatry, SMG-SNU Boramae Medical Center, Korea

The Internet user Cohort for Unbiased Recognition of gaming disorder in Early Adolescence (iCURE) study is an ongoing multidisciplinary prospective cohort study in Korea. The iCURE study had begun in 2014 and 2319 teenagers were enrolled to the cohort from 21 schools. The aim of the iCURE is to observe the natural and clinical courses of Internet gaming disorder (IGD) proposed DSM-5, and to find the risk and protective factors of IGD in child and adolescent.
In this presentation, the authors introduced the iCURE study and showed the results of an analysis on the baseline assessment; prevalence of IGD screening positive and clinical diagnosis, and association between Internet gaming behavior and IGD, etc.
In addition, they showed how the individuals' status had changed in the aspect of the IGD screening or diagnosis results via preliminary analysis on the 1-year follow-up data, where not only mental health or psychological health outcomes, but also physical health outcomes of the IGD were included.
In conclusions, IGD has significant implications for young people's health, both in IGD itself and in its impact on psychological and physical health. Therefore, preventive efforts are needed, and it is expected that such efforts would work.

046

SCREENING AND INTERVENTION NEEDS FOR INTERNET ADDICTION COMORBID WITH NEURODEVELOPMENTAL DISORDERS

R. So
Okayama Psychiatric Medical Center, Japan

We previously reported the high prevalence of Internet addiction (IA) defined by Young's Internet Addiction Test among a Japanese adolescent psychiatric clinic sample With ASD and/or ADHD in 2017. Our hypothesis is that adolescents with ASD and/or ADHD have a worse prognosis of IA as well as a high risk to be IA. If the hypothesis is proven, youth with ASD and ADHD needs appropriate screening and intervention for IA. To verify the hypothesis, we are conducting a 2-year follow-up study in 2018.
In the first place, I will introduce the detailed results of the preliminary cross-sectional study in 2017. The results include the risk and the characteristics of IA among youth with ASD and/or ADHD in a psychiatric clinical setting. The second topic is the results of the 2-year follow-up study in 2018 which investigated the natural course and the subjective treatment needs of IA among youth with ASD and/or ADHD. Finally, I will show our practice for youth with IA and their parents in Okayama Psychiatric Medical Center.

047

EFFECTIVENESS OF A SCHOOL-BASED BRIEF GROUP INTERVENTION FOR THE PREVENTION OF INTERNET ADDICTION

H. Nakayama, S. Higuchi
National Hospital Organization Kurihama Medical and Addiction Center, Japan

Aim: The purpose of this study was to evaluate the possible effect of a brief school-based group intervention to prevent IA.
Method: The study participants were all second-grade students in a men's private junior high school. We performed a single session intervention for each class. Questionnaire surveys were conducted just before and 2 months after intervention. Ninety-five students participated in all the procedures and were included in the data analyses.
Result: Both the average Internet use (AIU: Young's Internet Addiction Test [YIAT] 39 points or less) and problematic Internet use (PIU: YIAT 40 points or more) groups showed a significant increase in average sleeping time on weekdays but not on weekend days when the results of a follow-up survey were compared with those of the baseline survey. The average Internet use time spent on devices other than smartphones was significantly reduced between the two surveys only in the PIU group. However, the average Internet use time spent on smartphones did not change in either the AIU or the PIU group.
Conclusion: Because this type of brief group intervention was effective to some degree, its introduction should be recommended as a first step toward preventing IA.

MONDAY, SEPTEMBER 10 9:50 AM–11:20 AM

SYMPOSIUM

ROLE AND THERAPEUTIC POTENTIAL OF OXYTOCIN IN ALCOHOL ADDICTION

ORGANIZER/CHAIR: HOWARD C. BECKER CHAIR: ROSANA CAMARINI

048

ROLE OF OXYTOCIN IN THE MODULATING EFFECTS OF ENVIRONMENTAL ENRICHMENT ON ALCOHOL-RELATED BEHAVIORS IN MICE

R. Camarini[1], M. Rae[1], M. Almeida[1], A. Bailey[2]
[1]University of Sao Paulo, Brazil and [2]St. George's University of London, UK

Our laboratory has focused most of its research on how environmental enrichment (EE) may influence ethanol-elicited behaviors. Our studies showed that EE prevented and reversed ethanol-induced behavioral sensitization, decreased ethanol intake after an acute exposure to restraint stress, but increased ethanol-induced conditioned place preference (CPP) in both adolescent and adult mice. This latter effect seems to be oxytocinergic system-dependent. We have now investigated the effects of EE and carbetocin, an analogue of oxytocin (OT), on ethanol consumption before and after exposure to an acute predator stress. Predator stress exposure increased ethanol intake 1 week after stress. Mice exposed to EE showed reduced ethanol intake, suggesting that positive environments may exert a protective influence for reducing alcohol consumption. We tested the effects of both acute and chronic treatment with carbetocin before and after mice were exposed to a predator (Long-Evans rat). While carbetocin decreased ethanol intake before stress, mice treated with either acute (at high dose) or repeated doses of carbetocin showed greater intake of ethanol after stress. These results show important precautions regarding the use of carbetocin in chronic alcohol abuse as a result of psychosocial stress.

049

ROLE OF OXYTOCIN IN ALCOHOL SELF-ADMINISTRATION AND STRESS-INDUCED RELAPSE-LIKE BEHAVIOR IN MICE

H.C. Becker, C.E. King
Medical University of South Carolina, USA

We recently showed that systemic administration of the neuropeptide oxytocin (OXT) reduced binge-like alcohol drinking in mice. The present set of studies used operant conditioning procedures to examine effects of OXT on alcohol self-administration and stress-induced relapse-like behavior in male and female C57BL/6J mice. In one study, OXT (0.1–1 mg/kg; ip; 30 min pretreatment) reduced operant oral alcohol self-administration in a dose-related manner at doses that did not alter sucrose responding. In another set of studies, after establishing stable alcohol responding/intake, stable responding was then established under extinction training. Mice then were exposed 15 min to a predator odor (TMT) or received yohimbine (0.3 or 0.625 mg/kg) injection prior to reinstatement testing. OXT (1 mg/kg; 30 min pretreatment) blocked alcohol relapse-like responding (reinstatement of alcohol seeking behavior) provoked by exposure to the different stressors (TMT and yohimbine). In another set of studies, OXT-Cre mice were used to target hypothalamic OXT neurons using an AAV-hM4Dq excitatory DREADD virus. Chemogenetic activation of endogenous OXT release via injection of CNO (3 mg/kg) (but not vehicle) decreased binge-like drinking as previously shown for exogenous OXT treatment. A similar chemogenetic study is underway to examine effects on operant alcohol self-administration and stress-induced relapse-like behavior.

050

DEVELOPMENT OF SMALL MOLECULE OXYTOCIN LIGANDS FOR ALCOHOL DEPENDENCE AND DRUG ADDICTION

I.S. Mcgregor[1], M.T. Bowen[1], R. Foltin[2], S.J. Baracz[3], J.L. Cornish[3]
[1]University of Sydney, Australia, [2]Columbia University, USA and [3]Macquarie University, Australia

In 2010 our group reported that systemic injections of oxytocin inhibited both beer consumption and intravenous methamphetamine self-administration in rats. Our subsequent research documented a long-lasting inhibition of addictive behaviours as a result of brief oxytocin exposure. These results and others have lead to substantial clinical interest in intranasal oxytocin as a therapeutic for addictions. However, our own (unpublished) study of intranasal oxytocin in problem drinkers found only modest effects, most likely due to the relatively poor central penetration and bioavailability of oxytocin. Consequently, we have developed a range of small molecules that stimulate central oxytocin circuits. Our lead candidate, *SOC-1*, has remarkable effects in animal models of addiction. These include dose-dependent reductions in methamphetamine self-administration in rats and reduced prime-induced reinstatement of methamphetamine-seeking. In primate models, SOC-1 (2–4 mg/kg, IM) decreased cocaine self-administration and decreased operant alcohol self-administration in baboons at a dose of 6 mg/kg (P.O.). SOC-1 also prevented a range of nicotine withdrawal symptoms in mice. In addition, SOC-1 has powerful prosocial effects in animal models of autism and in the social interaction test, while being devoid of addictive properties itself. Our current activities are aimed at fast-tracking the passage of SOC-1 into the clinic.

051

THE OXYTOCIN SYSTEM IN ALCOHOLISM: CONVERGENT EVIDENCE FROM HUMANS AND RATS

A.C. Hansson[1], A. Koopmann[2], S. Uhrig[1], F. Kiefer[2], W.H. Sommer[1,2], SabineVollstädt-Klein[2], R. Spanagel[1]
[1]Institute for Psychopharmacology, Central Institute of Mental Health Mannheim, Uniklinikum Mannheim, University of Heidelberg, Germany and [2]Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health Mannheim, Medical Faculty Mannheim, Heidelberg University, J5, 68159 Mannheim, Germany

Oxytocin (OXT) is a neuropeptide which has important and well-documented roles in mammalian social behavior, reward, stress, learning and memory processes as well as behaviors related to drugs of abuse and alcohol.

Combining postmortem and *in vivo* methods, we present data on neuroadaptive changes of the OXT system in alcohol-dependent individuals in brain sites that are relevant for mediating alcohol reinforcement and addictive behavior and further studied the effects of OXT on alcohol-seeking behavior in dependent rats. Additionally, we analyzed the effect of intranasal administered OXT in non-treatment seeking heavy social drinkers by functional magnetic resonance imaging to measure neural reactivity to alcohol-related cues.

Overall, our data show an increase in OXT receptor expression (mRNA and binding sites) both in alcoholic patients and alcohol dependent rats, as well as a decrease in *Oxt* mRNA and OXT peptide in alcohol dependent rats. Furthermore, we could demonstrate that OXT decreases alcohol cue-reactivity; in rats at the behavioral level by the cue-induced reinstatement test and in heavy social drinkers upon cue exposure at the neural level.

This highly translational, multi-level approach underlines the importance of the OXT system in alcohol dependence. Our data suggest that oxytocin may positively affect treatment outcomes in alcoholics.

052

COMMENT FROM A DISCUSSANT
L.F. Vendruscolo
National Institute on Drug Abuse, USA

Dr. Vendruscolo will provide an overall synthesis of the presentations and highlight future directions for research in this area. He will discuss translational work integrating preclinical and clinical studies. He will also discuss the importance of determining exogenous versus endogenous oxytocin's effects, and peripheral versus central oxytocin's sites of action.

MONDAY, SEPTEMBER 10 1:00 PM–2:30 PM
SYMPOSIUM
ISBRA-JSPH SYMPOSIUM: PREVENTION OF HEALTH PROBLEMS DUE TO INADEQUATE ALCOHOL DRINKING – VIEWPOINTS FROM COMMUNITY TOTAL HEALTH
CHAIRS: TOMONORI OKAMURA AND HIDEYUKI KANDA

053

CANCER RISK AND ALCOHOL: GENE-ENVIRONMENT INTERACTION AMONG ASIAN
K. Matsuo
Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Japan

Alcohol is one of established risk factors for cancer. Alcohol is one of the important modifiable risk factors for cancer. According to International Agency for Research on Cancer, there have been convincing evidence for alcohol on the risk of cancer in head and neck, esophagus, colon and rectum, liver and breast. Although various mechanisms behind the association have been hypothesized, molecular epidemiological studies in decades revealed contribution of acetaldehyde in alcohol related carcinogenesis.
In East Asia, it is known that a functionally established single nucleotide polymorphism (SNP) in aldehydedehydrogenase-2 (ALDH2), rs671 (Glu504Lys), which has strong phenotypic change in acetaldehyde metabolism, is prevalent. The minor Lys-allele lead to reduced oxidation capacity leading to reduced tolerability to acetaldehyde. A gene-environment interaction observed in the studies considering this SNP with alcohol consumption has strongly indicated contribution of acetaldehyde. In this presentation, molecular epidemiological studies showing between rs671 SNP and alcohol consumption conducted in Japan will be introduced.

054

ALCOHOL AND CARDIOVASCULAR DISEASE, ITS RISK FACTORS, AND OTHER HEALTH DISORDERS IN THE COMMUNITY
A. Higashiyama[1], Y. Miyamoto[1], I. Wakabayashi[2], T. Okamura[3]
[1]National Cerebral and Cardiovascular Center, 2 Hyogo College of Medicine, Japan, [2]Hyogo College of Medicine, Japan and [3]Keio University, Japan

Alcohol drinking is related to cardiovascular disease (CVD), its risk factors, and other diseases, including cancer and injury. Japanese people drink much more alcohol compared to people in other Asian countries. According to the National Survey in 2015, 14% of male participants drink more than 40 g/day, and 8% of female participants drink more than 20 g/day. Accordingly, alcohol drinking is still our important matter of concern from the view point of public health.
The relationship between alcohol drinking and CVD has been considered to be J- or U-shaped, with a decreased risk in light-to-moderate alcohol drinkers and with an increased risk in heavy drinkers. And alcohol consumption has detrimental effects on hypertension, arrhythmia and haemorrhagic stroke. In addition to the relationships mentioned above, we introduce the results of epidemiological studies investigating the relationships between alcohol and CVD and its risk factors in various situations: e.g. among those with and without high level of serum gamma-glutamyltransferase (GGT), flushing (inactive ALDH2), hypertension, and increased HDL-cholesterol level.
We also introduce the updated program for lifestyle improvements to prevent lifestyle-related disease, published by Ministry of Health, Labor and Welfare.

055

ALCOHOL AND MINORS IN JAPAN
H. Kanda[1], Y. Osaki[2], Y. Kaneita[3], O. Itani[3], M. Jike[3], S. Nakagome[3], Y. Otsuka[3], S. Higuchi[4], T. Ohida[3]
[1]Department of Environmental Medicine and Public Health, Shimane University, Japan, [2]Division of Environmental and Preventive Medicine, Tottori University, Japan, [3]Department of Public Health, Nihon University, Japan and [4]National Hospital Organization Kurihama Medical and Addiction Center, Japan

Background: Early drinking is considered to result in making tolerant of alcohol consumption and a higher prevalence of alcohol related disorders in the later. Although Japanese law forbids alcohol drinking under 20 years old, teen drinking is frequently observed. Frequent observations are needed to examine trends in drinking rates among minors.
Objective: To clarify the trend of the prevalence in alcohol drinking among junior and senior high school students in Japan by the regular national-wide epidemiological study of adolescents.
Methods: We used national-wide data from the Japanese Youth Tobacco and Drinking Surveys by anonymous questionnaire, gathered from 1996 to 2014. Of all high schools in Japan, around 130 junior and 110 senior high schools were randomly selected in every survey. Participants were all students over 80,000 who belong to selected schools. Outcome measures in this study were life time drinking, current drinking within 30 days and weekly drinking.
Results: All rates of alcohol drinking among high school students in Japan decreased from 1996 to 2014. Those rates on drinking did not have gender differences in every survey.
Conclusions: Alcohol drinking rates among minors in Japan decreased gradually in recent years in both gender. It needs to continue careful monitoring of drinking prevalence.

056

ALCOHOL-RELATED PROBLEMS IN JAPANESE PRIMARY CARE

H. Yoshimoto
Department of Family Medicine, General Practice and Community Health, Faculty of Medicine, University of Tsukuba, Japan

Primary care facilities such as clinics and small hospitals treat many patients with physical, mental, and social problems related to alcohol. Regarding the frequency of alcohol problems in primary care, there were no differences between clinics and hospitals in a survey conducted in Okayama in 2000: alcohol abuse or dependence was identified in 12.6% of males and 1.9% of females. In a survey conducted in 2016, 23.8% of males and 2.3% of females had an AUDIT score of 10 or more. Nonetheless, there has been a lack of programs to actively address alcohol-related problems in primary care. This has been accompanied by issues in both undergraduate and post-graduate education, including, (1) underestimating the prevalence of alcohol-related problems, (2) the cultural belief that alcohol is essential for socialization, and (3) the stigma associated with patients with alcohol dependence and the difficulty in responding to their needs.
At primary care sites, the SBI/SBIRT framework makes it easier to handle alcohol-related problems, and the future management of these problems in Japan will depend in large part on the expanded use of SBI/SBIRT.
Hisashi Yoshimoto is a family physician, and an associate professor at the University of Tsukuba in Japan. He was involved in enacting an alcohol-related law in Japan, named the “Basic Act on Measures Against Alcohol-related Health Harm”. He is interested in disseminating the “Screening, Brief Intervention, and Referral to Treatment” (SBIRT) approach in colleges and primary care settings. He is also interested in alcohol-related injuries and other alcohol-related health problems associated with binge drinking and heavy drinking.

057

PUBLIC HEALTH POLICY ON HARMFUL HEALTH HAZARDS OF ALCOHOL USE IN JAPAN: THE POPULATION STRATEGY PERSPECTIVE

Y. Osaki, A. Kinjo, Y. Kuwabara
Division of Environmental and Preventive Medicine, Department of Social Medicine, Faculty of Medicine, Tottori University, Japan

In response to the 2010 “Global Strategy to Reduce the Harmful Use of Alcohol” and the “Global Action Plan 2013–2020” introduced by the WHO to prevent and control non-communicable diseases (NCDs), the Japanese Bill for the Basic Act on Measures against Alcohol-related Harm was passed in December 2013. The law was effected in June 2014. In 2016, the Cabinet Office devised the Basic Plan for Promotion of Measures against Alcohol-related Harm to promote concrete measures against hazards of alcohol use.
The Basic Plan includes comprehensive measures such as promotion of education (school education, workplace education, and education on medical care, nursing care, welfare, judicial affairs, etc.), dissemination of relevant information at driving schools, and prevention of inappropriate drinking (through advertising, sales, provisions, etc.). It also promotes medical examinations and health guidance (early intervention in the community and at the workplace), accessibility to and enhancement of the quality of medical care for alcohol-related harm, and the promotion of medical coordination (between internal medicine, emergency care, and specialized medical care). Guidance to those who, under the influence of alcohol, drive or become embroiled in other problems (violence, maltreatment, suicide attempt, etc.), consultation support (support for re-integration into society), securing of human resources, and promotion of research and study on the issue are also covered under this plan.
Increase in price of alcohol beverages, regulation on alcohol advertisements, and regulation on all-you-can-drink offers in restaurants are also necessary steps. However, improvement in these areas is difficult in Japan. Screening of alcohol-related harm, referring suspected alcohol-dependent patients to specialists according to the results of screening tests, and conducting brief interventions with problem drinkers are measures that need to be implemented as population strategy. We will promote these measures for the time being.

MONDAY, SEPTEMBER 10 **2:50 PM–4:20 PM**

SYMPOSIUM

INTERNATIONAL COMPARISON OF PREVENTION POLICY AGAINST ALCOHOLIC HEALTH DAMAGE – IN REFERENCE TO JAPANESE BASIC LAW – PART 1

ORGANIZER: ARO INO

ORGANIZER/CHAIR: NAOYUKI HIRONAKA CHAIR: MEGUMI GOTO

058

JAPANESE BASIC ACT ON MEASURES AGAINST ALCOHOL-RELATED HARM: FORMATION, SIGNIFICANCE, AND FUTURE

A. Ino
Kasumigaura Clinic, Japan

The Basic Act on Measures against Alcohol-related Harm (Act No. 109 of 2013) represents a first and important step toward the nationwide promotion of measures against alcohol-related harm in Japan. The Global Strategy to Reduce the Harmful Use of Alcohol, endorsed by WHO in 2010, facilitated social movements toward the enactment of this Act. A distinctive feature of this movement was the initiative of academic societies, which called for collaboration with civic and self-help groups that helped secure favorable political commitment. The former played a notable role in the banning of liquor vending machines. The latter organized an all-party parliamentary group on alcohol-related problems. The Basic Act stresses the mutual exchange of information and energy among different social systems. Thus, setting up a cooperation network is regarded as one of the most important tasks. After the promulgation of this Act, Japanese society started to change. Each local government created local plans for the promotion of measures. Some local governments introduced AUDIT in the medical checkup of staff. The practice of Screening, Brief Intervention, Referral to Treatment, and Self-help Group (SBIRTS) is becoming popular. In this still inchoate movement, the review of Japanese measures from an international standpoint is crucial.

059

PROCESS OF FORMULATING THE BASIC LAW AND ITS SIGNIFICANCE FOR INTERNAL MEDICINE AND GENERAL PRACTICE/FAMILY MEDICINE

H. Yoshimoto
Department of Family Medicine, General Practice and Community Health, Faculty of Medicine, University of Tsukuba, Japan

In Japan, where there is free access to medical care, internal medicine providers at clinics, small hospitals, and primary care facilities treat physical, mental, and social problems related to alcohol. Nevertheless, few programs actively address these issues. Important points include: (1) lack of education, (2) underestimating prevalence, (3) the cultural belief that socialization must involve alcohol, and (4) stigma. However, change is anticipated following the formulation of the Basic Act for Measures Against Alcohol-Related Health Harm. Many organizations, including the Japan Society of Hepatology, Japan Society of Gastroenterology, Japanese Medical Association, Japan Internal Medicine Association, and Japan Primary Care Association, were involved in the formulation of the new Act. This broad cooperation demonstrates the necessity of measures against alcohol-related health problems. The Basic Act requires physicians and other medical staff to provide high-quality medical treatment for those with alcohol-related health problems, to give advice on reducing or stopping alcohol consumption, and to secure the cooperation of medical institutions. Promoting collaboration between general and specialized medical institutions and providing training on alcohol-related problems, including brief intervention methods, will be necessary in the future.

060

HISTORY OF PSYCHIATRIC TREATMENT FOR ALCOHOL USE DISORDER AND THE IMPACT OF BASIC ACT FOR MEASURES AGAINST ALCOHOL-RELATED HEALTH HARM IN JAPAN

C. Iwahara, S. Higuchi
National Hospital Organization Kurihama Medical and Addiction Center, Japan

Previously in Japan, alcoholism was regarded as a personality problem, and the main treatment was to lock patients in closed psychiatric wards. Prior to the Tokyo Olympic Games, the Drunkenness Prevention Law was enacted to improve drinking morality. Based on this law, the first specialized treatment ward for alcoholism was developed at the National Kurihama Hospital (Kurihama Medical and Addiction Center) in 1963. This event marked the initiation of contemporary treatment for alcoholism, emphasizing the treatment of patients in an open ward on a voluntary basis. This method was called the "Kurihama style" and has been gradually expanded nationwide, although some hospitals continue to use closed wards.

After the enactment of the Basic Act for Measures Against Alcohol-Related Health Harm, the Japanese government launched a comprehensive program to increase treatment and consultation capacities nationwide. Based on this program, our center has been designated as the national center for three addictions: alcohol, drugs, and gambling. In addition to the designation of specialized treatment facilities and local hub facilities in all prefectures, this program is aimed at strengthening the activities of NGOs and self-help groups. Our presentation will cover the latest information on programs and other developments related to the Basic Act.

061

ESSENTIAL ELEMENTS OF EFFECTIVE ALCOHOL POLICIES AND THEIR IMPLEMENTATION IN THE WORLD

V. Poznyak
Department of Mental Health and Substance Abuse, World Health Organisation, Geneva, Switzerland

In 2010 Member States of the World Health Organization (WHO) endorsed the Global strategy to reduce the harmful use of alcohol that provides policy options for implementation at national level to reduce alcohol-related harm. In the text of the Global strategy more than a hundred of different policy options and interventions were grouped into ten recommended complementary target areas. More recently, within the framework of the global processes on prevention and control of noncommunicable diseases, WHO produced the list of the most cost-effective and effective policy options and interventions to reduce the harmful use of alcohol. Assessment of successes or failures in this area may include not only monitoring the overall levels of alcohol-related harm and alcohol consumption, but also monitoring the levels of implementation of the most cost-effective and effective policy options. A number of countries in the world achieved significant decrease in alcohol-related harm since 2010. The core elements of alcohol policy actions in these countries included, as a rule, implementation of the most cost-effective measures promoted by WHO. These measures are not implemented in isolation, but within a broader framework of alcohol policies to ensure their acceptance and support at national and community levels. The most recent WHO data indicate that the global alcohol-related targets are valid and achievable, but implementation of the most effective alcohol policy measures varies significantly in different parts of the world. Accordingly, the progress in reduction of alcohol consumption and alcohol-related harm is very uneven globally, and the global target of 10% of relative reduction in alcohol consumption may not be achieved without invigorated concerted efforts of all major stakeholders at national, regional and global levels.

MONDAY, SEPTEMBER 10 **4:30 PM–6:00 PM**

SYMPOSIUM

INTERNATIONAL COMPARISON OF PREVENTION POLICY AGAINST ALCOHOLIC HEALTH DAMAGE – IN REFERENCE TO JAPANESE BASIC LAW – PART 2

ORGANIZER: ARO INO

ORGANIZER/CHAIR: NAOYUKI HIRONAKA CHAIR: MEGUMI GOTO

062

THE HISTORY OF ALCOHOL RESEARCH IN THE UNITED STATES AND THE NIAAA

K.R. Warren
National Institute on Alcohol Abuse and Alcoholism, USA

Alcohol research in the U.S. began its growth in 1971 with the creation by the U.S. government of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Now located as one of 27 institutes of the National Institutes of Health (NIH) it receives funds for research and research training through an annual appropriation. The research is conducted both through the Institute's own research laboratories (20% of NIAAA's budget) with the remaining 80% expended on extramural science projects conducted in universities and private institution via a competitive peer review system with external scientists serving as reviewers and a secondary review by the Institute's National Advisory Council. In the current fiscal year (2018) over $500 million was provided to NIAAA.

The scope of NIAAA's research is broad from basic to clinical research on a range of alcohol problems ranging from metabolism to chronic organ pathologies; acute problems such as underage drinking and accidents; alcohol use disorder including new drug development and improved behavioral treatments; to prevention and policy research.

063

ALCOHOL POLICIES IN THE USA IN RELATION TO THE JAPANESE BASIC LAW: WHAT WE CAN LEARN FROM EACH OTHER

T.F. Babor
Department of Community Medicine, University of Connecticut School of Medicine, USA

In 2013, the Japanese government promulgated the Basic Law on Measures against Alcohol-Related Health Harm. The Basic Law has many desirable features, which in this presentation will be discussed in relation to major changes in alcohol policy that have been found to be effective in the United States. After describing long waves of alcohol consumption since the 18th century in the USA in relation to major changes in alcohol policy, this presentation will provide examples of successful alcohol policy changes in the modern era, including policies on the minimum alcohol purchase age, alcohol-impaired driving, alcohol taxes and strengthening of the overall alcohol policy environment. Also considered will be changes that have resulted in increased alcohol consumption and problems, including privatization of alcohol monopolies and reductions in alcohol taxes. The changes in Japanese policy will be compared to the findings from research on US alcohol policies. The presentation will close with a consideration of the role of policy research in the development of prevention, treatment and policy, and how the globalization of the alcohol industry requires greater collaboration among alcohol experts and policymakers at the national and international levels.

064

PUBLIC HEALTH MEASURES AGAINST ALCOHOL-RELATED PROBLEMS IN THAILAND
S. Assanangkornchai
Prince of Songkla University, Thailand

Alcohol consumption has been the top leading cause of burden of diseases in Thailand for several years. In response to this, Thailand has actively implemented several public health measures in the past decade. The Alcoholic Beverage Control Law, issued in Thailand in 2008 contains several acts, aiming to control drinking and alcohol-related harm among general population. In 2009, the national strategic plan on alcohol control was adopted to bring together all sectors to tackle alcohol-related problems, including five main strategies; (1) restrictions of access to retail alcohol by means of increased price and limiting times and places of sale; (2) changing social attitudes towards drinking by banning alcohol advertisements and social marketing to denormalise alcohol; (3) reducing alcohol-related harm by controlling drinking in high-risk situation, screening and treatment of individuals with alcohol-use disorders; (4) promoting area-based interventions and (5) developing effective management and supporting system. Changes and trends of some indicators of alcohol consumption and related problems, including the annual per capital consumption, prevalence of drinking in adults and adolescents and binge and regular drinking; and perceptions of related laws among general population will be presented in this symposium.

065

ALCOHOL POLICIES IN UK, FOCUSING ON EARLY HARM PREVENTION
I. Guerrini[1,2]
[1]South London & Maudsley NHS Foundation Trust, UK and [2]Institute of Psychiatry Psychology Neuroscience Kings College London, UK

Several nations world-wide have developed policies and implemented interventions to reduce the burden of alcohol related diseases and alcohol attributable deaths and disabilities. Screening and brief interventions for hazardous and harmful drinking have a good cost-effectiveness profile, as suggested in the WHO Global Status Report on Alcohol and Health-2014 (1), and it has been considered as a public health measure to improve health and reduce alcohol consumption in several national policies like in Japan and the U.K. In 2010 the NICE Guidance on Alcohol Use – Prevention (2) has pointed out the importance of early and preventative interventions which include price, availability, marketing, screening and brief intervention Some of these recommendations from NICE were subsequently incorporated in the UK Government Alcohol Strategy. Focus of this lecture is the impact of early interventions in different settings and their efficacy in reducing alcohol consumption. Screening and Brief interventions have been widely researched and recommended as cost-effective measures to reduce alcohol consumption in diverse populations and settings (primary care, antenatal services, criminal justice and emergency departments). The preventative efficacy of these interventions at populations level will be discussed.
1. WHO. Global status report on Alcohol and Health, 20142. NICE. Alcohol use: Prevention, 2010.

MONDAY, SEPTEMBER 10 9:50 AM–11:20 AM
SYMPOSIUM
MECHANISMS OF COMPULSIVE AVERSION-RESISTANT ALCOHOL DRINKING IN RODENTS
ORGANIZER/CHAIR: STEPHEN L. BOEHM

066

AVERSION- (QUININE-) RESISTANT ALCOHOL DRINKING IN MOUSE LINES GENETICALLY SELECTED FOR HIGH AND LOW ALCOHOL PREFERENCE DRINKING
N.J. Grahame, C.A. Houck
Department of Psychology, Indiana University – Purdue University Indianapolis, USA

Mechanisms underlying quinine-resistant (QR) alcohol drinking are not well understood. In a series of studies, we examined factors contributing to QR drinking in lines of mice selectively bred to prefer alcohol (High Alcohol Preferring, or HAP mice). HAP mice had access to two-bottle choice alcohol (10% v/v) and water, or saccharin and water, for 2–5 weeks. Quinine resistance develops more quickly (2 weeks) in our highest drinking line, cHAP (averaging BECs >200 mg/dL), than in a somewhat lower-drinking line, HAP2 (BECs around 100 mg/dL; 5 weeks). However, neither line developed QR saccharin drinking at a variety of concentrations, even after prolonged saccharin access. Using the cHAP mice with 2 weeks of alcohol drinking experience, we investigated effects of infusing the dopamine D1 antagonist SCH-23390 (3 micrograms per side) into the dorsolateral striatum (DLS) immediately prior to testing. This attenuated QR drinking ($p < 0.001$) but not baseline, non-bitter alcohol consumption. Together, these findings indicate that QR drinking in these animals requires long-term consumption of pharmacologically relevant amounts of alcohol and is not caused solely by consumption of a preferred taste. Furthermore, these data implicate dopaminergic signaling to the DLS in aversion-resistant, but not baseline free-choice alcohol drinking.

067

NEUROBIOLOGICAL MECHANISMS UNDERLYING LOSS OF CONTROL OVER ALCOHOL USE IN RATS
H. Lesscher[1], J. Smeets[1], M. Minnaard[1], G. Ramakers[2], G.V. Tilborg[3], R. Adan[2], L. Vanderschuren[1]
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Alcohol use disorder (AUD) is characterized by loss of control over alcohol use, but only a minority of individuals who drink alcohol develop AUD. Importantly, the mechanisms that determine loss of control over alcohol use and an individual's risk to develop AUD remain incompletely understood. Exaggerated involvement of the dorsolateral striatum (DLS) and reduced activity of the prelimbic cortex (PrL) have been proposed to contribute to habitual alcohol seeking and loss of control over substance use. We therefore assessed the contribution of these structures to the propensity to lose control over alcohol seeking in rats, using an intermittent two-bottle choice paradigm.
Using resting-state MRI, we observed differential neuronal connectivity between the DLS and PrL in low and high alcohol drinking rats, before the onset of alcohol consumption, which persisted after alcohol consumption. We next used optogenetics to determine the effect of excessive alcohol consumption on synaptic plasticity in a cortical-DLS projection. Preliminary analysis of optically-induced excitatory neurotransmission in DLS neurons showed increased facilitation of paired-pulse responses in the DLS in high alcohol drinking rats.
In conclusion, differential DLS-PrL connectivity predicts the degree of alcohol consumption, while prolonged alcohol consumption alters synaptic plasticity in glutamatergic cortical inputs to the DLS.

068

COMPULSIVE RESPONDING FOR ALCOHOL IS MORE AUTOMATIC AND MOTIVATED: INSIGHTS INTO OVERLAP OF COMPULSION AND HABIT CIRCUITRY
F.W. Hopf, D. Darevsky, S.A. Wegner, B. Hu, M. Gill, K.R. Vitale
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Intake that persists despite negative consequences, called compulsive drinking, is a major contributor to alcohol addiction and a pernicious obstacle to treatment. Thus, there is considerable interest and importance in understanding neural mechanisms that allow responding despite knowledge of bad consequences. Using lickometry to examine the microstructure of alcohol responding in rats, we find that compulsive intake involves less variable responding across many licking measures, ranging from bout organization to lick volume (reflecting better tongue control), consistent with the importance of automaticity and habit-like behavior for expression of compulsion. Compulsive responding also exhibits greater motivation, indicated by faster licking that is particularly pronounced at onset of each licking bout. With stronger challenge (higher quinine in alcohol), responding is more automaticity but faster licking becomes especially critical to maintain intake. More automatic responding combined with stronger bout start may reflect a strategy akin to putting one's head down and pushing through, which would allow intake while minimizing the need for monitoring or awareness. This strategy may also reflect a choice to act habitually, and may explain why the circuitry for expression of compulsive intake and habitual responding have such pronounced overlap, including the importance of anterior insula circuitry.

069

COMPULSIVE ALCOHOL SEEKING IS ASSOCIATED WITH AN INABILITY TO DISENGAGE DORSOLATERAL-DOPAMINE DEPENDENT CONTROL OVER BEHAVIOUR
C. Giuliano, D. Belin, B.J. Everitt
University of Cambridge, Department of Psychology, UK

While for some individuals drug taking may be on an occasional basis, some lose control over their drug use and are unable to stop despite deleterious consequences. Within the theoretical framework that with prolonged drug exposure the shift from voluntary to habitual drug seeking reflects a shift in neural control from ventral to dorsal lateral striatum (DLS), we investigated the DLS dopamine-dependent mechanisms in the development of compulsive alcohol seeking.
Alcohol-preferring P rats, whose phenotype was confirmed through an intermittent 2-bottle choice procedure, were implanted bilaterally with cannulae in the anterior DLS. They were subsequently trained instrumentally on a seeking-taking chained schedule of alcohol reinforcement until some individuals developed compulsive alcohol seeking. The inter-individual differences in the recruitment of DLS-dopamine-dependent control over seeking behaviour were investigated by intra-DLS infusing the DA receptor antagonist, alpha-flupenthixol (5–10–15 μg/side) soon after acquisition of instrumental responses for alcohol, after well-established alcohol seeking behaviour and after the development of punishment-resistant alcohol-seeking.
Well-established alcohol-seeking became reliant on DLS-dopamine-dependent mechanisms and predicted which rats developed compulsive alcohol-seeking. Moreover, alcohol-seeking was decreased by DLS dopaminergic receptor blockade selectively in compulsive rats.
The engagement of DLS dopaminergic mechanisms thus reflects the rigidity characterising the individual vulnerability to compulsive alcohol-seeking.

MONDAY, SEPTEMBER 10 1:00 PM–2:30 PM

SYMPOSIUM

TO BE OR NOT TO BE: TRANSCRIPTION AND TRANSLATION MECHANISMS UNDERLYING ALCOHOL USE DISORDERS
ORGANIZER/CHAIR: DORIT RON

070

MTORC1 IN THE ORBITOFRONTAL CORTEX CONTROLS ALCOHOL SEEKING AND HABIT
D. Ron
Department of Neurology, UCSF, USA

The mammalian target of rapamycin in complex 1 (mTORC1) plays an important role in dendritic protein synthesis, synaptic plasticity, learning and memory. We recently found that excessive alcohol intake and withdrawal activates mTORC1 in the rat orbitofrontal cortex (OFC) (Laguesse et al. 2017), a brain region that plays a role in decision making. This study was aimed to elucidate the role of mTORC1 in the OFC in alcohol-dependent behaviors. We found that inhibiting mTORC1 in the OFC of rats reduces alcohol seeking. We then hypothesized that mTORC1 in the OFC is required for either goal-directed or habitual alcohol seeking. To model goal-directed and habit-driven behaviors, respectively, we used an operant paradigm in which rats self-administered alcohol under a random ratio (RR) or a random interval (RI) schedule of reinforcement. We found that mTORC1 in the OFC is driving habitual but not goal directed responding for alcohol. Next, we elucidate the mechanism by which mTORC1 is activated by alcohol. We found that the enhancement of glutamatergic neurotransmission during withdrawal activates mTORC1 in the OFC which in turn drives habitual alcohol seeking. Together our results suggest that mTORC1 plays an important role in maladaptive habitual alcohol seeking.

071

COMMON MECHANISMS BETWEEN ETHANOL AND RAPIDLY ACTING ANTIDEPRESSANTS
K. Raab-Graham, C. Heaney, S. Namjoshi, S. Barth
Wake Forest Translational Alcohol Research Center, Physiology and Pharmacology, Wake Forest School of Medicine, USA

Comorbidity of alcohol use disorder (AUD) and major depressive disorder (MDD) in adults ranges from 12% to 30%, and can be explained by the self-medication hypothesis, which proposes that people turn to alcohol to alleviate their MDD symptoms. We have recently demonstrated that a single administration of ethanol produces an antidepressant-like behavioral effect, and that this effect is blocked with a metabotropic gamma-aminobutyric acid receptor (GABABR) antagonist. These data fit into the molecular rapid antidepressant pathway that we have characterized that demonstrates that GABABR-mediated mTORC1 activation is required for the antidepressant efficacy. Further, both the antidepressant Ro 25-6981 and Ethanol stimulate new protein synthesis of the subunit GABABR2, and increased surface expression of these receptors requiring Fragile X Retardation protein (FMRP). Through sequencing FMRP target mRNAs, FMRP regulated mRNA translation is required for mTORC1-dependent trans-synaptic signaling and new synapse formation. Collectively, these data support the self-medication hypothesis by demonstrating that ethanol utilizes the same biochemical signaling pathways as rapidly acting antidepressants. Notably, GABABR markers are decreased in AUD and MDD patient populations and animal models. These data suggest a critical role of this receptor in AUD, posing the question if repeated exposure to ethanol over time fails to elicit antidepressant properties.

072

GENOME-WIDE TRANSCRIPTIONAL CHANGES IN THE RAT HIPPOCAMPUS DURING WITHDRAWAL FROM CHRONIC ALCOHOL DRINKING IDENTIFIES ALTERED NEUROIMMUNE SIGNALING

A.W. Lasek, W.-y. Chen, H. Chen, Y. Chen, H. Zhang, H.R. Krishnan, C. Liu, D. Grayson, S.C. Pandey
Psychiatry, University of Illinois at Chicago, USA

Withdrawal from alcohol drinking causes transcriptional changes in the brain that may contribute to relapse. To find novel genes altered during withdrawal, we performed genome-wide analysis of transcripts in the rat hippocampus. Rats were fed an ethanol or control liquid diet for 15 days and withdrawn for 24 h. Hippocampal RNA was subjected to RNA-Seq and weighted gene co-expression network analysis to identify modules of co-expressed genes. Genes in module 1 were significantly higher during withdrawal and enriched in the "TNF signaling pathway" and "Epstein Barr virus Infection" by gene ontology analysis, indicating disruptions in neuroimmune signaling. To validate the RNA-Seq findings, hippocampal RNA and chromatin were analyzed by qPCR and chromatin immunoprecipitation, respectively. Expression of neuroimmune genes such as *Tnfrsf1a*, *Stat3*, and *Relb* were increased during withdrawal, consistent with the RNA-Seq results. Surprisingly, decreased acetylation of histone H3 was observed at the promoters of these genes, while treatment with the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA) during withdrawal normalized gene expression and histone acetylation. Our results demonstrate that withdrawal induces transcriptional changes in hippocampal neuroimmune genes and that some of these changes can be reversed by SAHA, suggesting epigenetic regulation of neuroimmune genes and possible involvement in alcoholism.

073

MOLECULAR BASIS OF FOR CHOOSING ALCOHOL OVER A NATURAL REWARD

M.A. Heilig
Center for Social and Affective Neuroscience, Sweden

Alcohol addiction leads to progressively increased choice of alcohol over healthy rewards, but the molecular basis of this process remains unknown. We established an exclusive choice procedure in rats, and used it for molecular discovery. Similar to rates of human alcohol addiction, only about 15% of outbred Wistar rats choose alcohol over an alternative high-value reward, a sweet solution. These animals display several traits reminiscent of clinical alcoholism, including high motivation to obtain alcohol as measured by progressive ratio breakpoints, and pursuit of this drug despite adverse consequences such as electric foot-shock or taste adulteration. Expression of the GABA-transporter GAT-3 is selectively decreased within the amygdala of alcohol choosing rats, while a viral-vector mediated knockdown of this transcript is sufficient to reverse choice preference of rats that originally chose a sweet solution over alcohol. On post-mortem analysis, GAT-3 expression is selectively decreased in central amygdala of alcohol dependent individuals compared to those who died of unrelated causes. Thus, impaired GABA-clearance within the amygdala contributes to core traits of alcohol addiction, appears to translate between species, and may offer targets for novel pharmacotherapies in this disorder.

MONDAY, SEPTEMBER 10 2:50 PM–4:20 PM

SYMPOSIUM

SYSTEMS BIOLOGY FOR ANALYSIS OF COMPLEX TRAITS INCLUDING ALCOHOLISM (THE NFPCDD SYMPOSIUM)

ORGANIZER/CHAIR: BORIS TABAKOFF CHAIR: PAULA L. HOFFMAN

074

THE NFPCDD SYMPOSIUM ON SYSTEMS BIOLOGY FOR ANALYSIS OF COMPLEX TRAITS INCLUDING ALCOHOLISM

B. Tabakoff[1], P.L. Hoffman[2]
[1]Skaggs School of Pharmacy & Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, USA and [2]Department of Pharmacology, University of Colorado Anschutz Medical Campus, USA

The advent of high throughput 'omics technology, particularly RNA-Seq has opened the doors to go well beyond DNA marker association studies (GWAS) to determine genetic factors that predispose complex traits (traits that are determined by the combined action of several or many gene products). Analytical processes have been devised to include transcriptome and proteome data with GWAS and QTL data to clarify which genetic loci contribute to expression of complex traits including alcoholism. The speakers in this symposium will present the rationale and the evolution of the statistical methods which allowed for inclusion of 'omics data in linking genotype to phenotype and will demonstrate how 'omics data can provide insight into the organization of functional networks in tissues and across tissues and provide the context in which the products of various genes function (network topology). Each speaker, Dr. Enrico Petretto, Dr. Mete Civelek and Dr. Laura Saba will present examples of the application of the systems biology approach to cardiovascular, and metabolic disorders and alcohol drinking behavior. Supported by the NFPCDD.

075

SYSTEMS-GENETICS TO COMPLEX DISEASES: FROM GENE NETWORKS TO DRUGGABLE TARGETS

E.G. Petretto[1,2]
[1]Duke-NUS Medical School, Singapore and [2]Imperial College London, UK

Systems-Genetics embraces a variety of integrative data modeling approaches for the analysis of a biological system as a whole. I developed an experimentally validated Systems-Genetics pipeline to identify the most relevant genetic drivers of disease as well as the underlying biological processes (e.g., a signaling pathway) dysregulated in disease. Applications to different diseases pinpointed new molecular targets for potential therapeutic intervention, including EBI2 regulating a pro-inflammatory gene network in type 1 diabetes, Kcnn4 and a macrophage multinucleation network underlying inflammatory disease and bone resorption, SESN3 regulating a proconvulsant gene network in epilepsy and DLG4 regulating white matter development of preterm infants.

More recently we focused on conserved pathways in the rat and human heart. We identified an E3 ubiquitin protein ligase as a positive *trans*-acting genetic regulator of a conserved gene network including extracellular matrix genes, which we detected as a pro-fibrotic transcriptional program in the heart of dilated cardiomyopathy patients. Using two *in vivo* models, we demonstrated that gene loss-of-function protects from developing exacerbated fibrosis down-stream of TGFβ receptor activation by chronic AngII treatment and in the infarcted heart. These Systems-Genetics approaches contributed to improve our *understanding of cardiovascular pathologies*, and can help identifying actionable *targets for therapeutic intervention*.

076

USING MULTI-OMICS DATA TO DETERMINE CAUSALITY AND CONSEQUENCES FOR PATHOLOGICAL TRAITS IN ANIMALS AND HUMANS

M. Civelek[1,2]
[1]Department of Biomedical Engineering, University of Virginia, USA and [2]Center for Public Health Genomics, University of Virginia, USA

Individual risk for cardio-metabolic disorders is strongly influenced by genetic risk and lifestyle, one of which is excess alcohol consumption. Genome-wide association studies (GWAS) identified hundreds of loci for cardio-metabolic traits. However, how these loci contribute to the disease process remains unknown. We use an integrated systems genetics approach to identify causal genes and pathways underlying the GWAS loci by combining multi-omics data from extensively phenotyped human and mouse cohorts. I will highlight one of our studies elucidating the molecular mechanism of a metabolic syndrome locus on chromosome 7q32.3. Combining human and mouse studies, we showed that this locus is associated with the transcription factor KLF14 in cis and 385 genes in trans. These associations were specific to adipose tissue. We showed that KLF14 regulates lipid uptake, proliferation, and maturation of adipocytes. These effects were observed only in females, yet they were not driven by the hormonal environment. While we discovered the KLF14 association through GWAS, the specificity of this association – with respect to sex, parent of origin, ethnicity, and tissue of action – is a reminder that risk prediction, or targeted medical treatment, based on genotype alone may fail to capture highly-relevant aspects of biological complexity.

077

THE QUANTITATIVE "OMICS" ANALYSIS OF COMPLEX ALCOHOL-RELATED TRAITS IN THE HYBRID RAT DIVERSITY PANEL

L.M. Saba[1], P.L. Hoffman[2], R. Lusk[1], B. Tabakoff[1]
[1]Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, USA and [2]Department of Pharmacology, School of Medicine, University of Colorado Anschutz Medical Campus, USA

We have used an integrative systems genetics approach, that takes into account genetic variation, and the effect of variation on phenotype and gene expression levels, to elucidate the genetic basis for the complex trait of alcohol consumption. With this approach, we identified a co-expression network associated with predisposition to voluntary alcohol consumption in the two-bottle choice paradigm using a subset of the Hybrid Rat Diversity Panel (HRDP). Based on common functionalities among genes, this network provided insight into the biological mechanisms important for differences in alcohol consumption. At the center of this network was an unannotated, likely non-coding, transcript. The integral role of this transcript in alcohol consumption was validated by developing a CRISPR/Cas9 "knockout" of the transcript and assessing its effect on alcohol drinking. Assessment of the brain transcriptome in the knockout rat model validated predicted changes in expression of other transcripts derived from the original HRDP data and provided insight into the influence of the non-coding transcript on transcription of protein-coding genes. The combination of the HRDP and the systems genetics techniques represents a powerful tool for modeling the complex relationships between DNA, RNA, and alcohol-related phenotypes. Supported by NIAAA R24AA013162, NIDA P30DA044223 and the Banbury Fund.

MONDAY, SEPTEMBER 10 **4:30 PM–6:00 PM**

SYMPOSIUM

PROMISING TARGETS OF ALCOHOL ADDICTION

ORGANIZER/CHAIR: A LESLIE MORROW

079

TRANSGENIC RAT LINES FOR REGION SPECIFIC INTERFERENCE WITH TARGET GENE EXPRESSION: EFFECT ON ALCOHOL-SEEKING BEHAVIOR

W.H. Sommer[1], S. Pfarr[1], L. Broccoli[1], K. Schönig[1], M. Klugmann[2], R. Spanagel[1], D. Bartsch[1], A.C. Hansson[1]
[1]Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany and [2]Translational Neuroscience Facility and Department of Physiology, School of Medical Sciences, UNSW Sydney, Australia

Validating the functional relevance of candidate mechanisms involves the demonstration of necessity as well as sufficiency for the process under study. These questions can be effectively addressed using various transgenic approaches. The use of these techniques is still mostly restricted to mice, although this model organism has severe limitations for medication development. Recent advances in genomic technologies have opened for a resurgence of rat models for mechanistic studies. Here, we present Camk2a-Cre driver rat lines that in combination with site specific viral gene transfer allow for time-, region- and cell-specific interference with the expression of candidate genes. For two previously established mechanisms of high relapse risk in alcoholism, namely increased expression of *Crhr1* in the amygdala or *Grm2* deficit in the medial prefrontal cortex, we demonstrated that overexpression or knockdown, respectively, in the specific brain regions of non-dependent rats is sufficient to drive excessive responding for alcohol cues.
In conclusion, virus-based conditional expression in transgenic Cre-driver rat lines is a key tool for assessing the function of different neural populations in alcohol-related behavior.

080

ALPHA-1 BLOCKADE AS PERSONALIZED TREATMENTS FOR ALCOHOL USE DISORDER
C.L. Haass-Koffler
Brown University, USA

Alcohol use disorder (AUD) affects individuals with a variety of endophenotypes. This heterogeneity may be in part responsible for different response to pharmacological treatment. There is a need to identify predictors for selecting "personalized" pharmacotherapies options. An example of such personalized approach is provided by the recent data suggesting a role of a1 blockers as treatments for AUD.
Given the involvement of noradrenergic activity in AUD the norepinephrine system is a promising pharmacological approach to treat AUD. Preclinical studies suggest that a1 blockade may be an effective pharmacological approach for AUD. Placebo-controlled studies showed that the a1 blocker prazosin reduced alcohol and decreased both stress- and cue-induced alcohol craving in AUD patients. We investigated the role of the a1 blocker doxazosin in AUD and found that it reduced alcohol drinking, although this effect was limited to those patients with high Family History Density of Alcoholism (FHDA). We also found that baseline BP moderated doxazosin's response in reducing alcohol drinking. These findings suggest that doxazosin may be an effective treatment for individuals with high FHDA (genetic marker) and with higher standing diastolic BP (biological/clinical assessment). In conclusion, the studies provide evidence that prazosin/doxazosin may represent novel effective treatments for AUD.

081

ENDOGENOUS NEUROSTEROID ALLOPREGNANOLONE INHIBITS TOLL-LIKE-4 RECEPTOR SIGNALING TO TARGET ALCOHOL ADDICTION
A.L. Morrow[1,2], I. Balan[3], M. Beattie[2], T.K. O' Buckley[2], L. Aurelian[3]
[1]Psychiatry and Pharmacology, UNC School of Medicine, USA, [2]Bowles Center for Alcohol Studies, USA and [3]Pharmacology, University of Maryland School of Medicine, USA

The endogenous neurosteroid (3α,5α)3-hydroxypregnan-20-one (3α,5α-THP, allopregnanolone) has protective activity in animal models of alcoholism, which involve excessive proinflammatory signaling through toll-like-4 receptors (TLR4). Thus, we examined the effects of 3α,5α-THP, and pregnenolone on LPS-induced TLR4 activation in both the periphery and the CNS. Monocytes/macrophages (RAW264.7) were used as a model of peripheral immune signaling and innately activated TLR4 in the ventral tegmental area (VTA) was studied in selectively bred alcohol-preferring (P) rats. LPS activated the TLR4 pathway in RAW264.7 cells as evidenced by increased levels of pTAK1, TRAF6, NFkB p50, phospho-NF-kB- p65, pCREB, HMGB1, and inflammatory mediators, MCP-1 and TNFα. Both 3α,5α-THP and pregnenolone (0.5–1.0 mM) substantially (~80%) inhibited these effects, indicating pronounced inhibition of TLR4 signaling. The mechanism of inhibition involves blockade of TLR4/MD-2 protein interactions in RAW246.7 cells. In VTA, 3α,5α-THP (15 mg/kg, IP) administration reduced TRAF6 (~20%), CRF (~30%), and MCP-1 (~20%) levels, as well as TLR4 binding to $GABA_AR$ α2 subunits (~60%) and MyD88 (~40%). The data suggest that inhibition of proinflammatory neuroimmune signaling underlies protective effects of 3α,5α-THP in immune cells and brain. Inhibition of pro-inflammatory TLR4 signaling may represent a new therapeutic target of 3α,5α-THP action in the periphery and the brain.

MONDAY, SEPTEMBER 10 **9:50 AM–11:20 AM**
SYMPOSIUM
CIFASD STUDIES ON THE GENETICS OF FASD
ORGANIZER/CHAIR: EDWARD RILEY

082

IDENTIFYING GENETIC MODIFIERS OF SUSCEPTIBILITY TO PRENATAL ALCOHOL EXPOSURE IN MICE
S.E. Parnell, K.E. Boschen
Bowles Center for Alcohol Sudies, University of North Carolina, USA

Not all children who are prenatally exposed to alcohol present with the characteristic craniofacial features of Fetal Alcohol Syndrome. While there are numerous factors that contribute to this variation, there is a strong genetic component to individual susceptibility to prenatal alcohol exposure. This genetic component is also present in mice, in that various strains of mice demonstrate a range of susceptibility to prenatal alcohol. Likewise, knocking out even one copy of certain genes can modify susceptibility to alcohol. We recently identified two closely related sub-strains of mice that differ in their response to alcohol. C57BL6J mice phenocopy the craniofacial and brain abnormalities observed in human FAS populations. However, the closely related strain, C57BL6N, does not exhibit these same effects. RNASeq was used to compare the transcriptomic differences between these strains when the embryo is at the critical developmental window for the severest craniofacial and brain defects. We identified 80 differentially expressed genes between the embryos of these strains. Subsequent work in mice lacking some of these genes demonstrate that we can alter susceptibility to prenatal alcohol. This work will be important in identifying genes that can be further tested in humans, and provide a better understanding of pathogenic mechanisms.

083

SYNERGISTIC GENE-ENVIRONMENT INTERACTIONS IN A ZEBRAFISH MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS
J.K. Eberhart, S. Tucker, Y. Fernandes, N. Mccarthy
Department of Molecular Biosciences, University of Texas at Austin, USA

Susceptibility to FASD is genetically modulated but the nature of these modifying loci is poorly understood. We have used genetic screens to identify mutants that are sensitive to normally subteratogenic doses of ethanol. Embryos mutant or heterozygous for *platelet-derived growth factor receptor alpha (pdgfra)* are exquisitely sensitive to ethanol-induced facial defects. Under control conditions, proper neural crest cell migration, but not survival, requires Pdgfra function. Following ethanol exposure, Pdgfra promotes the survival of neural crest cells. The PI3K pathway is the major Pdgfra effector and the PI3K/mTORC1 pathway has been shown to modulate ethanol teratogenesis. We have used CRISPR/Cas-9 to generate mutants altering mTORC1 function and are currently assaying the ethanol sensitivity of these mutants. Disruption of the essential mTORC1 complex member *raptor*, sensitizes embryos to ethanol-induced defects, while elevating mTORC1 function by disrupting *tsc1a* restores facial development in ethanol-treated *pdgfra* mutants and heterozygotes. In addition to structural defects, ethanol causes a variety of behavioral deficits, including those social in nature. We adapted an assay for ethanol-induced social defects to our genetic analyses. We have found that loss of *tsc1a* also protects against ethanol-induced social deficits. Collectively, our findings implicate the mTOR pathway in multiple aspects of FASD.

084

GENES AND DRUGS THAT REGULATE L1 SENSITIVITY TO ETHANOL MODIFY THE RISK FOR FASD

M.E. Charness[1,2,3], X. Dou[1,2]
[1]VA Boston Healthcare System, West Roxbury, MA 02132, USA, [2]Harvard Medical School, Boston, MA 02115, USA and [3]Boston University School of Medicine, Boston, MA, USA

Ethanol may cause FASD partly by inhibiting L1-mediated cell adhesion. FASD is a partial phenocopy of L1 mutations in humans, and drugs that block ethanol inhibition of L1 adhesion also prevent ethanol teratogenesis in mouse embryos. Ethanol inhibits L1 adhesion by interacting with an alcohol binding site in the extracellular domain of L1 (L1-ECD). Phosphorylation of multiple residues in the L1 cytoplasmic domain (L1-CD) decrease L1 sensitivity to ethanol by promoting the dissociation of L1 from ankyrin-G and the spectrin-actin cytoskeleton. Hence, genetic variants or drugs that regulate L1-ankyrin association might also regulate ethanol teratogenesis. Polymorphisms in ankyrin-G and p90rsk, a kinase that phosphorylates a residue in the L1-CD, are associated with principal components of facial dysmorphology in a CIFASD cohort of children with heavy prenatal ethanol exposure. Likewise, NAPVSIPQ, a peptide that blocks ethanol inhibition of L1 adhesion and prevents ethanol teratogensis in mice, potently stimulates EphB2, a kinase that phosphorylates the L1-CD at the ankyrin binding locus, leading to ankyrin dissociation from L1. These findings indicate that L1 association with ankyrin and the spectrin-actin cytoskeleton is necessary for L1 sensitivity to ethanol and ethanol teratogenesis. Genetic polymorphisms or drugs that alter L1-ankyrin association modify the risk for FASD.

085

CREATION OF AN ONLINE COLLABORATIVE INITIATIVE ON FETAL ALCOHOL SPECTRUM DISORDERS (CIFASD) REGISTRY FOR THE STUDY OF THE GENETICS OF FASD

T.M. Foroud, E. Rowe, L. Wetherill, T.-h.S. An
Department of Medical and Molecular Genetics, Indiana University School of Medicine, USA

While prenatal alcohol exposure is required for fetal alcohol spectrum disorders (FASD) it is clear that there is substantial variation in the clinical and physical manifestations of this teratogenic exposure. It is hypothesized that other factors, some of which may be genetic, contribute to this variation. Ongoing genetic studies have examined the role of common variation using genomewide SNP arrays as well as rare variation using whole exome sequencing. SNP analyses provided further support for several genes including PDGFRB and PDGFRA. One of the significant challenges in genetic studies of FASD is the ability to analyze data from large numbers of individuals to ensure sufficient power to detect genetic effects with small to moderate effect size. Given the diverse groups affected by FASD, it is essential that results are generalizable to the overall population. To address this challenge, a web portal has been developed that includes innovative online consenting methods and invites participants to complete a series of online protocols including 2D image acquisition. Participants will provide a saliva sample for DNA to be used in genetic studies. This innovative online approach will recruit over 2000 individuals over 5 years and will substantially improve the power of genetic studies.

MONDAY, SEPTEMBER 10 1:00 PM–2:30 PM

SYMPOSIUM

MECHANISMS OF MULTI-ORGAN INJURY BY ALCOHOL AND HIV-1 INTERACTIONS THROUGH THE GUT-LIVER-BRAIN AXIS
ORGANIZER/CHAIR: B. J. SONG CHAIR: MOHAMMED AKBAR

086

MECHANISMS OF MULTI-ORGAN INJURY BY ALCOHOL AND HIV-1 INTERACTIONS THROUGH THE GUT-LIVER-BRAIN AXIS

A. Keshavarzian, C. Forsyth, R. Voigt, M. Shaikh, P. Engen
Rush University Medical Center, Department of Internal Medicine, Chicago, IL, USA

Several epidemiological and clinical studies have demonstrated that HIV patients who have AUD have worse disease course than those without alcoholism even in virally controlled HIV patients treated with long-term antiretroviral therapy (ART). Since, non-AIDS events are the primary cause of mortality and morbidity in treated HIV patients, then it is reasonable to consider that alcohol worsen HIV disease course through increasing the frequency and/or severity of these non-AIDS co-morbidity like inflammation-driven metabolic syndrome, diabetes, cardiovascular disease (CVD), premature aging and neurodegenerative diseases. Several experimental studies have shown that Gut-derived inflammation may trigger systemic inflammation leading to poor immune reconstitution and low CD4 counts. Indeed, we and others have shown that HIV patients (even virally controlled treated patients) have pro-inflammatory dysbiotic intestinal microbiota and disruption of intestinal barrier integrity. Thus, excessive alcohol use can trigger and/or exacerbate gut-derived inflammation by promoting dysbiosis and/or gut leakiness to endotoxins. We and others have shown that alcohol abuse disrupts intestinal microbiota community composition and function leading to a pro-inflammatory dysbiotic microbiota community in both mice and human. We also showed that alcohol consumption disrupts intestinal barrier integrity leading to endotoxemia in alcoholics and alcohol fed mice and rats. In this symposium, we will present data demonstrating that both alcohol abuse and HIV can cause pro-inflammatory dysbiotic microbiota and disrupted intestinal barrier integrity and endotoxemia. These data provide compelling evidence for microbiota-directed intervention in HIV patients with AUD to determine if their disease course can be positively modified.

087

ROLE OF CYP2E1 IN PROTEIN MODIFICATIONS AND GUT LEAKINESS, LEADING TO LIVER INFLAMMATION AND BRAIN INJURY IN HIV-1 TRANSGENIC RATS

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We have recently characterized the functional roles of ethanol-inducible cytochrome P450-2E1 (CYP2E1) in promoting mitochondrial dysfunction and hepatocyte cell death in animal models of alcoholic and nonalcoholic fatty liver disease. In this Symposium, I will briefly describe the properties of CYP2E1 and its functional roles in promoting various post-translational modifications (PTMs, e.g., oxidation, S-nitrosylation, nitration, JNK-mediated phosphorylation, adduct formation, etc.) of many proteins in mitochondria and cytosols (including ER), contributing to their inactivation with mitochondrial dysfunction and ER stress and ultimately cell death in many tissues. I will also describe the recent results of the causal role of CYP2E1 in promoting alcohol-induced gut leakiness and inflammatory liver injury in rats and mice in a CYP2E1-dependent manner. Treatment with a specific CYP2E1 inhibitor or genetic deletion of *Cyp2e1* gene, as in the *Cyp2e1*-null mice, prevented alcohol-induced gut leakiness and inflammatory tissue injury. Finally, I will also describe the differential sensitivity to alcohol-induced gut leakiness and inflammatory liver injury in wild-type (WT) and HIV-1 transgenic (Tg) rats, mimicking the conditions of human HIV-1 infected people treated with anti-retroviral agents. Our results showed that the HIV-1 Tg rats were more sensitive to alcohol-induced gut leakage, leading to inflammatory fatty liver disease compared to age- and gender-matched WT rats. These results indicate the important role of gut leakiness in stimulating inflammatory liver injury in experimental animal models especially through the additive or synergistic interactions between alcohol and HIV infection. Furthermore, HIV-1 Tg rats could be a good animal model to study multi-organ injury through the gut-liver-brain interactions especially in the presence of ethanol exposure.

088

ALCOHOL AND HIV ASSOCIATED CHANGES IN THE GUT-LIVER-BRAIN AXIS: RELEVANCE TO HEPATIC INJURY AND NEUROINFLAMMATION

S. Barve
Department of Medicine, University of Louisville Medical School, Louisville, KY, USA

Background: Heavy alcohol use is common among people living with HIV-1 infection (PLWH). It is becoming increasingly evident that in both HIV-1 infection and chronic alcohol abuse alterations in gut microbiome (dysbiosis) and increased intestinal permeability and microbial translocation (MT) are major pathogenic drivers of local and systemic inflammation and organ injury. These findings underscore the importance of studying the interactive effects of heavy alcohol drinking and HIV-1 infection at the level of gut dysbiosis, gut permeability, peripheral inflammation and the development of hepatic injury and neuroinflammation.
Methods: Preclinical studies were conducted by employing a well-established animal model of ALD. Metagenomic analysis of the gut microbiome was performed on fecal DNA by amplification of the V3–V5 regions of the 16S rRNA gene, and large-scale parallel sequencing on the Illumina MiSeq platform. For clinical studies, plasma specimens obtained from HIV infected (RNA < 400 copies/mL) and uninfected individuals were analyzed for biomarkers of intestinal permeability, microbial translocation and systemic inflammation.
Results: Pre-clinical and clinical studies delineating the effects of alcohol and HIV-1 infection demonstrated the induction of gut microbial dysbiosis, characterized by a marked increase in the Proteobacteria phylum and a shift in the *Firmicutes/Bacteroidetes* phyla ratio. Pre-clinical studies demonstrated that alcohol-induced gut dysbiosis was associated with increased MT and systemic endotoxemia, leading to hepatic inflammation and injury, and neuroinflammation. Clinical studies showed that the plasma concentrations of markers of gut barrier damage (iFABP) and monocyte activation (sCD14 and sCD163) were significantly higher in HIV infected individuals when compared to the healthy controls. Notably, within HIV infected individuals alcohol consumption was associated with higher plasma iFABP and sCD14 levels suggesting that alcohol abuse increases microbial translocation and immune activation in HIV-1 infected individuals.
Conclusion: These studies emphasize the need for studying the interactive effects of heavy alcohol drinking and HIV-1 infection at the level of gut dysbiosis, gut permeability, microbial translocation, and peripheral inflammation leading to development of hepatic and neuronal disease.

089

INTERPLAY BETWEEN NEUROHIV AND BINGE EXPOSURE TO ALCOHOL

S. Chang
Institute of Neuroimmune Pharmacology and Department of Biological Sciences, Seton Hall University, South Orange, NJ, USA

Purpose: In the post-cART era, the percentage of heavy drinking among people living with HIV (PLWH) is close to ten-fold greater than that in the general population in US. The HIV-1 transgenic (HIV-1Tg) rat was created with a *gag*- and *pol*-deleted HIV-1 viral genome to mimic PLWH receiving combination anti-retroviral therapy (cART). HIV-1Tg rats exhibit cognitive impairment prior to the symptomatic signs of HIV infection. HIV-1Tg rat was characterized and used to study interplay of neuroHIV and binge exposure to ethanol (EtOH).
Methods: RNA deep sequencing analysis, flow cytometry, ELISA and behavior assessment were employed to characterize neuroimmune parameters, immunophenotyping, plasma level of inflammatory cytokines of the HIV-1Tg rats. We then examined the impacts of binge EtOH (4.8 g/kg/day, 52%, 3d, i.g.).
Data and Results: RNA deep sequencing analysis revealed that immune response, neurotransmission, and neuroplasticity related pathways were significantly changed in the brain of HIV-1Tg rats. Immuno-phenotying by flow cytometry revealed that HIV-1Tg rats suffered with inflaming aging. HIV-1Tg rats exhibited increased sensitivity to addictive substances, including alcohol, commonly abused by the PLWH. EtOH-induced enhancement of novelty seeking behaviors was significantly greater in the HIV-1Tg rats than control animals. In response to single cycle of binge EtOH, elevation of expression of various EtOH metabolite enzymes of the brain including CYP2E1 in the control rats was not observed in the HIV-1Tg rats. This may be the molecular mechanism underlying high sensitivity to EtOH of the HIV-1Tg rats. The level of plasma endotoxin was significantly higher in the HIV-1Tg rats than that in the control animals suggesting HIV-1Tg rats might experience the challenge associated with gut leaking. The locomotor activity deficits induced by giving five cycles of binge EtOH was associated with increased expression of inflammatory cytokines including IL-6, IL-18 and NfKB. These EtOH-induced effects were much more pronounced in the HIV-1Tg rats.
Conclusion: HIV-1Tg rat is an invaluable rodent model to study high prevalence of heavy drinking among PLWH on cART. The high level of plasma endotoxin of HIV-1Tg rat could reflect its gut leaking and lead to neuroinflammation. Elevation of neuroinflammation could contribute to transition of functional central nervous system to alcohol use disorders.

090

HOW HIV-1 INFECTION AND ALCOHOL LEAD TO NEURODEGENERATION: MECHANISMS AND INTERVENTIONS

Y. Persidsky
Lewis Katz School of Medicine, Temple University, Philadelphia, PA, USA

Despite immune recovery in individuals on antiretroviral therapy (ART), the frequency of HIV-associated neurocognitive disorders (HAND) remains high for reasons that are not well understood. Current understanding is that HIV-associated neurodegeneration is driven by chronic inflammatory responses outside of the brain due to blood brain barrier (BBB) injury as well as a low level of HIV replication in central nervous system (CNS) reservoir cells (macrophages, microglia). Alcohol misuse exacerbates HIV infection in humans and in animal models. There is an important connection between alcohol abuse and progression of HIV infection and its contribution to HAND, including BBB dysfunction and neuroinflammation. The causes of HIV-1-associated neurotoxicity include excitotoxic effects of glutamate, secretory products of chronically activated glial cells and oxidative stress, similar culprits to ones mediating alcohol-induced neuronal injury. Dysfunction of the BBB; a common feature of HIV-1 neurodegeneration) was documented in the setting of inflammation and chronic alcohol exposure in animal studies. Taken together, alcohol abuse and HIV-1 infection of the CNS could result in combined toxic effects leading to neuronal injury and cognitive dysfunction. While mechanisms of such injury are currently unknown, oxidative damage and glutamate imbalance contribute to neurodegeneration in both conditions. Recent findings in humans and animal models suggest that alcohol induces inflammatory processes in the brain leading to neurodegeneration. We have demonstrated alcohol-induced BBB impairment and delineated molecular mechanisms of this formerly unrecognized phenomenon. BBB compromise further promotes the neurodegeneration mediated by ethanol metabolism in human neurons and in human astrocytes. We showed alcohol exposure increased neuroinflammation in an animal model of HIV-1 encephalitis, a pathologic correlate of HAND. Therefore, therapeutic strategies aiming at reduction of neuroinflammation is a logical approach to ameliorate, or reverse, CNS injury in the setting of alcohol abuse and HIV-1 infection.

MONDAY, SEPTEMBER 10 2:50 PM–4:20 PM

SYMPOSIUM

BUILDING A GLOBAL ALCOHOL RESEARCH AGENDA FOR REPRODUCTIVE AND CHILD HEALTH: CLOSING INTERDISCIPLINARY GAPS TO ADDRESS THE NEEDS OF PEOPLE AFFECTED BY HIV/AIDS – PART 1

ORGANIZER/CHAIR: TATIANA N. BALACHOVA CHAIR: NIRANJAN SAGGURTI.

091

ALCOHOL USE AND ADVERSE HEALTH OUTCOMES FOR YOUNG HIV-INFECTED RUSSIAN WOMEN: ASSOCIATION BETWEEN PHOSPHATIDYLETHANOL AS A NOVEL BIOMARKER OF ALCOHOL CONSUMPTION, SEXUAL RISK, OTHER SUBSTANCE USE, AND ANTIRETROVIRAL MEDICATION ADHERENCE

R.J. Diclemente[1,2], J.L. Brown[3,4], L. Godfrey[4], A.K. Littlefield[5]
[1]Department of Socio-behavioral Sciences, College of Global Public Health, New York University, USA, [2]Center for Drug Use and HIV/HCV Research, USA, [3]Addiction Sciences Division, Department of Psychiatry & Behavioral Neuroscience, University of Cincinnati College of Medicine, USA, [4]Department of Psychology, University of Cincinnati, USA and [5]Department of Psychological Sciences, Texas Tech University, USA

This study assessed alcohol use among HIV-infected Russian women using ACASI technology to minimize self-report bias and an innovative biomarker, Phosphatidylethanol (PEth), to provide an objective and quantifiable measure of alcohol use over the prior 14 days. Participants were 250 young Russian women (18–35 years; Mean age = 30) recruited from an HIV clinical center in Saint Petersburg who completed assessments at baseline and 3-month follow-up. The majority (71.9%) had a positive PEth at baseline. On self-report measures, 25.4% reported heavy episodic drinking during the past month, and 27.9% exceeded the cut-off for hazardous drinking as measured by AUDIT-C. Comparing self-reported alcohol use and PEth biomarker, we observed marked underreporting of alcohol use. Of those participants denying alcohol consumption in the past 30 days, 52.9% tested PEth+ at baseline. However, underreporting of alcohol use at baseline did not predict underreporting at 3-month follow-up ($b = 0.94$, $p = 0.06$). Biologically-confirmed alcohol use was significantly associated with myriad risk behaviors and adverse health outcomes (e.g., poorer medication adherence, $p = 0.05$). Findings indicate alcohol use is prevalent and screening, assessment, intervention and referral to intensive alcohol treatment services may be needed to reduce alcohol use and its adverse health consequences.

092

ALCOHOL USE BY WOMEN LIVING WITH HIV (WLWH) IN UGANDA AND SOUTH AFRICA DURING PERICONCEPTION AND PREGNANCY PERIODS IS HIGH

L.T. Matthews[1], C. Orrell[2], G. Amanyire[3], M.B. Bwana[4], S. Asiimwe[1,5], A. Cross[2], N. Musinguzi[1], C. Psaros[1], J.A. Hahn[6], J.E. Haberer[1]

[1]Massachusetts General Hospital / Harvard Medical School, USA, [2]University of Cape Town / Desmond Tutu HIV Foundation, South Africa, [3]Makerere Joint AIDS Program, Uganda, [4]Mbarara University of Science and Technology, Uganda, [5]Kabwohe Clinical Research Center, Uganda and [6]University of California at San Francisco, USA

Background: Alcohol use is associated with poor adherence to antiretroviral treatment (ART) and poor infant outcomes.

Methods: WLWH enrolled in a cohort evaluating ART adherence in Uganda (UG) and South Africa (SA). Baseline blood measured phosphatidylethanol, an objective marker of alcohol intake. Women provided self-reported pregnancy plans, prior 3-month alcohol intake (AUDIT-C), and urine for b-HCG at enrollment, 6, and 12 months. We describe proportion of visits with hazardous alcohol use by self-report (AUDIT-C $\geq$ 3) among women at periconception (desiring pregnancy), prevalent/incident pregnancy, and non-pregnancy-related visits over 12 months; and proportion of women with hazardous alcohol use (AUDIT-C $\geq$ 3 or phosphatidylethanol $\geq$ 50 ng/mL) at enrollment.

Results: 625 women (median age 29; CD4 416) reported hazardous drinking at 32% and 8% of periconception, 25% and 4% of prevalent-pregnancy, 23% and 4% of incident-pregnancy, and 23% and 2% of non-pregnancy-related visits in South Africa and Uganda, respectively. At enrollment, hazardous drinking was observed among 47% (SA) and 32% (UG) of periconception, 36% (SA) and 18% (UG) of pregnant, and 43% (SA) and 14% (UG) of remaining women.

Conclusion: WLWH in Uganda and South Africa had hazardous alcohol use during periconception, pregnant, and non-pregnancy-related periods. Alcohol counseling for WLWH is important to supporting healthy pregnancies.

093

ALCOHOL USE AMONG HIV-INFECTED PREGNANT WOMEN AND CHILD OUTCOMES IN THE PEDIATRIC HIV AIDS COHORT STUDY (PHACS)

D. Jacobson[1], K. Tassiopoulos[1], P. Williams[2], G.R. Seage[1]

[1]Department of Epidemiology, Harvard T. H. Chan School of Public Health, USA and [2]Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health, USA

The PHACS Surveillance Monitoring for ART Toxicities Study (SMARTT) is designed to identify adverse events related to in utero antiretroviral treatment (ART) exposure among HIV-uninfected children born to HIV-infected mothers at 18 sites in the United States. The dynamic SMARTT cohort enrolls newborn/mother pairs, and static SMARTT enrolls older infants/children. Substance use, including alcohol, which are important potential exposures/confounders, are obtained from maternal interviews as well as biological specimens (meconium and urine). Children are followed up to age 18.

As of April 2018, 2810 newborns were enrolled into dynamic SMARTT. Approximately half of the children were male. Most children were Black or African American (67%), and 29% were of Hispanic ethnicity. Among 2648 newborns whose mothers provided self-reported information on substance use during pregnancy, 760 (29%) had substance use exposure at some point during the pregnancy. Substance use was highest during the first trimester and then decreased; cigarette smoking (18%) was the most frequently reported substance, followed by alcohol (9%) and marijuana (9%).

Age-appropriate neurodevelopment evaluations are conducted on all children. Of children assessed to-date, mean test scores across different evaluations are mostly within 5–10 points of general population norms.

094

ALCOHOL USE, PREGNANCY PLANNING, AND REPRODUCTIVE HEALTH CONCERNS IN PEOPLE LIVING WITH HIV/AIDS IN RUSSIA

A.Y. Marianian[1,2], E. Genich-Timofeeva[1], A.V. Atalyan[1], O.Y.A. Leshchenko[1], L.V. Suturina[1], T.N. Balachova[3]

[1]Federal State Public Scientific Institution (SC FHHRP), Russia, [2]Irkutsk State Medical Academy of Postgraduate Education – Branch Campus of the FSBEI FPE RMACPE MOH, Russia and [3]University of Oklahoma Health Sciences Center, USA

Background: Data on alcohol consumption and reproductive health among people living with HIV/AIDS (PLWH) are insufficient. The objective of this pilot study was to evaluate alcohol use and reproductive health among PLWH in Siberia, Russia.

Methods: A total of 50 females (F) and 35 males (M) LWH of childbearing age (18–44) were recruited for the study at Irkutsk Regional Infectious Disease Hospital, Russia.

Results: A total of 42.9%F and 28.6%M were receiving ART. The majority of participants (55.1% F, 71.4%M) were diagnosed with Hepatitis B or C. Compared to males, females were less likely to be married (14%F, 40%M, $p = 0.01$) and have intercourse regularly (48.9%F. 91.2%M, $p = 0.0001$). 100%F planned to become pregnant sometime in future compared to 42.9%M being interested in F partner's pregnancy ($p = 0.0001$). The most common methods of contraception reported by F and M were condoms and coitus interruption; 26.1%F and 20%M did not use contraception. Among females, 82.4% reported alcohol use, 36% use drugs regularly, and 68% smoke.

Conclusions: Although all women plan pregnancy in future, high prevalence of alcohol misuse and other health risk behaviors, comorbidities, and risk for unplanned pregnancies constitute significant concerns for reproductive health, prenatal exposure, and adverse child outcomes in PLWH.

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BUILDING A GLOBAL ALCOHOL RESEARCH AGENDA FOR REPRODUCTIVE AND CHILD HEALTH

D.A. Russo

National Institutes of Health, EKS National Institute of Child Health and Human Development, USA

NICHD has great interest in the impact of HIV/AIDS and antiretrovirals on reproductive and child health globally. There has been ongoing interest in mitigating the adverse effects of alcohol misuse in infectious disease contexts, especially HIV/AIDS in women and men of reproductive age and their offspring. Several of the HIV/AIDS networks and many of the individual grants and contracts supported by NICHD have alcohol measures and drug use incorporated into their clinical research topics. These studies have been supported by several NIH Institutes including NIAAA. Supported studies have also been active in assessing the various microbiomes of the women and offspring who are participating. For example, an ongoing global study in Africa compares breast feeding and the microbiome in HIV positive individuals. Adding an alcohol component to these research endeavors is a feasible and desirable way to leverage the robust and ongoing data sets available in the networks and studies. Perturbations in the microbiomes during alcohol misuse and ongoing infectious disease may reflect important developmental changes within these populations.

MONDAY, SEPTEMBER 10 4:30 PM–6:00 PM

SYMPOSIUM

BUILDING A GLOBAL ALCOHOL RESEARCH AGENDA FOR REPRODUCTIVE AND CHILD HEALTH: CLOSING INTERDISCIPLINARY GAPS TO ADDRESS THE NEEDS OF PEOPLE AFFECTED BY HIV/AIDS – PART 2

ORGANIZER/CHAIR: TATIANA N. BALACHOVA CHAIR: NIRANJAN SAGGURTI

096

ROLE OF ALCOHOL ABUSE, HIV-1 INFECTION AND VAGINAL MICROBIAL DYSBIOSIS IN THE REPRODUCTIVE HEALTH OF WOMEN

S. Barve, S. Ghare, L. Gobejishvili
Department of Medicine, University of Louisville, USA

The vaginal microbiome varies with hormonal changes, sexual activity, age, race and lifestyle factors including chronic alcohol abuse. Women with vaginal dysbiosis (altered microbiome) represented by a decrease in *Lactobacillus* spp. are at risk for serious and costly reproductive tract diseases, such as bacterial vaginosis, yeast infections, sexually transmitted infections, urinary tract infections, and HIV infection. The current findings indicate that up to 30% of new HIV cases could be averted if the composition of the vaginal microbiota was represented predominantly by lactic acid-producing *Lactobacillus* spp.

Findings from studies that have investigated an in-depth and accurate assessment of the vaginal microbiome in asymptomatic and HIV-1 infected women, using next-generation sequencing (NGS)-based metagenomic sequencing strategies, will be presented. It is becoming increasingly clear, that accurately defining the changes in the vaginal microbiome with regards to composition and function, both in the context of HIV-1 infection and alcohol abuse, are an essential prerequisite for (i) reducing the risk of acquisition of reproductive tract diseases and identifying factors that determine disease susceptibility and (ii) developing treatment strategies for management, modulation, and restoration of a robust vaginal microenvironment, that ultimately improves the health of women and their children.

097

ALCOHOL PHARMACOTHERAPIES TO IMPROVE ALCOHOL AND HIV TREATMENT OUTCOMES AFTER RELEASE FROM PRISON FOR WOMEN LIVING WITH HIV AND ALCOHOL USE DISORDERS IN THE UNITED STATES CRIMINAL JUSTICE SYSTEM

S.A. Springer
Department of Internal Medicine, Section of Infectious Disease, Yale School of Medicine, USA

Alcohol use disorders (AUD) and HIV are highly prevalent among women in the U.S. criminal justice system (CJS). The majority of women, however, are not screened for AUD nor are they offered relapse prevention at time of release. This abstract will review the positive impact alcohol pharmacotherapies could have on preventing relapse to alcohol use and HIV viral suppression after release to the community for HIV+ women involved in the CJS. An overview of HIV and substance use disorders among those incarcerated in the U.S CJS and the current medications to treat AUD will be given with a special emphasis on women. Further, results of the first study to evaluate the impact of an alcohol pharmacotherapy, extended-release naltrexone, on HIV viral suppression among 100 prisoners with HIV and AUD will be shown. Implications from this research will be discussed including implementing the use of alcohol pharmacotherapies as a means to achieve the United Nations Goals to end AIDS by 2030 as well as how to prevent HIV in high AUD and HIV prevalent areas globally.

098

ALCOHOL USE AND GENITAL TRACT INFECTIONS IN INDIA: LESSONS LEARNED FROM RESEARCH, COMMUNITY IMPLEMENTATION, AND BUILDING NATIONAL CAPACITY

N. Saggurti
Population Council, India

Alcohol is consumed by female sex workers (FSWs) for variety of reasons including insistence from clients and to cope with sex work related fatigue. On the other hand, genital tract infections are common among FSWs in India. However, interventions to address the interaction between alcohol and genital tract infections are limited primarily due to lack of evidence. The research that Population Council conducted in partnership with FSW-led community organisations during 2016–2017 ($N = 3500+$) helped examine the linkages; and develop programmatic strategies around alcohol related vulnerability. Bivariate and multiple logistic regression analyses indicated a significant association between alcohol use and genital tract infections (for e.g., having 6 or more drinks in one occasion versus no alcohol users: adjusted odds ratio- 3.11, $p < 0.01$) and unpack the reasons for alcohol use and circumstances leading to infections. Results of this research helped FSW-led organisations to develop programmatic strategies to primarily deal with clients' pressure for alcohol use. The presentation will share findings from the large-scale survey, learnings from development and implementation of community-led programme on alcohol and related vulnerabilities, which was done as part of a national AIDS control programme in India.

099

DISCUSSION ON ALCOHOL AND HIV RESEARCH FOR REPRODUCTIVE HEALTH: CLOSING GAPS BETWEEN DISCIPLINES AND SETTING RESEARCH AGENDA

K.J. Bryant
National Institutes of Health, USA

The role of alcohol use among mothers infected with HIV and its impact on developmental challenges for their children represents a major focus for research. The National Institute on Alcohol Abuse and Alcoholism (NIAAA, NIH) needs to build capacity in both domestic and international settings to achieve this high priority goal for women and their families for ending the HIV epidemic. This objective, to study co-morbidities among the highest risk populations, includes a range of ongoing observational, basic, and intervention research. Research can be integrated with other research on mothers who drink and are not HIV positive being carried out with NIAAA support and addresses the impact of maternal alcohol use on developmental delays among children such as Fetal Alcohol Spectrum Disorders (FASD). NIAAA has pioneered interventions among HIV+ mothers improving both maternal and child outcomes and has successfully disseminated these interventions in the context of a generalist home visits. In addition, NIAAA supports integrative research within informative cohorts such as the Pediatric AIDS Cohort Study. However, more needs to be done. The discussion will highlight the integrative and translational characteristics of this research and the need to better understand how dissemination of effective interventions can become successful.

MONDAY, SEPTEMBER 10 9:50 AM–11:20 AM

SYMPOSIUM

BINGE BEHAVIORS : ETIOLOGICAL MODELS AND UNDERLYING PSYCHOLOGICAL FACTORS

ORGANIZER/CHAIR: JOËL BILLIEUX

100

BINGE DRINKING – A BEHAVIORAL AND ELECTROPHYSIOLOGICAL APPROACH

P. Maurage[1,2], S. Lannoy[1,2], V. Dormal[1]

[1]Psychological Science Research Institute, Université Catholique de Louvain, Belgium and [2]Fund for Scientific Research, FSR/FNRS, Belgium

Binge drinking is a pattern of excessive alcohol consumption characterized by an alternation between intense intakes and abstinence periods, associated with various deleterious consequences. The cognitive deficits observed among binge drinkers have been largely reported during the last decade. Executive functions impairments, especially, have been identified as key factors in the emergence and maintenance of binge drinking habits. This talk will present new behavioral and electrophysiological data allowing to better understand the specific executive impairments associated with binge drinking. We will centrally underline that binge drinkers present a dissociation between impaired error-related processing (indexed by slower and blunted ERN, i.e. error-related negativity component) and preserved feedback processing (indexed by efficient FRN, i.e. feedback-related negativity component). We will also describe the first experimental observation of emotional impairments in this population, underlining that binge drinkers present reduced performance in an emotional facial decoding task including positive and negative emotional expressions. The influence of these new insights at theoretical, experimental and clinical levels will then be discussed, notably to underline, by means of recent results obtained using tDCS combined with cognitive remediation, the potential usefulness of joint neuropsychological/neuromodulation interventions among people presenting binge drinking habits.

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BINGE-WATCHING ENGAGEMENT AS DETERMINED BY MOTIVATIONS, IMPULSIVITY AND EMOTIONAL REACTIVITY: A CLUSTER ANALYTIC APPROACH

M. Flayelle[1], P. Maurage[2], C. Vögele[1], L. Karila[3,4], J. Billieux[1,5]

[1]University of Luxembourg, Luxembourg, [2]Université Catholique de Louvain, Belgium, [3]University Hospital Paul Brousse, France, [4]Université Paris Sud, France and [5]University Hospitals of Geneva, Switzerland

With the advent of on-demand viewing services, binge-watching (i.e. watching multiple episodes of a TV series in one session) has become the new normative way viewers consume TV shows. Yet, this behavioral phenomenon recently generated concerns regarding the negative outcomes associated with excessive binge-watching. Its psychological investigation, however, remains fragmentary, the few initial studies *a priori* conceptualizing this behavior as a new addictive disorder. The current study thus explores binge-watchers' psychological characteristics by identifying the different subtypes of TV series viewers based on their motivations for watching, impulsivity traits and emotional reactivity. A sample of 4039 TV series viewers was surveyed online via self-reported questionnaires. Then, hierarchical and non-hierarchical cluster analyses were undertaken and the validity of the clusters evidenced was investigated through comparisons for external correlates. Four clusters of viewers were identified: recreational TV series viewers, regulated binge-watchers, avid binge-watchers and unregulated binge-watchers. These preliminary results underline the heterogeneous and multi-determined nature of binge-watching. More crucially, our findings emphasize that high engagement in binge-watching is distinct from problematic binge-watching, thus reinforcing the proposal that conceptualizing binge-watching as an addictive disorder from the outset is of low relevance and might actually lead to the overpathologization of this popular leisure activity.

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INVESTIGATING FOOD CHOICE PROCESSES USING HAND MOVEMENTS IN BULIMIA NERVOSA AND BINGE EATING DISORDER

Z.V. Dyck[1], M. Schulte-Mecklenbeck[2], J. Blechert[3], C. Vögele[1]

[1]University of Luxembourg, Luxembourg, [2]University of Bern, Switzerland and [3]University of Salzburg, Austria

Navigating today's food environment requires frequent food choices. Eating-related psychopathologies are likely to moderate such food choices. Little is known, however, about food-related decision making processes in patients with binge eating behaviours. The present study aimed at investigating the time-course of the food choice process in patients with bulimia nervosa (BN) or binge-eating disorder (BED).

29 eating disordered patients (ED) meeting current DSM-5 criteria for BN ($n = 11$) or BED ($n = 18$) and 29 healthy controls (HC) participated in the study. A mouse-tracking paradigm was used to record continuous hand-movements during repeated forced choices between healthy and unhealthy foods. The degree of curvature in response trajectories during mouse-based choice was calculated as a metric of the competition between choice options.

When making a healthy food choice, ED participants were stronger attracted towards the unhealthy food option and they took more time to make a food choice than HCs. In addition, the curvature of their mouse trajectory was strongly positively related to the mean number of objective binge eating episodes per week.

In an environment with high food availability, not only behavioral food choices, but also choice processes, are altered in patients with recurrent binge eating behaviors.

MONDAY, SEPTEMBER 10 2:50 PM–4:20 PM

SYMPOSIUM

LONG-TERM CONSEQUENCES OF HEAVY DRINKING IN JAPAN, GERMANY AND U.S

ORGANIZER: MICHIE N. HESSELBROCK CHAIRS: VICTOR M. HESSELBROCK AND SUSUMU HIGUCHI

103

LIVER STIFFNESS PRIOR AND AFTER ALCOHOL DETOXIFICATION AS A NOVEL PROGNOSTIC MARKER IN HEAVY DRINKERS: FIRST DATA FROM A PROSPECTIVE COHORT

S. Mueller

Salem Medical Center and Center for Alcohol Research, University of Heidelberg, Germany

Background and Aims: We here present first data on the prognostic impact of liver stiffness (LS) on long-term survival of Caucasian drinkers primarily presenting for alcohol detoxification.

Method: Information of survival status was obtained in 225 (96.9%) of 232 screened patients that had presented for alcohol detoxification over a 10 year period from 2007 to 2017. All patients had LS measurements by transient elastography and routine lab tests.

Results: During the observation time, 28 patients (13.5%) passed away. In 19 patients, a cause of death could be identified which was liver-related in 11 cases (58%). LS ($r = 0.25$), bilirubin ($r = 0.29$) and INR ($r = 0.29$) were all highly associated ($p < 0.001$) with liver-related death but not with overall mortality. LS was also a significant and independent predictor of liver-related death ($p < 0.005$) in multivariate analysis. In 131 patients, we were able to assess laboratory markers and LS prior and after alcohol detoxification. To our surprise, LS after detoxification was significantly better in predicting death as compared to the initial LS (0.0004 vs. 0.0015).

Conclusion: We here show that LS predicts long-term mortality in heavy drinkers primarily presenting for alcohol detoxification.

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THE EFFECT OF SMOKING ON THE TREATMENT OUTCOME OF ALCOHOLIC PATIENTS WHO RECEIVED INPATIENT CBT

M. Kimura[1], A. Yoshimura[2], J. Yoneda[1], H. Maesato[1], T. Takimura[1], H. Nakayama[1], H. Sakuma[1], A. Yokoyama[1], S. Matsushita[1], S. Higuchi[1]
[1]National Hospital Organization Kurihama Medical and Addiction Center, Japan and [2]Department of Neuropsychiatry, Tohoku Medical and Pharmaceutical University, Japan

Purpose: This study aims to clarify the association between smoking and treatment outcomes among alcohol dependent patients who received inpatient Cognitive Behavioral Therapy (CBT).
Subjects and Methods: Subjects included 659 patients (556 male, 103 female) diagnosed as alcohol dependent who were admitted to Kurihama Medical and Addiction Center during 2014–2015. Most patients participated in an 8 week CBT-based treatment program. After discharge, each patient was sent a questionnaire by mail for 12 months, once a month for the first 6 months and every 2 months for the following 6 months. The relapse rate was estimated using Kaplan–Meier method and analyzed by log rank test.
Results: 376 participants were current smokers at admission, 147 participants had no smoking history and 136 were former smoker who had quit smoking. 463 patients answered their smoking status in the first month and 238 (51.4%) patients declared they smoked. Patients who smoked tobacco in the first month post-discharge were more likely to relapse (drink more than 60 g/day twice or more frequently a week) in the 12 months follow-up period ($p = 0.012$).
Conclusion: These results suggest the possibility that smoking is associated with the desire to drink and causes relapse in alcoholic patients.

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A 40 YEAR STUDY OF HEAVY DRINKING OUTCOMES IN HIGHLY EDUCATED MEN

M.A. Schuckit, T.L. Smith
Department of Psychiatry, University of California, San Diego, USA

This presentation describes results of drinking-related consequences in over 400 men from the San Diego Prospective Study who were selected at age 20 as drinking but not yet alcohol dependent university students, half of whom had an alcohol dependent parent and half of whom had no close relative with an alcohol use disorder (AUD). These men were followed about every 5 years through about age 60. Almost 50% of these men, most of whom went on to receive graduate degrees, developed an AUD, and most of these were persistent across their adult lives. Reflecting their relatively high socioeconomic status, less than 5% of these subjects have died, more than 80% had relatively successful careers, and at follow up the large majority were married and had adult children. However, compared to those who did not develop an AUD, those with multiple alcohol problems experienced more life challenges related to their heavy drinking including higher rates of failed marriages and impairments in earnings. The patterns of consequences and predictors of those outcomes are discussed.

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LONGTERM OUTCOMES IN ADULTS WITH ALCOHOL DEPENDENCE RE-ASSESSED AFTER AN AVERAGE OF 17 YEARS

K.K. Bucholz[1], V.M. Hesselbrock[2], M.N. Hesselbrock[2]
[1]Psychiatry, Washington U. School of Medicine, USA and [2]Psychiatry, University of Connecticut School of Medicine, USA

Purpose: This presentation investigates the long term outcomes of adults with Alcohol Dependence (AD) re-assessed after a mean of 17 years.
Methodology: Subjects were selected from participants in the Collaborative Study of the Genetics of Alcoholism who met criteria for AD and were 50 years or older at follow-up. 706 were interviewed (90% of located and living, 55% male, mean age 60.4) by telephone to obtain information on drinking patterns, problems and health status. Predictors from prior interviews and follow-up health characterized long term outcomes.
Results: 56% had drunk in the past year; others had not drunk for 1–5 years (8%), 5–10 years (6%), and over 10 years (30%). Individuals 60 and older, white, those with past psychiatric and drug comorbidities were more likely to be long-term nondrinkers (10+ years). No gender differences were seen. Long-term nondrinkers had better recent physical health, despite more baseline conduct, depression, comorbid cannabis and tobacco diagnoses; high blood pressure and brain injuries characterized current drinkers and past 10 year drinkers. Short term nondrinkers had elevated recent health problems and past opiate dependence.
Conclusions: Nondrinkers for 10+ years, despite greater past comorbidities, fared well based on recent health indicators compared to persistent drinkers and shorter term nondrinkers.

MONDAY, SEPTEMBER 10 4:30 PM–6:00 PM

SYMPOSIUM

THE CURRENT SITUATION OF INTERNET GAMING DISORDER FROM THE STANDPOINT OF YOUNG RESEARCHERS

ORGANIZER/CHAIR: YOKO NISHITANI CHAIR: TOMOHIRO SHIRASAKA

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INTERNET GAMING DISORDER IN CHILDREN AND ADOLESCENTS: AN UPDATED LITERATURE REVIEW

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Previous large-scale studies suggest that Internet Gaming Disorder (IGD) among children and adolescents has become an important public concern. Minors are known to be particularly susceptible to problematic internet gaming use due to age-related underdevelopment of cognitive control. Furthermore, online gamers were more likely than offline gamers to severely overuse internet gaming and to experience interpersonal problems. It has been shown that addictions have precursors during adolescence, therefore, prevention efforts must be established targeting minors who have their first experience with addictive substances and behaviors during pubescence. Since the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) IGD classification in 2013, studies of IGD have drastically increased. Thus, we performed an updated review of IGD in children and adolescents. Across studies, the presence of IGD had a negative effect on sleep and school work in minors. Additionally, family factors, including quality of parent-child relationship, were important social factors in minors with IGD. Finally, brain imaging studies indicated that impaired cognitive control in minors with IGD was associated with abnormal function in the prefrontal cortex (PFC) and striatum. Persistent pathological online game use since childhood may aggravate abnormal brain function, therefore, preventive care and early intervention have become increasingly important.

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A REPORT ON A TREATMENT PROGRAM FOR INTERNET GAMING DISORDER AMONG SOUTH KOREAN YOUTH

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Mounting evidence indicates that addicted gamers suffer from multiple comorbid psychiatric disorders. The problem is further complicated because computer usage is so pervasive in our society that the aim of treatment cannot be abstinence.
There is a general consensus that total abstinence from the Internet should not be the goal of the interventions and that instead, an abstinence from problematic applications and a controlled and balanced Internet usage should be achieved. The aim of the treatment is to help the patient manage the inappropriate behavior and still be able to use the technology. Here I introduce a multimodal treatment approach integrating various types of treatment in some cases even from different disciplines such as pharmacology, psychotherapy, and family counseling simultaneously or sequentially.
The inpatient treatment program, HORA helps patients relearn healthy coping skills in a contained environment. In addition, the HORA program is set up to address a wide variety of underlying issues which may contribute to the excessive internet game by connecting patients with community service providers knowledgeable in these areas during their stay at the center.

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SPOTLIGHTS ON INTERNET GAMING DISORDER AMONG UNIVERSITY STUDENTS IN EGYPT

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Internet addiction, or Problematic Internet Use (PIU), is considered a global phenomenon that has been a topic of increasing interest to clinicians, researchers and stakeholders in the recent years. There are general subtypes of Internet addiction that were categorized based upon the most problematic types of online applications, and they include addictions to Cybersex and internet pornography, Cyber-relationships, online stock trading or gambling, information surfing, and gaming. Internet Gaming Disorder (IGD) is included in DSM-5 as a "Condition for Further Study".
Despite its recognized potential hazards that warrants its inclusion in diagnostic systems, IGD is understudied in many societies. This presentation will overview recent studies on Internet Gaming Disorder in undergraduate students in Ain Shams University.
In a recent study by ELNahas et al. (2018) on 997 students around quarter of the sample experienced problematic gaming, with disordered gamers constituting 9.3% of the sample and risky gamers 15.9% of the sample while the rest were normal gamers.

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GAMING DEVICE USAGE PATTERNS AND INTERNET GAMING DISORDER AMONG YOUNG ADULTS IN SOUTH KOREA

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Gaming behaviors have been significantly influenced by smartphones. This study was designed to explore gaming behaviors and clinical characteristics across different gaming device usage patterns and the role of the patterns on Internet gaming disorder (IGD). Responders of an online survey regarding smartphone and online game usage were classified by different gaming device usage patterns: (1) individuals who played only computer games; (2) individuals who played computer games more than smartphone games; (3) individuals who played computer and smartphone games evenly; (4) individuals who played smartphone games more than computer games; (5) individuals who played only smartphone games. Data on demographics, gaming-related behaviors, and scales for Internet and smartphone addiction, depression, anxiety disorder, and substance use were collected. Combined users, especially those who played computer and smartphone games evenly, had higher prevalence of IGD, depression, anxiety disorder, and substance use disorder. These subjects were more prone to develop IGD than the reference group (Group 1). Smartphone only gamers had the lowest prevalence of IGD, spent the least time and money on gaming, and showed lowest scores of Internet and smartphone addiction. Our findings suggest that gaming device usage patterns may be associated with the occurrence, course, and prognosis of IGD.

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CLINICAL CHARACTERISTICS OF SOCIAL WITHDRAWAL (HIKIKOMORI) AND PROBLEMATIC INTERNET USE IN JAPAN

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Problematic internet use and related behaviors have been attracting the attention of mental health researchers and clinicians. Amongst students, problematic internet use may be a major factor in social withdrawal (Hikikomori). We conducted a survey of internet addiction and social withdrawal among students for different purposes.
Methods: Subjects were 864 high school students. And divided into three group for different purposes (1: Online game, 2: Social networking service [SNS], 3: The others). To examine the relationship between internet addiction and social withdrawal, we administered the Internet Addiction Test (IAT) and the UCLA Loneliness Scale (ULS), a measure of social isolation.
Results: For online game users considered addictive internet users, we found a significant correlation between the ULS and the IAT ($r = 0.682$, $p < 0.05$), suggesting that social isolation and internet addiction are associated with each other. For SNS group who were not addictive internet users, we found a negative correlation between the ULS and the IAT ($r = -0.265$, $p < 0.05$), suggesting that use of the internet for workers was not a compensatory behavior.
Conclusions: SNS users' loneliness did not appear to be related to their use of the internet, but amongst online game users with internet addiction, loneliness appeared to be associated with internet use.

TUESDAY, SEPTEMBER 11 9:55 AM–11:25 AM

SYMPOSIUM

TRANSGENIC ANIMAL AND PHARMACOLOGICAL STUDIES OF ALCOHOL METABOLITES, FROM PERIPHERAL ORGANS TO BRAIN

ORGANIZER: BIN GAO CHAIRS: KATHERINE JUNG AND LI ZHANG

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INTRODUCTION TO THE SYMPOSIUM

K. Jung
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Alcohol metabolism has been implicated in several human diseases and conditions. Pathologies associated with alcohol consumption occur in the general population, but are more prevalent in individuals with a mutant aldehyde dehydrogenase allele that confers impaired enzyme activity. It is important to note that alcohol and acetaldehyde are not the only substrates for their eponymous enzymes, and that the physiological functions of these enzymes, aldehyde dehydrogenase in particular, reach beyond their role in catabolizing alcohol. Investigators in his session will report insights into mechanisms by which aldehyde dehydrogenase 2 dysregulates the normal physiology of liver, heart, and brain.

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GENETIC DELETION OF ALDH2 EXACERBATES ALCOHOL AND CCL4-INDUCED LIVER INFLAMMATION AND FIBROSIS

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Approximately 35–45% of East Asians carry an inactive ALDH2 gene and exhibit acetaldehyde accumulation after alcohol consumption. However, the role of ALDH2 deficiency in the pathogenesis of alcoholic liver injury remains obscure. In this talk, I will discuss the effects of alcohol and/or carbon tetrachloride (CCl4) on liver injury and inflammation in ALDH2(−/−) mice. Compared with wild-type mice, ethanol-fed ALDH2(−/−) mice had higher levels of malondialdehyde-acetaldehyde (MAA) adduct and hepatic interleukin (IL)-6 expression but surprisingly lower levels of steatosis and serum alanine aminotransferase (ALT). *in vitro* incubation with MAA enhanced the lipopolysaccharide (LPS)-mediated stimulation of IL-6 production in Kupffer cells. Hepatic activation of the major IL-6 downstream molecule signal transducer and activator of transcription 3 (STAT3) was higher in ALDH2(−/−) mice than in wild-type mice. An additional deletion of hepatic STAT3 increased steatosis and hepatocellular damage in ALDH2(−/−) mice. Finally, ethanol-fed ALDH2(−/−) mice were more prone to CCl4-induced liver inflammation and fibrosis than ethanol-fed wild-type mice. In conclusion, ALDH2(−/−) mice are more susceptible to inflammation and fibrosis by way of MAA-mediated paracrine activation of IL-6 in Kupffer cells. These findings suggest that ALDH2-deficient individuals may be resistant to steatosis, but are prone to liver inflammation and fibrosis following alcohol consumption.

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ALDH2 AND OBESITY CARDIOMYOPATHY

J. Ren[1,2], Y. Zhang[1,2]
[1]University of Wyoming, USA and [2]Zhongshan Hospital Fudan University, China

Mitochondrial aldehyde dehydrogenase (ALDH2) is a mitochondrial enzyme with some promises in a number of cardiovascular diseases. Our study evaluated the impact of ALDH2 on cardiac remodeling and contractile property in high fat diet-induced obesity. WT and ALDH2 transgenic mice were fed low (10% calorie from fat) or high (45% calorie from fat) fat diet for 5 months. High fat diet intake promoted weight gain, cardiac remodeling (hypertrophy and interstitial fibrosis) and contractile dysfunction [reduced fractional shortening, cardiomyocyte function, and intracellular Ca^{2+} handling], mitochondrial injury (elevated O_2^- levels, suppressed PGC-1α and enhanced PGC-1α acetylation), elevated SUV39H, suppressed Sirt1, autophagy and phosphorylation of AMPK and CaM kinase II, the effects of which were negated by ALDH2. *In vitro* incubation of the ALDH2 activator Alda-1 rescued against palmitic acid-induced changes in cardiomyocyte function, the effect was nullified by the Sirt-1 inhibitor nicotinamide and the CaM kinase II inhibitor KN-93. The SUV39H inhibitor chaetocin mimicked Alda-1-induced protection again palmitic acid. Examination in overweight human revealed an inverse correlation between diastolic cardiac function and ALDH2 gene mutation. These data suggest that ALDH2 is an indispensable factor against cardiac anomalies in diet-induced obesity through a mechanism related to autophagy and facilitation of SUV39H-Sirt1-dependent PGC-1α deacetylation.

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ALDH2 SUPPRESSES CIRRHOSIS/FIBROSIS AND ALCOHOL-INDUCED HEPATOCELLULAR CARCINOMA VIA THE INHIBITION OF ACETALDEHYDE-DERIVED DNA DAMAGE AND MULTIPLE ONCOGENIC SIGNALING PATHWAYS

B. Gao[1], W. Seo[1], Y. Gao[1,2], T. Ren[1,2], S.-j. Kim[1], Y. He[1], D. Feng[1], J. Niu[2]
[1]NIAAA, NIH, USA and [2]Jilin University First Hospital, Jilin, China

An aldehyde dehydrogenase 2 (ALDH2) inactivating variant (termed ALDH2*2) is the most common single point variant in humans, existing in approximately 40–50% of East Asians. However, the effects of ALDH2 deficiency in the pathogenesis of liver disease progression and hepatocellular carcinoma (HCC) remain unclear. Mice with ALDH2 deficiency via the disruption of the *Aldh2* gene (*Aldh2* KO) globally or specifically in the liver, or knock-in of human *ALDH2*2* inactive variant (*ALDH2*1/*2*) did not affect CCl4-induced liver disease progression and HCC but markedly exacerbated CCl4-plus-ethanol-induced liver fibrosis and HCC. Compared to WT mice after CCl4-plus-ethanol challenge, *Aldh2* KO mice had greater levels of oxidative stress/lipid peroxidation, liver mitochondrial DNA damage, and oxidized DNA in the liver, as well as in the serum. Most of these mtDNA and oxidized DNA in the serum were detected in extracellular vesicles (EVs), which were higher in CCl4-plus-ethanol-treated *Aldh2* KO mice than WT mice. In addition, tumors from CCl4-plus-ethanol-treated *Aldh2* KO mice had higher levels of activation and expression of several oncogenic proteins (e.g. JNK, p38, TAZ, and Bcl-xL) than those from WT mice.

Conclusions: ALDH2 deficiency is associated with increased risk of HCC development in mice with CCl4-plus-ethanol treatment.

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PERINATAL AND INFANTILE DEVELOPMENT: CRITICAL STAGES FOR THE ANALYSIS OF ACETALDEHYDE'S MOTIVATIONAL PROPERTIES IN HETEROGENOUS RATS

J.C. Molina
Instituto de Investigacion Medica Mercedes y Martin Ferreyra, Argentina

Different studies indicate that early ontogeny is a vulnerable window relative to ethanol's positive reinforcing effects. Early sensitivity to ethanol reinforcement occurs within a particular pharmacokinetic context. Neonates exhibit a significantly higher activity of the central catalase system relative to adults. This system metabolizes ethanol into acetaldehyde; a metabolite that mediates ethanol reinforcement. Newborn mammals are also born with an immature liver that impedes high levels of peripheral acetaldehyde and its aversive gastrointestinal effects. These metabolic particularities suggest that early in development ethanol will primarily recruit positive reinforcing effects via its metabolite. Recent studies indicate that neonatal central exposure to acetaldehyde impedes later operant conditioning mediated through ethanol reinforcement. This inhibitory process is compatible with an unconditioned pre-exposure effect. Furthermore, central administration of acetaldehyde associated with an odor results in neonatal olfactory conditioned preferences; a phenomenon that is inhibited when ethanol or acetaldehyde are administered under the effects of D-penicillamine. D-penicillamine also inhibits early motor stimulatory effects of ethanol that are systematically observed in infants. This stimulatory effect has been associated with reinforcing effects of different drugs. The hypothesis under analysis also receives support when conducting a developmental meta-analytical approach indicating a positive correlation between central catalase activity and ethanol consumption.

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CELL-TYPE SPECIFIC DISTRIBUTION OF BRAIN ALDH2 AND ITS CONTRIBUTION TO CANNABIS AND ETHANOL-INDUCED SYNERGISTIC EFFECTS ON PSYCHOMOTOR IMPAIRMENT

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National Institute on Alcohol Abuse and Alcoholism, NIH, USA

Aldehyde dehydrogenase type 2 (ALDH2) is a key enzyme to metabolize alcohol. The abundance of brain ALDH2 is relatively low and its contribution to alcohol use disorder is unclear. Alcohol when used with other drugs can produce a serious synergy. The most common example is the interaction between ethanol (EtOH) and cannabis, which leads to a psychomotor impairment in humans. However, whether or not ALDH2 deficiency can alter cannabis-EtOH interaction has not been reported. To address this question, we examined the effect of Delta-9-tetrahydrocannabinnol (THC) on EtOH-induced incoordination and hypothermia in ALDH2 knockout (KO) mice. ALDH2KO mice were more sensitive than their wildtype littermates to THC and EtOH-induced discordination and hypothermia. The mRNA of brain ALDH2 is expressed in a region and cell-type specific manner. Microinjection of THC into cerebral ventricular or cerebellum potentiated EtOH-induced motor impairment and hypothermia. Such THC potentiation was significantly higher in ALDH2 KO mice, suggesting the involvement of brain ALDH2 in THC and EtOH interaction. Consistent with this idea, selective depletion of brain ALDH2 in GFAP positive cells exhibited an increased sensitivity to THC and EtOH-induced synergistic impairment of psychoperformance. Thus, brain ALDH2 contributes to the pathological mechanisms of THC and EtOH-induced impairment in psychomotor performance.

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COMENT FROM A DISCUSSANT: THE ROLE OF ALDH2 IN ALCOHOL MEDIATED DISEASES

H.K. Seitz
Centre of Alcohol Research University of Heidelberg, Germany

In this symposium the role of ALDH2 in various alcohol mediated diseases is addressed. ALDH2 deficiency is frequented in Asians (40% of Japanese are heterozygotes). When these individuals drink alcohol they develop a flush syndrome. In addition, when they drink chronically, they have a very high risk for cancer of the upper alimentary tract, but not for the liver and obviously they do not develop cirrhosis to a higher degree as compared to ALDH2 1/1 carriers. In contrast the data in animals are different. How can this be explained? Acetaldehyde may also play a role in alcohol dependency and fetal alcohol syndrome. It would be of interest to know the effect of drinking in ALDH2 deficient pregnant women on their fetus. All the similarities and differences between animal studies and humans will be discussed.

WEDNESDAY, SEPTEMBER 12 4:30 PM–6:00 PM

SYMPOSIUM

WHO-ISBRA SYMPOSIUM: ADVANCES IN ALCOHOL RESEARCH AND ALCOHOL POLICY DEVELOPMENTS

ORGANIZER: SUSUMU HIGUCHI CHAIR: VLADIMIR POZNYAK

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EFFECTIVE POLICY MEASURES TO REDUCE ALCOHOL-RELATED HARM: AN UPDATE OF THE BOOK, "ALCOHOL: NO ORDINARY COMMODITY"

T.F. Babor
Department of Community Medicine, University of Connecticut School of Medicine, USA

This presentation describes from a public health perspective the effects of alcohol consumption on population rates of alcohol problems, giving special attention to Japan, China, South Korea and the broader Asia Pacific region. The current situation in China and, to a lesser extent in other countries of Southeast Asia, can be described as ominous. Strong pressures toward modernization of the consumer economy and the normalization of alcohol use portend increased drinking in the Asian region. After reviewing the possible contributing factors to alcohol-related epidemics, the policy responses that are appropriate to the prevention of alcohol problems in the region will be discussed, based on recent evidence since the publication of the 2010 edition of "Alcohol: No Ordinary Commodity". It is concluded that policies that limit access to alcoholic beverages, discourage driving under the influence of alcohol, reduce the legal purchasing age for alcoholic beverages, limit marketing exposure and increase the price of alcohol, are likely to reduce the harm linked to drinking.

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MOVING BEYOND THE GREAT EXCEPTION: THE GLOBAL CHALLENGE OF REGULATING ALCOHOL

R. Room[1,2]
[1]Centre for Alcohol Policy Research, La Trobe University, Melbourne, Australia and [2]Centre for Social Research on Alcohol & Drugs, Department of Public Health Sciences, Stockholm University, Stockholm, Sweden

Alcohol is a leading risk factor globally in the burden of disease. The harm is to others as well as to the drinker, and to welfare as well as to health. Responsibility for alcohol problems is dispersed across government departments and professions and response systems, and even within public health oscillates among noncommunicable diseases, traffic injuries, violence, mental health, and drugs. At the national level, it often escapes regulation which is routine for other commodities, such as nutrition labelling or identification as a carcinogen, and is often not a priority in public health policies. Internationally, it is the great exception, with no treaty equivalent to the drug treaties or the tobacco convention. The main treaties affecting alcohol are trade treaties, which constrain national controls and push toward greater availability. A public health treaty on alcohol is needed, as a counterforce to trade treaties; to ensure comity so that nations don't undercut each other's domestic laws; to provide institutional commitment and staffing at the international level; and to coordinate public health responses to the multinationals. While this could be accomplished by including alcohol in the drug treaties, a more likely path is a Framework Convention on Alcohol.

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MEASURING AND PREVENTING ALCOHOL USE AND RELATED HARM AMONG YOUNG PEOPLE IN ASIAN COUNTRIES: A THEMATIC REVIEW

X.J. Xiang
Second Xiangya Hospital of Central South University, China

The paper reviews alcohol consumption patterns and alcohol-related social and health issues among 15–29-years old young people in Asian countries. Forty-one reports, reviews and journal papers were identified and included in the final review. The current drinking levels and prevalence among young people are markedly different between eight included Asian countries, ranging from 4.2% in Malaysia to 49.3% in China. In a majority of the selected Asian countries, over 15% of total deaths among young men and 6% among young women aged 15–29 years are attributable to alcohol use. Alcohol use among young people is associated with a number of harms, including stress, family violence, injuries, suicide, and sexual and other risky behaviours. Alcohol policies, such as controlling sales, social supply and marketing, setting up/raising a legal drinking age, adding health warning labels on alcohol containers, and developing a surveillance system to monitor drinking pattern and risky drinking behaviour, could be potential means to reduce harmful use of alcohol and related harm among young people in Asia. The research evidence holds substantial policy implications for harm reduction on alcohol drinking among young people in Asian countries – especially for China, which has almost no alcohol control policies at present.

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THE CHANGES IN ALCOHOL CONSUMPTION EPIDEMIOLOGY AND MARKETING, AND ITS IMPLICATION IN ALCOHOL POLICY IN KOREA

H.K. Lee, B. Lee, S. Lee
Department of Psychiatry, The Catholic University of Korea, Seoul, Korea

It has been well reported that Korean has enjoyed drinking hard liquor, like 'Soju'-Korean style diluted spirit. However, unfortunately, the alcohol policy of Korea were very weak. Firstly, the author presented how alcohol consumption pattern and alcohol marketing have been related each other regarding female drinking in Korea. Secondly, the author reviewed current status of alcohol policy in Korea, and thirdly suggested the necessities of the international collaborative policy research based on the trend of alcohol marketing and consumption.
As 'Soju' was very cheap and had relatively higher alcohol content, it is main kind of liquor which formed 60–90% of alcohol consumption in Korea. 'Soju' was liquor for man, because it has higher alcohol content, and easy to be drunken. However, as the alcohol content of 'Soju' decrease from 25% to 17% recently, and alcohol industry are conducting marketing targeted young female, female are also enjoy drinking 'Soju' recently. These changes have proved that drinking prevalence among young female were getting higher recently in Korea. The risk and protective factors for female drinking have changed much, so, more detailed alcohol policy reflecting the trend of alcohol marketing and epidemiology pattern are needed.

TUESDAY, SEPTEMBER 11 4:30 PM–6:00 PM

SYMPOSIUM

COMMON AND DIFFERENT MECHANISMS UNDERLYING DEPENDENCE ON ALCOHOL AND OTHER ADDICTIVE SUBSTANCES

ORGANIZER/CHAIR: KAZUTAKA IKEDA CHAIR: MICHIE N. HESSELBROCK

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CAN WE UNTANGLE ALCOHOL AND COMORBID SUBSTANCE DEPENDENCE?

V.M. Hesselbrock, M. Hesselbrock, G. Chan
Department of Psychiatry, University of Connecticut School of Medicine, USA

Alcohol dependence is often associated with other co-morbid psychoactive substance dependences, e.g., opiates, sedatives, stimulants, cocaine and marijuana. However, these comorbities vary by age, gender and other demographic factors. The interplay of alcohol dependence and co-morbid substance dependence on the disease course and resulting deleterious consequences is not well understood. This study investigated the prevalence of lifetime co-morbid substance dependence and alcoholism in relation to the age(s) of onset of different substance use milestones (including dependence), the psychosocial and medical consequences and healthcare utilization. Subjects were drawn from the Collaborative Study of the Genetics of Alcoholism study (COGA), a multi-site, national study with the probands identified through inpatient/outpatient treatment programs. COGA is designed as an extended family study to characterize the familial distribution of alcohol abuse/dependence and related phenotypes and to identify vulnerability genes for related phenotypes. To date, the sample includes over 13,000 adults. 9328 subjects (approximately 50% were women) were directly interviewed and selected for the analyses. The subjects were divided into three groups: 630 drug dependence only (7%), 3136 (34%) were dependent on both alcohol plus another substance, while the remaining 5562 subjects were neither alcohol nor drug dependent.

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TELOMERE SHORTENING IN PATIENTS WITH ALCOHOL OR OTHER ADDICTIVE SUBSTANCES DEPENDENCE

M.-c. Huang[1,2], S.-k. Lin[1], Y.-f. Lin[1]
[1]Department of Psychiatry, Taipei City Psychiatric Center, Taipei City Hospital, Taiwan and [2]Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taiwan

Telomere shortening, a useful biomarker for determining general aging status, has been considered to be linked with psychiatric and substance use disorders, in particular alcohol dependence. Existing data regarding the association of leukocyte telomere length (LTL) with methamphetamine or ketamine abuse remains paucity. We aimed to determine the association of LTL with chronic and heavy alcohol, methamphetamine, and ketamine abuse. Patients with alcohol dependence (AD), methamphetamine dependence (MD), and ketamine dependence (KD) were consecutively enrolled from a psychiatric hospital. We examined LTL for the three groups and the correlations with years, onset age, frequency or quantity, and severity of substance use, and childhood trauma were examined. In AD group, we also compared patients with and without the occurrence of delirium tremens (DT). We found compared to controls, patients with AD or MD had a shorter LTL. Higher childhood trauma and duration of substance abuse was associated with LTL. The LTL in AD patients with DT was shorter than those without DT. LTL in KD group will be reported in the conference. In conclusion, alcohol and other substance abuse accelerate cellular aging. Whether the TLT will be normalized after discontinuation of alcohol or substance needs to be investigated in the future.

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PREFERENCE FOR ALCOHOL WITHOUT DEPENDENCE RISK: COMPARISON WITH OTHER ADDICTIVE SUBSTANCES

H. Miyata[1], K. Sawa[2]
[1]Department of Psychiatry, Jikei University School of Medicine, Japan and [2]Department of Psychology, Graduate School of Humanities, Senshu University, Japan

Alcohol has a negative effect on human health. At the same time, humans have used alcohol as a tool for stress reduction or a lubricant of human relations. In general, not a few people have enjoyed alcohol without producing significant problems. The theme of this presentation is to discuss whether or not alcohol can promote any beneficial effects on mental function under the so-called proper use. For that purpose, we investigated whether ethanol (EtOH) could decrease impulsivity in the doses producing neither dependence nor motor performance by rats. In an intracranial self-stimulation (ICSS) experiment, "the lever-holding paradigm" was established to estimate impulsivity, where a number of reward gain per min is regarded to reflect impulsivity related to "action restraint", whereas a time for releasing the lever is regarded to reflect impulsivity related to "action cancellation". The results of the experiment indicated that EtOH had a potential to decrease impulsivity related to "action restraint" at a dose producing neither dependence nor motor performance. Together with these findings, a concept of the proper use of alcohol and a comparison with other addictive substances including nicotine and methamphetamine will be discussed.

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GIRK CHANNELS AS COMMON EFFECTORS IN SOME PATHWAYS OF ALCOHOL AND OTHER ADDICTIVE SUBSTANCES

K. Ikeda
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G-protein activated inwardly rectifying potassium (GIRK, Kir3) channel is one of the effectors in signal pathways from ethanol, opioid, dopamine, and other addictive substances. We found associations between genetic polymorphisms in the GIRK subunit genes and sensitivity to addictive substances in mice and humans. We found that fluoxetine and paroxetine, selective serotonin reuptake inhibitors (SSRIs), but not fluvoxamine, another SSRI, inhibited GIRK channels in Xenopus oocyte expression assays and reduced preference for methamphetamine in conditioned place preference tests using mice. In addition, we found that ifenprodil, a widely used drug for dizziness, also inhibited GIRK channels in Xenopus oocyte expression assays. Another research group has shown that ifenprodil reduced preference for addictive substances in conditioned place preference tests using rodents. Furthermore, we found that relapse rate and relapse risk scores were lower in alcoholics who received GIRK inhibition treatment than alcoholics with non-GIRK inhibition treatment. We also demonstrated an inhibitory effect of ifenprodil on alcohol use in patients with alcohol dependence in a prospective, randomized, controlled, rater-blinded study. These results suggest that GIRK channels are important molecules in the reward system and candidate targets for pharmacotherapy of drug and alcohol dependence.

TUESDAY, SEPTEMBER 11 9:55 AM–11:25 AM

SYMPOSIUM

DIVERSE ROLES OF NON-PROTEIN-CODING RNAS: ALCOHOL-MEDIATED NEUROINFLAMMATION, REGULATION OF NEURAL STEM CELL RENEWAL, AND EPIGENETIC REGULATION IN EARLY ONSET AND CHRONIC ALCOHOL USE DISORDERS

ORGANIZER/CHAIR: R. DAYNE MAYFIELD

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CHRONIC ALCOHOL-INDUCED MICRORNA-155 CONTRIBUTES TO NEUROINFLAMMATION IN A TLR4-DEPENDENT MANNER IN MICE

G. Szabo
University of Massachusetts Medical School, USA

Alcohol-induced neuroinflammation is mediated by pro-inflammatory cytokines and chemokines including tumor necrosis factor-α (TNFα), monocyte chemotactic protein-1 (MCP1) and interleukin-1-beta (IL-1β). Toll-like receptor-4 (TLR4)-induced nuclear factor-κB (NF-κB) activation contributes to the alcohol-induced neuroinflammation. MicroRNAs, particularly microRNA-155 (miR-155) is a major regulator of inflammation after TLR stimulation. We found that chronic alcohol feeding significantly increased miR-155 expression in the cerebellum and cortex of C57/Bl6 mice compared to pair-fed controls. miR-155 knockout mice were protected from the alcohol-induced increases in TNFα and MCP1 at the mRNA and protein levels. Inflammasome components, pro-IL-1β and pro-caspase-1, mRNA levels were reduced in miR-155 KO alcohol-fed mice compared to controls. NF-κB was activated in WT but not in miR-155 KO alcohol-fed mice after choric alcohol feeding. However, increases in caspase-1 and IL-1β were similar in alcohol-fed miR-155-KO and WT mice. TLR4-KO mice were protected from alcohol-induced increases in miR-155 and NF-κB activation. TLR4 stimulation with lipopolysaccharide in primary or immortalized mouse microglia increased miR-155 expression. These results suggest that chronic alcohol induces miR-155 in the brain in a TLR4-dependent manner. Alcohol-induced miR-155 regulates TNFα and MCP1 expression but not caspase-dependent IL-1β increase in neuroinflammation.

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A NOVEL PSEUDOGENE-ENCODED LONG NONCODING RNA MEDIATES FETAL ALCOHOL EFFECTS

R.C. Miranda, N. Salem, A. Tseng, A. Mahnke, C. Garcia
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Prenatal alcohol exposure is a leading cause of neurodevelopmental disability. Fetal neural stem cells (NSCs) are vulnerable to alcohol and undergo premature maturation following ethanol exposure. We investigated whether ethanol interfered with NSC renewal and the function of the pluripotency transcription factor, Oct4/POU5F1. The Oct4 family includes several lncRNAs, transcribed from pseudogenes. We identified Octpg9 as one Oct4-related nuclear-enriched lncRNA, present in NSCs at significantly higher levels than the parent Oct4 mRNA. Oct4pg9 is transcribed at significantly higher levels in NSCs than differentiating neurons. Ethanol exposure results in elevated levels of Oct4pg9, whereas Oct4 protein levels are reduced. We assessed the effect of elevated Oct4pg9 on NSC fate markers and compared it to the effects of ethanol. Oct4pg9 overexpression resulted in decreased Nestin but increased GLAST, DCX, NeuN and GFAP transcripts. This effect was mimicked by ethanol exposure. In contrast, Oct4pg9 knockdown results in elevated Oct4, REST and Nestin mRNA transcripts and downregulation of DCX mRNA. Oct4pg9 overexpression resulted in increased neurosphere size suggesting increased proliferation. These data suggest that ethanol-mediated elevation of Oct4pg9 shifts NSCs towards neuronal/oligodendrocytic fate. These data suggest that a novel lncRNA may regulate NSC renewal and mediate some of the teratogenic effects of ethanol.

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BDNF-AS IS A NOVEL LNCRNA THAT IS AN EPIGENETIC REGULATOR IN EARLY ONSET ALCOHOL USE DISORDERS

J.P. Bohnsack, T. Teppen, E.J. Kyzar, S. Dzitoyeva, S.C. Pandey
Department of Psychiatry, Alcohol Research Center on Epigenetics, University of Illinois at Chicago, USA

Adolescent alcohol use increases the likelihood of developing an alcohol use disorder (AUD) later in life, in part due to changes in BDNF signaling in the amygdala which drives increased drinking and comorbid anxiety. BDNF-antisense (*BDNF-As*) a naturally occurring long-noncoding RNAs (lncRNA), that decreases *BDNF* expression via an epigenetic mechanism by the recruitment of EZH2. However, it is unknown if there are changes in *BDNF-As* expression in human postmortem amygdala in individuals with AUDs. Our results indicate that *BDNF* is downregulated and *BDNF-AS* expression is upregulated in individuals who began drinking before the age of 21 (early onset) but not after the age of 21 (late onset). Analysis of the *BDNF* exon IX promoter and the overlap region of *BDNF-As* and *BDNF* exon IX using chromatin immunoprecipitations found that there was increased EZH2 and repressive H3K27me3 at both these loci only in the early onset group suggesting that *BDNF-As* recruits EZH2 to decrease *BDNF* expression. Our results demonstrate the novel role of *BDNF-As* in early onset alcohol use disorders and the PRC2 complex as a potential therapeutic target for the treatment of alcohol use disorders that begin with alcohol consumption early in life (Supported by NIAAA grants).

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NOVEL LONG NON-CODING RNAS INVOLVED IN ALCOHOL USE DISORDER

S.P. Farris[1], C.M. Borghese[1], E.A. Osterndorff-Kahanek[1], Y.A. Blednov[1], G.E. Homanics[2], R. Dayne Mayfield[1], R. Adron Harris[1]
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Long non-coding RNA (lncRNA), transcripts > 200 nucleotides not translated into protein, represent an abundant class of functional RNA molecules. Despite a growing catalog of lncRNAs, their involvement in alcohol use disorder (AUD) and other neuropsychiatric disorders remains unknown. We conducted RNA-Seq analysis of human postmortem brain tissue (n = 385 samples) to identify coordinate changes in coding and non-coding gene expression relevant for AUD. Focusing on novel long intergenic non-coding RNA (lincRNA), our analysis identified 132 lincRNAs altered in AUD. Select transcripts were prioritized for further validation by the level of brain expression, syntenic conservation across model organisms, and predicted molecular functions. Using *Xenopus laevis oocytes*, lincRNAs were evaluated in the presence of ion-channels using two-electrode voltage clamp recordings. Co-injection of a single lincRNA caused a selective reduction in NMDAR1/NMDAR2B expression, and an ~80% reduction in maximum NMDAR currents. To behaviorally test these findings *in vivo,* we generated a null-mutant mouse model using CRISPR/Cas9 genome editing technology. Consistent with actions on NMDAR, null mutants were more sensitive for loss of righting response to alcohol, and NMDAR antagonist ketamine. Overall, our findings demonstrate an important role of lncRNA in the pathophysiology of AUD and associated phenotypes. *Supported NIAAA (K99AA024836 and U01AA020926).*

TUESDAY, SEPTEMBER 11 2:55 PM–4:25 PM

SYMPOSIUM

EMERGING ROLE OF EPIGENETIC PROCESSES IN THE DEVELOPMENT OF ALCOHOL USE DISORDERS

ORGANIZER/CHAIR: SUBHASH C. PANDEY CHAIR: ANTONIO NORONHA

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LONG-LASTING EPIGENETIC MARK OF ALCOHOL HAS A DEVELOPMENTAL WINDOW

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Alcohol exposure (either prenatally or in the early postnatal period) can impact developmental pathways resulting in lasting structural and regulatory changes that predispose individuals to adulthood diseases including long-term hyper-responsiveness to stress with exaggerated circulating glucocorticoids, enhanced anxiety and depression and immune abnormalities. Dr. Sarkar group determined when does alcohol programming of stress axis begins and ceases? They found alcohol exposure during preconception, prenatal, postnatal, juvenile or prepubertal period, but not after pubertal period, significantly affects POMC gene methylation, gene expression and POMC endophenotypes (stress hyperresponse, anxiety, and/or immune abnormalities) in the adulthood. Genome-wide analysis identified changes in some key molecular substrates responsible for DNA methylation in the offspring. His presentation will show that alcohol developmental programming of the neuroendocrine immune axis expands from germ cell to adolescent brain.

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EPIGENETIC REPROGRAMMING REGULATES ENHANCER RNA AND ADULT PSYCHOPATHOLOGY AFTER ADOLESCENT ALCOHOL EXPOSURE

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Binge drinking is common in adolescence and increases risk for alcohol use and anxiety disorders in adulthood. Rats were exposed to 2 g/kg ethanol (2 days on/off; AIE) or intermittent n-saline (AIS) during postnatal days (PND) 28–41 and allowed to grow to adulthood for analysis of behavior and biochemical measures. Some adult rats were exposed to an acute challenge with 2 g/kg ethanol in adult hood, and another cohort was cannulated in the central nucleus of amygdala (CeA) and infused with *Kdm6b* siRNA prior to analysis.AIE increases anxiety-like behavior. AIE adult rats show reduced occupancy of both KDM6B and CREB binding protein (CBP), leading to increased H3K27me3 and deceased H3K27ac respectively, at the synaptic activity response element (SARE) site of the activity-regulated cytoskeleton-associated protein (*Arc*) gene in the amygdala. The SARE site encodes an enhancer RNA (eRNA) upstream of *Arc*, and AIE leads to decreased *Arc* eRNA. Knockdown of *Kdm6b* expression in the CeA provokes anxiety-like behavior in AIS rats and decreases *Arc*eRNA and mRNA expression, possibly via increased H3K27me3 and decreased H3K27ac at the SARE site. Adolescent alcohol exposure leads to epigenetic reprogramming at the *Arc* SARE site and synaptic remodeling in the amygdala that increases adult anxiety susceptibility (Supported by NIH-NIAAA grants).

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METHYLATION PROFILES DURING ACUTE ALCOHOL WITHDRAWAL IN A CLINICAL SAMPLE

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Withdrawal is a serious and sometimes life threatening event in alcohol-dependent individuals. It has been suggested that epigenetic processes may play a role in this context. Identification of genes involved in such processes may hint to relevant mechanisms underlying withdrawal.
In the present study we sought to longitudinally investigate epigenome-wide methylation patterns in 100 severely alcohol-dependent patients during alcohol withdrawal and after 2 weeks of recovery, and also in 100 matched controls. More than 850,000 methylation sites were assessed using Illumina EPIC bead chips. Reflecting the high quality of our methylation data, we found – consistent with earlier reports – that correlation of methylation age with biological age of assessed individuals was very high ($r = 0.9$).
We found pronounced genome-wide significant differences between patients in withdrawal and after 2 weeks, among them in genes which have been reported to play a role in withdrawal symptomatology in previous studies (*SLC29A1, FYN*).
As expected, methylation between patients and controls differed considerably, also in genes implicated in withdrawal (*FKBP5, BDNF, EFNA5*).
This epigenome-wide longitudinal methylation study conducted in the so far largest sample of severely alcohol-dependent individuals suffering from withdrawal symptoms replicates known and suggests novel genes, which may play a crucial role in alcohol withdrawal.

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ROLE OF HDAC IN BINGE DRINKING LIKE ETHANOL EXPOSURE-INDUCED ALTERATIONS IN ANXIETY, MEMORY AND SYNAPTIC PLASTICITY DURING ADOLESCENCE IN RATS

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Université de Picardie Jules Verne – UMR INSERM U1247 – GRAP, Amiens, France

Very few studies investigated the mechanisms by which limited number of binge drinking episodes has deleterious effects on memory and its cellular mechanism: synaptic plasticity. Here we used our double binge-like exposure model (3 g/kg) in adolescent rats to investigate the short term effects at 48 h on memory using the novel object recognition test, on anxiety in the light dark box test and on synaptic plasticity in hippocampus. We investigated the role of HDAC by using HDAC inhibitors to see whether the effects on both behavior and plasticity could be prevented by HDAC inhibition. We also measured the level of HDAC-2 protein expression and its acetylated forms. Since we recently dentified the crucial role of the GluN2B NMDA receptor subunit in the deleterious effect of binge drinking on synaptic plasticity we also tested if the HDAC inhibitor could have a beneficial effect through a modification on this NMDA subunit. In general our results demonstrated that an HDAC inhibitor is able to prevent the deleterious effect of binge-like ethanol exposure both at the behavioral level and at the cellular level. We identified a specific role of HDAC-2 and GluN2B in the deleterious effect of binge drinking during adolescence and our results open new therapeutic perspectives.

TUESDAY, SEPTEMBER 11 4:30 PM–6:00 PM

SYMPOSIUM

A ROLE FOR THE INSULAR CORTEX IN ALCOHOL USE DISORDERS?

ORGANIZER/CHAIR: ANGELO BIFONE CHAIR: WOLFGANG H. SOMMER

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INTRODUCTION: RESULTS FROM THE SYBIL-AA PROJECT – CHARACTERIZING THE ROLE OF INSULA IN ALCOHOLISM

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SyBil-AA is a highly interdisciplinary Horizon 2020 project on systems biology of alcohol addiction that combines leading experts in mathematical modeling and complex network science with experimentalist and clinicians in alcoholism research from seven EU countries and Israel (http://sybil-aa.eu). The objective is to provide a neurobiologically-defined discovery strategy based on the principles of systems medicine that uses mathematical and network theoretical models. To build predictive models of the 'relapse-prone' state of brain networks we use MRI, electrophysiology and neurochemical data from patients and laboratory animals. The mathematical models can then be tested through experimental procedures aimed to guide the network towards increased resilience against relapse. In this symposium we demonstrate the feasibility of our experimental strategy. First, using unbiased analyses of resting state fMRI data from humans and rats we found the insula to be a key network node for the relapse prone state in the alcoholic brain. Second, functional validation of this finding for ethanol responding was obtained by experimental interference with insula activity in both species. In this introduction I will briefly present the SyBil-AA project and summarize the current state of knowledge on a potential role of the insula in alcoholism.

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RESTING STATE FUNCTIONAL CONNECTIVITY OF THE INSULAR CORTEX IN RECENTLY DETOXIFIED ALCOHOLICS

A. Bifone[1,2], C. Bordier[1], C. Nicolini[1], G. Forcellini[1], G. Scuppa[1]
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Alterations of brain functional connectivity as measured by resting state functional MRI have been reported in Alcohol Use Disorders. However, the functional implications of alcohol-induced aberrant brain connectivity are not entirely understood. Here, we have applied graph theoretical methods to study the organization of functional connectivity networks in recently detoxified alcoholics, pre and post treatment with Naltrexone, and in healthy controls. Graph theory provides a powerful means to identify the circuits involved in the disorder and affected by treatment. A reduction of overall connectivity was observed in patients compared to controls, with specific effects in supramarginal, temporal and basal subnetworks. Significant between-group differences were detected in the connectivity of the anterior insular cortex, which appeared to play an exaggerated role in the integration of the functional connectivity networks in alcoholics. Naltrexone treatment resulted in partial normalization of the connectivity of the insula. Altogether, these results support the hypothesis of an exaggerated role of this region in the integration of interoception, emotions and decision-making in the alcohol dependent brain.

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REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) OF THE INSULA FOR TREATMENT OF ALCOHOL ADDICTION

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Centre for Social and Affective Neuroscience, Sweden

Background: The anterior insula has been suggested to be a critical area in integrating internal bodily information with motivational drives. Functional and anatomical changes in the insular cortex of alcohol dependent patients indicate a potentially important role of the insula in drug-seeking behavior. This study addresses the effect of rTMS of the insula on drug consumption and brain function.
Methods: Treatment-seeking patients (N = 35) received rTMS stimulation targeting the insula bilaterally. Half of the patients were assigned to sham and half to real rTMS stimulation, in a double-blind fashion. Pre and post treatment magnetic resonance imaging (MRI) scans were performed to measure anatomical and resting state brain activity. Seed-based resting state analysis was compared between sham and real rTMS groups.
Results: No difference in drug consumption scores was observed between groups. Seed-based resting state fMRI findings revealed an effect of stimulation. Whole-brain connectivity maps using insula seeds showed increased connectivity between bilateral anterior insulae and decreased connectivity between right posterior insula and the striatum. Compared to sham, real rTMS stimulation reduced left anterior insula to default mode network (DMN) connectivity. These findings suggest that real rTMS induced changes in insula activity and its relationship to DMN and striatum.

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CHEMOGENETIC INTERROGATION OF THE ROLE OF INSULA IN ALCOHOL CONSUMPTION

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The insula has been proposed to participate in the interoceptive effects of drugs, as well as decision-making processes underlying drug taking. However, the circuitry involving the insula and its connections in these functions remains to be clarified. Here, we used DREADDs (designer receptors exclusively activated by designer drugs) for either stimulating (Gq DREADDs) or silencing (Gi DREADDs) the insula and its efferent projections in alcohol-preferring AA (Alko Alcohol) rats trained to drink alcohol in an intermittent access paradigm. We accomplished pathway-specific DREADD manipulation by expressing FLEX-DREADDs in the insula following injections of retrograde AAV-Cre in the insula projections areas. In addition, in order to map insula connectivity, we expressed the Gq DREADD unilaterally in the insula and measured c-Fos expression in the insula output areas after DREADD activation. The data from these experiments illustrate the contribution of insula circuits to alcohol reinforcement.

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ALTERED INSULAR CORTEX CONNECTIVITY IN ALCOHOL POST-DEPENDENT RATS AND NORMALIZATION BY A D3 RECEPTOR SELECTIVE ANTAGONIST

G. Scuppa[1], S. Tambalo[1], S. Pfarr[2], W.H. Sommer[2,3], A. Bifone[1]
[1]Center for Neuroscience and Cognitive Systems, Istituto Italiano di Tecnologia, Rovereto, Italy, [2]Institute of Psychopharmacology, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany and [3]Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany

Recent research implicates the insular cortex (IC) in alcoholism, but its role is poorly understood. Using functional MRI, here we studied resting state functional connectivity (rsFC) in rats abstinent from chronic intermittent exposure to ethanol. Further, we evaluated the effects of SB-277011, a selective dopamine D3 receptor antagonist.
13 postdependent and 14 alcohol-naïve rats were administered SB-277011 or vehicle before fMRI (7T Bruker) in a within-subject design allowing one week between the two scan sessions. Resting state functional connectivity networks (RSNs) were extracted by group level Independent Component Analysis (ICA). A dual-regression analysis was performed using IC maps as spatial regressors. Correlation between RSNs were computed, converted to z-statistic and compared with a non-parametric test. Seed-based analysis was also performed within the Salience Network.
Ethanol exposure decreased functional connectivity between sub-regions of the IC and within the Salience Network, but strengthened connectivity between the IC and mesolimbic areas. Aberrant connectivity in postdependent rats was partially restored by SB-277011, which, conversely, had no significant effects in alcohol naïve rats.
Our findings demonstrate the crucial involvement of the IC in a rodent model of alcohol dependence and suggest a possible mechanism underlying the previously reported anti-addiction effects of SB-277011.

TUESDAY, SEPTEMBER 11 9:55 AM–11:25 AM

SYMPOSIUM

DYSREGULATION OF PROTEIN HOMEOSTASIS (PROTEOSTASIS): NOVEL MECHANISM IN ALCOHOL USE DISORDERS AND ORGAN INJURY

ORGANIZER/CHAIR: PRANOTI MANDREKAR CHAIR: ANDRAS OROSZ

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SQSTM1 IS IMPORTANT FOR ETHANOL-INDUCED LIPOPHAGY IN HEPATIC CELLS

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Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, USA

The activation of lipophagy in hepatocytes plays an important cytoprotective role in ethanol-induced liver injury. However, its exact mechanism is still not clear. Toward this end, we studied ethanol-induced lipophagy using immortalized murine AML-12 cells. We found that ethanol treatment elevated lipid content in these cells, which was affected by a series of chemical and genetic modulators of the autophagy pathway. We then analyzed the potential role of a key adaptor molecular p62/SQSTM1 in this process. We found that p62 and autophagosome marker LC3 were colocalized together on lipid droplets (LDs) following ethanol treatment. Knockdown of 62 caused a reduction in the colocalization of autophagosome with LDs and an increase in lipid accumulation, suggesting a critical role of p62 in ethanol-induced lipophagy. In addition, we found an increase in ubiquitin signals on LDs, which was colocalized with p62 following ethanol treatment. Moreover, the colocalization of p62 with perilipin and ubiquitin was observed by three-color immunofluorescence staining. Finally, lipophagy was significantly altered by perilipin knockdown, indicating that it could participate in this process as a potential recognition target. In conclusion, this study provides a potential explanation to the mechanism of protective lipophagy induced by ethanol.

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INHIBITING NLRP3 INFLAMMASOME AND IL-1BETA IN ALCOHOLIC LIVER DISEASE VIA THERAPEUTIC TARGETING OF THE PROTEOSTASIS CHAPERONE

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Department of Medicine, University of Massachusetts Medical School, USA

The chaperone machinery is crucial to prevent aggregation and promote efficient protein folding for maintenance of protein homeostasis. Activation of NLRP3 inflammasome complexes serve as scaffold to promote IL-1β production in alcoholic liver disease (ALD). Stress-mediated chaperone heat shock protein 90 (HSP90) facilitates NLRP3 inflammasome activation. We hypothesize that HSP90 is required for alcohol mediated NLRP3 inflammasome activity in the liver and its therapeutic targeting reduces active IL-1β in the alcoholic liver. C57BL/6J mice subjected to chronic-binge alcohol feeding. Specific HSP90 inhibitor, 17-DMAG intraperitoneally administered every alternate day or at the end of alcohol feeding and livers/cells subjected to analysis of inflammasome components. Further, bone marrow derived macrophages (BMDM) were stimulated with LPS $\pm$ ATP and 17-DMAG and analyzed for inflammasome expression. Chronic alcohol mediated induction of NLRP3 expression was restricted to liver macrophages, but not hepatocytes. Inhibition of HSP90, using 17-DMAG significantly inhibited NLRP3, ASC and pro-caspase-1 and IL-1β *in vivo. In vitro* studies confirmed that 17-DMAG reduced IL-1β and caspase-1 cleavage in BMDMs. Our results show that HSP90 is crucial in alcohol mediated NLRP3 inflammasome activation in liver macrophages. We demonstrate clinical relevance of HSP90 inhibition in preventing NLRP3 inflammasome and cytokine production in ALD.

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ACTIVATION OF THE HEAT-SHOCK PATHWAY MEDIATES DNA METHYLOME DYSREGULATION IN THE DEVELOPING BRAIN UPON PRENATAL ALCOHOL EXPOSURE

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We have shown that the Heat Shock Transcription Factors (HSFs), which act at crossroads between stress, epigenetics, and brain development (Chang et al. *Genes & Dev* 2006; Miozzo et al. *J Mol Biol* 2015), mediate adverse effects of PAE in the developing brain by impacting the expression of genes that are involved in neuronal migration (El Fatimy, *EMBO Mol Med* 2014). We have also unravelled a novel role of HSF2 in the establishment of addiction-like behaviour, in the adult brain. Studies conducted in rodent models or in humans have reported that prenatal alcohol exposure (PAE) causes genome-wide disturbances in DNA methylation showing differential DNA methylation regions (DMRs), which exhibit either hypomethylation or hypermethylation. This is which is suggestive of redistribution of DNA methyltransferases (DNMTs) – the enzymes responsible for DNA methylation – in a genome-wide manner through unknown mechanisms (Schang et al. Clinic Genet 2017). We also explore the role of the HSF pathway in the contribution to redistribution of DNMTs in a genome-wide manner and the functional consequences of this contribution in terms of neuromorphology and behaviour, with relevance to motivation and addiction-like traits.

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CELL-TO-CELL VARIABLE MOLECULAR RESPONSES FOR MAINTENANCE OF PROTEOSTASIS EPIGENETICALLY PROGRAM LIFE-LONG PATHOLOGICAL CONDITIONS IN FASD

K. Hashimoto-Torii
Children's National Medical Center, USA

Molecular responses that maintain proteostasis immediately after the environmental disturbances are crucial for the survival of cells and organisms. We recently demonstrated that such acute molecular response of the developing neurons against environmental burden, including ethanol, is a stochastic event and therefore quite variable between the cells. However, it is still unknown if such heterogeneous acute molecular response is involved in the epigenetics of cell-to-cell variable cellular pathology. By tracing the descendent neurons of such cells that experienced acute differential molecular stress response, we examined physiological differences that are epigenetically marked between the neurons in mouse offspring that had been exposed to alcohol prenatally (PAE mouse). Single cell RNA-sequencing revealed sustained pathological characteristics that are associated with robust activation of Heat Shock signaling, a major stress responsive signaling. Among such defined gene signatures, the expression of Kcnn2 in primary motor cortex shows negative correlation with the motor skill learning ability in PAE mouse. Furthermore, the Kcnn2 blocker improved motor learning deficits. Altogether, the results suggest that cell-to-cell variable molecular responses for maintenance of proteostasis at acute phase may epigenetically program life-long pathological conditions such as sustained changes in gene expressions in the neuron that lead to cognitive problems in PAE mouse.

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ETHANOL-INDUCED DISORGANIZATION OF GOLGI APPARATUS AND ALTERED PROTEIN TRAFFICKING: ROLE OF DEFECTIVE RAB3D FUNCTION

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We and others have shown that ethanol (EtOH) treatment interferes with important intracellular protein and lipid transport pathways, including altered transport through the Golgi apparatus. Our current work is focused on alcohol-impaired Golgi function, characterized by the presence of disorganized (fragmented Golgi) and EtOH-impaired flow of membrane components from the *trans*-face of Golgi apparatus to the cell membrane. These impairments would contribute to the previously identified accumulation of newly synthesized proteins in the cytoplasm which, in conjunction with dysregulated hepatic autophagy, would promote cytotoxicity and hepatocellular injury. Of central importance to this fragmentation phenomena is that a small GTPase, Rab3D, which is involved in secretion and exocytosis of proteins from the trans-Golgi membranes, through interaction with its partners, appears to play a central role in the organization of Golgi apparatus. Our recent data shows that in cultured cells, animals, and in human tissue, chronic EtOH exposure critically decreases the content of Rab3D and knockdown of Rab3D in liver cells results in Golgi disorganization. We are currently pursuing the central hypothesis that EtOH exposure, with Rab3D downregulation, contributes to trans-Golgi disorganization via its fragmentation and autophagy-mediated Golgi membrane lysis, leading to impaired endocytic and exocytic protein trafficking and subsequent liver injury.

TUESDAY, SEPTEMBER 11 2:55 PM–4:25 PM

SYMPOSIUM

ALCOHOL AND ORGAN DAMAGE: BRIDGING THE GAP BETWEEN BENCH AND BEDSIDE – PART 2: BENCH

ORGANIZER/CHAIR: KENICHI IKEJIMA CHAIR: GAVIN E. ARTEEL

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THE ROLE OF ENDOPLASMIC RETICULUM STRESS ON ALCOHOLIC LIVER INJURY IN A MURINE MODEL OF CHRONIC-BINGE ETHANOL FEEDING

M. Suzuki, K. Kon, M. Morinaga, A. Uchiyama, T. Aoyama, H. Fukada, S. Yamashina, K. Ikejima
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Background: We examined the role of ER stress and oxidative stress in the early phase of alcoholic liver injury using chronic-binge ethanol (EtOH) mouse model and 4-phenyl butyric acid (PBA), chemical chaperon.
Methods: Male KK-A^{y} mice were fed Lieber-DeCarli diet (5% EtOH) for 10 days. Some mice were given PBA at the same time. On day 11, mice were gavaged with a single dose of EtOH (4 g/kg BW).
Results: Chronic-binge EtOH massively induced steatohepatitis with apoptosis of hepatocytes, and serum ALT was significantly elevated at 9 h after binge. PBA significantly reduced apoptosis of hepatocytes and elevation of serum ALT after binge. PBA also significantly attenuated increased hepatic expression of 4-hydroxy-2-nonenal and mRNA for spliced XBP1, CHOP, HO-1 and TNF-α after chronic-binge EtOH. Elevation of serum ALT or overexpression of mRNA for spliced XBP1, CHOP, HO-1 and TNF-α were not observed, whereas mRNA for BiP and unspliced XBP-1 was significantly increased before binge. PBA completely inhibited the pre-binge expression of mRNA for BiP and unspliced XBP-1.
Conclusion: PBA ameliorated chronic-binge EtOH-induced liver injury through reduction of ER stress during chronic EtOH exposure, followed by minimizing lethal ER stress signal and oxidative stress after EtOH binge.

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LYSOSOMAL BIOGENESIS AND ALCOHOLIC PANCREATITIS

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Impaired autophagy has been implicated in experimental and human pancreatitis but the mechanisms remain largely unknown. We investigated the role and mechanisms of transcription factor EB (TFEB), a master regulator of lysosomal biogenesis, in the pathogenesis of pancreatitis. We utilized a chronic plus acute alcohol binge and a cerulein mouse model to induce pancreatitis. We analyzed autophagic flux, TFEB nuclear translocation, lysosomal biogenesis, inflammation and fibrosis in GFP-LC3 transgenic mice, acinar cell-specific Atg5 and TFEB knockout (KO) mice as well as human pancreatitis pancreas. We found that both alcohol and cerulein induced mouse pancreatic edema, elevated expression of inflammatory cytokines, increased infiltration of inflammatory cells in pancreas and increased serum amylase and lipase. Both alcohol and cerulein decreased transcription factor EB (EB) and impaired autophagic flux in mouse pancreas. Inhibition of autophagy by leupeptin (a lysosomal protease inhibitor) markedly exacerbated alcohol-induced pancreatitis. Furthermore, genetic deletion of Atg5 or TFEB specifically in mouse pancreatic acinar cells led to severe pancreatitis regardless of alcohol feeding. These results indicate a critical role of TFEB-mediated lysosomal biogenesis in maintaining acinar cell homeostasis and provide strong evidence that impaired TFEB-mediated lysosomal biogenesis may lead to impaired/insufficient autophagy resulting in pancreatitis.

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MACROPHAGE INHIBITORY FACTOR (MIF) ATTENUATES HEPATIC STEATOSIS, BUT PROMOTES HEPATIC CARCINOGENESIS

N. Horiguchi[1], S. Kakizaki[1], D. Takizawa[1], D. Uehara[1], T. Kobayashi[1], Y. Yamazaki[1], K. Sato[1], G. Bin[2], T. Uraoka[1]
[1]Gunma University of Medicine, Internal Medicine of Gastroenterology and Hepatology, Japan and [2]NIAAA/NIH, USA

Background: Macrophage inhibitory factor (MIF) has been identified as an upstream activator of the innate immune response which mediates the recruitment macrophages via CD74 receptor. Although it is well-known macrophage plays essential role in the development of metabolic syndrome, the precise role of MIF on NAFLD is not clear. In this study, we examined the role of MIF on murine NAFLD model.
Methods: MIF-knockout mice (MIF-KO) and wild-type mice (WT) were fed with fed either control or high fat diet for 24 and 72 weeks.
Results: In high-fat diet model, High-fat feeding up-regulated MIF and CD74 mRNA expression in WT liver. High-fat-fed MIF-KO showed significantly higher liver/body weight ratio, higher ALT levels (liver damage) and triglyceride accumulation (steatosis) with decreased AMPK activation compared with WT. In addition, high-fat-fed MIF-KO showed worse liver fibrosis with immunohistochemistry with elevation of TIMP1 mRNA. After 72 weeks high-fat feeding, this hepatic fibrosis became more apparent in MIF-KO compared with WT. On the other hand, WT developed significantly higher number of liver tumors in spite of less fibrosis, less steatosis.
Conclusions: MIF attenuated hepatic steatosis and fibrosis, but promoted hepatic carcinogenesis. These results suggest that MIF plays unique role in the development of NAFLD.

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TRANSITIONAL CHANGES TO THE MATRISOME AND ALCOHOLIC LIVER DISEASE, MORE THAN COLLAGEN AND FIBROSIS

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It is well known that fatty liver disease increases in extracellular matrix (ECM) deposition. The majority of current research has focused on collagenous scarring during end-stage liver disease. However, several ECM proteins accumulate rapidly in response to injury and may contribute to hepatic damage. For example, fibrin ECM to rapidly accumulates in the sinusoidal space of the liver after alcohol or inflammation. Work by our group has demonstrated that fibrin ECM contributes to steatosis, inflammation and fibrosis in several models of experimental liver disease. Furthermore, the hepatic ECM responds dynamically to stress. The term "transitional tissue remodeling" describes changes of matrix proteins occurring in response to injury that do not alter the overall architecture of the organ. The nature and magnitude of these changes to the ECM are currently poorly understood. Using proteomic approaches, we have characterized changes to the ECM proteome ("matrisome") in response to stress. Several ECM proteins responded similarly to unique stresses (e.g., LPS and ethanol), whereas there are also proteins that respond uniquely to individual stresses. These results therefore also serve as a foundation for future analyses in hepatic models of liver disease, as well as a foundation for predictive modeling of the impact of these changes.

MONDAY, SEPTEMBER 10 4:30 PM–6:00 PM

SYMPOSIUM

ALCOHOL AND ORGAN DAMAGE: BRIDGING THE GAP BETWEEN BENCH AND BEDSIDE – PART 1: TRANSLATIONAL

ORGANIZER/CHAIR: KENICHI IKEJIMA CHAIR: GAVIN E. ARTEEL

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HEPATOCYTE-DERIVED EXTRACELLULAR VESICLES CONTAIN MICRORNA BARCODE TO CONTROL A UNIQUE TRANSCRIPTOME PROFILE OF ACTIVATED STELLATE CELLS IN ALCOHOLIC HEPATITIS

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Extracellular vesicles (EVs) have been growingly shown to play important roles in cell-to-cell communication and as biomarkers. We recently reported that hepatocyte-derived EVs (Hep-EVs) are increased in circulation in a murine model and in patients with mild alcoholic steatohepatitis (Hepatology 2017). Here the study was extended to characterize EVs released by hepatocytes isolated from a murine model of neutrophilic alcoholic hepatitis (AH) with advanced fibrosis and to determine the microRNA composition of these EVs via miR-seq for their potential roles in modulating hepatic stellate cells (HSC) phenotype. We found that Hep-EVs and circulating EVs were significantly increased in AH mice. The miR-seq analysis detected differentially expressed miRNAs in Hep-EVs from AH mice (AH-Hep-EVs). Some up-regulated miRNAs (miR-126 etc.) are known to target IκBα genes and contribute to liver fibrogenesis. Treatment of mouse primary HSCs with AH-Hep-EVs up-regulated *bona fide* HSC activation markers and more importantly, some of 344 genes uniquely and differentially regulated in HSCs from AH model which are also predicted targets of identified miRNAs (miR-25 etc.). These results support the notion that Hep-EVs contribute to HSC activation and liver fibrosis in AH via delivery of a specific miRNA cargo to facilitate a unique transcriptome profile in activated HSCs.

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MECHANISMS OF HEPATOCELLULAR FAILURE IN ALCOHOLIC HEPATITIS

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Hepatocellular failure is a hallmark finding in patients with alcoholic hepatitis (AH). Current therapy with steroids is not fully effective and targeted therapies are needed. Most research has been focused on the role of inflammation. In contrast, the mechanisms underlying hepatocellular failure and the subsequent poor regenerative response in AH are unknown. It is urgently needed to identify the molecular mechanisms underlying the hepatocellular failure and the subsequent poor regenerative response in AH. High through-put technology has become the "gold standard" for the unbiased approach to uncover new mechanisms in human disease. We have used RNA sequencing of liver biopsies and plasma proteomics from a well characterized cohort of patients with different stages of Alcoholic Liver Disease. Preliminary data suggests that progression of early forms of ALD to AH is characterized by a profound decrease in the function of Liver enriched transcription factors that closely correlates with disease severity in AH patients. Quantification secreted protein which are targets of Liver-enriched Transcription Factors (LETF) in plasma of patients with AH could be useful applied for more precise patient stratification and prognosis. This translational research approach has provided new insights for future AH treatment with new targeted therapies in the era of personalized medicine.

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MICROBIOTA AND LIVER DISEASE

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The intestinal microbiota and the human body have a symbiotic relationship. A disruption of this delicate homeostasis between host and microbes can lead to disease. Chronic liver disease is associated with an increase in microbial numbers and changes in the bacterial and fungal composition. We have recently demonstrated that chronic alcohol consumption is associated with altered intestinal fungi (mycobiota) and translocation of fungal products. The contribution of dysbiosis to alcoholic liver disease goes beyond a dysfunction of the intestinal barrier. Microbial metabolites are equally important for the progression of liver disease. For example, changes in bile acid profiles, lower bacterial synthesis of butyrate and saturated long-chain fatty acids contribute to ethanol-induced liver disease. Restoration of intestinal homeostasis and eubiosis is an effective strategy for attenuation of alcohol-related liver disease. Recent preclinical studies emphasized the importance of intestinal inflammation for the onset of gut barrier disruption and microbial translocation for alcoholic liver disease. In conclusion, the gut microbiota represents an excellent target to prevent the onset and progression of liver disease.

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PREVENTIVE EFFECTS OF L-CARNITINE ON HIGH-FAT DIET-INDUCED STEATOHEPATITIS IN OBESE AND DIABETIC MICE

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Background: The pharmacotherapy for non-alcoholic steatohepatitis (NASH), occurs frequently with obesity and insulin resistance, has not been established. Here we examined the effect of L-carnitine, which is required for mitochondrial free fatty acid (FFA) transport/oxidation, on murine steatohepatitis using high-fat diet (HFD)-fed obese and diabetic mice.
Methods: Male KK-A^y mice were fed an HFD for 5–8 weeks. Addition of L-carnitine to drinking water was started at 4 weeks of HFD feeding in some mice.
Results: The treatment with L-carnitine ameliorated HFD-induced severe hepatic steatosis with enhanced 4-HNE expression. L-carnitine significantly prevented serum ALT elevation, hyperglycemia and hyperinsulinemia caused by HFD. L-carnitine inhibited HFD-induced serine phosphorylation of IRS-1 in liver. The increased expression of mRNA for SREBP-1c, HO-1, TNF-α, MCP-1, iNOS in liver of HFD-fed mice was also inhibited by L-carnitine. Hepatic content of β-hydroxybutyrate, products of the FFA oxidation, was increased by L-carnitine. Lipidomics analysis using tandem mass spectrometry revealed that L-carnitine to HFD-fed mice diminished hepatic content of cell toxic diacylglycerols and increased cell protective lipids including unsaturated fatty acid and sphingomyelin.
Conclusion: The treatment with L-carnitine attenuates oxidative stress and suppresses inflammatory responses in steatohepatitis via activation of β-oxidation, changes of hepatic lipid composition and reduction of lipotoxicity.

TUESDAY, SEPTEMBER 11 9:55 AM–11:25 AM
SYMPOSIUM
YOUNG INVESTIGATOR'S SYMPOSIUM IN ASIA 1
ORGANIZER/CHAIR: SUNG-GON KIM

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RATE OF BLACKOUT AND ITS NEGATIVE CONSEQUENCES IN UNIVERSITY STUDENTS

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Introduction: A blackout, by alcohol intake that impairs long-term memory, is a phenomenon reportedly experienced by 35% of the population in Korea, 52% and 50% of the male and female university students, respectively. Being a precursor for injury risk, we investigated the rates and its negative effects on male and female university students.
Methods: Using a self-completed questionnaire, subjects were asked about blackout experiences and their negative effects.
Results: 40.4% (190, 88 males and 102 females) of 470 subjects surveyed had experienced a blackout. Twenty of the male and 28 of the female students had experienced a blackout in the past 4 weeks among whom, in terms of the negative consequences of the latest blackout, 61.2% and 53.3% of the male and female students respectively reported that they could not remember how they had returned home, 13.6% of them arguments and physical and personal fight, 8.7% physical injuries, 3.9% sexual-related problems, 8.3% of the female students an argument or physical fight, 7.5% physical injuries and 0.8% sexual-related problems.
Conclusion: 40.4% of the students surveyed had experienced blackout, and about 23% of them reported serious problems related to blackout, which suggests more systematic anti-drinking education is required for Korean university students.

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PREDICTIVE FACTORS FOR TREATMENT FAILURE IN REDUCING ALCOHOLIC CONSUMPTION BY CASE MANAGEMENT FOR ALCOHOLICS LIVING IN PERMANENT RENTAL APARTMENTS

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Introduction: Based on the results showing that there are more alcoholics in low-income bracket, case management (CM) was begun from 2011 for them. As a result, the treatment failure rate was 43–44% by WHO criteria. Therefore, we investigated the predictive factors for the treatment failure in order to maximize successful CM treatment.
Methods: Thirty-nine subjects from both Sasang-gu and Saha-gu were treated by four social workers using CM. Failure was defined when the level of risk was maintained or increased by WHO criteria. Their clinical characteristics including age and gender were collected.
Results: The subjects who were failed by CM (TF) were 17 (43.6%). Compared with clients who were treated successfully, TF quit drinking for fewer days in terms of a longer abstinent period, during CM ($p = 0.025$), higher population in TF never attempted to quit drinking while CM ($p = 0.051$), and more TF lived with family members ($p = 0.092$).
Conclusion: These results showed that a shorter abstinence period, never attempting to quit drinking while in CM, and living with family were predictive factors for failure in treating alcoholics by CM. It is supposed that inducing patients to try to quit drinking and encouraging them to keep abstinent longer are important for successful treatment.

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CHANGES IN THE DRINKING BEHAVIOR OF KOREAN WOMEN DURING THE PREVIOUS 20 YEARS

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Objective: According to the national statistical office of the Republic of Korea, prevalence of alcohol use of Korean women is increasing. However, there are few studies on the changes in drinking behavior of pregnant women. The purpose of this study is to investigate the drinking behavior of Korean pregnant women in 2017 and to compare changes of drinking status with results of the study conducted in 1997 and 2008.
Methods: Pregnant women at one obstetrics and gynecology hospital and one university hospital were subjects of the study. They completed some questionnaires.
Results: The rate of pregnant women drinking alcohol before pregnancy was 78.5% in 1997, 85.2% in 2008, and 80.9% in 2017 ($p = 0.002$). The rate of pregnant women drinking alcohol during pregnancy decreased from 57.6% in 1997 to 40.7% in 2008 and decreased to 27.2% in 2017 ($p < 0.001$). The rate of pregnant women drinking alcohol after knowing about the pregnancy decreased in 2017 (7.4%) compared to 2008 (24.0%) ($p < 0.001$).
Conclusion: According to results of the study in 2017, the rate of pregnant women drinking alcohol after pregnancy decreased compared to 1997 and 2008. Also, the rate of pregnant women drinking alcohol after knowing about their pregnancy in 2017 decreased compared to 2008.

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SENSIBLE AND NATURAL ALCOHOLISM PREVENTION PROGRAM FOR YOU (SNAPPY), A SUITE OF WEB-BASED SCREENING AND BRIEF INTERVENTION TOOLS FOR EXCESSIVE ALCOHOL CONSUMPTION

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Excessive alcohol consumption is a worldwide public health concern which can lead to serious physical and mental illnesses. Screening and brief intervention are said to be effective in reducing alcohol consumption. However, in Japan as well as foreign countries, few people lead to conventional face-to-face treatment.
To overcome the treatment gap, we have developed a suite of web-based screening and brief intervention tools named SNAPPY. SNAPPY-CAT (Computer Advise Technique) is a self-screening program AUDIT developed in 2014. SNAPPY-PANDA (Preventive Apparatus for Not Driving under the influence of Alcohol) is a calculator for alcohol consumption and time to break down alcohol to be a sober driver developed in 2015. SNAPPY-BEAR (Brilliant Education program for Addiction Recovery) is a series of short clips on YouTube to learn how alcohol can affect mind and body developed in 2017. Currently, we are developing SNAPPY-DOC (Diary On Computer) which is an alcohol diary program to review personal drinking habits and record the daily alcohol consumption.
In our presentation, we will show the detailed contents of the SNAPPY-DOC and a protocol outline of a randomized controlled trial to investigate the effect of SNAPPY-DOC on alcohol consumption and health condition among at medical institutions and occupational areas.

TUESDAY, SEPTEMBER 11 2:55 PM–4:25 PM

SYMPOSIUM

THE CURRENT SITUATION AND TREATMENT SYSTEMS FOR DRUG ADDICTION IN ASIA

ORGANIZER/CHAIR: TOMOHIRO SHIRASAKA CHAIR: TOSHIKAZU SAITO

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DRUG ABUSE IN MALAYSIA

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In Malaysia, illicit drug use is considered a major social threat. On the 19th February 1983, the Prime Minister declared that drugs as the nations number one enemy, and a threat to national security after the tremendously escalated numbers of drug users in the country. Methadone maintenance therapy (MMT) was not supported by government for many years as it was thought to compromise the nation's goal of becoming a drug-free society by 2015. However, the government finally approved the MMT in late 2005 after the escalation of the HIV epidemic and the desire for locally driven evidence-based harm reduction strategies. Currently, there were 811 MMT centres (446 government facilities and 365 private setting) in this country that provided treatment for total of 65,259 heroin dependence patients.

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TREATMENT SYSTEM OF DRUG ADDICTION IN TAIWAN: MOVING FORWARD ON A WANDERING JOURNEY

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Previously Taiwanese people with drug addiction were taken to be criminals and would be sentenced of imprisonment without adequate medical intervention. Since 1998, the Narcotics Elimination Act was modified to the Narcotics Hazard Prevention Act under the consideration of disease model of addiction. Controlled drugs are classified into four schedules based on their potential for habitual use, dependency, abuse, and danger to the society. Smuggling, trafficking, transporting, or making drugs were still criminal behaviors, but people with pure drug addiction were considered to be "patient-offenders" instead of inmates. Medical intervention was incorporation of deferred persecution. Nonetheless, lack of flexibility of treatment program and shortness of community resources are two major weakness of current status.
Beyond the judicial system, people with drug addiction could seek medical treatment voluntarily. However, the "addiction" category is not included in the coverage of current Taiwan National Health Insurance. Besides, the stigma and the undereducated addiction medical model for patients are also the obstacles for adequate treatment.
We have conquered many steps in drug addiction management in Taiwan in recent decades, though there are still many barriers on the road. Multidisciplinary works are needed for the journey of recovery with patients of drug addiction.

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TREATMENT SYSTEM FOR DRUG ADDICTION IN INDONESIA: CHALLENGING SYSTEM FOR DEVELOPING COUNTRY

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The illicit drug use continues to increase in developing countries, including Indonesia. According to National Narcotics Board study (2014), projected prevalence of drug use in 2016 was about 4 million people (2.21%). The susceptibility of drug abuse was inseparable from unconducive social environment, urbanization, poverty, and social stress. Drug addiction was suspected as impingement of stress problems. The role of law and correctional institutions still weren't optimal provide support to prevent eradication of drug addiction, and illicit drug trafficking. Outdated view, stigma, and discrimination were common to people with drug addiction, leading to inadequate quality treatments, undermining the development of drug addiction therapy facilities, and investment recovery programs. Efforts should be made to mitigate the problem of addiction substance by considering cost-effective treatments include substance dependence prevention by focusing on the social risk factors as early identification of hazardous substances use. This task couldn't be done alone by health services, it needed community involvement in primary health care, close coordination with social services. Replacement of dangerous drugs with controlled substitution in therapeutic workspace is necessary to reduce drug addiction problems. Government support in law and regulation related to illicit drug trafficking was also a necessary support to manage of drug addiction in Indonesia.

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CONSIDERATIONS ON THE PRESENT TREATMENT SYSTEMS AND ISSUES OF DRUG ADDICTION IN JAPAN

M. Kido
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According to Ministry of Health, Labor and Welfare, number of consulting about drug addiction at health center and mental health and welfare centers was increasing and decreasing, and 4 years ago, it was achieved 11,048 cases 4 years ago, and it tends to decreasing. Most of drug addiction is methamphetamine and organic solvent. In Japan, drug addiction is regarded as criminal not mental disorder, so Japan has the highest level in police control. The number of arrests breaking Stimulants Control Law is increasing year by year. On the other hand, the treatment system of drug addiction is behind. This is why the number of drug addiction is increasing. In this situation, the new approach of treatment for drug addiction named Serigaya Methamphetamine Relapse Prevention Program (SMARRP) was introduced in 2006 and this method is spreading in Japan. In this presentation we introduce "SHIKARRP" that is administered in Nara prefecture, and how effective the method is. Then, we discuss about the future prospects of treatment system of Japan.

TUESDAY, SEPTEMBER 11 4:30 PM–6:00 PM

SYMPOSIUM

LEARNING FROM THE DIFFERENCES REGARDING THE RELATIONSHIP BETWEEN SOCIAL STRUCTURES AND SUBSTANCES USE

ORGANIZER/CHAIR: MASUO TANAKA CHAIR: TETSUJI CHO

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CHANGES IN TREATMENT FOR ALCOHOL USE DISORDER IN JAPAN

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In Japan, the patients with alcohol use disorder (AUD) tend to be less likely to visit medical care settings on their own. Although abstinence is the most ideal approach to recovery, it is hard to stay abstinent. When their treatment goal is hard to achieve, they tend to drop out from treatment easily. Therefore, the concept of "harm reduction" has been suggested. This concept can be viewed as the prevention of adverse consequences of drinking alcohol without necessarily reducing their consumption. People who have difficulty starting from abstinence, harm reduction could be a key to start treatment.

We investigated the hardships of living in the persons with AUD at multi-center in Japan. Our results suggested clinicians need to focus on not only drinking problem but also the hardships of living in the clinical settings and need to enhance coping skill for craving and so on. The Japanese guideline for diagnosis and treatment of AUD published in 2017 included the concept of "harm reduction" for the first time. Since more people with AUD are expected to visit medical care at their earlier stage, medical staffs need to understand the concept "harm reduction" and how to make good treatment alliance with them.

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DIFFERENT CHARACTERISTICS OF AUD BETWEEN THE US AND JAPAN

H. Sakuma
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The US census shows the morbidity from Alcohol Use Disorder (AUD) is six times greater in the US than in Japan. Genetic factors, age, comorbidities and other parameters differ among individuals with AUD. Although ADH1B and ALDH2 alleles are strong protective factors, AUD in some East Asian countries is still high even when accounting for their large ADH1B and ALDH2 genotype frequencies. Culture plays a significant role in the etiology of AUD; examples include the context of consuming alcohol, the perceived peer pressure, and/or the customs leading to binge drinking. In this presentation, I will focus on the translational difference of AUD between the US and Japan. Epidemiological features, cultural background and treatment situations will be discussed. In the US, the novel self-help groups and personalized approach for addiction recovery are likely becoming a mainstream path in the next decade. In contrast, combining the use of self-help groups with intermediate-term inpatient treatments, psychoeducational treatment in clinics, and halfway houses are becoming more popular in Japan. Since the US and Japan differ in many ways, I will discuss their communality and differences related to AUD.

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CURRENT SITUATION ON SUBSTANCE USE DISORDERS IN BOSNIA AND HERZEGOVINA

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Substance abuse causes tremendous social, health and safety problems in the Bosnia and Herzegovina. Data on the number of addicts are imprecise and based on estimations related on different studies. One reliable indicator of drug use prevalence among youngsters is available from The European School Survey Project on Alcohol and Other Drugs. Data shown that cannabis was the most frequently used illicit substance, followed by sedatives and inhalants. Furthermore, lifetime use of any drug among adult population was 3.8%. The central prevalence of the IDU population has been 0.47. During 2017 one research was conducted which shown proportion of patients with substance-related problems (68.1% alcohol dependency; 17.6% opiate dependency; 1.9% gambling; 4.4% misuse of benzodiazepines). Treatment programme for addictions is a complex multi-component process which contains of development of motivation, pharmacological therapy, individual psychotherapy, family counselling and occupational therapy, group social therapy, therapeutic communities and various support groups. However, a very complicated political structure of the country, insufficient financial support, stigmatization, insufficient staffing and number of treatment centers are objective obstacles for treatment.

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IRELAND'S ALCOHOL PROBLEM: A PUBLIC HEALTH ISSUE

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Ireland's National Self-Harm Registry (NSHRI) is the world's first national registry for intentional self-harm, which was established within the National Suicide Research Foundation. Since 2006, they have provided full coverage of self-harm presentations in all general hospital emergency departments (ED). NSHRI reports have consistently highlighted concerns on how alcohol is the most important risk factor associated with self-harm and suicide – bringing alcohol further into the spotlight in the realm of Ireland's public health.

Ireland has ranked third for binge drinking in an analysis of 194 nations by the WHO in 2014. NSHRI data highlighted that almost one-third of all self-harm presentations to the ED involved alcohol (34% of men and 29% of women). Reports also indicated that the rates of self-harm peaked on public holidays – especially St. Patrick's and New Year's Day – and the day after. Such peaks would not have occurred if alcohol were not involved.

These findings will aid policy makers in the ongoing debate regarding the Public Health Alcohol Bill, which will set: minimum unit pricing, restrictions on advertising/promotions, separation of alcohol products in outlets, and health labeling of alcohol. Passing of the Bill will help in reducing suicide and self-harm in Ireland.

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SYMPOSIUM

BINGE DRINKING: FROM RISK TO CONSEQUENCES

ORGANIZER/CHAIR: JOHN CRABBE

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BEHAVIORAL FACTORS PREDICTING THE RISK OR RESILIENCE TO CONSUME ALCOHOL AND LOSE CONTROL OVER ALCOHOL SEEKING IN RATS

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Alcohol use disorder (AUD) is characterized by loss of control over alcohol seeking. Importantly, AUD often originates during adolescence. Altered brain development, social context and personality traits are thought to play an important role in the onset of AUD, but only few studies have systematically investigated this. Social play behaviour, abundantly present in young mammals, is important for social, cognitive and emotional development. Impaired social play behaviour may therefore cause long-lasting changes in brain reward circuits which increases the risk for AUD.

We assessed the effect of age of onset of alcohol use and individual differences in social play on the development of AUD-like behaviour. Conditioned suppression of alcohol seeking, as a measure for alcohol use in the face of adversity, was less pronounced in rats with adolescent-onset alcohol consumption, compared to adult-onset animals. Rats showing high levels of social play behaviour as juveniles, later consumed more alcohol. However, they showed intact conditioned suppression of alcohol seeking, unlike rats that displayed low levels of social play, reflecting a lack of control over alcohol seeking.

Taken together, these data suggest a complex relationship between age, social play behaviour and the development of AUD-like behaviour in rats.

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A ROLE FOR PHOSPHODIESTERASE TYPE 4 (PDE4) IN BINGE-LIKE DRINKING

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Introduction: Recent studies provide evidence for phosphodiesterase (PDE) inhibitors in the regulation of alcohol drinking in mice, rats, and humans. We investigated the role of PDE4 in high-intensity, binge-like alcohol drinking in High Drinking in the Dark mice (HDID-1).

Methods: HDID-1 female mice experienced 8 weeks of a 4-days/week Drinking in the Dark (DID; ethanol or water) paradigm. NAc tissue was processed for multiplex qRT-PCR ($n = 6$ mice/treatment/time point) to determine whether ethanol altered expression of PDE4. We next tested whether rolipram (0, 5, 7.5, or 10 mg/kg) or apremilast (0, 20, or 40 mg/kg) reduced DID ($n = 11$–12/sex/dose). To determine whether inhibition of PDE4 in the NAc was sufficient to reduce DID, we administered apremilast intra-accumbens (0 or 2 μg, via bilateral cannulae; $n = 15$–17/group). We also test the effects of apremilast on intake of other fluids and tastants.

Results: Chronic binge-like drinking increased Pde4b expression in the NAc ($p < 0.01$). Rolipram and apremilast reduced binge-like drinking (both drugs $p < 0.0001$) and BALs (rolipram $p < 0.05$; apremilast $p < 0.0001$). Further, intra-NAc administration of apremilast selectively reduced ethanol intake ($p < 0.05$). These data provide support for the use of apremilast as a potential new therapeutic for the treatment of high-intensity binge-like drinking.

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MATERNAL ALCOHOL BINGE DRINKING INDUCES MOLECULAR ALTERATIONS IN THE BRAIN AND BEHAVIORAL DYSFUNCTIONS IN OFFSPRING MICE

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Binge alcohol drinking during pregnancy and breastfeeding may lead to a wide range of long-lasting morphological and behavioral deficiencies known as fetal alcohol spectrum disorders (FASD), associated with a higher risk of later developing neuropsychiatric disorders. We assessed the effects of maternal binge alcohol consumption during prenatal and early postnatal periods on cognitive, locomotor, anxiety and alcohol-reward behaviors in adulthood. Pregnant C57BL/6 female mice were exposed to an experimental procedure modelling binge alcohol drinking (drinking-in-the-dark test) throughout gestation up to weaning. Then, adult male offspring were behaviorally tested. Early alcohol exposure induced age-dependent changes in spontaneous locomotor activity, motor coordination impairments, spatial working memory dysfunction and anxiogenic-like effects. Furthermore, alcohol-exposed mice showed attenuated alcohol-induced conditioned place preference. These changes were associated with an up-regulation of pro-inflammatory markers and diminished expression of some structural myelin proteins in the brain of adult mice. In addition, cytochrome c oxidase quantitative histochemistry revealed changes in neural metabolic capacity in some brain areas and disrupted functional brain connectivity. Finally, increased neurogenesis was found in the hippocampus of alcohol-exposed offspring, suggesting neuroadaptive effects due to early alcohol exposure. Our results demonstrate that maternal binge-like alcohol exposure produces long-lasting behavioral and molecular alterations in the brain.

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ASSOCIATION BETWEEN EXCESSIVE ALCOHOL USE AND ALCOHOL-RELATED INJURIES – A MULTICENTER CROSS SECTIONAL STUDY OF COLLEGE STUDENTS IN JAPAN

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Introduction: Alcohol-related injuries in college students are a major public health problem worldwide. However, there are few reports on alcohol-related injuries in college students in Asian countries. We clarified the association between excessive drinking and alcohol-related injuries in Japanese college students.
Method: This was a cross-sectional study with a self-administered questionnaire. From January to March 2013, we sampled all college students and graduate students aged 20 years or older during annual health examinations at three universities in Japan. The questionnaire assessed frequency of alcohol drinking, amount of alcohol consumed per day, binge drinking during the past year, alcohol-related injuries during the past year, and demographic data. Logistic regression analysis was conducted on the association between excessive alcohol use and alcohol-related injuries.
Result: A total of 2177 completed the questionnaire. There were 181 excessive weekly drinkers, 1151 binge drinkers, and 107 people with a history of alcohol-related injuries in the past year. In the logistic regression analysis, binge drinkers (odds ratio 25.6 [8.05–81.4]) and excessive weekly drinkers (odds ratio 3.83 [2.41–6.09]) had a history of significantly more alcohol-related injuries, even after adjusting for age and sex.
Conclusion: Alcohol-related injuries in college students in Japan were strongly associated with excessive drinking.

TUESDAY, SEPTEMBER 11 2:55 PM–4:25 PM

SYMPOSIUM

NOVEL TECHNOLOGIES AND INTEGRATED APPROACHES FOR OBTAINING AND USING REAL-TIME ALCOHOL CONSUMPTION DATA COLLECTED IN NATURALISTIC ENVIRONMENTS

ORGANIZER/CHAIR: SUSAN E. LUCZAK CHAIR: VIJAY A. RAMCHANDANI

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INTRODUCTION TO THE SYMPOSIUM

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Division of Metabolism and Health Effects, National Institute on Alcohol Abuse and Alcoholism, USA

This conference brings together biomedical researchers devoted to understanding and alleviating alcohol addiction and the negative consequences of alcohol consumption. Advances in technology in several domains have opened up the possibility of new tools and techniques that may benefit alcohol research and treatment. This session brings together investigators who will report on tools that will enable accurate measurement of alcohol consumption, along with others applying techniques based on modern communication technologies to maximize the use of this data in research and addiction treatment. The introduction to the session will provide an update on progress in designing and developing wearable alcohol biosensors that will provide accurate and real time measures of blood alcohol content.

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A NOVEL POPULATION-BASED MODEL APPROACH TO ESTIMATING BREATH ALCOHOL CONCENTRATION (BRAC) FROM TRANSDERMAL ALCOHOL CONCENTRATION (TAC) BIOSENSOR DATA

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Alcohol biosensor devices have been developed to measure transdermal alcohol concentration (TAC) in nearly continuous fashion in naturalistic settings. Because TAC data are affected by physiological and environmental factors, there is not a simple formula to convert TAC into easily-interpretable metrics like breath alcohol concentrations (BrAC). Here, we report on a novel mathematical framework for obtaining estimated BrAC (eBRAC) from TAC data using population data to determine model parameter values via a random diffusion equation. We test the efficacy of this method using data from a single subject with multiple drinking episodes and from multiple subjects with single drinking episodes. For each dataset, we used a set of drinking episodes to construct the population model, and then tested the model with another set of randomly-selected episodes. We compared raw TAC data to model-simulated TAC curve, raw breath analyzer BrAC data to model eBrAC curves with credible bands, and report episode summary scores (e.g., peak, times of peak, area under the curve) and the percent of raw BrAC captured within the eBrAC credible bands. Results are promising and provide initial proof-of-concept for constructing, fitting, and using a population-based model to obtain estimates and error bands for BrAC from TAC.

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USING EMA AND SENSOR DATA TO UNDERSTAND THE RELATIONSHIPS BETWEEN DRINKING AND EMOTIONAL STATES AMONG PERSONS LIVING WITH HIV (PLWH)

Y. Wang, E. Porges, R. Cook
University of Florida, USA

Alcohol use and mental health comorbidities (e.g., depression) are both common among persons living with HIV (PLWH), and often co-occur, leading to detrimental health consequences. Interventions for alcohol use and mental health problems for PLWH tend to have low efficacy, partly due to a lack of continuous care outside of clinical settings. A better understanding of the relationship between alcohol use and negative emotions on a day-to-day basis would provide valuable information for improving interventions in PLWH. Thus, in this study, we employed a 2-week ecological momentary assessment (EMA) research design to examine the real-time relationship between emotional states and drinking in 50 PLWH. We used a smartphone-based program to capture emotional states and a wearable transdermal alcohol biosensor (SCRAM-CAM) to capture concurrent drinking. Mood was measured at 3 random prompts/day, one daily prompt (e.g., 10 am every day), and one time during each drinking episode. We will present preliminary quantitative data linking mood and drinking, describe qualitative data on participants' feedback on the research procedure, and discuss the advantages/challenges in obtaining and analyzing multisource real-time data in real-world environments. We will conclude with future applications of such an integrative EMA methodology, including the potential of biosensor-assisted mobile health interventions.

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ALTERNATE REPRESENTATIONS OF SUBJECTIVE EFFECTS: AN ECOLOGICAL STUDY OF SIMULTANEOUS ALCOHOL AND MARIJUANA USE

K.M. Jackson[1], H.R. White[2], A.W. Sokolovsky[1], K.L. Hayes[1]
[1]Brown University, USA and [2]Rutgers University, USA

Most young adult alcohol and marijuana users have used them simultaneously, often citing enhanced subjective effects (SEs) as a reason for combined use, but whether simultaneous alcohol and marijuana (SAM) use actually leads to greater SEs than either substance alone remains uncertain. This study examined associations between alcohol and marijuana use and SEs among college students (N = 343) enrolled in an 8-week ecological protocol. Participants completed up to five daily reports using a Smartphone. SEs (from "Not at all" to "Very" drunk/high) were assessed using a graphical interface from which we computed daily intercept (level), slope, and quadratic functions. Number of drinks and marijuana use occasions were recorded; a categorical variable indicated whether participants had engaged in alcohol, marijuana, SAM, or no use. Controlling for quantity of alcohol and marijuana, categorical use pattern significantly predicted SEs such that SEs were greatest for marijuana use, especially when alone. Slope also was greatest for marijuana use, followed by SAM use; alcohol use alone did not significantly differ from non-use. Acceleration (Quadratic) was greatest for SAM use. Overall, alcohol does not appear to greatly enhance SEs when consumed with marijuana, although combined use may accelerate getting high/drunk which is concerning given SAM use consequences.

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TESTING THE EFFICACY OF THE MOBILE INTERVENTION FOR DRINKING IN YOUNG PEOPLE (MIDY): AN ECOLOGICAL MOMENTARY INTERVENTION TO REDUCE YOUNG ADULTS ALCOHOL USE IN THE EVENT

C.J. Wright[1,2], P.M. Dietze[1,2], P.A. Agius[1,2,3], E. Kuntsche[4,5,6], M. Livingston[7,8], O.C. Black[2], R. Room[7,9], M. Hellard[1,2], M.S.C. Lim[1,2,10]
[1]Burnet Institute, Australia, [2]School of Public Health and Preventive Medicine, Monash University, Australia, [3]Judith Lumley Centre, La Trobe University, Australia, [4]Addiction Switzerland, Switzerland, [5]Behavioural Science Institute, Radboud University, The Netherlands, [6]Faculty of Education and Psychology, Eötvös Loránd University, Hungary, [7]Centre for Alcohol Policy Research, La Trobe University, Australia, [8]Department of Clinical Neurosciences, Karolinska Institutet, Sweden, [9]Centre for Social Research on Alcohol and Drugs, Stockholm University, Sweden and [10]Melbourne School of Population and Global Health, University of Melbourne, Australia

Introduction: Smartphones offer new opportunities to collect data and deliver health interventions, including during events such as risky single occasion drinking (RSOD). This study aimed to evaluate an ecological momentary intervention (EMI), comprised of mobile ecological momentary assessments (EMA) and SMS feedback, delivered during drinking events.
Method: We implemented a Randomised Controlled Trial with three arms: an EMI group; an assessment-only group (EMA) and; a control group that received no contact. We used random-effects mixed modelling to provide estimates of differences in mean number of standard drinks consumed at the most recent heavy drinking occasion (peak RSOD), assessed at baseline and 12-week follow-up.
Results: A total of 269 were randomised into the three groups; 101 of these followed through with registration. Between baseline and follow-up, the EMI group showed a small, non-significant increase in peak RSOD while the EMA and Control groups both showed a non-significant decrease. There no significant differences between groups.
Conclusions: Our study showed no significant differences in RSOD between groups of young adults receiving EMI, EMA or no contact. A small sample meant that only substantial differences could have reached significance. Our study highlights further areas for investigation into the effects of EMI on RSOD.

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DISCUSSION

K.J. Sher
Department of Psychological Sciences, University of Missouri, USA

Dr. Ken Sher will lead the discussion. He will begin with a brief review of the issues highlighted in the various talks along with the limitations and promise of the presented work. He will then consider the kinds of novel findings that real-time, ambulatory assessments of drinking are likely to generate in the next few years and their importance for both basic and intervention research. He will conclude by describing emerging technologies that hold great promise for moving the field forward, and noting the types of new skills researchers will need to optimally exploit these new technologies.

TUESDAY, SEPTEMBER 11 4:30 PM–6:00 PM

SYMPOSIUM

THE FACT AND ISSUE OF ALCOHOL USE AMONG ASIAN ADOLESCENCES – FOR THE PURPOSE OF FUTURE COLLABORATION ON YOUTH RISK BEHAVIOUR MONITORING
ORGANIZER/CHAIR: YONEATSU OSAKI

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ALCOHOL AND DRUGS ABUSE AMONG ADOLESCENT IN INDONESIA

K.S. Kurniasanti
Department of Psychiatry, University of Indonesia, Indonesia

Drug and alcohol abuse was an emerging issues among adolescents in Indonesia. According to National Narcotics Board in 2014, prevalence of substance and alcohol abuse was about 4.02 million people (2.18%), with an increasing estimation up to 5 million people (2.56%) in 2020. Prior drug abuse surveys conducted from 2006 to 2011 shows that rates of abuse were higher among men, tend to be higher in city rather than in district area, and increase along with its education level. The common drugs and substances was abused by teenagers were marijuana, shabu-shabu, alcohol and ecstasy. Regarding alcohol consumption in Indonesia, there were counterfeit alcoholic drinks that is cheaper and easier to get. Nevertheless, they were illegal and endangered lives. 15% of overall substance abuse were intravenous drug users. This data associated with AIDS incidents in Indonesia, which 52% were adolescents and young adults. Alcohol and substance abuse among adolescents had a serious impacts, such as: substance addiction, overdose deaths, injection-related hazards, cost implications, and other widespread social problems. To overcome this problems, it was important to create promotive and preventive program, obligatory reporting about alcohol and drugs abuse and addiction, and long-term hospitalization for child-specific rehabilitation programs according to their developmental stage.

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ALCOHOL USE AMONG ADOLESCENTS IN KOREA
S. Roh
Department of Psychiatry, Hanyang University College of Medicine, Korea

Korea Centers for Disease Control & Prevention have conducted the nation-wide web-based survey on youth risk behavior annually since 2005. The most recent data on 62,276 middle and high school students showed that current drinking rates of male and female adolescents are 18.2% and 13.7%, respectively, both of which are continuously in decreasing tendency in recent 3 years. High-risk drinking rates of male and female adolescents are 8.8% and 7.6%; problematic drinking 6.8% and 5.3%, respectively. Middle school students get alcoholic beverage mainly from home, whereas high school students buy it at convenience store. Forty-two percent of male students and 40.5% of female students took a school-based alcohol prevention education last 12 months.
Adolescents who used alcohol, cigarettes, and drugs are engaged in suicidal ideation 3.69 times and more likely to have had more sexual intercourse than those who didn't. High-risk drinking due to mental health problem in female students was higher than that in male.
The socioeconomic costs of alcohol drinking among adolescents were estimated to be 387.5 billion KRW (0.05% of GDP) including 48.3% for reduction of productivity from drinking and hangover, 39.4% for future income loss from premature death, and 6.7% for hangover costs.

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PREVALENCE, CHARACTERISTICS, AND FACTORS ASSOCIATED WITH ALCOHOL USE AMONG ADOLESCENTS IN THAILAND: A REVIEW OF PUBLISHED DATA
W. Atsariyasing
Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

The purpose of this study is to examine the prevalence, characteristics, and factors associated with alcohol use among adolescents in Thailand. Articles were identified through electronic databases. Fifteen articles were eligible for the study. The prevalence of past-30-day alcohol drinking increased from 14.3% (19.6% males and 9.9% females) in 2008 to 22.2% (27.0% males and 17.9% females) in 2015. The prevalence of lifetime alcohol intoxication also increased from 11.8% in 2008 to 24.3% in 2015. The peak age of starting to drink alcohol was 15 years, and the main reason for first drinking was wanting to try alcohol. The most popular places for drinking were at parties and at home. Factors that were consistently found to be associated with alcohol use included low grade point average, having family members with substance or alcohol problems, attitudes toward alcohol drinking, and positive outcome expectations of alcohol use.

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THE FACTS AND ISSUES OF ALCOHOL USE AMONG ADOLESCENTS AND YOUTH IN JAPAN
A. Kinjo, Y. Kuwabara, A. Imamoto
Division of Environmental and Preventive Medicine, Department of Social Medicine, Faculty of Medicine, Tottori University, Japan

Problem drinking is higher in persons who had developed the habit of alcohol use in their adolescence and this is true in Japan as well. Therefore, preventing adolescents from beginning alcohol use is highly significant to reduce harmful use of alcohol both in the youth and general population. The percentage of students who had an alcoholic drink during the past 30 days was approximately 5% in junior high school and 10% in senior high school in Japan (as per the national school-based survey in 2014). A remarkable decline in alcohol use among students was observed for two decades. Introducing the need for age-verification during alcohol sale is considered effective in making it difficult for adolescents to obtain alcoholic beverages. However, several issues remain. Current issues of alcohol use among adolescents and youth are: (1) the percentage of alcohol use among females has reached a level comparable with that of males (reduction in gender gap); (2) the percentage of alcohol use has not decreased only for the students who smoked tobacco (accumulation of risk behavior); and (3) taking measures for preventing binge drinking is insufficient, although the percentage of binge drinking is higher in youth.

TUESDAY, SEPTEMBER 11 9:55 AM–11:25 AM

SYMPOSIUM

UPDATE OF ALCOHOL DEPENDENCE/ALCOHOL USE DISORDER AND THEIR TREATMENT IN US, EU, AND JAPAN
CO-SPONSORED BY OTSUKA PHARMACEUTICAL CO., LTD.
CHAIR: TOSHIKAZU SAITO

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CURRENT SITUATION AND FUTURE TASKS FOR THE TREATMENT OF ALCOHOL DEPENDENCE IN JAPAN
S. Higuchi
National Hospital Organization Kurihama Medical and Addiction Center, Japan

A growing recognition of the magnitude of alcohol-related problems and the development of a global strategy by the WHO, contributed in 2013 to the Japanese government's enactment of the Basic Act on Measures against Alcohol-related Health Harm, and its subsequent implementation. Separate legislation, related to the legalization of casinos in this country, the Act on Measures against Gambling Addiction, will soon become law. These legislative changes have inspired plans by the Japanese government to strengthen treatment and consultation capacity, both qualitatively and quantitatively, for those individuals suffering from addictions, and their families. The target population for the treatment of alcohol dependence (AD) at specialist and non-specialist treatment facilities is expected to cover less severe cases, in order to broaden treatment coverage. For this purpose, new guidelines for the diagnosis and treatment of substance dependence will be published. Furthermore, reduction in alcohol consumption in addition to abstinence as the treatment goal for AD has been accepted and clinically implemented. This is expected to further address the clear treatment gaps for AD. My presentation will summarize the current situation in the treatment of AD and suggest future actions that may address some of the related treatment issues in Japan.

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TRENDS IN THE TREATMENT OF ALCOHOL DEPENDENCE IN THE EU

J. Chick
Edinburgh Napier University and Castle Craig Hospital, UK

In England people scoring 20+ on AUDIT (i.e. definitely alcohol dependent) seldom received treatments specific for alcohol dependence. Instead many receive prescriptions for anxiety and depression because any help they receive is in primary care or general psychiatry, because addiction isn't recognized or specialist services are few. Austerity has closed services and beds in the UK more than in other EU countries.

UK sales of specific medicines for alcohol dependence are few compared to e.g. sales of antidepressants (ratio 1:3500); acamprosate sales have plateau'*d* (prescribed 3–4 times more than disulfiram). Off-label topiramate and baclofen have adherents throughout the EU – baclofen has a long history in Italy, and is widely used in France where a special temporary licence was obtained. In Austria and Italy, GHB is used for withdrawal and relapse prevention.

Mutual aid groups aimed at abstinence are widely available in France; in Madrid their effectiveness was shown in a recent controlled study. AA groups exist throughout the EU but some professionals do not help their patients to attend. There has been a growing acceptance by specialists that, for some patients, reduction rather than abstinence is a helpful goal, widening the menu of available therapies.

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THE CURRENT STATUS OF ALCOHOL USE DISORDER AND ITS TREATMENT IN THE U.S.

R.M. Swift
Brown University Center for Alcohol and Addiction Studies, USA

Over the past decade there has been a shift in attitudes about alcohol use disorder diagnosis and treatment in the U.S. Four main factors account for this change.

First, the opioid crisis has increased awareness and acceptance of substance use disorders as an illness that requires treatment. The idea of "Medication Assisted Treatment" (MAT), originally applied to opioid treatment, is being applied to alcohol treatment as well. Second, there has been a shift in the U.S. paradigm of abstinence as the only acceptable treatment, to now accept harm reduction as an outcome. Both NIAAA in its funded grants and the US FDA in its guidance for pharmacotherapy clinical trials accept reductions in heavy drinking as an acceptable treatment outcome. Third, the Affordable Care Act (Obamacare) gave health care coverage, including coverage for SUDs, to more than 20 million Americans who did not have coverage. Fourth, there is an increasing prevalence of alcohol use disorder. Because of the requirement for only two positive criteria along with the addition of "craving" in DSM V, it may be easier to receive the diagnosis of alcohol use disorder with DSM V. However, it is also likely that U.S. citizens are drinking more alcohol.

TUESDAY, SEPTEMBER 11 2:55 PM–4:25 PM

SYMPOSIUM

ALCOHOL MISUSE EFFECTS ON BRAIN STRUCTURE FROM ADOLESCENCE TO SENESCENCE: *IN VIVO* MRI, INDICES FOR IDENTIFYING AT-RISK YOUTH, POSTMORTEM BRAIN-BANK MATERIAL FOR VALIDATING *IN VIVO* FINDINGS AND ENABLING GENETIC INVESTIGATIONS

ORGANIZER/CHAIR: EDITH V. SULLIVAN CHAIR: ADOLF PFEFFERBAUM

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LONGITUDINAL STUDIES OF ALCOHOLISM-RELATED BRAIN STRUCTURAL CHANGES FROM ADOLESCENCE TO SENESCENCE

A. Pfefferbaum[1], E.V. Sullivan[2]
[1]SRI International, Menlo Park, CA, USA and [2]Psychiatry, Stanford University School of Medicine, USA

Development of the human brain continues throughout adolescence, into young adulthood and follows an inexorable decline from about age 30 to senescence. During those years of normal changes, alcohol dependence has the potential of altering normal brain structural trajectories. Through longitudinal study, we have found that adolescents who initiate heavy drinking, even without meeting criteria for alcohol dependence, show acceleration of the normal decline in cortical gray matter volumes that are salient in frontal and parietal regions. Older adults who do meet criteria for alcohol dependence exhibit age-alcohol interactions, where selective regional frontal cortical volumes are subject to accelerated aging. Other regions, including medial frontal, parietal, and hippocampal volumes, show premature aging. Although comorbidities of drug dependence or human immunodeficiency virus and hepatitis C virus infections can compound the volume deficits, age-alcohol interactions can occur even in alcohol dependents free of such comorbidities. Thus, adolescents who initiate appreciable drinking are vulnerable to the potential of disturbing trajectories of normal brain development, and older alcohol dependent individuals are at heightened risk of accelerated frontal tissue loss and cognitive compromise. Support: NIAAA (U01AA017347, R01AA010723, R01AA005965, R01AA017923, U01AA021697, K05AA017168).

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LEVEL OF RESPONSE TO ALCOHOL MEASURED ON THE SELF-RATING OF THE EFFECTS OF ALCOHOL QUESTIONNAIRE IN KOREAN MEDICAL STUDENTS

A. Stadlin[1,2], Y. Park[2], B. Lee[3], S. Kim[2], M.A. Schuckit[4]
[1]College of Medicine, Ajman University, United Arab Emirates, [2]College of Medicine, Chungbuk National University, Korea, [3]Department of Psychology, Chungbuk National University, Korea and [4]Department of Psychiatry, University of California San Diego, USA

Low level of response (LR) to alcohol is a risk factor for alcohol-use disorder (AUD). Self-Rating of Effects (SRE) scores are robust predictors of the quantity and frequency of alcohol use, alcohol-related problems, and the development of alcohol dependence. This study is the first attempt to develop and validate a Korean version of SRE. Korean medical students aged 18+ were recruited. Demographics, first-time alcohol-use history, AUDIT-KR and gender differences were studied. Nicotine, drug use, and internet addiction patterns were also ascertained. Psychological well-being were assessed using the Center for Epidemiologic Studies Depression (CES-D) and Kessler Psychological Distress Scale – K6 (Kessler K6). The Korean SRE was in accord with earlier reports, the overall SRE scores correlated with the three individual time points and internally consistent. 55% of the study subjects scored greater than 4.5 (69% male vs. 31% females), suggestive of low LR to alcohol and thus at risk of developing AUD. Males are more at risk. SRE correlated with AUDIT scores. The Korean SRE is valid and matched other reports. It can be implemented in large-scale nation-wide studies throughout Korea.

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USING HUMAN POST-MORTEM BRAIN TISSUE TO ADVANCE THE UNDERSTANDING OF ALCOHOL-RELATED BRAIN DAMAGE

J.J. Kril, J. Stevens, D. Sheedy, T. Mccrossin, C. Smith, M.V. Roijen, C.D. Sousa, G.T. Sutherland
Sydney Medical School, University of Sydney, Australia

Human post-mortem brain tissue is essential for testing hypotheses regarding the aetiology of alcoholism and alcohol-related brain damage, and for confirmatory studies that support the findings of *in vivo* human and animal investigations. The authenticity of findings using human brain tissue depends, in part, on the accurate classification of cases and controls used in such studies. In addition to extensive pathological screening, cases from the NSW Brain Tissue Resource Centre (BTRC) undergo comprehensive clinical characterisation using a combination of prospective and retrospective information. To aid in the classification of cases where case notes are sparse or information contradictory, the BTRC has recently undertaken the measurement of brain phosphatidylethanol (PEth) using an LC-MS technique modified for application to brain tissue. PEth has proven to be a useful biomarker for monitoring alcohol use in people with alcohol use disorders and is helpful for determining recent alcohol consumption in the post-mortem cohort. This advance, together with work towards the application of newly developed techniques such as Matrix Assisted Laser Desorption/Ionization (MALDI) imaging mass spectrometry and imaging mass cytometry, expands the repertoire of techniques that can be applied to human post-mortem brain tissue and improves the characterisation of tissues made available to researchers. Support: NIAAA (R28 AA012725)

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COMBINING GWAS AND TRANSCRIPTOME DATA TO DEFINE GENES AND PATHWAYS IN ALCOHOLISM

R. Dayne Mayfield[1], M. Kapoor[2], S.P. Farris[1], J.C. Wang[2], S. Bertelsen[2], H. Edenberg[3], Y. Liu[3], R. Adron Harris[1], A. Goate[2]
[1]Waggoner Center for Alcohol and Addiction Research, The University of Texas at Austin, Austin, TX, USA, [2]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA and [3]Biochemistry/Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, USA

Alcohol dependence (AD) is a complex disorder with high heritability (50–60%). The excessive use of alcohol induces changes in global gene expression across different tissues including brain. RNA sequencing was used to compare the transcriptomic organization of prefrontal cortex in 143 post-mortem brain samples including 66 uncomplicated alcoholics and 77 matched controls. We identified 481 genes that were differentially expressed between alcoholics and controls. Pathway analysis identified gene enrichment for GADD45 signaling, interferon signaling and inflammatory response. Co-expression analysis clustered genes into 52 distinct modules, one of which contained 731 genes positively correlated with alcoholism classification (DSM4/DSM5) and alcohol consumption. This module was also significantly correlated with age and the number of years of drinking. Age-corrected module-trait correlation analysis improved the association signal for DSM4/DSM5 and case-control classification, indicating that this module was significantly correlated with alcoholism independent of age. SNPs overlapping with this module were highly enriched for association signals with age at onset of AD in the Collaborative Studies on Genetics of Alcoholism (COGA) European American dataset. Interestingly, this gene module was highly enriched for genes related to immune function. By leveraging power from transcriptomic and GWAS data, we identified novel genes and networks associated with alcoholism. Support: NIAAA (U01AA020926 and R01AA012404)

TUESDAY, SEPTEMBER 11 4:30 PM–6:00 PM

SYMPOSIUM

NEW PERSPECTIVES IN THE PHARMACOTHERAPY OF ALCOHOL DEPENDENCE

ORGANIZER/CHAIR: KARL F. MANN CHAIR: SUSUMU HIGUCHI

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A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 3-PARALLEL-GROUP COMPARISON TRIAL TO INVESTIGATE THE EFFECT OF NALMEFENE ON ALCOHOL CONSUMPTION REDUCTION IN PATIENTS WITH ALCOHOL DEPENDENCE IN JAPAN

S. Higuchi[1], H. Miyata[2]
[1]National Hospital Organization Kurihama Medical and Addiction Center, Japan and [2]Department of Psychiatry, Jikei University School of Medicine, Japan

Nalmefene, an opioid receptor modulator, is approved in Europe for patients with at least high WHO drinking risk level (men: >60 g/day; women: >40 g/day), however no prospective study has been reported for patient with high or very high DRL. In this study, patients were randomly assigned to Nalmefene 20 mg (248 pts), 10 mg (184 pts) or placebo (245 pts) from 80 clinical practices in Japan. Compared with placebo, significant reductions in heavy drinking days were observed from baseline to Week 12 with nalmefene 20 mg (difference: −4.34 days per month; 95% confidence interval [CI]: −6.05, −2.62; $p < 0.0001$) and nalmefene 10 mg (difference: −4.18 days per month, 95% CI: −6.05, −2.32; $p < 0.0001$). There was also a reduction in total alcohol consumption in both treatment groups at Week 12 compared with placebo ($p < 0.0001$). Treatment-emergent adverse events (AEs) occurred in 87.9%, 84.8% and 79.2% of patients receiving nalmefene 20 mg, 10 mg and placebo, respectively. The majority of AEs were mild or moderate in severity. This prospective study demonstrated that nalmefene 20 and 10 mg were effective in reducing alcohol consumption and were well tolerated in alcohol-dependent patients with high or very high DRL.

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CAN WE LIMIT TENDENCY OF DOCTORS TO INAPPROPRIATE DIAGNOSIS AND PHARMACOTHERAPY IN ALCOHOL AND SUBSTANCE MISUSING PATIENTS?

J. Chick
Edinburgh Napier University and Castle Craig Hospital, UK

Alcohol and substance use disorders (SUD) can mimic anxiety disorder, depression or bipolar disorder. 80% of patients admitted to addictions clinics have already been prescribed a psychiatric medication - mostly SSRIs but often an antipsychotic; 33% have been prescribed two or more. SSRIs have minimal efficacy on depression in alcohol use disorder and in early onset patients tend to increase risk of relapse. SSRIs have been linked to aggression.

For ADHD, increasingly commonly already diagnosed in patients referred for addiction treatment, diagnostic criteria overlap greatly with symptoms seen in SUD (and in many other psychiatric conditions - 11 according to the UK Royal College of Psychiatrists). Psychometricians state that scales for ADHD cannot detect malingerers. Students fake ADHD to obtain amphetamines - sometimes to sell on. SUD in prisoners is more preceded by personality disorder than ADHD. Longitudinal studies find surprisingly low childhood attention deficit symptoms in those who acquire adult diagnosis of ADHD. Stimulant treatment of ADHD in SUD lacks evidence of efficacy - many adult ADHD patients misuse or divert their medications.

This narrative review suggests we must help our psychiatric colleagues resist the pressure from patients and relatives that ends in irrational prescribing when SUD is present.

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REDUCED DRINKING FOR ALCOHOL DEPENDENT PATIENTS, WHAT IS THE EVIDENCE IN PHARMACOTHERAPY TRIALS?

Karl F. Mann[1], Active Working Group[2]
[1]Heidelberg University, Mannheim, Germany and [2]Medical University of South Carolina, Charleston, SC, USA

Many individuals with alcohol dependence do not seek treatment, they are unwilling or unable to engage in abstinence. Thus, allowing for alternative treatment options offering drinking reduction goals could be an important step to decrease the treatment gap.
The presentation will discuss results of controlled studies testing this alternative approach. Sustained drinking reductions were shown for patients following behavioral treatments and pharmacotherapy. With reduced drinking, long-term improvements have been reported regarding mortality rates, incidence of alcohol-associated injuries and accidents, levels of mood symptoms, quality of life, social functioning, along with significant weight reduction, a normalization of systolic and diastolic blood pressure, slowed progression of alcohol-attributable liver fibrosis, and recovery of ventricular heart function.
Recently, the clinical value of a shift in WHO risk levels of drinking with respect to improvement in functional outcomes has been validated in a clinical sample (see Witkiewitz, this symposium) and a population-based sample of drinkers. There is growing recognition that harm reduction outcomes including reduced alcohol consumption need to be considered in addition to abstinence for defining treatment success.
In conclusion, while abstinence remains the safest treatment goal for individuals with AD, reduced drinking approaches may be an important extension in the treatment of AD.

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ALTERNATIVE ENDPOINTS IN ALCOHOL CLINICAL TRIALS: THE WORLD HEALTH ORGANIZATION DRINKING RISK LEVELS

K. Witkiewitz
University of New Mexico, USA

The goal of the current study was to examine the correspondence between levels of alcohol consumption, as measured by the World Health Organization (WHO) drinking risk levels, and experiences of drinking-related consequences, mental health, blood pressure, and liver function tests during treatment among individuals receiving treatment for alcohol dependence in the COMBINE study (n = 1383). Results indicated reductions in WHO risk levels were associated with significantly fewer alcohol related consequences, greater mental health, and improvements in physical health functioning, including reduced blood pressure and better liver function. Importantly, even a one level decrease in WHO risk drinking levels predicted statistically and clinically significant decreases in the risk of experiencing a variety of alcohol related consequences, improvements in mental health, and improvements in blood pressure and liver function. The results from the current study provide evidence of reductions in WHO risk levels as a viable alternative to abstinence as an endpoint for alcohol clinical trials. The paper will also discuss the application of WHO risk levels in clinical practice and provide guidance for clinicians on the targets for alcohol risk reduction that are most likely to be associated with meaningful reductions in alcohol related consequences and improvements in mental and physical health.

WEDNESDAY, SEPTEMBER 12 9:55 AM–11:25 AM

SYMPOSIUM

UNDERSTANDING NEURAL CIRCUITS UNDERLYING NATURAL AND ETHANOL REWARD

ORGANIZER/CHAIR: IGOR PONOMAREV

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MECHANISMS ENCODING SEXUAL AND ETHANOL REWARD WITHIN THE DROSOPHILA NERVOUS SYSTEM

G. Shohat-Ophir[1], S. Zer-Krispil[1], J. Ryvkin[1], L. Shao[2], A. Shmueli[1]
[1]The Faculty of Life Sciences and The Multidisciplinary Brain Research Center, Bar Ilan University, Israel and [2]HHMI Janelia Research Campus, 19700 Helix Drive Ashburn, VA 20147, USA

Given the importance of reproduction for survival, actions that promote successful mating induce pleasurable feeling and are positively reinforced. This principle is conserved in *Drosophila*, where successful copulation is naturally rewarding to males, induces appetitive memories, increases brain levels of Neuropeptide F (NPF, the fly homologue of Neuropeptide Y) and prevents ethanol from being perceived as rewarding. It is not clear which of the multiple sensory and motor responses performed during mating induce the perception of reward. Here we tested the ability of ejaculation to mimic the rewarding value of full copulation, by activating neurons that express the neuropeptide corazonin (CRZ), and subsequently measured different aspects of reward. We show that activating Crz-expressing neurons is rewarding to male flies, as they exhibit place preference to a zone that triggers stimulation of Crz-neurons and display conditioned preference for an odor paired with the activation. Repeated activation of Crz-neurons increases *npf* levels and reduces ethanol consumption. To explore mechanisms that process reward, we analyzed the transcriptome of our neuronal populations known to process reward in response to sexual deprivation and successful mating. The analysis revealed many differentially regulated genes, including wnt signaling, synaptic plasticity, innate immunity and genes related to aggressive behavior.

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CIRCUITS AND MOLECULES DRIVING CUE-INDUCED ALCOHOL PREFERENCE

E. Petruccelli, K.R. Kaun, K.M. Scaplen, N. Ledru, G. Chiefallo
Department of Neuroscience, Brown University, USA

Investigating the anatomical and molecular makeup of memory circuits is key to understanding how memories for rewarding stimuli are remembered, and can be manipulated to influence decisions. The genetic accessibility afforded in *Drosophila* provides an ideal platform to understand how molecules act within reward circuits to form appetitive memories, and how drugs of abuse such as alcohol can manipulate these circuits to induce cravings. Here we describe a how expression of memories for the intoxicating properties of alcohol requires a remarkably complex multilevel circuit whereby dopamine directly, and indirectly via the mushroom body, modulates the activity of glutamatergic and cholinergic output neurons. We then reveal lasting molecular changes induced by alcohol-cue training in the mushroom body nuclear transcriptome. This included alternative splicing of transcripts associated with addiction, synaptic plasticity, axon guidance, dendrite development, innate immunity and lipid biosynthesis. This suggests a wide diversity in lasting molecular changes associated with alcohol-cue training in a memory circuit. Together this work provides a neuromolecular snapshot of how alcohol can affect the dynamic molecular and circuit mechanisms required for behavioral decisions.

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LASTING EFFECTS OF INCREASING NUCLEUS ACCUMBENS ACTIVITY ON BINGE-LIKE ALCOHOL DRINKING AND THE TRANSCRIPTOME

A.R. Ozburn
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Neurobiological mechanisms that underlie binge drinking are not well understood. We used Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to chronically alter neuronal activity in the nucleus accumbens (NAc) and measure Drinking in the Dark (DID). We found that activating the excitatory DREADD with clozapine-n-oxide (CNO) for 28 days significantly decreased binge-like drinking, an effect which persisted during a 7 days vehicle wash-out period. We did not observe these changes in mice expressing the inhibitory DREADD (or in mCherry control group). To further study the behavioral plasticity observed in mice that received chronic stimulation of the NAc, we performed another study (in which mice either had water or ethanol, and received either vehicle and CNO or vehicle only) and replicated our behavioral findings. We performed RNA Seq to assess the effects of chronically increasing NAc activity on the transcriptome. We found significant changes in a number of plasticity-related genes that were altered in vehicle treated ethanol drinking mice and ameliorated in ethanol drinking mice that received CNO treatment. In conclusion, chronic stimulation of NAc produces lasting reductions in DID and ameliorates the effects of DID on a molecular level. This work aims to develop potentially therapeutic strategies for reducing harmful drinking.

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THE EFFECTS OF THE PDE4 INHIBITOR APREMILAST ON CELLULAR PHYSIOLOGY AND ETHANOL DRINKING

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PDE4 is a promising target for the treatment of alcohol use disorder, with several groups demonstrating efficacy of PDE4 inhibitors in reducing ethanol intake in rodents. However, it is less clear whether these compounds are effective in ethanol-dependent animals and little is known regarding possible mechanisms of action. Therefore, we tested the FDA-approved PDE4 inhibitor, apremilast, in a mouse model of ethanol dependence – the chronic intermittent ethanol vapor model. Apremilast (20 mg/kg, p.o.) administration prior to drinking sessions reduced ethanol consumption by air controls and ethanol vapor-exposed mice, indicating that apremilast also is efficacious in ethanol-dependent mice. To investigate how apremilast impacts function in a brain region implicated in ethanol reward, we performed slice electrophysiology to record from nucleus accumbens medium spiny neurons. Apremilast differentially regulated membrane excitability, depending on the subtype of MSN and location within the NAc. This varied influence on excitability may reflect differences in sensitivity to the synaptic inputs that regulate MSN excitability, as apremilast increased excitatory input while also promoting GABA signaling. Notably, these electrophysiological effects of apremilast mirror those of ethanol in several respects, suggesting that apremilast may reduce consumption in both non-dependent and dependent mice by potentiating acute pharmacological actions of ethanol.

WEDNESDAY, SEPTEMBER 12 2:55 PM–4:25 PM

SYMPOSIUM

A NEW ERA OF ALCOHOLISM RESEARCH FOR UNVEILING NEURAL, COGNITIVE, AND GENETIC DYSFUNCTIONS; FROM BASIC TO BEDSIDE

ORGANIZER/CHAIR: SHIGENOBU TODA CHAIR: MING CHYI HUANG

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HOW IS A HABIT DEVELOPED OR UNDEVELOPED?: IMPLICATIONS FOR A CRITICAL ROLE OF ATTENTION DURING A GOAL-DIRECTED PROCESS OF OPERANT LEARNING IN RATS

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Many workers become alcoholism after retirement despite their long alcohol history. What does prevent alcoholism during their working days?
To address this question, we focused on habit. A habit is immediately output by a specific stimulus without requiring explicit attention and is considered to be responsible for compulsivity in addiction. The operant training with distinct schedules result in different consequences; the subject with random interval schedule is given one reward averagely per a certain interval in a random manner and is prone to be a habit. Meanwhile, the subject with fixed interval (FI) schedule is rewarded in every fixed interval by lever pressing on timing and is resistant to be habitual. We hypothesized that the temporal attention for the interval could prevent habit formation. To verify this, we prepared a cohort of rats with FI schedule for which the timing of lever pressing was informed just before by an auditory cue, thus the subjects need not pay attention to the interval. With this modification, the cohort developed habit rapidly. Thus, it is speculated that a temporal attentional restriction prevents habit formation, which could explain the reason why the retired workers are more prone to be alcoholism, at least in part.

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HOW SOCIAL DEPRIVATION DIFFERENTIALLY AFFECTS ALCOHOL INTAKE BEHAVIOR AMONG MALE AND FEMALE MICE?

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Early social experience has been consistently shown increase alcohol consumption, perhaps by influencing stress systems. A complex relationship exists between alcohol-drinking behavior and stress. There are well-known sex differences in the epidemiology of alcohol dependence; however, the relationship between stress and alcohol consumption is poorly understood. There obviously exist sex differences in sensitivity and responsiveness to stress, and then these differences will be reflected in drinking behavior. Curiously, in most acute stress models alcohol consumption is most often reduced, rather than increased, as it is following chronic social isolation of adolescent rodents. This may suggest that other factors influence the interaction between stress and alcohol exposure. Genetic factors also have a substantial influence on alcohol consumption, but only a limited set of such genetic influences on stress-induced alcohol consumption have been examined.
Our experiment was based on the hypothesis that the effects of chronic stress on ethanol consumption would be influenced by both sex and the functioning of opioid receptor systems. To characterize alcohol consumption of μ-opioid receptor knockout- and wild type mice exposed to social isolation stress and evaluate the effects of opioid signaling into the link between the stress and alcohol consumption.

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IDENTIFICATION OF GENETIC POLYMORPHISMS ASSOCIATED WITH HUMAN SENSITIVITY TO ADDICTIVE SUBSTANCES AND ITS CLINICAL APPLICATION

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Addictive substances, such as ethanol, nicotine, cocaine, heroin, and methamphetamine, could cause substance use disorders by their rewarding effects. One of the key mechanisms in the rewarding effects of various addictive substances is the opioid system, which is also known to be involved in antinociceptive effects. To date, various candidate genetic polymorphisms have been reported to be associated with individual differences in sensitivity to addictive substances, including opioids, or vulnerability to or severity of substance use disorders. In our previous human studies, several single-nucleotide polymorphisms (SNPs) within or close to regions of the genes related to opioid signaling have been identified as possible candidates associated with human opioid sensitivity. Among them, the rs2952768 SNP, close to the *CREB1* gene that encodes cyclic adenosine 3′,5′-monophosphate responsive element binding protein 1, also exhibited associations with vulnerability to severe drug dependence in patients with methamphetamine dependence, alcohol dependence, and eating disorders and a lower "Reward Dependence" score on a personality questionnaire in healthy subjects. Whereas we are currently conducting a clinical study for individualized pain treatment utilizing those SNPs to predict individual opioid sensitivity, such personalized medicine will be hopefully applied for the treatment of substance use disorders including alcoholism in the future.

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A REPORT OF THE FUNCTIONAL MRI STUDY WITH SEVERE ALCOHOL USE DISORDER (AUD) PATIENTS

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We had a functional MRI (fMRI) study to investigate the difference between Alcohol use disorder (AUD) patients and healthy people with visual tasks.
24 patients with severe AUD and 15 healthy controls (HC) participated in this study. We presented visual cues using drink images. We used a block design. In total, we presented eight stimuli for 4 min in each fMRI session. We used SPM12 software to analyze Blood Oxygen Level Dependent (BOLD) signals of fMRI data.
We had a group analysis between AUD patients and HC. We detected an interaction effect between brain activation of AUD patients and HC at left precuneus, right precuneus and left posterior cingulate cortex (PCC). With a multiple comparison, AUD had significantly lower responses to the image of someone drinking juice than HC in left precuneus and left PCC ($p = 0.036$, $p = 0.044$), while AUD had significantly higher responses to the image of someone drinking alcohol than HC in left PCC ($p = 0.044$).
These results suggest that the responses to the behavior of drinking alcohol may be associated with drug craving in patients. Severe AUD patients may have strong responses when they see someone drinking alcohol.

MONDAY, SEPTEMBER 10 1:00 PM–2:30 PM

SYMPOSIUM

CHRONIC ALCOHOL INDUCES PLASTICITY IN STRIATAL AND LIMBIC CIRCUITS

ORGANIZER/CHAIR: NICHOLAS W. GILPIN

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DRUG-INDUCED DYSFUNCTION IN DORSOMEDIAL STRIATUM AND IN DECISION-MAKING

B.W. Balleine
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The smooth integration of cognitive and emotional processes is necessary for everyday decisions. Dysfunction of this integrative capacity accompanies many major psychiatric conditions and neurodegenerative disorders. It is also powerfully affected by exposure to various drugs in a manner that precipitates the poor decision-making associated with addiction. Here I will discuss recent evidence that the neural bases of cognitive-emotional integration in normal decision-making is mediated by a network centred on the dorsomedial striatum, how this network is affected by exposure to various drugs, notably alcohol, cocaine and methamphetamine, how these effects result in the symptoms associated with addictive disorders, and the implications these views have for treatment.

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PREFRONTAL CONTROL OVER COMPULSIVE-LIKE ETHANOL-SEEKING

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A clinical hallmark of AUD sufferers is that alcohol drinking persists despite an awareness of the potential adverse consequences that may occur as a result. Prior studies in rodents have identified the medial prefrontal cortex (mPFC) as a key source of top-down control over subcortical regions, such as the nucleus accumbens (NAc) and basolateral amygdala (BLA), that encode the positive and negative valence of ethanol (EtOH)-related stimuli. In this study, we used *in vivo* single-unit electrophysiological recordings and circuit-specific optogenetic manipulations to examine the role of the mPFC and mPFC-inputs to the NAc and BLA in a mouse assay of punished EtOH self-administration. We found encoding of punished-avoidance of EtOH self-administration in neurons in the ventral, but not dorsal, subregion of the mPFC, and showed that optogenetic photosilencing of the ventral mPFC or projections from this area to the NAc shell prevented punished suppression of EtOH self-administration. These findings provide evidence for a key neural circuit for controlling punished suppression of EtOH self-administration, with implications for understanding the biological basis of compulsive drinking in AUDs.

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ALCOHOL DEPENDENCE IMPACTS VENTRAL TEGMENTAL AREA PROJECTIONS TO CENTRAL AMYGDALA

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The neural adaptations that define excessive alcohol drinking in alcohol-dependent individuals may include interactions between mesolimbic reward circuits and brain stress circuits. Here, we focused on dopaminergic and non-dopaminergic projections from the ventral tegmental area (VTA) to the central nucleus of the amygdala (CeA), regions important for mediating acute alcohol reinforcement and dependence-induced escalation of alcohol drinking, respectively. Little is known about the VTA-CeA circuit, even under basal conditions; therefore, we combined retrograde tracing and immunohistochemical experiments in rats to demonstrate that the CeA receives both dopaminergic and non-dopaminergic projection neurons from VTA and the neighboring substantia nigra (SN). We then used slice electrophysiology and cFos immunohistochemistry to test the effects of alcohol dependence on activity and activation profiles of CeA-projecting neurons in VTA and SN. Our data indicate that alcohol dependence perturbs midbrain projections to the amygdala, raising the possibility that this circuit is involved in mediating behaviors (e.g., escalated alcohol drinking) associated with alcohol dependence. We explore this possibility by utilizing chemogenetics to investigate the role of the VTA-CeA circuit in operant alcohol self-administration in alcohol-dependent and non-dependent rats. These studies were supported by NIH grants R01 AA023305, R01 AA026531, T32 AA007577, and F32 AA025831.

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EXCESSIVE ALCOHOL DRINKING DISRUPTS STRESS COPING THROUGH ALTERATIONS IN BNST DYNORPHIN

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Excessive alcohol intake can lead to dynamic changes in stress coping behavior and stress-related neural mechanisms. We aim to explore how long-term intermittent alcohol (IA) changes how mice react to a variety of stressors and if the dynorphin (DYN)/kappa opioid receptor (KOR) system influences these aberrant behaviors. After 8 weeks of IA, mice show reduced ability to cope with a repeated forced swim stress and deficits in active coping in response to a fox-derived TMT predator odor compared to H_2O-drinking mice. Further, we found that KOR antagonist norBNI could restore stress coping in the repeated forced swim and responses to predator odor. To next determine which DYN/KOR populations may drive these altered stress reactions after chronic alcohol, c-Fos was used to map activity in DYN neurons using a transgenic reporter strain of mouse (preprodynorphin-IRES-Cre:: Rosa26-flox-stop-L10a-eGFP). Among other corticolimbic areas, the dorsal bed nucleus of the stria terminalis (dBNST) showed the highest c-Fos interaction between alcohol history and stress. We next performed excitability and synaptic transmission experiments using whole cell patch clamp recordings of dBNST DYN neurons. Overall, IA robustly silenced synaptic drive while the combination of IA and stress significantly increased excitability and glutamatergic activity in DYN-containing cells in the dBNST.

WEDNESDAY, SEPTEMBER 12 9:55 PM–11:25 PM

SYMPOSIUM

GENETIC STUDIES ON THE DEVELOPMENT AND CONSEQUENCES OF ALCOHOL USE DISORDERS

ORGANIZER/CHAIR: SACHIO MATSUSHITA CHAIR: AKITOYO HISHIMOTO

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THE ROLE OF SYSTEM XCT IN ADDICTION

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System xCT is a chloride-dependent cysteine-glutamate antiporter which is coded from SLC7A11 gene. It is related to non-vesicular glutamate release and the extracellular glutamate level regulation. Many CNS diseases are caused from dysfunction of glutamate, and we want to focus on the role of system xCT and extracellular glutamate level in addiction. We started from animal model study with alcohol-dependence mice, not only highly expression of system xCT but also high extracellular glutamate level were noted in alcohol-dependence wild type mice. However, obviously low expression of system xCT and significant lower extracellular glutamate level were noted in xCT knockout mice compared to wild type mice. Our hypothesis is that addiction is associated with disruption of glutamate hemeostasis, and we try to investigate it more from a clinical pilot study. We checked the gene expression in a group of opioid dependence patients and “X drug” was prescribed accompany with methadone for them. “X drug” has the function in xCT inhibition, we recorded their withdrawal symptoms and the dosage of methadone using in this pilot study. Gradually decreased of methadone dosage was noted in some patients, hence, further researches related to SLC7A11 gene expression and addiction treatment by xCT inhibitor are needed and expected.

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ALCOHOL-RELATED POLYMORPHISMS AND RISK FOR SUICIDE IN THE JAPANESE POPULATION

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Recent mega genome-wide association studies (GWASs) have confirmed the genetic involvements of ALDH2, ADH1B, KLB and GCKR in excessive alcohol consumption which is a potential risk factor for suicide as suggested by a number of epidemiological studies. Interestingly, we previously reported the association of two popular single nucleotide polymorphisms (SNPs) (ALDH2 rs671 and ADH1B rs1229984) with completed suicide; however, the sample size was relatively small (<300) and our findings had not been updated by any other suicide studies due to the extreme difficulty in collecting suicide samples. We now retain about 1000 samples of suicide completers, one of the largest sample sizes worldwide. Then, we further investigate whether alcohol-related SNPs strongly identified by past GWASs have statistical effect on the genetic components of suicide. Here, we report the possibility of genetic correlation between alcohol consumption and suicide.

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PERCEIVED RESPONSE TO ALCOHOL AS A PHENOTYPE FOR RISK OF ALCOHOL RELATED PROBLEMS IN YOUNG JAPANESE ADULTS

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Background: A Low level of Response (LR) to alcohol is genetically influenced and is a possible predictor of alcohol use disorder (AUD). This presentation will examine: (1) the relationship between the genetic variation of alcohol dehydrogenase (*ADH1B*) and aldehyde dehydrogenase (*ALDH2*) and subjective response to alcohol and (2) the association between the subjective response to alcohol and AUD risk in Japanese young adults studied prospectively.
Methods: Subjects included 424 healthy Japanese college students. Using the alcohol clamp method, we infused diluted alcohol for 3 h. The LR to alcohol was assessed using the Biphasic Alcohol Effects Scale (BAES) every 30 min during the infusion procedure. Subjects have been followed using the Alcohol Use Disorder Identification Test (AUDIT).
Results: Subjects with inactive *ALDH2* showed stronger sedative subjective responses to alcohol than those with active *ALDH2*. Examining the relationship between subjective response to alcohol and AUDIT scores at follow up revealed that subjects with higher AUDIT scores showed stronger stimulant, but weaker sedative, subjective responses to alcohol than those with lower AUDIT scores.
Conclusion: Our findings suggest that a subjective stimulant response to alcohol predicts later alcohol related problems among healthy young Japanese adults, but this effect is not related to genotype.

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ABERRANT TELOMERES IN ALCOHOL DEPENDENCE, MOOD DISORDER AND SUICIDE

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Heavy drinking leads to premature aging and precipitates the onset of age-related diseases. However, whether alcohol dependence accelerates biological aging at a cellular level remains unclear. Here, we addressed this question by focusing telomere length in peripheral blood leukocytes of alcoholic subjects with their types of genetic variants related to alcohol dependence and other clinical characteristics. Further, we are also investigating the association of telomeres with mood disorders and suicide in which alcohol dependence is frequently comorbid.

WEDNESDAY, SEPTEMBER 12 2:55 PM–4:25 PM

SYMPOSIUM

THE ROLE OF GLYCINERGIC MECHANISMS FOR ETHANOL'S MECHANISM OF ACTION AND FOR CONTROLLING ALCOHOL INTAKE

ORGANIZER/CHAIR: BO SÖDERPALM CHAIR: LUIS AGUAYO

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ROLE OF ALPHA1 AND ALPHA2 SUBUNITS IN ETHANOL MEDIATED POTENTIATION OF GLYCINE RECEPTORS IN NUCLEUS ACCUMBENS

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The glycine receptor (GlyR), a ligand-gated ion channel, is known to play a critical role for inhibitory neurotransmission in brainstem and spinal cord. In these regions, most of the GlyRs are synaptically located and several studies have shown that GlyRs are potentiated by low and clinically-relevant concentrations of ethanol. Interestingly, in recent years much more attention has been focused on the presence of GlyRs in supraspinal regions. These GlyRs are mainly found in non-synaptic regions, although some GlyRs are still expressed at the synapsis. Recent data from several laboratories have shown that GlyRs are important in the brain reward system and that α_1 and α_2 are the predominant subunits expressed in the nucleus accumbens (nAc). Here, we report that GlyR receptors activated in dissociated neurons are sensitive to ethanol, with the largest effect in D1 MSNs. The effects of ethanol were concentration dependent (10–100 mM) and were associated to potentiation of tonic, but not phasic currents (mIPSC and eIPSCS). The effects of ethanol in D1 MSNs were associated to a reduction in the number of action potentials in a concentration- and strychnine-dependent manner suggesting that the potentiation of GlyRs in these neurons actually reduces neuronal excitability.
Supported by NIH R01AA025718.

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ROLE OF TAURINE FOR ETHANOL'S INTERACTION WITH GLYCINE RECEPTORS CONTROLLING DOPAMINE IN THE NUCLEUS ACCUMBENS

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Glycine receptors in the nucleus accumbens, the terminal region of the mesolimbic dopamine system, have been demonstrated to be of importance for ethanol-induced dopamine elevation as well as ethanol consumption in rats. Ethanol is also known to induce a release of the endogenous amino acid taurine in the nAc, and it was previously demonstrated that if the ethanol-induced elevation of taurine is prevented the dopamine increase following ethanol administration is lost. To better understand the role of taurine for ethanol's ability to increase nucleus accumbens dopamine we designed a series of *in vivo* microdialysis studies, in freely moving Wistar rats, aiming to explore the mechanism underlying ethanol-induced elevation of taurine. Here we found that the increase of extracellular taurine following ethanol administration likely derives from astrocytes and may be released via volume regulated anion channels as a consequence of an ethanol-induced alteration of osmotic conditions. These studies further implicates taurine and glycine receptors as prominent participants in the dopamine elevating properties of ethanol.

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CHRONIC INTERMITTENT VOLUNTARY ALCOHOL ADMINISTRATION ELEVATES GLYCINE SIGNALS IN THE LATERAL HABENULA OF RATS

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Withdrawal from chronic excessive alcohol administration often results in a negative affective state that has been linked to a propensity for relapse drinking and dependence. Recently we found that this state was alleviated by activating the strychnine-sensitive glycine receptors (GlyRs) in the lateral habenula (LHb), a brain region critically involved in processing aversive signals.

To study the underlying mechanisms, we examined the effects of pharmacological manipulations of GlyRs on LHb neurons. Glycine (3–1000 μM) suppressed spontaneous firing and EPSCs (sEPSCs) of LHb neurons in brain slices from rats at 24 h withdrawal from chronic alcohol administration, whereas, at 3–30 and 50–1000 μM respectively induced excitation and inhibition in LHb neurons of alcohol Naïve rats. Also, at 3–30 and 50–1000 μM respectively induced excitatory and inhibitory currents in LHb neurons of both groups rats.

Interestingly, strychnine induced depolarizing currents in LHb neurons of both groups of rats and a mixed result on firing and sEPSC frequency. Sarcosine also produced a mixed result on firing, sEPSC frequency and membrane currents.

Together, these results suggest that glycine signals have been elevated in the LHb of rats withdrawn from chronic excessive alcohol administration, which may contribute to the negative state during withdrawal.

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A HUMAN LABORATORY TRIAL ASSESSING HIGH-DOSE GLYCINE FOR REDUCING ALCOHOL CRAVING IN ALCOHOL DEPENDENT SUBJECTS

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The glycine system is under investigation as treatment target for alcohol use disorder. The biological rationale derives from animal studies showing that glycine receptors are access points for alcohol to the mesolimbic dopamine system and that elevated brain glycine levels reduce ethanol intake in rats. This translational laboratory trial investigated the effect of glycine supplementation with individual dosing (0.12 g/kg/day) using a laboratory paradigm with alcohol challenge in a double-blind, placebo-controlled manner. 56 subjects with alcohol use disorder were randomized to glycine or placebo for 5 days and participated in an alcohol challenge study on the sixth day. Glycine treatment significantly elevated s-glycine levels by 125% (from 248.4 to 557.7 μmol/L) compared to placebo (from 243.8 to 247.4 μmol/L). *Results* – Headache and tiredness were the most prevalent adverse events. Glycine did not change priming-induced craving or alcohol consumption in alcohol dependent subjects. Yet suboptimal dosing/poor CNS penetration and limitations in study design may have hindered a sound evaluation of the treatment. Given the strong preclinical efficacy but again a lack of clinical success to date it could be advantageous to combine glycine-based therapy with another pharmacological approach, in a similar manner as glycine is investigated as adjuvant therapy in schizophrenia.

WEDNESDAY, SEPTEMBER 12 4:30 PM–6:00 PM

SYMPOSIUM

HIV AND ALCOHOL CO-MORBIDITIES: PATHOGENESIS AND TREATMENT

ORGANIZER/CHAIR: NATALIA A. OSNA AND PATRICIA E. MOLINA

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ALCOHOL-SIV/HIV-ART INTERACTIONS & METABOLIC COMORBIDITY PATHWAYS

P.E. Molina, L. Simon, D.A. Welsh, A.M. Amedee, R.W. Siggins, T.F. Ferguson, M.M. Brashear, S.D. Primeaux
Comprehensive Alcohol-HIV/AIDS Research Center, Louisiana State University Health Sciences Center, USA

Background: Persons living with HIV (PLWH) have higher prevalence of heavy alcohol consumption. Antiretroviral therapy (ART) increases risk for comorbidities and these can be exacerbated by chronic heavy alcohol consumption. Previously, we reported subclinical insulin resistance in chronic binge alcohol (CBA)-administered, (SIV)-infected non-human primates (NHP).

Methods: We studied the impact of CBA and at-risk alcohol consumption on tissue-specific metabolic alterations in NHP and their translational relevance. PLWH (N = 365; 69% male; 84% African American; mean age 48.2 $\pm$ 10 years), in care were enrolled in our translational study.

Results: In NHP, CBA decreased adipocyte cell size, and increased collagen expression and mast cell number in mesenteric adipose tissue. ART decreased expression of mTOR, rpS6, and PTEN, and increased phosphorylation of hepatic AMP-activated protein kinase α and hepatic gene expression of key gluconeogenic and adipogenic enzymes. In PLWH, 40.3% of subjects had AUDIT $\geq$ 8 and 48.5% met IR criteria (HOMA-IR $>$ 1.9). Insulin sensitivity index (McAuley index) was associated with increasing AUDIT and phosphatidylethanol levels.

Conclusions: Results from NHP show altered mesenteric adipose tissue phenotype and enhancement of hepatic adipo- and gluconeogenic capacity. Translational findings suggest a positive association of heavy alcohol consumption and metabolic dysregulation in PLWH.

Research support: NIH/NIAAA P60AA009803, UH2AA026198, UH2AA026226.

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ALCOHOL POTENTIATES HIV-INDUCED EXTRACELLULAR VESICLES (EV) RELEASE: CONTRIBUTION TO LIVER INFLAMMATION AND FIBROSIS

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Liver-related morbidity and mortality at HIV-infection is increased by excessive alcohol consumption, and about 48% of HIV-infected persons are alcohol abusers. The damaging effects of HIV on liver cells are partially related to the HIV-triggered hepatocyte killing potentiated by alcohol. We hypothesize that alcohol exposure makes hepatocytes HIV- permissive and triggers hepatocyte apoptosis, providing activating signal to liver non-parenchymal cells (NPC). Here, primary human hepatocytes were plated on custom gels resembling differential liver stiffness and infected with HIV. HIV-infection was more prominent in ethanol-exposed hepatocytes determined by reverse transcriptase levels, HIVgagRNA and HIV integration into host DNA. Furthermore, ethanol treatment induced apoptosis in HIV- infected hepatocytes as indicated by enhanced caspase 3 cleavages and by M30 CytoDeath ELISA. The effects of ethanol on apoptosis induction were mimicked by UV exposure of HIV-infected hepatocytes. Obtained apoptotic bodies (AB) were engulfed by macrophages and hepatic stellate cells (HSC). We observed activation of inflammasome in macrophages (NRLP3, caspase 1, IL-1β and IL-18 mRNA increase) and pro-fibrotic changes in HSC. We conclude that ethanol increases expression of HIV in hepatocytes hepatocyte apoptosis. Engulfment of these AB by NPC cells promotes liver inflammation and fibrosis progression.

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ALCOHOL AND HIV-INFECTION INDUCED EPIGENETIC HISTONE MODIFICATIONS IMPAIR CD4+ T LYMPHOCYTE GENE EXPRESSION: RELEVANCE TO HIV-1 PATHOGENESIS

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Similar to the population at large, many patients with human immunodeficiency virus type 1 (HIV-1) infection also abuse alcohol. Several studies suggest that chronic alcohol abuse can further exacerbate the immune abnormalities induced by HIV, and hence be an important predisposing factor to opportunistic infections like tuberculosis and certain types of cancer, often associated with HIV-AIDS. Importantly, akin to HIV-1 infection, chronic alcohol consumption results in the depletion and loss of function of $CD4^+$ T lymphocytes, which regulate all aspects of the innate and adaptive immunity, and determine organ-specific immunological responses. Hence, the present work investigated HIV-1 and alcohol-induced epigenetic mechanisms underlying immunosuppressive changes in FasL and IL-2 gene expression.

CD4+ T cells exposed to alcohol and HIV-1 infection demonstrated the establishment of a distinct promoter histone profile for FasL and IL-2 genes. These distinct promoter histone modifications including histone H3 acetylation, methylation and phosphorylation played a critical regulatory role in activating FasL while concomitantly decreasing IL-2 gene expression. Taken together, the present work identifies key regulatory epigenetic mechanisms that constitute a significant component of alcohol and HIV-1 induced immunosuppression that can exacerbate the pathogenesis of secondary bacterial and viral infections.

Grant Support: This work is supported by NIH/NIAAA grants.

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NEUROPATHOLOGICAL MECHANISMS OF ALCOHOL, SIV, AND ANTIRETROVIRAL THERAPY: ENHANCED SUSCEPTIBILITY OF THE FRONTAL CORTEX IN RHESUS MACAQUES

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Alcohol use represents a major exacerbating factor for HIV-related cognitive deficits, and persons living with HIV/AIDS (PLWHA) are more likely to be heavy alcohol drinkers. We hypothesize that pathological changes in the striatum and frontal cortex underlie alcohol- and HIV-associated cognitive deficits. To investigate mechanisms whereby alcohol facilitates cognitive deficits in PLWHA, we developed and utilized a rhesus macaque model of chronic binge alcohol (CBA) exposure and simian immunodeficiency virus (SIV) infection (with and without anti-retroviral therapy, ART). We conducted gene expression analyses in the striatum and frontal cortex of male macaques as a neurobiological measure of potential neuropathology. As an extension of our work in males, we also measured alterations in cognitive behavior (via novel object recognition tests) and plan to measure gene expression in CBA/SIV/ART-administered female rhesus macaques, including an investigation of the contribution of ovarian hormones via inclusion of ovariectomized (OVX) animals. Our work in male rhesus macaques discovered that SIV infection is associated with greater inflammatory gene expression in the striatum and reduced growth factor signaling in the frontal cortex, while CBA administration is associated with reduced growth factor signaling in both the striatum and frontal cortex. Importantly, ART reduces inflammatory gene expression in both the frontal cortex and striatum, but does not ameliorate CBA-associated suppression of growth factor signaling. Our behavioral findings in female macaques indicate that CBA/SIV/ART/OVX animals demonstrate a reduced ability to discriminate a novel object compared to control (water-exposed and intact) animals, indicative of deficits in recognition memory. We also find that CBA/SIV/ART-administered animals spend significantly less time with the novel object relative to a familiar object, which may reflect either cognitive deficits or anhedonia-like behavior. Future gene expression analyses of female striatum and frontal cortex tissue will be directly compared with our findings in males. Overall, our results are consistent with the increased prevalence of frontal cortex-associated cognitive deficits in PLWHA in the era of widespread ART and lead to the prediction that restoration of brain growth factor signaling may be beneficial for cognitive deficits in PLWHA who drink alcohol.

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TRIAL OF ZINC SUPPLEMENTATION TO IMPROVE MARKERS OF MORTALITY AND HIV DISEASE PROGRESSION IN HIV-POSITIVE DRINKERS IN RUSSIA

E. Blokhina[1], M.S. Freiberg[2,3], D.M. Cheng[3], N. Gnatienko[3], D. Lioznov[1], S.M. Coleman[3], M.F. Doyle[4], T. Yaroslavtseva[1], E. Krupitsky[1], J.H. Samet[3]
[1]Pavlov First State Medical University, Russia, [2]Vanderbilt University Medical Center, USA, [3]Boston University, USA and [4]University of Vermont, USA

We conducted a double-blinded randomized placebo-controlled trial of zinc supplementation among HIV-positive, ART- naïve heavy drinkers recruited 2013–2015 in St. Petersburg, Russia. We randomly assigned 254 participants to receive zinc (15 mg men; 12 mg women) or matching placebo, daily for 18 months. VACS index score (predictor of total mortality) increased between baseline and 18 months in both arms, the increase was smaller in the zinc (0.49 point) than in the placebo group (5.5 point); adjusted mean difference in change between groups was −4.68 points (95% confidence interval [CI] −9.62, 0.25; $p = 0.06$). Mean CD4 cell counts decreased between baseline and 18 months in both zinc (−128.8) and placebo (−176.2) groups; adjusted mean difference in change between groups was 41.8 (95% CI −20.3, 103.8; $p = 0.19$). At 18 months there was no significant difference in mean log-transformed Reynolds risk score ($p = 0.85$). The zinc intervention group had lower levels of biomarkers of inflammation and microbial translocation (IL-6, D-dimer, sCD14) at 18 months; these results were not statistically significant ($p = 0.30$, $p = 0.14$, $p = 0.56$, respectively). Additional analyses examining factors such as the role of ART use, the short-term impact of zinc, and impact among those with zinc deficiency are needed to further understand these findings.

WEDNESDAY, SEPTEMBER 12 9:55 AM–11:25 AM

SYMPOSIUM

TRANSLATIONAL RESEARCH ON THE NEURODEVELOPMENTAL EFFECTS OF PRENATAL ALCOHOL EXPOSURE AND TREATMENT STRATEGIES FOR FETAL ALCOHOL SPECTRUM DISORDERS

ORGANIZER/CHAIR: JEFFREY R. WOZNIAK CHAIR: JENNIFER D. THOMAS

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EVALUATING THE EFFECTIVENESS OF MINOCYCLINE TREATMENT FOLLOWING PRENATAL ALCOHOL EXPOSURE: IMPACTS ON BEHAVIOUR AND IMMUNE FUNCTION

T.S. Bodnar, J. Weinberg
The University of British Columbia, Canada

Prenatal alcohol exposure (PAE) has an impact on immune function. Studies in animal models have shown that following PAE, cytokine levels are increased in the brain during the early postnatal period, a critical window for brain development. As a result, it is suspected that some of the long-term effects of PAE may be due to early-life disturbances in the neuroimmune system.

We hypothesized that administration of an anti-inflammatory would have beneficial impacts on the developing neuroimmune system and result in normalization of adult outcomes in PAE animals. To test this hypothesis, following PAE, offspring were administered minocycline and tested in the Barnes Maze (spatial learning/memory test). In addition, the response to immune challenge (lipopolysaccharide; LPS) was examined. Results indicate that PAE animals show deficits in performance in the Barnes Maze and show a heightened cytokine response to LPS, Importantly, minocycline administration appears to normalize both performance in the Barnes Maze and the cytokine response to challenge.

Taken together, as altered immune function/neuroimmune signaling may underlie some of the effects of PAE, findings from this study may have implications for understanding long-lasting deficits associated with FASD and support investment into immune-based intervention strategies.

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THYROID FUNCTION IN PREGNANT WOMEN WITH MODERATE TO SEVERE ALCOHOL CONSUMPTION IS RELATED TO INFANT DEVELOPMENTAL OUTCOMES

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Fetal alcohol spectrum disorders have estimated global prevalence of 2–5% of births. Preclinical studies demonstrate that alcohol consumption during pregnancy interferes with thyroid hormone availability and function, negatively impacting exposed offspring.
Methods: This pilot study was embedded in the Drakenstein Child Health Study, a birth cohort study investigating early biological and psychosocial determinants of child health in South Africa. 19 mothers and their children with no alcohol exposure and 21 with moderate-severe prenatal alcohol exposure (PAE) were assessed. Maternal exposure history and blood samples collected in mid-pregnancy. Children assessed for growth and Bayley III Scales of Infant and Toddler Development (BSID III) at 6 and 24 months old.
Results: In abstinent pregnant women, free thyroxin (FT4) was significantly correlated with scores on cognitive measures at 6 and 24 months and with gross-motor skills at 24 months, but not for those with PAE. In PAE, maternal FT3 significantly correlated with scores on children's socio-emotional development at 24 months.
Discussion: Thyroid function in PAE is not sufficiently disrupted to lead to alterations in peripheral FT4 and FT3 levels. However, the contrast in findings between PAE and abstinent dyads suggests that such disruption is present, and may contribute to adverse neurodevelopment.

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CHOLINE ALTERS HIPPOCAMPAL DEVELOPMENT: IMPLICATIONS FOR THE TREATMENT OF FETAL ALCOHOL SPECTRUM DISORDERS

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Prenatal alcohol exposure can lead to a variety of behavioral and cognitive problems. Importantly, supplementation with the essential nutrient choline can reduce the severity of deficits on hippocampal-dependent behaviors and alter hippocampal structure and function, even when administered after alcohol exposure has ceased. Recently, we found that choline mitigates ethanol-related increases in ceramide, suggesting that choline may protect against neuroinflammation. The present study examined whether choline modifies immune function in the hippocampus of subjects exposed to alcohol during early development. Sprague-Dawley rats received 5.25 g/kg/day alcohol or sham intubations from postnatal days (PD) 4–9, a developmental period equivalent to the human third trimester. Subjects received 100 mg/kg/day choline chloride or saline from PD 10–30. On PD 35, hippocampal cytokine levels were measured. Choline reduced cytokines IL-4, IL-5, and IL-10 in both alcohol-exposed and control subjects. Although alcohol did not alter baseline cytokine levels, further studies will determine if choline supplementation protects against alcohol-related increases in cytokines during immune challenges. These data suggest that choline may protect against alcohol-related damage, in part, by altering neuroimmune function, findings that have important implications as choline is explored as a treatment for fetal alcohol spectrum disorders. Supported by AA012446 (JDT); AA022460 and AA007789 (JW).

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CHOLINE AS A NEURODEVELOPMENTAL INTERVENTION FOR CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS

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University of Minnesota, USA

In pre-clinical models, choline supplementation has been shown to attenuate the neurodevelopmental, cognitive, and behavioral effects of prenatal alcohol exposure. Possible mechanisms of action include epigenetic effects, acetylcholine enhancement, and effects on phospholipids and neuronal cell membranes. Over the past 6 years, we have been conducting a series of double-blind, randomized controlled trials of choline in 2–5 year old children with FASD using neurocognitive outcome measures. Our initial pilot work established the relative safety and tolerability of choline supplementation. There were no serious adverse events and compliance was high (participants received a dose on 88% of the days in the 9-month study). A follow-up study (n = 60) examined global cognitive functioning and sequential memory after 9 months of choline supplementation or placebo. Results showed a significant improvement in sequential memory, but more so for 2–3 year olds compared to 4–5 year olds. We will present these results in detail and will present preliminary analyses from the follow-up data for children who were seen again at 2–4 years post-termination (ages 4–9 years) for cognitive evaluation. Results suggest sustained benefits from choline compared to placebo: greater improvement was seen on working memory and non-verbal processing ability on the Stanford-Binet.

WEDNESDAY, SEPTEMBER 12 2:55 PM–4:25 PM

SYMPOSIUM

ALCOHOL-INDUCED ORGAN DAMAGES

ORGANIZER/CHAIR: TOSHIKAZU SAITO CHAIR: SEBASTIAN MUELLER

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DYSFUNCTION OF AUTOPHAGY IS INVOLVED IN THE PROGRESSION OF ALCOHOLIC AND NON-ALCOHOLIC FATTY LIVER DISEASES

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Autophagy, one of protein degradation system, contributes to maintain cellular homeostasis and cell defense. Loss of autophagy in mice induces inclusion formation composed of keratins, ubiquitin, and p62 in hepatocytes. Mallory-Denk bodies represent hepatic inclusions were observed in diverse chronic liver diseases such as alcoholic and non-alcoholic steatohepatitis. Recent evidences indicated that accumulation of autophagic substrate p62 accelerates development and progression of liver tumors. Here, we disclose the data that hepatic steatosis impairs autophagic function in both hepatocytes and Kupffer cells. Hepatic steatosis blunts autophagic proteolysis via impairment of autophagic acidification and cathepsin expression in hepatocytes. Thus, accumulation of autophagic vesicles was observed in hepatocytes from NAFLD model. On the other hand, autophagic induction was suppressed in Kupffer cells from NAFLD model. TNFα production by Kupffer cells after LPS treatment was upregulated by suppression of autophagy. These results indicated that suppression of autophagy by hepatic steatosis sensitizes Kupffer cells to endotoxin. Furthermore, an increase in M1 macrophage which is inflammatory macrophage phenotype was linked to inclusion formation in hepatocytes from NAFLD patients. In conclusion, impairment of autophagic function is implicated in the pathogenesis of non-alcoholic fatty liver disease.

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ALCOHOL-RELATED IRON OVERLOAD: ROLE OF NOX4 IN HEPATIC IRON SIGNALING
I. Silva, V. Rausch, T. Peccerella, G. Millonig, H.-K. Seitz, S. Mueller
Center for Alcohol Research, University of Heidelberg and Salem Medical Center, Heidelberg, Germany

The exact regulation of the liver-secreted peptide hepcidin, the key regulator of systemic iron homeostasis, is still poorly understood. It is potently induced by iron, inflammation, cytokines or H_2O_2 but conflicting results have been reported on hypoxia. In this study, we first show that pronounced (1%) and mild (5%) hypoxia strongly induces hepcidin in human Huh7 hepatoma and primary liver cells at the transcriptional level via STAT3 using hypoxia chamber and enzymatic hypoxia by the GOX/CAT system. siRNA silencing of JAK1, STAT3 and NOX4 diminished the hypoxia-mediated effect while a role of HIF1α could be clearly ruled out by the response to hypoxia-mimetics and competition experiments with a plasmid harboring the oxygen-dependent degradation domain of HIF1α. Specifically, hypoxia drastically enhances the H_2O_2-mediated induction of hepcidin strongly pointing towards an oxidase as upstream control of hepcidin. We finally provide evidences for an efficient regulation of hepcidin expression by NOX4 in hepatocytes. In summary, our data demonstrate that hypoxia strongly potentiates the peroxide-mediated induction of hepcidin via STAT3 signaling pathway. Moreover, oxidases such as NOX4 or UOX can induce hepcidin.

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MASKED HEMOLYSIS AS IMPORTANT FACTOR OF IRON OVERLOAD IN ALD
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Center for Alcohol Research, University Hospital Heidelberg and Salem Medical Center, Germany

Background: 50% of ALD patients develop hepatic iron overload (HIO) and anemia, however, the underlying mechanisms including hepcidin response are poorly understood. Herein, we introduce hemolysis as novel factor in disrupting hepcidin regulation and eventually causing iron overload.
Method: Hepcidin, molecular and laboratory iron markers were studied in ALD patients (n = 831). The effect of hemolysis was further studied in C57BL/6 mice using two different phenylhydrazine (PHZ) treatment regimens and an erythrophagocytosis model.
Results: Indirect evidence for hemolysis (anemia, ferritin, LDH, MCV, CD163) as cause for HIO was found in 16.4% of heavy drinkers. Despite higher ferritin levels as compared to controls, hepcidin was not adequately upregulated in hemolytic patients suggesting a suppressive effect. Using a murine model of severe PHZ-induced hemolysis (anemia, transaminases, LDH) we confirmed suppressed hepcidin levels by 50%, whereas mild hemolysis increased hepcidin. The same concentration-dependent hepcidin response could be detected in an erythrophagocytosis model using primary isolated as well as THP-1 macrophages. At physiological low levels of oxidized erythrocytes hepcidin was induced while it was strongly suppressed at higher pathological levels.
Conclusion: Our data suggest that suppression of hepcidin by masked hemolysis seems to be an important novel factor contributing to HIO in ALD patients.

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ALCOHOLIC LIVER INJURY: CLINICAL ASPECTS IN RELATION TO PATHOGENESIS AND HEPATOCARCINOGENESIS
M. Taniai
Department of Internal Medicine and Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan

Recent studies revealed the pathophysiological influence of microbiome to many diseases including non-alcoholic fatty liver diseases (NAFLD) and alcoholic liver disease (ALD) by molecularbiological tools using 16S ribosomal RNA (rRNA) gene such as terminal restriction fragment length polymorphism (TRFLP) and next generation sequencer (NGS). On other hand, the incidence of hepatocellular carcinoma (HCC) associated with NAFLD and ALD has gradually been increasing. The aim of this talk is to clarify and summarize the knowledge about pathophysiological aspects of microbiome and characteristic features of HCC in patients with ALD. We investigated samples from patients clinicopathologically diagnosed as ALD and healthy controls matched with age and sex. Five mg of feces were collected for analysis. TRFLP and analysis by NGS were employed. We observed differences were abundant at phylum, family and genus levels between ALD patients and control subjects, and the microbial variability in ALD was significantly decreased and very simplified, and in all cases who stopped drinking, dysbiosis dramatically improved. Dysbiosis was also associated with the severity of ALD. Next, we investigated clinical profiles of HCC patients with ALD and/or NAFLD. ALD-HCC patients were significantly younger, with lower rate of complicated obesity or cirrhosis, and higher rate of males and complicated non-hepatic cancer.

WEDNESDAY, SEPTEMBER 12 4:30 PM–6:00 PM

SYMPOSIUM

ALCOHOL USE DISORDERS AND COMORBID CONDITIONS

ORGANIZER/CHAIR: ISMENE L. PETRAKIS

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ALCOHOL USE DISORDER AND CO-MORBID SMOKING: EARLY PREDICTORS OF END OF TREATMENT SMOKING AND DRINKING IN A TRIAL OF VARENICLINE TARTRATE
S.S. O'Malley[1], L. Fucito[1], K. Bold[1], S. Muvvala[1], A. Zweben[2], R. Gueorguieva[1]
[1]Yale School of Medicine, USA and [2]Columbia School of Social Work, USA

Patients with alcohol use disorder have high rates of cigarette smoking that predict poorer treatment outcome. To address this important comorbidity, we completed a clinical trial of varenicline tartrate, an approved treatment for smoking cessation, and found that varenicline in combination with medication management led to reduced heavy drinking in men and increased the percentage of patients who quit smoking compared to placebo. In a secondary analysis of this data, we examined: (1) early responses measured within the first 4 weeks of treatment (i.e., phase of counselling focused on medication management prior to Week 5 alcohol goal setting) and (2) whether these responses predicted improvements in smoking and drinking outcomes at the end of treatment. As expected, early improvements in drinking and smoking predicted their respective outcomes. To understand whether varenicline had direct effects on heavy drinking or indirect effects via reductions in smoking, mediational analyses were conducted. Taken together, these secondary analyses suggest that early responses could be used to guide clinical decision-making for patients with alcohol use disorder and co-morbid cigarette smoking.

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SUPPORTIVE TEXT MESSAGES FOR PATIENTS WITH ALCOHOL USE DISORDER AND COMORBID DEPRESSION. SIX MONTH RANDOMISED CONTROLLED TRIAL WITH AFTERCARE

C.K. Farren, H. O'Reilly, A. Hagerty, V. Agyapong, D. Mcloughlin
Department of Psychiatry, Trinity College Dublin, Ireland

Alcohol use disorder (AUD) and mood disorders commonly co-occur, with a range of negative outcomes due to the comorbidity. Mobile phone technology has the potential to provide personalised support for such patients and potentially improve outcomes in this cohort. We recruited 174 patients with AUD and depression and randomised 96 to an intervention of twice daily supportive text messages ($N = 47$) post in-patient rehabilitation and treatment versus treatment as usual (TAU) ($N = 49$) for a 6-month period with a further 6-month follow-up. Retention was 90% at 3 months, 75% at 6 months, 60% at 9 months, and 65% at 12 months. Drinking was reduced in the intervention group at 3 and 6 months to a non-significant extent relative to the TAU group. Depression was significantly reduced at 3 months in the intervention group relative to TAU, and this difference was not sustained at 6 months. There were no difference in drinking and mood measures at the 9 and 12 month follow-up points. These findings suggest some benefits in treatment outcomes during the course of the treatment trial in this difficult to treat group.

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PHARMACOLOGIC TREATMENT OF AUD AND COMORBID POSTTRAUMATIC STRESS DISORDER (PTSD): IMPACT OF PTSD ON TREATMENT OUTCOMES

I.L. Petrakis
Department of Psychiatry, Yale University School of Medicine, USA

Alcohol use disorder commonly occurs with co-morbid posttraumatic stress disorder (PTSD). The presence of comorbid condition complicates the outcome of the other disorder and those with comorbidity have worse PTSD outcomes and higher rates of relapse. Our group has conducted several pharmacotherapy studies to identify effective medication treatment of patients with AUD and PTSD. Most recently we completed a 12 week, outpatient, randomized, placebo controlled clinical trial of the noradrenergic medication prazosin as treatment of PTSD and alcohol use outcomes for patients with comorbid condition. Overall study results suggested the prazosin-treated group had no better outcomes than the placebo-treated group in either alcohol use outcomes or PTSD symptoms. In a secondary analysis of this data, we examined whether drinking influenced PTSD symptoms. Unexpectedly, abstinence was associated with worse symptoms of PTSD. While causality cannot be determined, further analyses will try to understand the relationship between drinking and PTSD symptoms. The implications of this will be discussed.

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IMPACT OF PSYCHIATRIC COMORBIDITY ON TREATMENT OUTCOME FOR INPATIENTS WITH ALCOHOL DEPENDENCE

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[1]National Hospital Organization Kurihama Medical and Addiction Center, Japan and [2]Division of Psychiatry, Tohoku Medical and Pharmaceutical University, Japan

Individuals with alcohol dependence (AD) often have comorbid psychiatric disorders, which may affect their treatment outcome. We evaluated psychiatric comorbidities among inpatients with AD, and assessed whether the comorbidities influence their treatment outcomes after discharge. 637 individuals participated in the study, and 313 completed one year follow up; 56 had depression (17.9%), 66 had anxiety disorder (21.1%) as assessed by MINI, and 86 met the criteria of severe ADHD (28.7%), 23 met mild ADHD (7.7%) assessed by Adult ADHD Self-Report Scale. Abstinence rate estimated by Kaplan-Meier method among all participants was 30.9% at 12 months after discharge. Individuals with these comorbidities showed a significantly lower abstinence rate than those without them (Log-rank test, with depression; $p = 0.020$, anxiety disorder: $p = 0.021$, ADHD scale; $p = 0.014$). Moreover, we investigated the effectiveness of acamprosate or disulfiram among inpatients with each comorbidity. No significant differences on the abstinence rate during follow up were observed. The clinical implications of these findings will be discussed.

WEDNESDAY, SEPTEMBER 12 9:55 AM–11:25 AM
SYMPOSIUM
THE CURRENT SITUATION AND TREATMENT SYSTEMS FOR ALCOHOLICS IN PACIFIC COUNTRIES
ORGANIZER/CHAIR : TOMOHIRO SHIRASAKA CHAIR : HISATSUGU MIYATA

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THE CURRENT SITUATION AND TREATMENT SYSTEMS FOR ALCOHOLISM IN KOREA

E. Na, W.J. Jeong
Addiction Treatment Center, Department of Psychiatry, Maeumsarang Hospital, Korea

The consumption of alcohol has an important role within the social structure and culture of Korea. Such customs resulted in high alcohol consumption rate and risky patterns of drinking in adolescents as well as adults. On the bright side, the total prevalence rate of alcohol use disorder (AUD) and the proportion of alcohol-related crime, which are directly related to the functional impairment due to alcohol use, show a declining trend in recent years. However, it is important to note that the rate of diagnosed AUD increases steadily in the certain demographic groups including women, adolescents, and elderly people. Moreover, the harmful alcohol use creates significant social costs, and the use of mental health services remains low despite its slight uptick. Regarding the treatment services use patterns for people with hazardous drinking habits and AUD in Korea, the key features are larger portion of inpatient treatment than outpatient treatment; greater re-admission rate, lesser outpatient visit rate after discharge, and lower rate of registration for community mental health services when compared to patients with severe mental illness. This presentation will provide updated information on the current situation and treatment systems for Alcoholics in Korea using data sources referenced by national databases.

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SURVEY OF THE RELATIONSHIP BETWEEN ALCOHOL-RELATED COGNITIVE DYSFUNCTION AND CEREBRAL BLOOD FLOW

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Background: In Japan, the nationwide survey estimated that the number of individuals with alcohol dependence syndrome was 1.09 million. One notable finding is the steep increase of alcohol consumption among elder person. Alcohol-related brain dysfunction has become a serious social problem in Japan. It is a form of dementia caused by long-term, excessive consumption of alcoholic beverages, resulting in neurological damage and impaired cognitive function. In this presentation, focus on the Alcoholics, we conducted a survey of alcohol-related cognitive dysfunction and relating cerebral blood flow (CBF) by the RI scintigraphy.
Method: Subjects were 21 alcoholics and 34 healthy controls. To evaluate regional patterns of CBF, *Z*-score analysis was carried. To evaluate regional patterns of CBF alterations, two-sample *t*-test values were calculated on a pixel-by-pixel basis between Alcoholics and to normal control. To evaluate their correlation between the CBF and Frontal Assessment Battery (FAB) was examined using Pearson's correlation coefficient.
Results: Compare with the normal control, we found that alcoholics have a significant reduction of the blood flow at medial frontal lobe and we found a significant correlation between the FAB scale and the CBF decreasing ($R^2 = 0.4685$, $p < 0.05$) suggesting that frontal dysfunction and frontal blood flow are associated with each other.

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DETECTION OF ALCOHOL USE DISORDER IN A GENERAL HOSPITAL

W. Ratta-Apha[1], N. Sitdhiraksa[1], P. Pariwatcharakul[1], N. Saisavoey[1], W. Wansrisuthon[2], L. Thongchot[3], N. Sanguanpanich[3]
[1]Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, [2]Medical Record Division, Siriraj Hospital, Thailand and [3]Department of Health Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

Alcohol use disorder is implicated in various diseases and associated with trauma and injuries. Previous evidence showed that alcohol-related problems are under-evaluated and undiagnosed. Here we collected the evidence of the under-detected of alcohol-related problems, the accuracy of diagnosis by physicians, and the accuracy of coding by medical coders for alcohol-related problems in a general hospital. Furthermore, we interviewed the patients about reporting to physicians regarded their drinking experience and reasons why they did not report earlier their drinking history to their physicians. The results of the present study support the need to enhance physician awareness regarding alcohol-related problems in this setting.

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THE USE OF GABAERGIC SUBSTANCES IN BUPRENORPHINE MAINTENANCE TREATMENT

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Background: GABAergic substances, particularly benzodiazepines and alcohol, are commonly used among patients receiving opioid agonist therapies (OAT). Risks of combined use benzodiazepines or alcohol and OAT include overdose mortality, addiction to benzodiazepines or alcohol, and decreased OAT treatment retention. In this study, we focused on the use of benzodiazepines in buprenorphine maintenance treatment.
Methods: We conducted a retrospective cohort study utilizing a cohort of individuals receiving at least one buprenorphine prescription between 2012 and 2015. Benzodiazepine prescription was the main independent variable. Outcomes included non-fatal and fatal overdose, all-cause mortality, and buprenorphine treatment discontinuation.
Results: Of the 53,365 individuals who received buprenorphine treatment, 22% received at least one concurrent benzodiazepine prescription. Concurrent benzodiazepine prescription was associated with an increased risk of non-fatal overdose (adjusted hazard ratio [AHR] = 1.45; 95%CI 1.11–1.88) and fatal overdose (AHR = 1.90; 95%CI 1.11–3.23), a decreased risk of buprenorphine discontinuation (AHR = 0.85; 95%CI 0.83–0.88), and was not associated with all-cause mortality (AHR = 1.13; 95%CI 0.76–1.68).
Conclusions: Receipt of benzodiazepines was associated with increased risk of overdose but also decreased risk of buprenorphine discontinuation in individuals receiving buprenorphine. Further evaluation of the potential risks and benefits of treatment with benzodiazepines is needed in this population.

WEDNESDAY, SEPTEMBER 12 4:30 PM–6:00 PM

SYMPOSIUM

EMERGING ISSUES ON ADDICTION IN INDONESIA

ORGANIZER/CHAIR: KRISTIANA SISTE KURNIASANTI

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PRESCRIPTION DRUGS ABUSE IN INDONESIA: NEW PHENOMENON, HOW TO HANDLE?

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Psychiatry Department, University of Indonesia/Cipto Mangunkusumo Hospital, Indonesia

Background: The number of drug use in Indonesia is increasing every year. The prevalence of drug abuse in 2016 is more than six million people. The new problem that arises today in Indonesia is prescription drugs misuse which have become the drug of choice as well. Prescription drug misuse as benzodiazepine classes, anticholinergic, analgetics has a serious impact on medical problems, therefore it needs to be handled well.
Purpose and Goal: To explain the risk and serious impact of prescription drugs misuse and both physically, psychologically, socially and comorbidities impairment. Handling prescription drugs also very challenging, hence it needs to be handled professionally in every aspect, community and cross department.
Specific Points to be Discussed: List of prescription drugs in Indonesia, the serious impact on medical problems: lead drugs addiction, overdose deaths and withdrawal effect, cost implications which may include dealing with adverse outcomes such as dependence, widespread social problems of drug abuse. Comorbidities, mental and behavior disorder problems as well. Programmes to handle, like preventive and promotive program from national treatment programmes, clear guideline for prescribing drugs, clear government regulations to band the drug-free sale, obligatory reporting about addict, and long-term hospitalization for rehabilitation program.

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SMARTPHONE ADDICTION AMONG YOUNG PEOPLE: IS IT REAL IN INDONESIA?
E. Hanafi, K.S. Kurniasanti, I. Kusumadewi, T. Wiguna
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Smartphones are a type of mobile phone that provides a variety of services through applications. The use of smartphones is feared will cause a serious impact, as an addiction, because of portability and the price is more affordable than other technologies. Up to date, many smartphone users reported that withdrawal symptoms in the absence of smartphone. If it is left untreated, this could disrupt work and school functions. Medical students are one of the most vulnerable populations to have this problem. This session aims to clarify how relevant is smartphone addiction in young people in Indonesia and discuss about its related factors.
A cross sectional research was conducted with medical students of several universities in Indonesia as its samples. Smartphone Addiction Scale, Indonesian Version, was used to measure the risk of smartphone addiction among medical students. Some demographical factors were also analyzed to find out their relations with the high risk group. The results would be compared to similar researches in other countries.

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NATIONAL TREATMENT PROGRAM TO MANAGE EMERGING ISSUES ON ADDICTION
I. Firmansyah
National Narcotic Board, Indonesia

The results of drug research in the 17–18 year age group of students in Sweden and Italy, showed the number of drug abusers about 15% and 43%. Cannabis, glue, dextromethorphan, painkillers, benzodiazepine and methamphetamine are a type of drug that most abused children and adolescents in Indonesia. Approximately 2.6% of junior high school students have an equivalent of using narcotics, and 4.7% of senior high school students have ever used narcotics.
Prior to rehabilitation the assessment is undertaken to obtain a more comprehensive and comprehensive overview of clinical and deeper problems as a child begins, undergoes, and completes the program. Assessment is done by using Teen Addiction Severity Index.
The main methods used were Psychotherapy as well as group therapy performed to increase motivation to follow the program through Motivational Interviewing and cognitive changes as well as deviant behavior through Cognitive Behavior Therapy, as well as Therapeutic Community with modified based on needs plus intervention biopsychosocial, occupational therapy, religious sessions.
PANSS-EC is used to assess the condition of Agitation. In child-specific rehabilitation programs, there are important things that must be available that is education according to age and ability of children. The child is tested for IQ test.

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ADDICTION MODULE FOR UNDERGRADUATE STUDENTS SCHOOL OF MEDICINE ATMA JAYA CATHOLIC UNIVERSITY OF INDONESIA
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Background: Addiction is a chronic relapsing condition involving brain circuits mediating reward, motivation, and memory. Limited exposure to addiction medicine topics during medical education is considered as a cause of medical doctors' negative attitude towards patients with addiction. It is imperative for medical graduates to possess good understanding of addiction medicine topic in order to develop a positive attitude towards the patients. Acknowledging this call, the School of Medicine Atma Jaya Catholic University of Indonesia developed a competency-based Addiction Medicine training as an elective block in the undergraduate education.
Objective: The purpose of this study was to evaluate the curriculum content of addiction medicine block to determine necessary changes and revision.
Method: This study used the Delphi method, to develop a consensus list of topics that need to be covered in addiction medicine block. The list of topics was the reference to evaluate the curriculum content of the current addiction medicine block. Participants were the addiction medicine scholars who contribute as a lecturer in addiction medicine.
Result: List of topics need to be covered are the science and clinical aspects of addiction, the 'new trend' in addictions, clinical skills training.
Keywords: addiction, addiction medicine block, addiction module, undergraduate education.

WEDNESDAY, SEPTEMBER 12 2:55 PM–4:25 PM

SYMPOSIUM

YOUNG INVESTIGATOR'S SYMPOSIUM IN ASIA 2

ORGANIZER: SUNG-GON KIM CHAIR: WOO-YOUNG JUNG

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THE CHARACTERISTICS OF ALCOHOLICS VISITING A COMMUNITY COUNSELING CENTER
E.J. Min[1], S.G. Kim[1,2]
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Objectives: The therapeutic approach for a patient with alcohol dependence should match the patient's characteristics, as found before treatment initiation. However, most services provided for these patient by hospitals and community counseling centers do not usually differ. We conducted this study to evaluate drinking history and cognitive function of patients within each institution, in order to design an effective treatment approach.
Methods: Alcohol-dependent patients visiting a community counseling center (CCC) and a university hospital (UH) were included as study subjects and were investigated for demographics and drinking history. In addition, we performed neuropsychological test.
Results: Significant differences were found in terms of duration of drinking, blackouts resulting from drinking, and blackout duration between the patients visiting a CCC and a UH (drinking duration, 22.74 ± 13.47 vs. 33.14 ± 13.75, $p < 0.05$, and blackout duration, 9.79 ± 9.41 vs. 18.43 ± 13.21, $p < 0.05$). Patients visiting a CCC started drinking at an earlier age than the patients visiting a UH (11% vs. 32%, $p < 0.10$). The patients visiting a CCC center had an executive function disability for IQ ($\chi = 2.95$, $p = 0.08$).
Conclusion: These findings suggest that different therapeutic services should be offered based on the patient's characteristics.

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A STUDY ON SELECTION FACTORS OF HOSPITALS BEFORE HOSPITALIZATION OF KOREAN ALCOHOL-DEPENDENT PATIENTS

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To increase the likelihood of hospitalization for alcohol-dependent patients who need to be, but are not, hospitalized, it is critical to know the thoughts (needs) of such patients. Therefore, if they are admitted to the hospital, we investigate the factors they consider in choosing a hospital.
We carried out a self-administered questionnaire survey of alcohol-dependent patients that attended the Community Addition Management Center in Busan (a total of four places). Respondents selected three factors from 11 hospitalization decision factors. A total of 82 respondents were interviewed, and we analyzed the results from 64 patients, excluding 18 who did not correctly choose hospital decision factors.
The top 4 factors selected as the determinants of hospital admission were 'Expertise in treating addiction (19.8%), Hospital cost (15.6%), Variety of treatment programs (10.9%), Hospital facilities (10.9%)'.
Since a relatively wide variety of factors have been investigated, hospitals conducting inpatient treatment for alcohol-dependent patients need to be aware of and accept inpatient hospital decision factors selected by the patients based on these results. If there are an alcohol-dependent patients in the community, these results can be used to guide hospitals according to their individual characteristics and to increase the possibility of inpatient treatment.

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EFFECTS OF EXPERIENCING THE TEMPLE STAY PROGRAM ON DRINKING BEHAVIOR IN KOREAN ALCOHOL-DEPENDENT PATIENTS

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Introduction: This study investigated the effect of participation in the program on alcohol abuse among participants who experienced the Temple Stay program provided by the Community Addiction Management Center.
Methods: We conducted a follow-up survey of 42 alcohol-dependent patients who had attended more than one Temple Stay program at Busan Poisoning Management Integrated Support Center 2013–2016. Effects of drinking frequency, alcohol consumption, drinking and alcohol use, spirituality, happiness, and satisfaction with life were investigated by phone, email, letters, and face-to-face.
Results: Subjects of the study included 18 subjects; it excluded those not in contact with family members. Experiencing the Temple Stay program has been revealed to help reduce the number of alcoholic beverages and drinking days in alcohol-dependent patients and to improve life satisfaction, happiness, and spirituality.

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SURVEY FINDINGS ON THE CIRCUMSTANCES AND ATTITUDES OF CHUGGING AMONG JAPANESE YOUNG ADULTS

H. Itoh[1], S. Katuno[2,3], N. Naruse[3,4], S. Namiki[3], N. Nishioka[3,5], S. Matsushita[1,3], K. Kitagaki[3,6]
[1]National Hospital Organization Kurihama Medical and Addiction Center, Japan, [2]Wakayama Medical University, Japan, [3]Japan Society of School Health, Japan, [4]Saitama Psychiatric Medical Center, Japan, [5]Hyogo University of Teacher Education, Japan and [6]Tokyo University of Pharmacy and Life Sciences, Japan

Objective: We investigated the circumstances and attitudes of young adults concerning Chugging (drinking an alcoholic beverage without pausing to breathe) in order to create effective prevention strategies.
Method: A data from 1500 individuals aged between 20 and 24 was collected through an online survey in December 2016. For each age group, 150 men and 150 women were recruited.
Results: The rate of women with drinking experiences was higher than men (men: 81.7%, women: 84.9%), but more men reported experiences of Chugging (men: 29.3%, women: 24.1%). Chugging was encouraged more by friends of similar ages than by older individuals. Approximately 30–40% reported feeling Chugging is unenjoyable. Participants with experience of Chugging were more likely to feel confident about their ability to judge whether to call an ambulance in emergency situations. However, they were also more likely to engage in risky drinking that involves blackout.
Discussion: Although 30–40% of young adults do not enjoy Chugging, it is frequently encouraged by their friends. People with experience of Chugging think they know how to respond in emergencies, but they also tend to engage in risky drinking. Accordingly, dissemination of information about the risks of Chugging from high school ages is essential in prevention of the risky drinking behaviors.

WEDNESDAY, SEPTEMBER 12 9:55 AM–11:25 AM

SYMPOSIUM

HOW SHOULD WE PROMOTE A STRATEGY FOR HEALTHY DRINKING?

ORGANIZER/CHAIR: KOSHI NAKAMURA CHAIR: KOHJI TAKADA

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ALCOHOL USE IN ASIA AND PUBLIC HEALTH APPROACHES FOR REDUCING ALCOHOL-RELATED HARM IN JAPAN

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The harmful use of alcohol can bring negative health and social consequences not only to drinkers themselves, but also to their family members and the others. At the same time, alcohol-related harms are greater in people who exhibit societal vulnerability factors. Therefore, public health approach is important for preventing and reducing the harmful use of alcohol.
Alcohol consumption in Asia has not been as high as European countries; however, per capita alcohol consumption is expected to grow in Asian countries by 2025. The alcohol consumption among adolescent and women also should be paid attention in Asia.
Japan government, in respond to the Global Strategy to Reduce the Harmful Use of Alcohol adopted by World Health Organization in 2010, enacted the Basic Act on Measures against Alcohol-related Harm in 2014 and launched the Basic Plan for Promotion of Measures against Alcohol-related Harm in 2016. The Basic Plan especially focuses on two issues. One is to spread correct knowledge particularly for vulnerable people such as minors, expectant and nursing mothers. The other key is to develop comprehensive care and support system from early intervention to specialized medical service for all who suffers from Alcohol-related Harm and his/her family members.

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THE USE OF ALCOHOL MIXED WITH CAFFEINATED BEVERAGES IN TAIWANESE MANUAL WORKERS

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Taiwanese manual workers have used caffeinated alcoholic beverages (CAB) at work for more than 40 years. The drinking context was different from CAB drinking among young adults in Europe, Australia, and America. Around 20% of manual labors used CAB, mostly at work for the purpose of energy boosting. We reviewed documents and found that CAB was inadequately and only managed by Food and Drug Administration in Taiwan instead of the Ministry of Labor, and regulations concerning alcohol drinking at work were scarce and poorly implemented. Survey data from the Institute of Labor, Occupational Safety and Health, Taiwan showed that CAB drinkers were associated with work-related injury, piece-rated pay, low job control, and long working hours. We also conducted an experimental study and found that CAB consumption was associated with acute impairments in motor functions. Through in-depth interviews, we found that outsourcing employment leads to difficult implementation of alcohol control policies in workers and hence CAB consumption was popular. In conclusion, CAB management at workplace is necessary and should take the specific drinking context into considerations.

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SAFETY/HEALTHY DRINKING PROGRAM: HOW DOES IT WORK IN THE THAI CONTEXT?

W. Arunothong
Department of Psychiatry, Lampang Regional Hospital, Lampang, Thailand

Compared with other Asian countries, Thailand is not a drinking country. Thai people do not routinely drink alcohol with meals or during the daytime over weekends. Generally, they drink when there is a special occasion, ceremony, or festival. A national survey on alcohol use in 2013 revealed that 63% of Thai people were lifetime abstainers. The 12-month prevalence of alcohol use disorder was 5.3% and the lifetime prevalence was 18%.

Although it seems the drinking situation in Thailand is not a concern, consequences of drinking on health, society, and economics are burdens, and require attention. Measures, including a minimum legal drinking age, limiting time to sell alcohol, limiting screen time for alcohol advertising, and raising the alcohol tax have been implemented to discourage underage and new drinkers. For those who drink and cannot quit, the safety/healthy drinking program is promoted. Health volunteers, primary healthcare officers, and healthcare providers at the community hospitals are trained to use this program. The program focuses on education about drinking behaviors, a standard drink, self-monitoring, and risks of drinking.

Regarding the Thai context, the safety/healthy drinking program does not mean to encourage abstainers to drink safety, but it is for regular drinkers who cannot quit.

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ESTABLISHING ALCOHOL CESSATION PROGRAM IN MALAYSIA SETTING: INTEGRATING PSYCHODYNAMIC CONSTRUCTS IN THE MODULE

H. Zakaria
The National University of Malaysia, Malaysia

In Malaysia, alcoholism is a major public issue despite the majority of the citizens are Muslim. It was reported the per capita consumption was relatively high for Asia. Despite the increase of alcohol problems, there is a lack service provision. Most of the interventions are pharmacologically based with individual psychotherapy. Alcoholic Anonymous group is available but it is only limited in big cities. Treatments for people with alcoholism require multimodal approach. The interventions in group setting is preferred. In this presentation, the speaker will introduce the program developed to help people with alcohol problem. The module utilizes the multimodal approach of balancing cognitive restructuring, correcting cognitive distortions, along with uncovering, interpretative and supportive interventions helps them to understand their behavior and gain higher levels of functioning. Psychodynamic factors such as attending to affective regulation, identifying insecure attachment, and creating opportunities for reparative emotional experiences are integrated into the modules. The psychodynamic formulations and constructs in the treatment of addictions would be discussed. The speaker would also highlight the role of integrating and combining psychotherapy modalities such as CBT, supportive, psychodynamic and motivational interviewing in the complex care of persons who engage in the harmful use of alcohol.

WEDNESDAY, SEPTEMBER 12 **2:55 PM–4:25 PM**

SYMPOSIUM

DISASTERS AND ADDICTIVE BEHAVIORS
ORGANIZER/CHAIR: SACHIO MATSUSHITA
CHAIR: KRISTIANA SISTE KURNIASANTI

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CANNABIS ABUSE IN TEEN SURVIVORS WHO LOST SIGNIFICANT FIGURES IN EARTHQUAKE AND TSUNAMI1

S.B. Marwan Iskandar
University of Indonesia, Indonesia

Over decades, the province of Nanggro Aceh has been frequently overwhelmed by protracted conflicts and followed by tsunami tragic disaster, which have caused great casualty and tremendous social impacts, as well as becoming the remarkable world's interest. Such disasters can certainly lead to various kinds of mental health problems including those related to drug abuse. There are some age groups that are susceptible toward the impact of a disaster, one of them are children and adolescents. After the disaster, the loss of significant figures causing discomfort for survivors especially for children and adolescents. This feeling may continue until adulthood. Maybe some are able to cope by developing coping strategies that are adaptive, and some are mal-adaptive which cause to drug abuse. There were five tsunami survivors who came to my private clinic with cannabis abuse problem. All of them are the survivor at the age of adolescents (13–15 years old). They have lost their significant figures such as mother, father, parents, grandmother and adoptive parents. They are advised to get counseling at the recipient institution of mandatory report in Aceh mental hospital in order to get legal protection.

Keywords: Cannabis, Abuse, Survivors, Tsunami, Aceh

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ALCOHOL-RELATED PROBLEMS IN FUKUSHIMA: MULTIDIMENSIONAL EFFECTS CAUSED BY THE NUCLEAR DISASTER

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There are substantial differences between natural and nuclear disasters in terms of the psychosocial impacts associated with many factors such as human or material losses. Although the Great East Japan Earthquake was a major natural disaster, the impact of the subsequent nuclear accident occurring in Fukushima seemed to affect residents' mental health for long time. These effects included not only posttraumatic responses but also chronic psychiatric symptoms such as depression and alcohol abuse, which could also contribute to self-destructive behaviors such as suicide. Fukushima Medical University has been conducting a longitudinal survey named "Mental health and Lifestyle Survey" for 210,000 evacuees since 2012, about 1 year after the disaster. The results in the first several years, in spite of serious data in the first survey year, showed decreasing patterns in many outcomes: general mental health conditions, traumatic responses and so on. However, they recently tended to remain unchanged. Moreover, the prevalence of people at risk of alcohol abuse reached approximately 15–18% in recent years. Such alcohol-related issues and suicidal behaviors among evacuees will be focused in the symposium. In addition, we will refer current mental health care system and interventions provided in Fukushima.

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ALCOHOL USE, MENTAL HEALTH AND PHYSICAL HEALTH STATUS IN BEREAVED FAMILIES OF THE SEWOL FERRY DISASTER IN KOREA

J.-a. Yun
Department of Psychiatry, Eulji University Hospital, Korea

The Sewol ferry accident that occurred in April 2014 was one of the most tragic human-made disasters in Korean history. This study examined the overall mental and physical health consequences related alcohol problem of the bereaved families after the Sewol ferry accident.
Data from a cross-sectional survey were obtained 18, 30 and 42 months after the disaster. Sociodemographic variables and psychiatric symptoms including alcohol use status were ascertained at each time point. General physical health examinations were also conducted every year.
At 42 months after the disaster, more than 50% of bereaved fathers and 16.3% of mothers had problematic alcohol use. Only alcohol use was associated with the erosive gastritis and gastric ulcer and any psychiatric symptoms were not associated with alcohol use.
Especially, bereaved families with high alcohol problem through all 3 years showed less complicated grief and embitterment than those with low alcohol problems.
For bereaved families, alcohol problem influenced to their physical health negatively. While, there was not proportional linear relationship between alcohol drinking and psychiatric symptoms.
Considering the cultural and social context of alcohol drinking seemed to be important for understanding their alcohol problem and it might be directly connected their physical health.

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THE IMPACT OF THE GREAT EAST JAPAN EARTHQUAKE ON ALCOHOL AND HYPNOTIC USE AND GAMBLING BEHAVIORS IN DISASTER-STRICKEN AREAS

S. Matsushita[1], H. Sakuma[1], T. Takimura[1], Y. Osaki[2], S. Higuchi[1]
[1]National Hospital Organization Kurihama Medical and Addiction Center, Japan and [2]Division of Environmental and Preventive Medicine, Tottori University, Japan

Introduction: A huge earthquake and subsequent tsunami struck north eastern Japan in 2011 and caused widespread damage. We investigated drinking and hypnotic use as well as gambling behaviors in disaster-stricken areas (DSA) and performed follow-up study.
Subjects and Methods: The subjects were 3600 people living in Miyagi and Iwate prefectures where the damage caused by the tsunami was most severe and 2000 people living outside the DSA. Drinking and substance use and gambling behaviors were investigated in 2011. Subjects living in Miyagi and Iwate prefectures were followed up in 2014.
Results: Frequencies of heavy alcohol use and prevalence rate of alcohol use disorders did not differ between subjects living in the DSA and those outside the DSA. The prevalence of hypnotic use was higher in women living in the DSA than those living outside the DSA and this trend was the same at follow-up. The percentage of subjects with high South Oaks Gambling Screen scores was higher in men living in the DSA than those living outside the DSA, but this difference disappeared at follow-up.
Conclusion: These results suggest that in the DSA, gambling problems increased temporarily in men while hypnotic use increased in women and was sustained at follow-up.

WEDNESDAY, SEPTEMBER 12 9:55 AM–11:25 AM
SYMPOSIUM
THE E:MED CONSORTIUM USES A SYSTEMS MEDICINE APPROACH TO PREDICT FOR ALCOHOL USE DISORDERS TRAJECTORIES, TREATMENT RESPONSES AND MODE OF ACTION FOR NEW ANTI-CRAVING DRUGS
ORGANIZER/CHAIR: RAINER SPANAGEL CHAIR: HAMID R. NOORI

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DEFINING INDIVIDUAL RISK PROFILES IN ADOLESCENTS THAT ARE PREDICTIVE OF ALCOHOL USE DISORDERS LATER IN LIFE

S. Desrivières
King's College London, UK

Prevention and intervention of alcohol binging in adolescents and treatment of alcoholism are major unmet challenges affecting our health care system and society alike. Defining individual risk profiles in adolescents that are predictive of alcohol use disorders later in life is fundamental to tackling these challenges. Data from the IMAGEN cohort, which is a longitudinal cohort of typically developing adolescents, will be presented that defines the individual risk for alcohol binging, abuse and dependence on the basis of neurobehavioral, genomic and epigenetic phenotypes.

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DEFINING RISK AND RESILIENCE FACTORS FOR THE COURSE OF ALCOHOL USE DISORDERS

K. Charlet
National Institute on Alcohol Abuse and Alcoholism (NIAAA)/National Institutes of Health (NIH), USA

Here we will translate the results of neuroimaging and genetic analyses from our adolescent risk sample (IMAGEN; previous talk) to adult disease trajectories by examining related MRI-paradigms tagging the same functional brain systems in both samples (e.g. reward system, inhibitory control system, emotion processing, working memory).

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PREDICTING DISEASE TRAJECTORIES AND TREATMENT RESPONSE IN RATS WITH BASELINE ACTIVITY AND DRINKING DATA

R. Spanagel, V. Vengeliene
Central Institute for Mental Health, Germany

The theory of critical transitions and especially the ability to predict abrupt changes by early-warning signals is seen as a promising avenue to study disease dynamics. Here, we acquired intense longitudinal data sets of drinking behaviour and locomotor activity in a rat model of alcohol addiction and used a multi-scale computational approach to demonstrate a critical transition from controlled baseline alcohol consumption to excessive alcohol drinking. This state transition is preceded by a critical slowing down scenario (an early-warning signal) during early deprivation. At later deprivations no further state transitions can be observed. However, if new experimental variables are introduced like a choice situation between alcohol and sucrose or aversiveness with quinine further transitions can be seen in subsets of animals which demonstrates clear and predictable trajectories into addictive behavior. We propose that our approach has the potential to make important contributions to the understanding of disease onset in general and can be translated to the clinical situation by the appropriate use of wearable and mobile biomedical sensing technology. In terms of treatment response we further show that prior baseline consumption levels correlate with treatment response to nalmefene which provides an avenue for precision treatment.

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PREDICTING NEUROCHEMICAL RESPONSES AND MECHANISMS OF PUTATIVE ANTI-CRAVING DRUGS

H. Noori
Max Planck Institute for Biological Cybernetics, Germany

Current pharmacological treatment for AUD is inadequate, with often insufficient efficacy and undesirable side-effects. One reason for this is that the multi-scale links between molecular drug action and neurobehavioural drug effects, namely the intermediate network response patterns, are still elusive. Here, we use a big data approach from neurotransmitter response patterns of 259 different compounds to address this question. Data from experiments comprising 110,674 rats are presented in our (Syphad-database www.syphad.org). Chemoinformatics analyses of the neurochemical fingerprints suggest that predicted drug-target interactions reflect brain region related neurochemical fingerprints. In conclusion neurobiological mechanism of new anti-craving drugs are difficult to predict in terms of their chemical similarity with already clinically used drugs such as acamprosate or naltrexone but can be better captured by their molecular drug-target interactions.

THURSDAY, SEPTEMBER 13 9:00 AM–10:30 AM

SYMPOSIUM

VENTRAL HIPPOCAMPUS CIRCUITS AND ALCOHOLISM-RELATED BEHAVIOR

ORGANIZER/CHAIR: JACQUELINE M. BARKER CHAIR: WILLIAM C. GRIFFIN

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THE ROLE OF THE VENTRAL HIPPOCAMPUS IN APPROACH-AVOIDANCE CONFLICT RESOLUTION – RELEVANCE TO ADDICTION

R. Ito, A. Schumacher, D. Nguyen
Department of Psychology, University of Toronto Scarborough, Canada

Addictive behaviors are characterized by the persistence of drug- or alcohol-seeking in spite of the negative consequences of such an action. One way of conceptualizing this maladaptive behavior is to consider it as a manifestation of aberrant approach-avoidance conflict resolution, with the propensity to approach taking precedence over avoidance behavior. Indeed, we have recently shown that approach motivation is enhanced, while avoidance motivation is diminished in rats that had undergone repeated, subchronic exposure to cocaine. The present set of studies provides evidence that the ventral hippocampus plays a key role in the regulation of approach-avoidance conflict decision making in rats. We demonstrate that subfield-specific pharmacological or optogenetic inactivation of the ventral hippocampus leads to differential control over approach-avoidance behaviors when animals are exposed to motivationally bivalent (conflicting) cues. More specifically, transient inactivation of the CA3 led to an increase in approach tendency, while inactivation of the CA1 led to increased avoidance behavior in the face of a motivational conflict, indicating that the ventral hippocampus exerts bidirectional control over approach-avoidance resolution. These results have implications for the neural substrates underlying addictive behaviors in which approach tendencies predominate, and implicate the ventral hippocampus as a potential target of therapeutic intervention.

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THE ROLE OF THE VENTRAL HIPPOCAMPAL TO ACCUMBENS PATHWAY ON ETHANOL DRINKING IN ETHANOL DEPENDENT AND NON-DEPENDENT MICE

W.C. Griffin[1], A.K. Olsen[1], H.L. Haun[1,2], H.C. Becker[1,2,3]
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Previous work demonstrates that ethanol dependence disrupts glutamatergic tone in the nucleus accumbens (NAc) and one glutamate source in the NAc is the dense innervation by the ventral subiculum (vSub) of the hippocampus. We evaluated the role of the vSub-NAc pathway on ethanol drinking using male C57BL/6J mice that underwent surgery to infuse excitatory or inhibitory DREADD-expressing viruses in the vSub and implant guides above the NAc. Next, mice were trained to drink ethanol in a limited access paradigm and then experienced alternating weekly cycles of chronic intermittent ethanol (CIE) vapor or air (CTL) exposure with weeks of drinking. As expected, CIE mice increased ethanol intake relative to CTL mice (3.92 ± 0.28 vs. 2.56 ± 0.14 g/kg; $p < 0.05$). Activating the vSub-NAc pathway by intra-NAc clozapine-N-oxide injection reduced ethanol drinking in the CIE group (51% decrease; $p < 0.05$), while inactivation showed a trend to increase drinking in CTL mice ($p = 0.068$). Data from other mice indicated that activating excitatory and inhibitory DREADDs produced expected changes in glutamate transmission and cFos expression in NAc. These data indicate that activating the vSub-NAc pathway reduces ethanol drinking and inactivating the pathway may increase drinking, consistent with the role of the hippocampus in behavioral inhibition.

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REGULATION OF BEHAVIORAL FLEXIBILITY BY VENTRAL HIPPOCAMPUS PROJECTIONS

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Individuals with alcohol use disorders (AUDs) have impairments in behavioral flexibility and exhibit an overreliance on habitual response strategies. Converging evidence indicates that chronic alcohol exposure promotes the development of habitual behavior, potentially via dysregulation of glutamate signaling in the nucleus accumbens shell (NAcS). Pharmacological regulation of mGluR2/3 signaling both systemically and within the NAcS can restore the ability to flexibly update behavior when contingencies change (i.e., goal-directed actions). While the contribution of prefrontal and striatal subregions in the regulation response strategy selection is well-established, only recently has a role for the ventral hippocampus (VHc), which sends extensive glutamatergic projections to the NAcS, been considered. We investigated the role of glutamatergic projections from the VHc in the expression of contingency-mediated reward seeking using a chemogenetic strategy. Selectively silencing VHc projections restored the use of action-outcome contingencies to guide behavior, while sparing cue-guided behavior and extinction learning. The ability of the VHc to promote habitual response strategies may be in part mediated by selective projections to the NAcS. Together these findings implicate glutamatergic projections from the VHc in the loss of behavioral flexibility and suggest that deficits in VHc function may contribute to overreliance on habitual response strategy observed in AUDs.

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THE VENTRAL HIPPOCAMPUS MAY REPRESENT A NEXUS FOR MALADAPTIVE SYNAPTIC ALTERATIONS ASSOCIATED WITH ALCOHOL USE DISORDER AND COMORBID ANXIETY DISORDERS

J.L. Weiner, S.E. Ewin, J.W. Morgan, N.P. Mcmullen, F. Nierre, S. Barth, A.G. Almonte
Department of Physiology and Pharmacology, Wake Forest School of Medicine, USA

Despite the frequent co-occurrence of anxiety/stressor-related disorders and alcohol use disorder (AUD), the neural substrates underlying this comorbidity are not well understood. The ventral hippocampus (vHC) plays an integral role in negative affective states like anxiety, however little is known about the contribution of the vHC to the maladaptive behaviors associated with these disorders. This talk will focus on recent findings that rodent models of AUD vulnerability and alcohol dependence both promote increases in glutamatergic synaptic excitability in the CA1 region of the hippocampus that are largely restricted to the ventral domain of this brain region. In both models, these changes are also associated with decreases in vHC synaptosomal expression of SK channels, which are known to buffer synaptic excitability at these synapses. Chemogenetic evidence will also be presented demonstrating that selective inhibition of the excitatory projection from the basolateral amygdala to the vHC significantly attenuates anxiety-like behaviors and measures of operant ethanol self-administration. Collectively, these data point to the vHC as a convergent site for synaptic dysregulation associated with comorbid anxiety disorders and AUD and begin to identify vHC-dependent circuits that may contribute to the behavioral phenotypes associated with this dual diagnosis.
Supported by NIH grants P50AA26117, R37AA17531, R01AA10422.

THURSDAY, SEPTEMBER 13 10:50 AM–12:20 PM

SYMPOSIUM

MODULATION OF REWARD MECHANISMS BY ALCOHOL
ORGANIZERS/CHAIR: ESA R. KORPI CHAIR: ELISABET JERLHAG HOLM

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EXPLOITING BRAIN DOPAMINE (DA) SYSTEMS FOR DEVELOPMENT OF NEW TREATMENT MODALITIES FOR ALCOHOL USE DISORDER (AUD)

B. Söderpalm, H. Lidö, A.D. Bejczy, C. Nilsson-Wallmark, L. Adermark, K. Danielsson, R. Stomberg, M. Ericson
University of Gothenburg, Sweden

We have proposed a nAc-VTA-nAc neurocircuitry underlying alcohol-induced DA activation involving ethanol-induced activation of glycine receptors in the nAc, and, secondary to this, acetylcholine-mediated activation of nicotinic receptors (nAChRs) in the VTA, resulting in increased DA release in the nAc. Manipulations of both these receptor populations modulate alcohol intake in the rat. Recently, we and others translated these findings to humans by showing that the partial nAChRs agonist varenicline reduces alcohol consumption in AUD with an effect size twice that of acamprosate and naltrexone. This effect may be produced by varenicline's blocking of ethanol's activation of the mesolimbic DA system via nAChRs in the VTA, and by varenicline slightly raising DA levels. We suggest that a further DA elevation by addition of the DA/NA reuptake inhibitor bupropion may boost this effect resulting in an effect size three times that of available pharmacotherapies. Indeed, in rats varenicline and bupropion failed to influence the alcohol deprivation effect (ADE),whereas the combined treatment abolished the ADE. Further, an additive effect on DA output in nAc was observed. We will perform a national, multicenter, randomized, placebo-controlled trial on the effects of varenicline and bupropion, alone or in combination, on alcohol consumption in AUD, starting in 2019.

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MODULATION OF VTA NEUROPLASTICITY AND REWARDING BEHAVIORS OF ETHANOL BY GABA-B RECEPTOR PAMS

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[1]Department of Pharmacology, University of Helsinki, Finland and [2]CNS Research, Research and Development, Orion Pharma, Finland

Dopamine neurons in the ventral tegmental area (VTA) are believed to be among the earliest targets of ethanol (EtOH) and other drugs of abuse. The drug sensitivity can be demonstrated by persistent memory-like neuroplasticity of VTA DA neurons induced ex vivo by single doses of EtOH and other drugs. The orthosteric agonist of $GABA_B$ receptors baclofen has shown efficacy in alcoholism, but it is also sedative. To further evaluate the impact of $GABA_B$ receptors on this neuroplasticity, we tested the ability of baclofen and two structurally diverse $GABA_B$ positive allosteric modulators (PAMs) to suppress VTA neuroadaptations and reward-related behaviors. Treatment of mice with baclofen, rac-BHFF or ORM-compound alone within wide dose ranges failed to induce glutamate receptor neuroplasticity in the VTA DA neurons. Pretreatment with the high-efficacy PAM rac-BHFF at non-sedative doses effectively reversed both EtOH- and cocaine-induced plasticity and attenuated their self-administration. Pretreatment with the low-efficacy PAM ORM-compound only reversed EtOH-induced neuroplasticity and attenuated its self-administration, but had no effects on cocaine. These findings suggest that low-efficacy $GABA_B$ receptor PAMs might be worthwhile to be further studied in preclinical models and to be tested as pharmacological treatments of alcoholism, while they might not work in stimulant addiction.

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ETHANOL ACUTE EFFECTS ON THE STRIATAL GABAERGIC PROJECTIONS TO THE SUBSTANTIA NIGRA PARS RETICULADA AND THE GLOBUS PALLIDUS

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The GABAergic striatum projections to the Substantia Nigra (SNr) and the Globus Pallidus (GP) mediate action selection and specific effects of ethanol on these synapses may be associated with alcohol use disorders. We used transgenic mice, optogenetic and whole-cell patch clamp recording to evaluate acute ethanol effects on striatonigral and striatopallidal GABAergic synapses. To directly study the effects of ethanol on presynaptic dynamics in GABAergic nerve terminals, we employed a brain slice photometry using the genetically encoded calcium sensor, GCaMP6f. Mice harboring the open reading frame for ChR2 or GCaMP6f, under the control of Cre-recombinase, were bred with either EY262-Cre (for D1R expressing medium spiny neurons; MSNs) or A2A-Cre (for D2R expressing MSNs) driver mice and coronal slices containing the SNr or GP were prepared. We found that while 50mM ethanol depressed inhibitory postsynaptic currents at striatonigral synapses, it slightly potentiated IPSCs at striatopallidal synapses. Using GCamP6f photometry, we found that ethanol induces a transient decrease in stimulus-evoked calcium in all projections analyzed. These findings indicate that although all synapses showed an alcohol-induced inhibition of the presynaptic calcium activity, there are specific pharmacological effects of ethanol at the GABAergic synaptic outputs from the striatum, probably due to post-synaptic changes.

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GUT-BRAIN PEPTIDES AND ALCOHOL USE DISORDERS: ROLE OF REWARD MECHANISMS

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Glucagon-like peptide 1 (GLP-1), and neuromedin U (NMU) are well-established appetite-reducing gut-brain peptides. Even though several studies have linked these anorexigenic peptides with alcohol reward and alcohol use disorder (AUD), the mechanisms of action are poorly defined. When it comes to GLP-1, our very recent data show that local injection of the GLP-1 receptor agonist, Ex4, into either the nucleus accumbens shell (NAc) or laterodorsal tegmental area (LDTg) attenuates alcohol-induced locomotor stimulation, the memory consolidation of alcohol reward and decreases alcohol intake. On the contrary, these behaviours do not involve GLP-1 signalling in the anterior/medial VTA. We further demonstrate that bilateral infusion of NMU into NAc shell reduces alcohol-induced locomotor stimulation, the memory consolidation of alcohol reward and decreases the intake of both alcohol and peanut butter in rodents. In addition, both ventral tegmental area and LDTg were identified as a novel site of action for NMU's anorexigenic properties based on the ability to reduce chow intake. Collectively, these data identify brain reward areas of importance for the ability of both GLP-1 and NMU to regulate alcohol-mediated behaviours. Moreover, these data contribute to the suggestion that gut-brain peptides may be a target for treatment of AUD.

THURSDAY, SEPTEMBER 13 9:00 AM–10:30 AM
SYMPOSIUM
NOVEL MECHANISMS OF ETHANOL-INDUCED DAMAGE TO THE DEVELOPING BRAIN
ORGANIZER/CHAIR: CARLOS F. VALENZUELA CHAIR: CONSUELO GUERRI

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ALCOHOL-INDUCED MICROCEPHALY INVOLVES A REDUCTION IN RETINOIC ACID SIGNALING IN THE HEAD-INDUCING PRECHORDAL MESENDODERM

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Severe forms of Fetal Alcohol Spectrum Disorder (FASD) exhibit microcephaly and its associated mental disabilities. We recently showed that acetaldehyde, the oxidation product of ethanol, reduces retinoic acid (RA) biosynthesis by competing for the retinaldehyde dehydrogenase (RALDH) activity. *Xenopus* embryos treated with ethanol, acetaldehyde or the RALDH inhibitor, DEAB, affect gene expression and induce microcephaly similarly. Using axis induction assays, we show that RA is needed for head formation during early gastrula. This function corresponds to the RA in Spemann's organizer and the cells migrating out of it. We also show that RA inhibition also leads to abnormal morphogenetic movements and delays in prechordal mesendoderm migration, the inducer of anterior neuroectoderm. We studied the RA-producing enzymes RALDH2 and RALDH3 during gastrula, and identify RALDH3 is the key enzyme involved in the production of RA for head formation. These observations suggest that, in addition to its known teratogenic effect on head development, RA also has a positive regulatory role in forebrain induction during early gastrula and this activity is inhibited by ethanol. This novel activity of RA signaling is in agreement with the proposed reduction of this signal in DiGeorge/VeloCardioFacial, Vitamin A Deficiency and FASD syndromes and the resulting microcephaly.

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ROLE OF THE TLR4 IMMUNE RESPONSE IN ALCOHOL-INDUCED BRAIN DYSFUNCTIONS IN A MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS (FASD)

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Prenatal ethanol exposure affects the developing brain, inducing neural impairment, and cognitive/behavioral dysfunctions. Inflammation during brain development has recently involved in the pathogenesis of early brain injury and cognitive dysfunctions. We demonstrated ethanol activates the TLR4 immune response, triggering neuroinflammation, brain damage and cognitive dysfunctions in the developing adolescent brain. Here, we assess if by activating the TLR4 response, maternal alcohol consumption during pregnancy triggers the release of cytokines and chemokines in both maternal sera and brains of fetuses/offspring, which impairs brain ontogeny and causes cognitive dysfunctions. We use WT and TLR4-KO fetal and offspring mice exposed to alcohol during gestation and lactation. We show that maternal alcohol intake during gestation and lactation increases the levels of IL-1β, IL-17, MIP-1α and fractalkine in maternal sera, amniotic fluid and brains of fetuses/offspring, effects that are associated with an increase in microglia markers and a reduction in some synaptic and myelin proteins in brains of offspring (PND0, 20, 66). Long-term behavioral impairments (elevated plus-maze, passive-avoidance tests) are also demonstrated in 66-day-old alcohol-exposed pups. Elimination of TLR4 by TLR4-KO mice abolishes most of these effects in alcohol-treated dams and their offspring. These results suggest that immune system activation might underlie some neurodevelopmental defects in FASD.

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EXPOSURE OF MICE TO ETHANOL DURING THE THIRD TRIMESTER-EQUIVALENT PERIOD DAMAGES HIPPOCAMPAL INTERNEURONS

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Department of Neurosciences, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

Developmental ethanol exposure causes a variety of deficits collectively known as Fetal Alcohol Spectrum Disorders (FASDs). Studies indicate that the GABA neurotransmitter system is a major target of developmental ethanol exposure. GABAergic interneurons are the main source of GABA in the brain and are particularly vulnerable to a variety of insults. Here, we used transgenic mice expressing the Venus yellow fluorescent protein to characterize the impact of ethanol exposure (via vapor inhalation) during the third trimester-equivalent (postnatal days 2–9) on these interneurons. We found that ethanol exposure reduces the number of Venus positive interneurons in the hilus, CA3 and CA1 regions of male but not female adult mice. Moreover, we found that a single exposure to ethanol at postnatal day 7 increases the number of Venus positive neurons that co-stain for activated caspase 3 in the hilus, granule cell layer, CA3 and CA1 regions. We are currently characterizing the functional impact of these effects using slice electrophysiological techniques. Overall, this study demonstrates that ethanol exposure during the equivalent to the last trimester of human pregnancy has a deleterious effect on hippocampal interneuron viability, which may contribute to the neurobehavioral deficits associated with FASDs. Supported by NIH grants R37-AA015614 and P50-AA0022534.

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PRENATAL ALCOHOL EXPOSURE ALTERS WHITE MATTER MICROSTRUCTURE IN NEONATES AND 2 YEAR OLDS

K.A. Donald[1], S.H. Joshi[2], A. Roos[1], K.L. Narr[2], C. Wedderburn[3], R.P. Woods[2], J.-P. Fouche[1], J.C. Ipser[1], H.J. Zar[1], D.J. Stein[1]
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White matter (WM) alterations in adolescents with prenatal alcohol exposure (ALC) are established. Following previous findings of altered WM in exposed neonates, we compared diffusion metrics, in ALC to healthy controls (CON) at two time points during the understudied early years.
Subjects were recruited through the Drakenstein Child Health Study: 23 ALC and 41 CON neonates; 14 ALC and 19 CON 2 years-olds. Diffusion weighted MRI images were acquired on a Siemens MRI-scanner during natural sleep. Average diffusion measures were extracted for regions of interest based on previous findings. Welch's *t*-test tested group differences between groups separately at both time-points.
Significant group differences were found in the left cingulum AD (ALC > CON; $t(39.48) = 2.12$, $p = 0.04$) which persisted in this region at 2 year follow-up with reduced FA (ALC < CON, $t(26.73) = 2.19$, $p = 0.036$). Other regions were also affected at the neonatal time-point. Developmental outcomes were correlated with WM metrics.
Reversal of the expected direction of effects of WM metrics in neonates compared to previous findings in older populations and at 2 years of age, here, may suggest that WM developmental trajectories in CON and ALC may intersect later in childhood. The rate of WM change is nonlinear and is confounded by alcohol exposure.

THURSDAY, SEPTEMBER 13 10:50 AM–12:20 PM
SYMPOSIUM
ADOLESCENT ALCOHOL ABUSE: RISKS, MECHANISMS OF PATHOLOGY AND CONSEQUENCES
ORGANIZER/CHAIR: FULTON T. CREWS

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ADOLESCENT INTERMITTENT ALCOHOL EXPOSURE ENHANCES SENSITIVITY TO FUTURE STRESS EVENTS THAT PROMOTE ABNORMAL FEAR-RELATED BEHAVIOR IN ADULTHOOD

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It is becoming increasing apparent that abuse of alcohol during adolescence has long lasting effects of brain and behavior in adulthood. In the present study, we investigate the effect of adolescent alcohol exposure on fear-related behavior in adulthood. Using a rodent model of binge-like adolescent intermittent alcohol (AIE) exposure by vapor inhalation, we observed that exposure to a fear conditioning paradigm in adult rats subjected to AIE leads to alterations in memory consolidation resulting in deficits in fear extinction learning and the recall of extinction memories. However, treatment with an mGluR5 positive allosteric modulator (CDPPB) during fear extinction training attenuated these deficits in extinction learning and retention. In addition, when AIE exposed rats subsequently experienced a single episode of acute stress, we observed a synergistic effect of AIE and acute stress on alterations of fear behaviors. Taken together, these findings suggest that adolescent alcohol abuse may increase the vulnerability development of postsynaptic stress disorders (PTSD) and alcohol use disorders (AUD), and identify potential therapeutic targets for the treatment of these comorbid disorders.

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ALCOHOL BINGEING IN YOUNG ADULTS IS ASSOCIATED WITH ALTERED BRAIN REGIONAL FMRI RESPONSES TO ATTENTIONAL, DECISION MAKING AND EMOTIONAL CHALLENGES; PREDISPOSING FACTORS

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Binge drinking (BD) is associated with increased impulsivity and altered emotional processing. Young adults ($n = 30$) with differing levels of BD were tested for their ability to inhibit a pre-potent response and to delay gratification under neutral or fearful emotional influences. Resting-state functional connectivity was also examined. Higher BD was associated with enhanced activation in pre-central gyrus and superior parietal lobule during successful response inhibition, indicating compensatory mechanisms. In a fearful context, higher BD was associated with decreased frontal and parietal activation, suggesting that emotional context facilitated inhibitory control. Delayed gratification was associated with lower frontopolar activation. Resting-state functional connectivity revealed that the higher the incidence of BD, the lower the coupling of the right supramarginal gyrus to the Ventral Attentional Network (VAN). BD was associated with more effortful response inhibition, which was facilitated by emotional context. BD was also associated with disrupted functional connectivity within the VAN, denoting disrupted attentional processing. Despite our knowledge of the associations between BD and cognitive as well as emotional alterations, the factors that actually predispose to BD remain unclear. The present talk will discuss these findings within the context of identifying potential endophenotypes associated with risk for the development of alcohol addiction.

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BINGE-LIKE ETHANOL TREATMENT IN ADOLESCENCE IMPAIRS AUTOPHAGY AND HINDERS SYNAPTIC MATURATION: ROLE OF THE NEUROIMMUNE ACTIVATION

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Adolescence is a developmental period in which remodeling and changes in synaptic plasticity and neural connectivity take place in some brain regions. A different mechanism participates in adolescent brain maturation, including autophagy processes that play a role in synaptic development and plasticity. Alcohol abuse in adolescence causes activation of TLR4 response, triggering neuroinflammation, neural damage and behavioral alterations. We evaluated whether binge ethanol drinking alters autophagy pathways by contributing to adolescent synaptic dysfunctions, and whether the immune receptors TLR4 participate in these events. By using wild-type (WT) and TLR4-deficient (TLR4-KO) adolescent mice treated intermittently with ethanol (3.0 g/kg) for 2 weeks, we observed that binge-like ethanol exposure in adolescence impairs autophagy machinery by increasing autophagy inhibitor mTOR, lowering LC3-II levels and accumulating p62. Inhibition of mTOR by rapamycin restores the ethanol-induced changes in the levels of excitatory scaffolding synaptic proteins (PSD-95 or SHANK3) in the prefrontal cortex of WT mice. Down-regulation of autophagic pathway was also observed in the proteomic analysis of exosomes isolated from cortexes of ethanol-treated WT mice. The effects of ethanol were prevented in TLR4-KO, suggesting the involvement of this receptor in the effects of ethanol on synaptic and cognitive alterations associated with binge alcohol in adolescence.

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NEUROIMMUNE ACTIVATION BY ADOLESCENT ALCOHOL EXPOSURE AND IN HUMAN ALCOHOLIC BRAIN

F.T. Crews[1], W. Liu[2], R. Vetreno[2], M. Broadwater[2], L. Coleman[2]
[1]Director of The Bowles Center for Alcohol Studies, UNC – Chapel Hill, USA and [2]The Bowles Center for Alcohol Studies, UNC – Chapel Hill, USA

Adolescent alcohol exposure alters brain development which increases risks of alcohol use disorder. Using adolescent intermittent ethanol exposure (AIE) in rats, we found increased expression of multiple neuroimmune genes, e.g. genes known to signal in the immune system, in the brain. HMGB1, a key cytokine like molecule, and its receptors, e.g. TLR4 and RAGE, as well as other Toll-like receptors were induced in the cortex by AIE and persisted into adulthood. Studies of post-mortem human brain find increased expression of HMGB1, TLR, RAGE in addition to multiple other neuroimmune genes in individuals with alcohol use disorder (AUD). Further, expression in human cortex parallels life-time alcohol consumption consistent neuroimmune gene induction by ethanol contributing to ethanol's progressive and persistent conjunction with increases in alcohol use leading to AUD. In parallel with increased neuroimmune gene expression, cholinergic neurons (ChAT+IR) and serotonergic neurons (5HT+IR) were reduced following AIE. In addition, AIE reduced adult brain PFC connectivity as assessed by rsfMRI and produced reversal-learning deficits consistent with loss of PFC function. Taken together these studies suggest adolescent alcohol exposure leads to long lasting changes in the adult brain that could increase risks of adult AUD (Funded by the NADIA of NIAAA).

THURSDAY, SEPTEMBER 13 9:00 AM–10:30 AM

SYMPOSIUM

EPIGENETIC MECHANISMS OF ALCOHOL TOXICITY

ORGANIZER: A LESLIE MORROW CHAIR: RAJESH MIRANDA

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MICRORNA BIOMARKERS AND MEDIATORS OF PRENATAL ALCOHOL EFFECTS

R.C. Miranda[1], A. Tseng[1], A. Mahnke[1], A. Wells[2], N. Walter[3], N. Newman[3], K. Grant[3], C. Kroenke[3], A. Allan[4], C. Chambers[2]
[1]Texas A&M University, USA, [2]University of California, San Diego, USA, [3]Oregon Health & Science University, USA and [4]University of New Mexico, USA

In a study of pregnant women in Ukraine, we identified 11 miRNAs which were significantly elevated in the plasma of mothers whose infants were affected by maternal alcohol consumption (HEa) compared to those infants who were unaffected (HEua) or unexposed (UE). Pathway overrepresentation analysis indicated that these miRNAs influence pathways related to fetal and placental growth and maturation, including the epithelial-mesenchymal transition (EMT) pathway. We now report that these miRNAs predict effects of prenatal alcohol exposure on placental EMT genes in primate but not mouse. In cell culture models of human trophoblast cells, overexpression of these maternal miRNAs retarded trophoblast invasion and inhibited EMT genes. Our data collectively suggest that these miRNAs may have emerged as evolutionarily recent regulators of placenta growth and maturation, and consequently a primate-specific epigenetic regulator of fetal growth that may explain infant growth restriction due to prenatal alcohol exposure.

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PRECLINICAL EVALUATION OF NEW HDAC INHIBITORS IN ANIMAL MODELS OF ALCOHOL USE DISORDERS

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Recent preclinical research suggested that histone deacetylase inhibitors (HDACIs) and specifically class I HDAC selective inhibitors might be useful to treat alcohol use disorders (AUDs).Our objective was to find a new inhibitor of the HDAC-1 isoenzyme and to test its efficacy in an animal model of AUDs. We prepared new derivatives bearing sulfonylhydrazide-type zinc-binding group (ZBG) and evaluated these compounds *in vitro* on HDAC-1 isoenzyme. The most promising compound was tested on ethanol operant self-administration and relapse in rats. We showed that the alkylsulfonyl-hydrazide-type compound (ASH) reduced by more than 55% the total amount of ethanol consumed after one intracerebroventricular microinjection, while no effect was observed on motivation of the animals to consume ethanol. In addition, one ASH injection in the central amygdala reduced relapse. Our study demonstrated that a new compound designed to target HDAC-1 is effective in reducing ethanol intake and relapse in rats and further confirm the interest of pursuing research to study the exact mechanism by which such inhibitor may be useful to treat AUDs.

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HDACS MEDIATE ETHANOL MECHANISMS OF ETHANOL DEPENDENCE INVOLVING GABA-A RECEPTOR FUNCTION AND EXPRESSION

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[1]Bowles Center for Alcohol Studies, UNC School of Medicine, USA and [2]Psychiatry and Pharmacology, UNC School of Medicine, USA

Alcohol dependence is characterized by withdrawal symptoms that contribute to morbidity and addiction. $GABA_A$ receptor ($GABA_AR$) adaptations contribute to many withdrawal symptoms associated with alcohol dependence. $GABA_AR$ hypofunction results from decreases in *Gabra1* expression, that is dependent upon increased *Hdac2* and *Hdac3* expression. Administration of the HDAC inhibitor Trichostatin A (TSA) after chronic ethanol exposure prevents the decrease in *Gabra1* expression in the medial prefrontal cortex (mPFC). TSA administration prevented the physiological manifestations of $GABA_AR$ hypofunction in layer 5 pyramidal neurons in the prefrontal cortical slice preparation, including reductions in activity dependent sIPSC frequency and adaptations in decay tau in both male and female rats. Such changes were found in the mPFC projection to the central nucleus of the amygdala as well as other mPFC projections. The molecular underpinnings of these adaptations appear to involve selective upregulation of HDAC2 and HDAC3 association with the *Gabra1* promoter that accompanies a decrease in H3 acetylation of the *Gabra1* promoter and the reduction in $GABA_AR$ α1 subunit expression. The results show how chronic ethanol exposure regulates the highly prominent $GABA_AR$ α1 receptors and the functions they modulate by an epigenetic mechanism that represents a potential treatment modality for alcohol dependence.

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MOLECULAR BIOMARKERS OF GENE EXPRESSION AND EPIGENETIC MIRNAS IN AUD

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Numerous genetic studies in alcohol use disorder (AUD) have associated candidate gene variants, including those of the dopaminergic pathway coding, the dopamine reuptake transporter, DAT1 and the D2 receptor, DRD2 gene. However, the expression of these genes in AD is poorly studied. It is rare to have brain samples to evaluate the expression of these genes. However, these expression in the blood could be a good biological marker for the diagnostic or the prognostic in abstinence. Furthermore, differences in gene expression, under the control of epigenetic factors, have been highlighted. Thus, expression of non-coding microRNAs (or miRNAs), binding to messenger or transcribed RNA targets, will regulate gene expression without genetic modification as has been observed in animal models and patients.
The main objective of our project is to quantify the gene expression genes involved in the dopaminergic pathway, including DAT1 transporter and DRD1 to DRD5 receptors genes, as well as, to identify and measure the miRNAs that targeted these genes from the blood of AUD patients from the Environment, Behavior, Suicide and Alcohol (ECSA) cohort and compared to controls.
This research work was supported by the Fondation pour la recherche en alcoologie (FRA).

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DIFFERENTIAL METHYLATION OF ALDH2 GENE PROMOTER IN PATIENTS WITH AUD

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The single nucleotide polymorphism (SNP) rs886205 in ALDH2 is located between two promoter elements: a negative and a positive regulator. We have previously reported differential methylation of CpGs in the negative regulatory region in the two allele variations of rs886205 SNP. Another CpG island, in the positive regulatory region of the ALDH2 promoter, extends through the SNP rs886205 and a nuclear receptor response element (NRRE). We observed a significant difference in the methylation of analyzed CpGs between alcohol-dependent patients and controls. Patients with AA ($n = 52$) or GG/GA ($n = 31$) genotype differed significantly in baseline methylation levels as well as in methylation kinetics during withdrawal. The reporter gene assays showed a significant effect of genotype on ALDH2 expression as well as an interaction between genotype and methylation. Further, we observed a significant genotype-dependent effect of estrogen receptor alpha ($ER\alpha$) and retinoic acid receptor alpha/retinoid x receptor alpha ($RAR\alpha/RXR\alpha$) heterodimer. We also observed an interaction between DNA methyltransferases (DNMTs) and Retinoic acid receptors. DNMT3a upregulated the transcription of A-genotype when co-transfected with $RAR\alpha/RXR\alpha$. DNMT3b acted by counteracting the effect of SNP, indicating the involvement of DNMT3b methylation in rs886205 mediated effect on the transcription.

THURSDAY, SEPTEMBER 13 10:50 AM–12:20 PM

SYMPOSIUM

MECHANISMS, BIOMARKERS AND TARGETS FOR THERAPY IN ALCOHOL-ASSOCIATED LIVER INJURY: FROM GENETICS TO NUTRITION

ORGANIZER/CHAIR: IRINA A. KIRPICH CHAIR: KUSUM KHARBANDA

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LOVE YOUR LIVER: HOW TO PROTECT IT FROM, OR TREAT IT AFTER, ALCOHOL-INDUCED INJURY

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Chronic heavy alcohol consumption can result in a spectrum of alcoholic liver disease (ALD), ranging from fatty liver, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinomas. In addition, alcoholic hepatitis can result from acute over chronic consumption. Some studies, on the other hand, suggested that moderate drinking may delay the progression of fatty liver to fibrosis in obese individuals.

While abstinence is the cornerstone of ALD treatment, the presentation will discuss potential treatments for ALD from manipulation of the gut microbiota with diet or probiotics to the use of corticosteroids in alcoholic hepatitis. The discussion will also focus on the use of antioxidants; nutrition including Zinc; pentoxifylline; PPAR agonists; endocannabinoids; anti-TNF therapy, therapies targeting inflammation, apoptosis, fibrosis; hepatoprotectants (Betaine, SAMe, Silybin, Silymarin, UDCA); new therapeutic options such as caspase-, CCR2-, and MAPK-inhibitors, FXR agonists and Galectin-3 antagonists; sirtuins, and liver transplantation. Furthermore, since chronic alcohol consumption causes mitochondrial impairment, mitochondrial-targeted agents such as triphenylphosphonium cation ligated ubiquinone Q10 and vitamin E, Szeto-Scheller peptides, and superoxide dismutase mimetic-salen manganese complexes will be discussed.

Emerging herbs with potential clinical applications such as curcumin, *Carthamus tinctorius, Bragzhun, Swertia chirayita, Swertia mussotii, Halenia elliptica, Herpetospermum pedunculosum,* and *Phyllanthus emblica*, will be addressed.

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PLASMA RESOLVIN D1 LEVELS ARE REDUCED IN ALCOHOLIC HEPATITIS: A POSSIBLE MECHANISM OF AND POTENTIAL THERAPY FOR ALCOHOLIC LIVER DISEASE

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Background and Aims: Alcoholic liver disease is a global health problem. Alcoholic hepatitis (AH) is associated with high mortality (up to 40% of severe AH patients die within 6 months). However, there is currently no FDA-approved therapy for any stage of ALD. Resolvins are a novel class of lipid metabolites with anti-inflammatory and pro-resolution of inflammation properties which might be beneficial for patients with ALD. In the current study, we evaluated resolvin levels in patients with severe AH and also tested if resolvin administration would attenuate experimental AH in mice.

Results: Decreased plasma levels of resolvin D1 (RvD1) were found in patients with severe AH (MELD score = 25.25 $\pm$ 0.75) on the day of hospital admission as compared to healthy individuals. RvD1 levels in AH patients reached control group levels following 1 month of therapy and remained at similar levels after a 6-month follow up. In mice, RvD1 treatment markedly decreased ethanol and LPS-induced liver injury. Mice treated with RvD1 also had a reduced hepatic pro-inflammatory response.

Conclusion: An imbalance in critical beneficial lipid mediators may contribute to the liver pathology associated with AH and may represent a novel therapeutic target in the management of ALD.

Funding: NIH NIAAA.

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DEFECTIVE METHYLATION REACTIONS PROMOTE THE PATHOGENESIS OF ALCOHOLIC LIVER INJURY: PREVENTION BY BETAINE ADMINISTRATION

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[1]University Nebraska Medical Center, USA and [2]VA Medical Center, USA

Alcoholic liver disease (ALD) is a major health care problem worldwide. We have previously shown that chronic ethanol exposure alters several of the multiple steps in methionine metabolism in the liver to ultimately lower the hepatocellular S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH) ratio. This decrease in the ratio impairs the activity of several critically important SAM-dependent methyltransferases resulting in the generation of many hallmark features of early alcoholic liver injury such as steatosis, apoptosis, accumulation of damaged proteins and altered signaling events. We further showed that betaine administration can preserve the hepatic SAM:SAH ratio and thereby attenuate alcoholic steatosis and other features of hepatic liver injury.

In expanding our findings to other organs and tissues of relevance to ALD, we found similar reduction in SAM:SAH ratio in the white adipose tissue (WAT) and intestine as seen in the liver. This reduction in the ratio impairs specific methylation-dependent pathway(s) to produces detrimental effects in these two organs which ultimately results in progressive liver injury. Betaine administration averts the development of ethanol-induced liver damage by preserving intestinal and WAT SAM:SAH ratio and preventing WAT hyperlipolysis and intestinal barrier dysfunction.

To conclude, betaine is a promising therapeutic in the treatment of alcoholic liver injury.

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PANETH CELL DYSFUNCTION MEDIATES ALCOHOL-INDUCED DYSBIOSIS AND HEPATITIS IN MICE: ROLE OF ZINC DEFICIENCY

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Paneth cells in the intestinal crypts are zinc-enriched exocrine cells, and function as an important regulator in microbiota homeostasis by secreting antimicrobial peptides (AMPs). The present study aimed at determining if Paneth cell dysfunction accounts for alcohol-induced dysbiosis and hepatitis and if zinc deficiency mediates the alcohol effect on Paneth cells. Chronic alcohol feeding caused dysbiosis at the gut-liver axis along with the development of endotoxemia and hepatitis in mice. Expression of AMPs and the bactericidal activity of Paneth cells were significantly reduced in the ileum of the alcohol-fed mice along with reduction of cellular zinc levels. Matrix metallopeptidase 7 (MMP7) knockout mice, which are deficient in active α-defensins, showed more severe gut dysbiosis, endotoxemia and hepatitis along with reduced intestinal bactericidal activity. Zinc deficiency both in alcohol-fed mice and Paneth cell-containing intestinal crypts reduced Paneth cell AMPs along with suppression of p-STAT1 and p-STAT3. Paneth cell specific-knockout of ZIP8, a Paneth cell-predominant zinc transporter, led to decreased cellular zinc levels in Paneth cells and reduced the production of α-defensins. The present study suggests that Paneth cell inactivation due to zinc deficiency serves as a pathophysiological factor in the development of alcohol-induced gut dysbiosis, endotoxemia and hepatitis.

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RELEVANCE OF GENETICS IN ALCOHOLIC LIVER DISEASE (ALD)
D. Seth
Royal Prince Alfred Hospital and Centenary Institute, Australia

Alcoholic liver disease is a multi-step and multi-factorial process. More than 90% of chronic drinkers develop alcoholic steatosis but why only up to 20% ever progress to cirrhosis is unknown. In addition to the amount of alcohol intake, female gender and ethnicity increase risk for ALD. A battery of genetic, epigenetic, and environmental factors are suspected to operate during ALC pathogenesis impacting cellular injury, inflammation and impaired hepatic regeneration. Investigations for genes known to operate during ALC pathogenesis remain largely unconfirmed. Recent genome-wide searches have identified several polymorphisms in genes PNPLA3 (rs739409), TM6SF2 (rs58542926) and MBOAT7 (rs641738) associated with the risk of developing alcoholic liver cirrhosis. However, all these gene variants were first identified in non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH). Most recently, associations were reported between variants in HSD17B13 and SAMM50 with liver diseases, including ALD and NAFLD. Interestingly, all polymorphisms identified so far in chronic liver diseases, are involved in lipid metabolism/processing. This indicates that lipids play an important role in chronicity underpinning inflammation and fibrogenesis. These shared risks indicate non-specificity to alcohol-induced liver disease. Given the clinical and histopathological commonalities between the two diseases, it is intriguing that they may share genetic risk factors and heritability.

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BIOMARKERS FOR ALCOHOLIC HEPATITIS: IMPLICATIONS FOR DIAGNOSIS AND THERAPY
C.J. Mcclain
University of Louisville, USA

Alcoholic hepatitis (AH) consists of a constellation of clinical and biochemical findings. Unfortunately, clinically available biomarkers are generally non-specific for the diagnosis of AH, and there are no blood biomarkers that clearly distinguish AH from other forms of liver disease, such as drug-induced liver injury (DILI). Moreover, there are no clinically available biomarkers that reflect the magnitude of cell death or the particular form of cell death (apoptosis vs. necrosis). While serum AST/ALT levels reflect severity of injury in many liver diseases, such as DILI, they appear to be less useful in AH. Importantly, AST/ALT and other biomarkers do not distinguish AH from decompensated cirrhosis without AH, and this is a major problem for clinicians that can adversely impact treatment decision making. Thus, new biomarkers are needed. The optimal biomarker would be easy to obtain, easy to perform and would serve multiple functions. In this talk, we discuss examples of biomarker sources including serum/plasma/whole blood, urine, stool, breath/saliva and cell-based assays. We also discuss biomarker functions, including diagnosis, disease severity, prognosis, mechanisms, response to therapy, and companion diagnostics/personalized medicine. Lastly, we review potential new biomarkers such as CK 18, acrolein, soluble receptor for IL-33, augmenter of liver regeneration, and others.

THURSDAY, SEPTEMBER 13 9:00 AM–10:30 AM
SYMPOSIUM
RECENT STUDIES ON ALCOHOL USE DISORDERS IN JAPAN AND KOREA
ORGANIZER: SUNG-GON KIM CHAIR: KEYSEOUNG LEE

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CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE IV GENE POLYMORPHISMS IN KOREAN ALCOHOL-DEPENDENT PATIENTS
W.-y. Jung
Department of Psychiatry, Pusan National University Yangsan Hospital, Korea

Objective: The purpose of the present study is to compare the frequency of calcium/calmodulin-dependent protein kinase IV (CAMKIV) genotypes and alleles between alcohol dependence (AD) and control subjects.
Methods: The present study includes 281 AD patients and 139 control subjects. Seven single nucleotide polymorphisms of CAMKIV gene known to show significant separation ratio in Asians were searched in SNP database and previous studies. Polymerase chain reaction and restriction fragment length polymorphism techniques were used to analyze genotype of CAMKIV gene SNPs.
Results: Major TT genotype and T allele frequencies of rs25917 in AD patients were significantly higher than those of control subjects (genotype, $p = 0.002$; allele, $p = 0.001$). Major CC genotype and C allele frequencies of rs117590959 in AD patients were also significantly higher than those of control subjects (genotype, $p < 0.001$; allele, $p = 0.001$). Major genotypes of rs25917 ($p = 0.002$; odds ratio = 3.13) and rs11790959 ($p = 0.002$; odds ratio = 3.22) showed significantly higher odds ratios associated with AD than minor genotypes in logistic regression.
Discussion: These results suggest that CAMKIV might be a candidate AD gene. Further research is needed to discover the precise relationship between CAMKIV and AD and the function of each SNP.

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PREDICTING FACTORS OF LONG-TERM FOLLOW-UP IN TREATING ALCOHOLICS WITH NALTREXONE OR ACAMPROSATE IN KOREA
S.Y. Huh
Department of Psychiatry, Pusan National University Yangsan Hospital, Korea

Objective: Alcohol use disorder is common, its lifetime prevalence is 12.2% in Korea. Despite high prevalence, it has a high recurrence rate. One study reveals 82.1% recurrence rate within 3 months after discharge. Another study reveals 80.3% recurrence rate within 6 months after discharge. To prevent recurrence, medication is critical. In Korea, naltrexone and acamprosate are authorized. But two medications have different mechanisms and actions. So we investigated the predicting factors of long-term follow-up in treating alcoholics with naltrexone or acamprosate in Korea.
Methods: A retrospective study was conducted. From 2008.11 to 2017.5, we studied patients diagnosed with alcohol abuse or alcohol dependence at PNUYH. We examined prescribed days of naltrexone or acamprosate, and factors of patients that maintained at least 180 days. For all the obtained data, logistic regression analysis was conducted.
Results: In the naltrexone group, treatment duration was longer for those highly educated, with more medical disease, prescribed more other psychotropics, and diagnosed as alcohol abuse than alcohol dependence. In the acamprosate group, treatment duration was longer for those prescribed fewer other psychotropics.
Conclusion: Predicting factors were different in long-term follow-up patients prescribed naltrexone or acamprosate. A well-designed study will be needed to accurately evaluate predicting factors according to the type of drug.

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DIFFERENCE OF EXECUTIVE DYSFUNCTION BETWEEN ALCOHOL DEPENDENCE & SCHIZOPHRENIA IN COMPARISON WITH TRAUMATIC BRAIN INJURY AND NORMAL CONTROL SUBJECT

K. Lee
Incheon ChamSarang Hospital, Korea

The purpose of this study is, by the evaluation of neuropsychological test, to identify how different executive dysfunction of the frontal lobe in alcohol dependence patients (alcoholics) with schizophrenia (SPR) compare to that of traumatic brain injury (TBI) and healthy controls (controls).
We enrolled 93 subjects consist of 24 alcoholics, 22 SPR, 24 TBI and 23 controls matched for age, educational level, and premorbid IQ. The subjects were evaluated by socio-demographic and clinical characteristics. We administered Korean versions of the Wechsler Adult Intelligence Scale (k-WAIS), EXIT (Executive intelligence test) which consists of stroop, verbal fluency, figural fluency, auditory verbal learning test (AVLT) and Wisconsin Card Sorting Test.
Alcoholics and SPR showed poorer IQ, EIQ, and WCST than controls. Alcoholics showed better performance than that of SPR at EIQ, stroop interference, and verbal fluency but there was no difference at AVLT and WCST. Interestingly in SPR, verbal fluency showed poorer performance compared with controls and alcoholics and decreased to the level of TBI but in alcoholics, figural fluency showed a lower score than SPR and decreased to the level of TBI.
Both alcohol dependence and SPR accompanied with executive dysfunctions. But there were differences in the domain of verbal fluency and figural fluency between alcoholics and SPR patients.

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THE EFFECTS OF BRIEF INTERVENTION AT A WORK PLACE

H. Maesato, M. Itoh
National Hospital Organization Kurihama Medical and Addiction Center, Japan

Background: Research on the use of a BI at workplace, and its association with the genotype of alcohol metabolizing enzymes is scarce. The aim of this study is to evaluate an efficacy of a BI at a workplace, and to assess impacts of the genotype of these enzymes on the intervention results. Since the study is ongoing, preliminary findings will be reported.
Method: 43 employees of a private company participated in a BI at their workplace. Participants were divided into a control and a BI group. Their annual health check results, the genotypes, and pre and post AUDIT scores were used for the analyses.
Results: The average AUDIT scores were decreased by – 0.2 (control) versus – 2.7(BI) in 6 months. Based on item level comparisons between pre and post AUDIT scores in the BI group, significant differences on "frequency of heavy episodic drinking" ($p = 0.008$) and "frequency of being unable to stop drinking" ($p = 0.020$)" were found. The genotype of ALDH2 did not have significant impacts on AUDIT scores at any points on both groups.
Conclusion: The AUDIT scores were significantly decreased in the BI group, compared with the control group, but not due to the genotype of alcohol metabolizing enzyme.

THURSDAY, SEPTEMBER 13 10:50 AM–12:20 PM

SYMPOSIUM

RECENT CLINICAL STUDIES ON GENETIC POLYMORPHISMS OF ETHANOL-METABOLIZING ENZYMES IN JAPAN AND KOREA
ORGANIZER: SUNG-GON KIM CHAIR: SACHIO MATSUSHITA

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AN ASSOCIATION STUDY ABOUT ALCOHOL METABOLISM AND ITS EFFECTS ON COGNITION AND SUBJECTIVE ALCOHOL EFFECT IN POPULATIONS WITH DIFFERENT ALDH2 GENOTYPES

S.-g. Kim[1,2], W.-y. Jung[2], H.-k. Kim[2]
[1]Psychiatry, Pusan National University, Korea and [2]Psychiatry, Pusan National University Yangsan Hospital, Korea

Objective: After alcohol consumption, ALDH2 genotype and age and gender differences of Breath Alcohol Concentration (BrAC) were analyzed, and changes in cognition and subjective alcohol effect (SAE) were analyzed according to time of change relative to the change of BrAC.
Methods: The study was conducted on 50 male and 54 female subjects, divided by ALDH2 genotypes and age group for healthy social drinkers. BrAC, cognition and BAES were measured just before alcohol drinking (male: 0.6 g/kg of BW; female: 0.4 g/kg of BW), and then 8 times after drinking.
Results: There was a significant difference in BrAC according to ALDH2 genotype and gender. In cognition, cancellation test revealed that ALDH2 1*2 genotype had significantly higher points (attention durability) than 1*1 genotype, and error (impulsivity) was significantly lower. In drinking effect, there was no difference in ALDH2 genotypes in BAES (STI), but BAES (SED) was significantly increased in ALDH2 1*2 group than 1*1.
Conclusion: These means that BrAC was significantly affected by ALDH2 genotype and gender, and ALDH2 1*2 group showed different effects by drinking from 1*1 group in cognition and SAE. Therefore, in public health aspect, when guidelines on drinking is established, those factors need to be considered.

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SLOW-METABOLIZING ADH1B AND INACTIVE HETEROZYGOUS ALDH2 INCREASE VULNERABILITY TO FATTY LIVER AND DECREASE VULNERABILITY TO CIRRHOSIS IN JAPANESE MEN WITH ALCOHOL DEPENDENCE

A. Yokoyama
National Hospital Organization Kurihama Medical and Addiction Center, Japan

Background: Genetic polymorphisms of alcohol dehydrogenase-1B (ADH1B; rs1229984) and aldehyde dehydrogenase-2 (ALDH2; rs671) affect BMI, body fat, lipid metabolism, and liver injury in alcoholics.
Methods: We evaluated associations between the presence of fatty liver and cirrhosis and ADH1B/ALDH2 genotypes in 1604 Japanese alcoholic men without HBs antigen and anti-HCV antibody.
Results: Fatty liver was diagnosed when ultrasonography showed both hepatorenal contrast and liver brightness. Cirrhosis was diagnosed based on clinical examinations including imaging studies. Age-adjusted usual alcohol intake did not differ according to ADH1B or ALDH2 genotypes. The adjusted OR of slow-metabolizing *ADH1B*1/*1* carriers (28% of the subjects) was 1.61 (1.27–2.03) for fatty liver and 0.52 (0.37–0.72) for cirrhosis in comparison with the *ADH1B*2* allele carriers, and that the OR of inactive heterozygous *ALDH2*1/*2* carriers (16% of the subjects) was 1.43 (1.08–1.89) for fatty liver and 0.56 (0.36–0.87) for cirrhosis in comparison with the *ALDH2*1/*1* carriers.
Conclusions: The *ADH1B*1/*1* genotype and the *ALDH2*1/*2* genotype were positive determinants of fatty liver and negative determinants of cirrhosis in the subjects. These results may partly explain the long-known difference in a major histological type of alcoholic liver disease between Western countries (steatohepatitis) and Japan (alcoholic liver fibrosis without histological features of steatohepatitis).

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IDENTIFICATION OF RISK FACTORS FOR ALCOHOL DEPENDENCE USING THE AIA MODEL: COMORBID PSYCHIATRIC AND PERSONALITY DISORDERS

M. Itoh, T. Yonemoto, F. Ueno, C. Iwahara, Y. Yumoto, H. Nakayama, H. Maesato, M. Kimura, S. Matsushita, S. Higuchi
National Hospital Organization Kurihama Medical and Addiction Center, Japan

Background: Despite the potentially severe reactions, some individuals with inactive ALDH2 and active ADH1B go on to become alcoholics, and it is hypothesized that they have risk factors for developing alcohol use disorders (AUDs). To identify such risk factors, we compared the prevalence of comorbid psychiatric disorders among male alcoholics according to ALDH2 and ADH1B genotypes.
Method: The subjects were 120 male alcoholics with inactive ALDH2, 106 alcoholics with active ALDH2 matched for age and ADH1B genotype, 200 age-matched healthy males recruited using an Internet advertisement. Alcoholics were divided into 4 groups according to their ALDH2 and ADH1B genotypes.
Results: Alcoholics with inactive ALDH2 and active ADH1B had a significantly higher prevalence of attention-deficit/hyperactivity disorder (ADHD) than the other 3 groups. The prevalence of agoraphobia and panic disorder were significantly higher among the alcoholics with active ALDH2 and usual ADH1B than in the other 3 groups.
Conclusions: ADHD may be a risk factor for AUDs. With regard to agoraphobia and panic disorder, it is hypothesized that adverse reactions due to inactive ALDH2 after alcohol consumption resemble symptoms of these disorders, and therefore, the disorders might be associated with reduced risk for becoming AUDs in individuals with inactive ALDH2.

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INFLUENCE OF GENETIC VARIATION IN ETHANOL-METABOLIZING ENZYMES ON ALCOHOL USE AND DIAGNOSIS OF ALCOHOL DEPENDENCE AMONG JAPANESE MALE ALCOHOLICS

T. Yonemoto, M. Itoh, F. Ueno, Y. Yumoto, C. Iwahara, H. Nakayama, H. Maesato, M. Kimura, S. Matsuhita, S. Higuchi
National Hospital Organization Kurihama Medical and Addiction Center, Japan

Introduction: Genetic variations of ethanol-metabolizing enzymes have been implicated in alcohol use patterns and alcohol dependence (AD) risk. Previous studies have shown that individuals with aldehyde dehydrogenase-2 (ALDH2)*1/*2 genotype and alcohol dehydrogenase 1B (ADH1B) *1/*2 or *2/*2 genotype acted as genetic deterrents of AD and lower alcohol consumption. However, the possible influence of genetic variations of these enzymes on alcohol use patterns, alcohol consumption and AD severity has not been elucidated.
Methods: The subjects were 164 male alcoholics. Semi-structured interviews were conducted using the SSAGA- II to obtain comprehensive information.
Results: AD tended to be delayed in alcoholics with ALDH2*1/*2 genotype. The alcohol consumption measures were almost the same for the two ALDH2 groups and for the three ADH1B groups. The severity of dependence was almost similar for the two ALDH2 groups. However, there was significantly higher matching against the tolerance items in the case of the ALDH2*1/*2 genotype group in relation to DSM-IV.
Conclusion: These results suggested that the ALDH2 genotype had little effect on alcohol use patterns among alcoholics. The results suggested that the validity of tolerance as one of the diagnostic criteria of AD needs to be examined in relation to Asian alcoholics.

MONDAY, SEPTEMBER 10 2:50 PM–4:20 PM
SYMPOSIUM
ALCOHOL & OPIOIDS: INTERSECTING MECHANISMS AND TREATMENT OPPORTUNITIES FOR PAIN MANAGEMENT AND ADDICTION
ORGANIZER/CHAIR: SCOTT EDWARDS CHAIR: MARCIN WOJNAR

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ANOTHER IMPORTANT PIECE IN A COMPLEX PUZZLE? EXPLORING SIGNIFICANCE OF PAIN IN ALCOHOL DEPENDENCE

M. Wojnar[1,2,3], A. Jakubczyk[1,3], M. Kopera[1,3], M. Nowakowska[3], J. Zaorska[3], J. Skrzeszewski[4]
[1]Department of Psychiatry, Medical University of Warsaw, Poland, [2]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA, [3]Szpital Nowowiejski, Warsaw, Poland and [4]Primary Care Services Bemowo, Warsaw, Poland

The use of alcohol is commonly considered a useful pain self-management strategy, with more than 25% of individuals with various pain symptoms reporting the use of ethanol for the purposes of analgesia. In this presentation, associations between physical pain and well-recognized risk factors of alcohol dependence: sleep problems, depression, emotion dysregulation and impulsivity will be discussed. Moreover, results of recent research study investigating tolerance of pain as well as pain sensitivity in the group of Polish alcohol-dependent individuals will be revealed. This study showed that in comparison to controls alcohol-dependent individuals were significantly more likely to use ethanol for analgesic purposes ($p = 0.00014$). Moreover, AD patients were characterized by significantly lower pain tolerance ($p < 0.001$) and lower pain threshold, i.e. higher pain sensitivity ($p < 0.001$). Moreover, analysis of the data suggests a significant discrepancy between results of behavioral and questionnaire measures of physical pain in alcohol dependent patients.

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OPIOID USE AND PAIN: MECHANISMS OF HEAVY DRINKING RELAPSE AMONG PATIENTS WITH ALCOHOL DEPENDENCE

K. Witkiewitz, V. Votaw, K. Vowles
University of New Mexico, USA

Identifying factors that predict a return to heavy drinking (i.e., relapse) following alcohol treatment is critical for the development of relapse prevention interventions. Physical pain is common among individuals with alcohol use disorders (AUDs) and opioid and other drug use is often comorbid with AUD, yet few studies have examined whether pain and opioid use might predict alcohol relapse. The goal of the current study was to examine the associations between physical pain and opioid use in the prediction of heavy drinking relapse in the COMBINE study ($n = 1383$ patients with alcohol dependence). Results indicated significant associations between physical pain, opioid use, and alcohol relapse. Opioid misuse was highly comorbid with cannabis and other drug use, however opioid misuse predicted the worst outcomes. Results also indicated that opioid misuse mediated the effects of pain on alcohol relapse, and medication adherence mediated the effects of opioid misuse on relapse. Opioid misuse predicted significantly lower medication adherence, particularly to naltrexone, which predicted worse outcomes. Accordingly, clinicians should screen for physical pain and opioid misuse in patients with alcohol dependence and consider pain and opioid misuse as potential risk factors for alcohol relapse.

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GLUCOCORTICOID-MEDIATED PLASTICITY UNDERLIES NEGATIVE EMOTIONAL STATES AND COMPULSIVE ALCOHOL AND OPIOID USE

S.A. Carmack
Intramural Research Program, National Institute on Drug Abuse, USA

Drug addiction is a chronic disease characterized by cyclical periods of compulsive drug use and seeking, quitting, and the emergence of a persistent negative emotional state (e.g. anxiety, pain) during drug abstinence. We hypothesized that repeated, intense cycles of drug intoxication and withdrawal lead to glucocorticoid-dependent downregulation of hypothalamic-pituitary-adrenal (HPA) axis function and sensitization of extrahypothalamic stress systems; and that these allostatic changes contribute to negative emotional states that drive compulsive drug taking and seeking. We found that chronic administration of the glucocorticoid receptor antagonist mifepristone blocked the development of compulsive-like alcohol or heroin taking and seeking in rat models of drug dependence. Chronic mifepristone treatment also prevented the emergence of heroin withdrawal-induced hyperalgesia. Additionally, acute treatment with mifepristone or the selective glucocorticoid receptor antagonist CORT113176 reduced drug intake in rats already dependent on alcohol or heroin. Glucocorticoid receptor antagonists may reduce alcohol and opioid intake and seeking by normalizing reward and stress systems. We propose that opioid and alcohol dependence share a similar mechanism of action in terms of dysregulation of the HPA axis and sensitization of brain stress systems and that glucocorticoid-mediated plasticity represents a novel therapeutic target for the treatment of stress-related psychiatric disorders.

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CENTRAL AMYGDALA CIRCUITS MEDIATE HYPERALGESIA IN ALCOHOL-DEPENDENT RATS

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[1]LSU Health Sciences Center – New Orleans, USA and [2]The Scripps Research Institute, USA

Humans with alcohol use disorder (AUD) report more pain and report drinking to reduce pain, although the neurobiology underlying these effects is not well understood. The periaqueductal gray (PAG) receives inputs from multiple forebrain regions that are likely important for modulating the activity of the descending inhibitory pain pathway. Using behavioral, optogenetic and electrophysiological techniques, we examined the role of CeA projections to PAG in mediating nociception. Optogenetic inhibition of CeA, as well as optogenetic inhibition of CeA projections to PAG produced thermal hyperalgesia, as measured by the Hargreaves test. We show that alcohol-dependent rats exhibit thermal hyperalgesia during alcohol withdrawal, and that photo-activation of CeA axon terminals within PAG rescues this withdrawal-induced thermal hyperalgesia. We also report that alcohol-dependent rats sacrificed during withdrawal exhibit reduced inhibition of vlPAG neurons evoked from CeA inputs, relative to alcohol-naïve controls, and that mu-opioid receptor function in vlPAG "filters" local inhibition onto putative projection neurons. Finally, we performed experiments that identified melanocortin-4 receptor (MC4R) signaling in CeA as a potential mediator of alcohol withdrawal hyperalgesia in rats. Collectively, our findings demonstrate that altered CeA-to-PAG circuit function and/or brain MC4R system plasticity may mediate alcohol withdrawal hyperalgesia. *Funding*: I01BX003451 R01AA023305, R01AA026531, T32AA007577, F32AA025831, R01AA015566.

THURSDAY, SEPTEMBER 13 10:50 AM–12:20 PM

SYMPOSIUM

METHAMPHETAMINE EPIDEMIC IN THE PHILIPPINES AND COUNTERMEASURES TO OVERCOME PROBLEMS

ORGANIZER/CHAIR: TAKAYUKI HARADA CHAIR: IVANHOE ESCARTIN

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PROJECT FOR INTRODUCING EVIDENCE-BASED RELAPSE PREVENTION PROGRAM TO DRUG DEPENDENCE TREATMENT AND REHABILITATION CENTERS IN THE PHILIPPINES

I. Escartin
Department of Health, Philippines

In the Philippines, residential treatment and rehabilitation services for drug dependents are provided at 45 Treatment and Rehabilitation Centers (TRCs) accredited by the Department of Health (DOH). The Therapeutic Community model has predominantly been adopted at these TRCs; however, its effectiveness has not been sufficiently explored.

In response, the Philippine Government initiated a five-year project to introduce an evidence-based relapse prevention program to TRCs with the technical support of Japan International Cooperation Agency (JICA) in December 2017. The primary objective of the project is to strengthen DOH's capacity to effectively deliver facility-based drug dependence treatment and rehabilitation services. It particularly aims at: (1) establishing a relapse prevention model and a training system for its nationwide dissemination, (2) demonstrating the model's effectiveness by scientific researches, and (3) strengthening DOH's capacity in monitoring and evaluation for treatment and rehabilitation services for drug dependents.

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DETERMINANTS OF RELAPSE RISKS AMONG DRUG USERS PARTICIPATING IN TREATMENT PROGRAMS AT RESIDENTIAL FACILITIES AND COMMUNITIES IN THE PHILIPPINES

S. Kanamori[1,2]
[1]Japan International Cooperation Agency, Japan and [2]The University of Tokyo, Japan

In the Philippines, drug dependence treatment services are provided at residential Treatment and Rehabilitation Centers (TRCs) and at the community level by local governments. The relapse among drug users has not been studied in any drug using populations.

A questionnaire composed of Stimulant Relapse Risk Scale (SRRS) and questions on personal profiles was administered with Shabu users at 14 government TRCs ($n = 1062$) and drug users in the communities ($n = 254$).

A stepwise linear regression indicated a statistically lower SRRS scores among the TRC patients who stayed longer period ($p = 0.01$). The SRRS scores of drug users registered at the local governments were higher among the following categories: high school incomplete or below ($p = 0.006$), working in farming/fishing/forestry industry ($p = 0.026$), prior experience of TRC admission ($p = 0.002$), and those diagnosed as alcohol dependents ($p = 0.003$). The SRRS scores were lower among housewives ($p = 0.042$).

The study result implied the positive impact of the patients' stay at TRCs in reducing relapse risks, while it needs to be validated by further longitudinal studies. It also showed higher relapse risk groups in the community by educational attainment, occupation, prior experience of TRC admission and alcohol dependence, suggesting the need to design prevention and treatment programs targeted to high-risk populations.

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ASSESSING THE SEVERITY OF DEPENDENCE AMONG DRUG USERS PARTICIPATING IN TREATMENT PROGRAMS AT RESIDENTIAL FACILITIES AND COMMUNITIES IN THE PHILIPPINES

A. Villaroman
Department of Health, Philippines

In the Philippines, more than a million drug users have surrendered and registered to the local authorities since the government's nationwide campaign to eliminate illegal drug use started in 2016. Majority of the surrendered drug users participate in community-based programs; however, severely dependent drug users are sent to residential services provided at Treatment and Rehabilitation Centers (TRCs).

A questionnaire survey was conducted with patients admitted at 14 government TRCs (n = 1770) and surrendered drug users registered at three local authorities (n = 308) to identify drugs used and severity of dependence based on Drug Abuse Screening Test 20 (DAST20).

The drugs used by TRC patients and surrendered drug users during the past one year were predominantly Shabu (95.6% and 85.7%, respectively). 47.6% of the TRC patients fell into the substantial or severe category in DAST20 scores, whereas, 47.7% of the surrendered drug users none or low category. Participants in the intermediate category accounted for 37.9% and 39.9% of the TRC patients and the surrendered drug users, respectively.

A policy recommendation could be made toward developing treatment services in between the community-based and the residential programs for Shabu users in the Philippines.

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RECOVERY CLINICS AND RECOVERY HOMES: RAPID DEVELOPMENT OF A PUBLIC-SECTOR, COMMUNITY-BASED, FULLY VOLUNTARY MEDICAL TREATMENT MODEL OF ADDICTION CARE IN THE PHILIPPINES

P. Banys[1,2], F. Paulin[1]
[1]European Union – EPOS, Philippines and [2]University of California at San Francisco (UCSF), USA

Prevailing public-sector models of care are based on extended compulsory detentions in residential Drug and Alcohol Treatment and Rehabilitation Centers (DATRC's). Since July 2016, over 1.3 M citizens have surrendered in *Operation Knock and Plead* as drug users or drug "pushers." The DOH, in collaboration with international consultants, has developed a program of six Recovery Clinics (RC's) and associated Recovery Homes (halfway-houses) to serve as regional models for expansion of community-based services. The design offers medical privacy and confidentiality protections assured by pre-existing privacy laws. There is no penalty, nor prejudicial treatment, for premature dropouts. Patients may receive multiple episodes of care. Relapses and slips are considered a part of chronic relapsing disorders and typically call for renewed services. The *Matrix Model* of stimulant treatment developed at UCLA is the core of the recovery curriculum; and, individualized assessments form the core of professional medical care. An Electronic Medical Record (EMR) is under development to support a Management Information System (MIS) and a clinical record. In 2019, it is expected that one of the Recovery Clinics will be named as a Center of Excellence (CoE) and will serve as the premier training resource for communities that want to develop their own clinics.

THURSDAY, SEPTEMBER 13 9:00 AM–10:30 AM

SYMPOSIUM

ALLOSTERIC MODULATOR DRUGS AS POTENTIAL TREATMENTS FOR ALCOHOL USE DISORDERS

ORGANIZER/CHAIR: ROBERT M. SWIFT CHAIR: CAROLINA HAASS-KOFFLER

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DESIGN, SYNTHESIS AND CHARACTERIZATION OF SMALL MOLECULE GROUP II METABOTROPIC GLUTAMATE RECEPTOR ALLOSTERIC MODULATORS

N.D.P. Cosford
Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA

Recent findings suggest that neuroadaptations in glutamatergic transmission produced by repeated exposure to drugs of abuse such as cocaine or nicotine are likely to contribute to the maintenance of addictive behaviors including drug use, craving and relapse to drug taking in humans. Specifically, it has been shown that repeated cocaine exposure alters the function of the Group II metabotropic glutamate $mGlu_2$ and $mGlu_3$ receptors. Furthermore, nicotine increases glutamatergic neurotransmission by activating excitatory nicotinic acetylcholine (nACh) receptors located on presynaptic glutamatergic terminals. The Group II mGlu receptors, which couple to $G_{i/o}$ proteins to negatively regulate the activity of adenylyl cyclase, are primarily localized presynaptically and modulate glutamate release [1]. Brain regions implicated in different aspects of drug abuse and drug dependence, including the cerebral cortex, hippocampus, striatum, amygdala, frontal cortex and nucleus accumbens display high levels of $mGlu_2$ and $mGlu_3$ receptor binding, suggesting a role for the $mGlu_{2/3}$ receptor subtypes in the development of cocaine dependence and as potential targets for therapeutic agents. We recently reported our preliminary results on a novel series of $mGlu_2$ receptor positive allosteric modulators (PAMs) [2]. Using the $mGlu_2$ receptor PAM 3′-((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yloxy)methyl)biphenyl-4-carboxylic acid (biphenyl indanone-A, BINA) [3] as a starting scaffold we designed and synthesized new $mGlu_2$ receptor PAMs that are significantly more potent than BINA *in vitro* and possess superior drug-like properties. We also recently reported the design, synthesis and characterization of $mGlu_{2/3}$ receptor PAMs with *in vivo* activity [4]. From these two series we have identified compounds which are active in behavioral models of self-administration in rats, providing proof-of-concept for the use of Group II mGlu receptor PAMs for the treatment of drug dependence.

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DEVELOPMENT OF CORTICOTROPIN RELEASING FACTOR BINDING PROTEIN ALLOSTERIC MODULATORS

C.L. Haass-Koffler
Brown University, USA

The corticotropin releasing factor exerts its effects by acting on its receptors and on the binding protein (CRFBP), and has been implicated in alcohol use disorder (AUD). Identification of the contribution of each protein that mediates CRF effects is necessary to design effective therapeutic strategies for AUD. A series of *in vitro* chimeric experiments using CRF-receptor 2 (CRFR2) and CRFBP were performed to define the allosteric modulation of CRF on CRFR2. To establish the CRFBP role in receptor signaling, we developed a novel chimeric cell-based assay and showed that that CFRBP full-length (FL) can stably be expressed on the plasma membrane. We discovered that only CRFBP (10 kD) is able to potentiate CRFR2 CRF-intracellular Ca^{2+} release. We miniaturized the cell-based assay, where we have expressed CRFBP (10 kD) on the plasma membrane fused as a chimera with CRFR2a to develop a high-throughput screening (HTS) assay. We screened >350,000 compounds that resulted in the identification of two lead negative allosteric modulators of the CRFBP (10 kD)-CRFR2 complex are able to blunt CRF-induced potentiation of *N*-Methyl-D-aspartic acid receptor (NMDAR)-mediated synaptic transmission in dopamine neurons in the ventral tegmental area. These results provide evidence of the first specific roles for CRFR2 and CRFBP in the modulation of neuronal activity.

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LONGITUDINAL NEUROIMAGING OF MGLU5 DURING ALCOHOL ABSTINENCE

A. Hillmer[1,2], G. Angarita[1], D. Scheinost[2], I. Esterlis[1], N. Nabulsi[2], Y. Huang[2], J. Krystal[1], R. Carson[2], S. O'Malley[1], K. Cosgrove[1,2]
[1]Department of Psychiatry, Yale University, USA and [2]Department of Radiology and Biomedical Imaging, Yale University, USA

This work aimed to measure metabotropic glutamate receptor 5 (mGlu5) levels with positron emission tomography (PET) imaging using [^{18}F] FPEB, a radioligand that binds to an allosteric site on mGlu5, during early and extended alcohol abstinence. Subjects who met DSM-5 criteria for alcohol use disorder (n = 10) were admitted inpatient and monitored for study duration. Imaging data were acquired during early abstinence (4–11 days since last drink), and a second time for a subset of subjects (n = 8) during extended abstinence (22–28 days since last drink). A single set of images was acquired for sex-matched controls (n = 10). MGlu5 availability was indexed by [^{18}F] FPEB distribution volumes (V_T) measured at steady state throughout the brain. During early abstinence, [^{18}F] FPEB V_T values (units of mL/cm^3) in sample regions of frontal cortex, putamen, hippocampus, and cerebellum did not significantly differ from [^{18}F] FPEB V_T values in control subjects. In extended abstinence, changes in [^{18}F] FPEB V_T from early abstinence were highly variable. Alcohol craving ratings pooled across both timepoints were positively correlated with [^{18}F] FPEB V_T ($p < 0.001$) in regions of frontal cortex. These preliminary data suggest that dynamic changes in mGlu5 availability occur during alcohol abstinence with a possible relationship between mGlu5 availability and alcohol craving.

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EFFECT OF THE MGLUR5 MODULATOR GET 73 ON ALCOHOL PHARMACOKINETICS AND PHARMACODYNAMICS AND ALCOHOL CRAVING IN A HUMAN LABORATORY MODEL

R.M. Swift[1], C. Haass-Koffler[1], R. Cacciaglia[2]
[1]Brown University Center for Alcohol and Addiction Studies, USA and [2]Laboratorio Farmaceutico CT, Italy

To better understand how the mGluR5 negative allosteric modulator (NAM) GET 73 reduces alcohol consumption, and to determine its safety, we conducted a placebo-controlled, within-subjects crossover study with GET 73. Twenty non-treatment seeking alcohol dependent subjects were screened for medical and psychiatric suitability. Those eligible were randomized to the 14-day inpatient study, receiving 3 days of treatment with GET 73 or placebo, followed by a 7-day outpatient washout, followed by 3 days of the alternate medication. Under each drug (GET 73 or placebo) condition, on the second treatment day (Day 2 and Day 12), participants received an oral dose of alcohol to bring BAC to 0.12 g/L. Alcohol pharmacokinetics and pharmacodynamics (intoxication, impairment, mood, sedation, etc.) were monitored and compared between drug and placebo conditions. On Day 3 and Day 13, participants received a laboratory alcohol cue-reactivity (craving) session, followed by alcohol self-administration. The results showed that GET 73 was safe and did not affect alcohol pharmacokinetics in these alcohol-dependent subjects. GET73, compared to placebo decreased blood pressure and subjective craving in response to alcohol cues. Cortisol levels were lower during GET73 treatment, compared to placebo. There was no difference in alcohol self-administration with GET73 treatment, compared to placebo.

THURSDAY, SEPTEMBER 13 10:50 AM–12:20 PM
SYMPOSIUM
NEW INSIGHTS ON THE NEUROBIOLOGY OF ALCOHOLISM: A STEP FORWARD FOR MEDICATION DEVELOPMENT
ORGANIZER/CHAIR: ROBERTO CICCOCIOPPO CHAIR: KOJI TESHIMA

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ALCOHOL DEPENDENCE AND WITHDRAWAL DYSREGULATE THE AMYGDALAR GABAERGIC SYNAPSES

M. Roberto, R.R. Patel, S. Khom, F.P. Varodayan
Department of Neuroscience, The Scripps Research Institute, USA

Using ex vivo slice electrophysiology, we investigated whether alcohol dependence and withdrawal alter noradrenergic (NE) regulation of the rat medial central amygdala (CeA) GABAergic synapses. The locus coeruleus noradrenergic projection innervates the CeA and its activity mediates some of the somatic and affective aspects of alcohol withdrawal. Both norepinephrine and its adrenergic receptors (α1, α2, and β) are abundantly expressed in the CeA. Notably, prazosin (α1 antagonist) reduced the number of drinking days and drinks per day of alcoholic patients, while atenolol and propranolol (β antagonists) reduced their craving, withdrawal tremors and stress. Here, we found that NE increases GABA release in the CeA of naïve male rats, but has mixed effects (increases or decreases it) in alcohol-dependent animals. NE's dual effects stem from differences in adrenergic receptor subtypes (α1 activity increases GABA release and β activity decreases it). Notably, after two weeks withdrawal from the chronic ethanol exposure, NE consistently increases CeA GABA release similar to the effects observed in naïve rats. These findings identify a temporal adrenergic receptor subtype-specific activation in alcohol dependence and highlight the importance of the CeA noradrenergic system as a key site of dysregulation.
Supported by NIH/NIAAA AA025408, AA015566, AA006420, AA017447, AA013498, AA021491.

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STIMULI CONDITIONED TO ALCOHOL CONSUMPTION DURING WITHDRAWAL PRODUCE COMPULSIVE-LIKE BEHAVIOR IN TESTS OF ALCOHOL SEEKING AS MEASURED BY RESISTANCE TO PUNISHMENT AND TOLERANCE OF INCREASED WORKLOAD

F. Weiss, O.O. Kozanian
The Scripps Research Institute, USA

We have reported previously that environmental stimuli conditioned to alcohol consumption during withdrawal episodes elicit significant alcohol seeking during abstinence in rats. More importantly, in these animals, stimuli conditioned to alcohol availability before dependence induction (i.e., in the nondependent state) lost their efficacy to elicit alcohol seeking. Extending these findings, we now show that stimuli conditioned to the effects of alcohol consumption over repeated withdrawal episodes induce pervasive compulsive-like alcohol seeking. Rats responding for these stimuli showed: (i) *resistance to punishment* by footshock, maintaining responding at significantly higher rates and current intensities than nondependent rats, and (i) *willingness to expend increased effort* by maintaining responding over increasing fixed ratio requirements for presentation of these stimuli. Stimuli conditioned to alcohol consumption after completion of withdrawal did not sustain punished responding or willingness to tolerate increased effort. Therefore, a dependence history alone (without withdrawal-related conditioning) is not sufficient to reveal punishment- and effort-resistant alcohol seeking. These finding suggest that stimuli that become conditioned to alcohol consumption during withdrawal episodes are of major motivational significance, presumably because alcohol attains a qualitatively different and more potent reinforcing dimension in dependent subjects compared to its effects in nondependent subjects. Support: NIH/NIAAA AA021549 (F.W.); T32AA007456 (O.K.).

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NOCICEPTIN RECEPTOR ANTAGONISM DECREASES ALCOHOL DRINKING AND SEEKING IN MALE AND FEMALE MARCHIGIAN SARDINIAN ALCOHOL-PREFERRING (MSP) RATS

R. Ciccocioppo[1], A.M. Borruto[1], Y. Fotio[1], S. Stopponi[1], F. Weiss[2], M. Petrella[1], L. Soverchia[1], A. Masi[1], N. Cannella[1]
[1]University of Camerino, Italy and [2]The Scripps Research Institute, USA

The reinforcing and rewarding properties of alcohol are mediated by several neurochemical pathways including the Nociceptin/OrphaninFQ (N/OFQ) peptidergic/NOP receptor system.
To shed light on the therapeutic potential of NOP antagonism in alcoholism we examined the effect of selective receptor blockade on 10% alcohol drinking and on cue and stress (yohimbine) induced reinstatement of alcohol seeking in male and female msP rats. To detect the mode of action of NOP antagonists, experiments at the neurocircuitry level were also conducted. Results demonstrated that systemic blockade of NOP leads to a significant reduction of alcohol consumption and seeking both in males and female msP rats. Microinjection studies revealed that alcohol drinking was attenuated following selective blockade of NOP in the ventral tegmental area (VTA) and in the central amygdala (CeA) but not in the nucleus accumbens. Yohimbine-induced reinstatement of alcohol seeking was blocked by NOP antagonism in the VTA and CeA. Whereas cue-induced relapse was attenuated after injection of the antagonist into the VTA only.
Our results demonstrate that NOP antagonism is a new suitable pharmacological approach to treat excessive alcohol drinking and relapse. The CeA and the VTA are the neuroanatomical substrates that mediate these effects. *Grant support (AA017447 and AA014351)*

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ML375 A NOVEL NEGATIVE ALLOSTERIC MODULATOR (NAM) OF (M_5) MUSCARINIC RECEPTOR (MACHR) ATTENUATES ALCOHOL DRINKING AND SEEKING IN GENETICALLY SELECTED IP RATS THROUGH MODULATION OF DORSOLATERAL STRIATUM M5 RECEPTORS

A.J. Lawrence[1,2], A. Berizzi[3], C.J. Perry[1,2], D.M. Shackleford[3], C.W. Lindsley[4], C.K. Jones[4], N. Chen[1,2], P.M. Sexton[3], A. Christopoulos[3], C.J. Langmead[3]
[1]Florey Institute of Neuroscience & Mental Health, Australia, [2]University of Melbourne, Australia, [3]Monash Institute of Pharmaceutical Science, Australia and [4]Vanderbilt Center for Neuroscience Drug Discovery, USA

Alcohol use disorders (AUDs) remain a major health risk within society, and both relapse and heavy drinking are still poorly controlled with current medications. Here we demonstrate that a centrally active and selective negative allosteric modulator (NAM) for the rat M_5 muscarinic receptor (mAChR), ML375, decreases ethanol self-administration and attenuates cue-induced reinstatement of ethanol-seeking in iP rats. Importantly, ML375 did not affect sucrose self-administration or general locomotor activity. Based on the expression profile of M_5 mAChRs in the brain and the distinct roles different aspects of the dorsal striatum have on long and short term ethanol use, we studied whether intra-striatal microinjection of ML375 modulated ethanol intake in rats. In iP rats with an extensive history of ethanol intake intra-dorsolateral (DL), but not intra-dorsomedial (DM), striatal injections of ML375 reduced ethanol self-administration to a similar extent as varenicline, which has preclinical and clinical efficacy in reducing the reinforcing effects of ethanol. These data implicate the DL striatum as a locus for the effects of cholinergic-acting drugs on ethanol-seeking in rats with a history of long-term ethanol use. We provide direct evidence that the M_5 mAChR is a potential novel target for pharmacotherapies aimed at treating AUDs.

TUESDAY, SEPTEMBER 11 2:55 PM–4:25 PM
SYMPOSIUM NOVEL FINDINGS FROM BENCH TO BEDSIDE – GLUMATE HYPOTHESIS FOR ADDICTIVE DISORDER – CO-SPONSORED BY EISAI CO.,LTD
CHAIR: HIDEHIKO TAKAHASHI

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THE ROLE OF GLUTAMATE ACTIVITY AT AMPA RECEPTORS IN ADDICTIVE DISORDER

T. Takahashi
Department of Physiology, Yokohama City University School of Medicine, Japan

The glutamate homeostasis imbalance leads impaired communication between prefrontal cortex and the nucleus accumbens (NAc) that can be associated with some addictive disorder such as substance use disorder. Chronic alcohol consumption results in strengthened excitatory neurotransmission and increased α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor signaling in animal models. Several findings revealed that the surface expression of AMPA receptors were increased in the NAc and inhibition of AMPA receptor attenuated alcohol self-administration. Most recently, the AMPA receptor PET probe has developed by Yokohama City University and supported such evidences that the glutamate activity at AMPA receptors may be the key role in facilitating alcohol consumption. This session will introduce novel findings from the perspective of translational research and discuss the possibility of future treatment option based on the glutamate homeostasis imbalance.

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ANTI-CRAVING DRUG AND THE STRUCTURE OF CRAVING

H. Miyata
Department of Psychiatry, Jikei University School of Medicine, Japan

In this session, the structure of craving is reviewed, and the possible mechanism of the anti-craving drugs is discussed from the perspective of the effects of these drugs on the structure of craving. Craving is hypothesized to be composed of three determinants. 1) The first is the primary reinforcing property of a substance of abuse, the neural mechanism of which is mediated by the stimulating effects of the substance on the brain reward system. 2) The second determinant is the secondary reinforcing property of a substance of abuse (conditioned aspects of the environment associated with substance taking). 3) The third determinant to elicit craving is the negative affective motivational property during withdrawal. With regard to the neural mechanism of the negative affective property during withdrawal, compensatory desensitization of the reward system that mediates the primary reinforcing property is considered to form a basic component of craving. Several neural systems are reported to be involved in the compensatory desensitization of the reward system. For example, hypofunction of dopamine, opioid, or GABA system, or hyperfunction of glutamatergic system are the candidates of responsible regions mediating withdrawal-elicited craving. Therefore, the drug which recover the above neural dysfunction are expected to alleviate craving.

SUNDAY, SEPTEMBER 9 1:30 PM–3:00 PM

ISBRA-WHO WORKSHOP

DEFINING AND DIAGNOSING DISORDERS DUE TO SUBSTANCE USE AND ADDICTIVE BEHAVIOURS: FOCUS ON ICD-11 AND ITS COMPARISONS WITH ICD-10 AND DSM-5

FACILITATOR: VLADIMIR POZNYAK

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CLINICAL ASPECTS OF TAXONOMY OF SUBSTANCE USE DISORDERS: BETWEEN SEMANTICS AND LOGIC, ICD-11 AND ITS COMPARISON WITH ICD-10 AND DSM-5

W.E. Kosmowski
Department of Psychiatry CM Bydgoszcz, Nicolaus Copernicus University, Poland

The aim is to describe selected aspects of semantics and logic of diagnostic systems to facilitate their use in clinical practice. Important features of classification are: transparency, intelligibility, unambiguity, ease of use. ICD-10 (also ICD-11) leads to long and non-specific diagnoses; DSM-5 uses simpler wording. There are different criteria for classification: anatomical; pathological – by disease processes; etiological – by causes; clinical – by symptoms. Yet in ICD-11 vascular dementia is moved to neurocognitive disorders, Wernicke-Korsakoff syndrome – to nutritional deficiency. Mild alcohol use disorder (DSM-5, 2 symptoms) is not necessarily concordant with alcohol abuse (F10.1 – ICD-10). The new version of the classification is longer, more complicated, difficult for making diagnoses. The term "alcohol abuse" (ICD-10) is replaced by a longer "harmful pattern of use of alcohol" (ICD-11). Using psychiatric classification requires knowledge of general and specific psychopathology, and examination methods. This can be more or less difficult, more or less ambiguous, depending on the diagnostic system. The translation of the new classification should not be based on a simple comparison of diagnostic codes, but on the analysis of symptoms and course of diseases. ICD-11 should be refined: simpler terms, standardized criteria for the division of disorders into categories.

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GAMBLING AND GAMING DISORDER AS ADDICTION BEHAVIOR IN ICD-11 AND DSM-5: SIMILARITIES AND DIFFERENCES

K.S. Kurniasanti
Psychiatry, Universitas Indonesia, Indonesia

Discussion on definition and diagnostic criteria of gambling and gaming disorder as behavioral addiction continue as this issues were included in ICD-11 draft and DSM-5. This paper will review similarities and differences of gambling and internet gaming disorder in ICD-11 and DSM-5. Pathological gambling was changed to gambling disorder in DSM-5, listed on substance-related and addictive disorder chapter. Internet gaming disorder was included on DSM-5 in section of "condition for further study". In ICD-11, gambling disorder and gaming disorder was grouped on substance and gambling disorder. In DSM-5 and ICD-11, certain criteria were common in gambling and gaming disorder including preoccupation, progressive loss of control, recreational activity negligence, continuation of gaming or gambling despite negative consequences. Contrary with DSM-5, ICD-11 doesn't include tolerance and withdrawal as diagnostic criterion of gaming disorder, it was in line with experience in clinical practice that patients with online game addiction often have no tolerance and withdrawal symptoms. ICD-11 and DSM-5 include 12-months period to diagnose either gambling or gaming disorder, but in ICD-11 diagnosis can be established within a brief time if symptoms were severe. Whereas there was update in ICD-11, research on internet addiction and development of internet addiction questionnaires in adolescents is important as we are doing in Indonesia.

SUNDAY, SEPTEMBER 9 3:30 PM–5:00 PM

ISBRA-WHO WORKSHOP

ALCOHOL AND DRUG EPIDEMIOLOGY TO INFORM POLICY DEVELOPMENT: HOW TO CONDUCT RELEVANT EPIDEMIOLOGICAL RESEARCH ON SUBSTANCE USE AND SUBSTANCE USE DISORDERS

FACILITATOR: HANS JÜRGEN RUMPF

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PROFILE OF ALCOHOL-DEPENDENT PATIENTS ADMITTED IN DEADDICTION WARD OF A TERTIARY LEVEL HOSPITAL IN NEPAL

S.B. Pant, S. Dhungana, S.P. Ojha, M. Chapagai, P. Tulachan
Department of Psychiatry and Mental Health, Institute of Medicine, Tribhuvan University Teaching Hospital, Nepal

Introduction: Alcohol dependence is a global problem worldwide and is very commonly seen in Nepal. Multiple factors account for this problem varying from biological, psychological to social. This study was conducted to find out the diagnostic profile, socio- cultural determinants, motivation level and other variables related to alcohol dependence in hospital admitted patients.
Methods: A cross- sectional study carried out in patients diagnosed as alcohol dependence and admitted in the deaddiction ward of Tribhuvan University Teaching Hospital over a period of eight months.
Results: A total of 86 patients were admitted and 48% for the diagnosis of alcohol dependence-complicated withdrawal while remaining 52% were admitted for uncomplicated withdrawal. The total duration of alcohol intake was 7.5 ± 4.2 years. In stage of motivation for change, majority of the patients i.e. 43% were in precontemplation phase, 27.9% were in the contemplation phase, 9.3% were in preparation phase, and 19.8% were in the action phase. More than 70% of patients with complicated withdrawal belonged to nuclear family when compared to uncomplicated withdrawal.
Conclusion: In this study, we assessed the overall profile of patients admitted with alcohol dependence so that this data can be used for better management of our patients in future.

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ALCOHOL DRINKING AND RISK OF CANCERS: FINDINGS FROM THE CHINA KADOORIE BIOBANK

P.K. Im[1], L. Yang[1], I.Y. Millwood[1], Y. Guo[2], Z. Bian[2], L. Li[3], Z. Chen[1]
[1]Nuffield Department of Population Health, University of Oxford, UK, [2]Chinese Academy of Medical Sciences, Beijing, China and [3]Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China

Background: Large-scale prospective evidence on alcohol and cancer risks for drinking guideline development from Chinese population is sparse.
Methods: The nationwide China Kadoorie Biobank cohort recruited 512,713 adults aged 30–79 years during 2004–2008. Information on alcohol drinking was collected by baseline questionnaire, with incident cancer events (n = 27,531) collected through death and disease registries and health insurance records to 2017. Cox regression yielded adjusted hazard ratios (HR) relating alcohol consumption to cancer risks.
Results: Overall, 33% of men and 2% of women drank alcohol weekly at baseline. Among male weekly drinkers, each 20 g of alcohol intake/day was associated with a HR of 1.10 (95%CI:1.08–1.11) for overall cancers, and increased risks of cancers in oesophagus (1.22 [1.19–1.25]), lip, oral cavity and pharynx (1.15 [1.09–1.21]), liver (1.11 [1.07–1.16]), lung (1.06 [1.03–1.10]) and colon-rectum (1.05 [1.00–1.10]). Starting drinking regularly at younger age increased stomach cancer risk. Compared with non-daily drinkers, daily drinkers experienced increased risks of oesophageal (1.76 [1.39–2.22]) and colorectal cancers (1.25 [1.00–1.56]) after adjusting for total weekly consumption. Among men consuming >280 g/week, compared with drinking outside of meals, drinking with meals was associated with lower liver cancer risk (0.62 [0.42–0.91]).
Conclusions: Drinking guidelines should incorporate the combined roles of consumption level and drinking patterns on cancer risks.

MONDAY, SEPTEMBER 10 9:50 AM–11:20 AM
ISBRA-WHO WORKSHOP
RELIABLE AND ACCURATE BRIEF ASSESSMENT OF ALCOHOL USE AND ALCOHOL USE DISORDERS IN HEALTH CARE SETTINGS
FACILITATOR: JOHN B. SAUNDERS

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ASSESSING ALCOHOL USE IN PATIENTS WITH COMORBID MENTAL HEALTH DISORDERS IN JAPAN: EARLY INTERVENTION OF ALCOHOLISM FROM THE GENERAL HOSPITAL IN JAPAN

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[1]Department of Psychiatry, Teine Keijinkai Hospital, Sapporo, Japan and [2]Psychiatric Institute, Hokujinkai Medical Corporation, Japan

In Japan, the nationwide survey for assessing the prevalence of alcoholics was 1.09 million. Despite the huge number of potential patients, Alcoholics who visit the psychiatric hospital are only 40 thousand. In other words, low of consultation rate is the big problem in Japan. A lot of alcoholics go to internal medicine, emergency, orthopedics, but they do not attend psychiatric hospitals. Therefore, we set up alcoholics' expert clinics in the general hospital for early intervention. Alcohol has several effects on health. Insomnia, cognitive impairment, anxiety disorder are caused by alcohol use. Especially High rates of major depressive disorder occur in heavy drinkers and those who abuse alcohol. Alcohol misuse is associated with several mental health disorders and alcoholics have a very high suicide rate. We need to use psychological tests (M.I.N.I., MMSE, HAM-D) to assess mental disorders for alcohol users. In this presentation, I will describe the detail methods and tips of the intervention.

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SELF-REPORTED DSM-5 ELEVEN CRITERIA TO ASSESS ALCOHOL USE DISORDER: IS IT A RELIABLE AND ACCURATE BRIEF ASSESSMENT? EVIDENCE FROM A COMMUNITY-BASED SAMPLE

S. Baggio[1,2], S. Rothen[1], F. Sporkert[3], J.-B. Daeppen[3], G. Gmel[3], K. Iglesias[4]
[1]Geneva University Hospitals, Switzerland, [2]University of Lausanne, Switzerland, [3]Lausanne University Hospital, Switzerland and [4]HES-SO University of Applied Sciences and Arts of Western Switzerland, Switzerland

Aims: Short reliable screening tools of alcohol use disorder (AUD) are crucially needed for population-based assessments, but current measures are likely to be misinterpreted by respondents. This study aimed to test the quality of the widely used self-reported DSM-5 AUD and to propose a suitable alternative measure.
Methods: Participants were recruited based on a stratified random selection of the Swiss Cohort Study on Substance Use and Risk Factors (200 participants). Assessments included a clinical interview (gold standard) based on the Diagnostic Interview for Genetic Studies (DIGS) and self-reported alcohol measures.
Results: Preliminary results showed that the current diagnostic threshold for AUD (more than 2 symptoms) lacks in specificity. The best alternative was to include DSM-5 AUD symptoms and alcohol-related consequences with a cut-off score of 5 or more.
Conclusions: Self-reported DSM-5 AUD should not be used as a binary variable designed to classify individuals as disordered alcohol users because it has led to a high proportion of false positives. An acceptable alternative is to use an 'alcohol-related harm' measure, including AUD symptoms and alcohol-related consequences. These findings will help to reduce the use of unreliable self-reported scales and may have a large impact on future alcohol research.

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DEATH CAUSED BY HIGH CONCENTRATION AND MIXED FORMULA ALCOHOL IN INDONESIA

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Psychiatric Division of Pambalah Batung General Hospital, Indonesia

Indonesia is facing challenges from multiple sources of addiction, not least of which is alcohol. While alcohol is regulated in Indonesia significant problems have arisen due to the availability of illegal alcohol, known as oplosan, which is distributed through the black market. This illegal alcohol is characterized by high concentrations of methanol, often exceeding 70%.
Problems associated with illegal alcohol consumption have become a national issue, surfacing as recently as April 2018, when 107 deaths were reported in Java and Kalimantan Island due to the consumption of alcohol with high concentrations of methanol.
However, fatalities are not solely caused by methanol concentration. The health impact been exacerbated when the alcohol has been combined with other substances, such as energy drinks, soda, and even mosquito repellent. Victims seem not to consider or understand the lethal consequence of high concentration methanol. This may be a product of poor economic backgrounds and low levels of education. The frequency of consumption of high concentration methanol alcohol in Indonesia is high, due to the affordability of illegal alcohol and lack of police enforcement. Moreover, individuals who drink occasionally are not considered to be suffering from addiction. As a result, healthcare professionals lack tools to deal with these cases. We believe that concise assessment tools and rapid interventions can make a significant difference. In this, we trust that WHO can play a part in ameliorating the situation.

MONDAY, SEPTEMBER 10 1:00 PM–2:30 PM
ISBRA-WHO WORKSHOP
TRANSLATING EVIDENCE INTO PRACTICE IN DIFFERENT HEALTH CARE SYSTEMS: FOCUS ON BRIEF INTERVENTIONS AND COGNITIVE BEHAVIOURAL THERAPIES IN THE MANAGEMENT OF ALCOHOL USE AND ALCOHOL USE DISORDERS
FACILITATOR: MARGARET MURRAY

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MINDFULNESS-BASED RELAPSE PREVENTION FOR ALCOHOL USE DISORDER: A NOVEL APPROACH FOR TREATMENT IN DIVERSE HEALTH CARE SETTINGS

K. Witkiewitz, C. Roos, E. Stein, A. Wilson, V. Votaw, M. Kirouac
University of New Mexico, USA

Introduction: Relapse to heavy drinking is common following alcohol use disorder treatment, and there is a clear need for interventions that target predictors of the alcohol relapse process. Mindfulness-Based Relapse Prevention (MBRP) incorporates mindfulness practices within a cognitive-behavioral relapse prevention approach. The ultimate goal of MBRP is to increase awareness of triggers and automatic reactions in the service of reducing the risk of relapse to heavy drinking during and following alcohol treatment.
Method: Review of four randomized clinical trials of MBRP for alcohol and substance use disorders in diverse settings. We have conducted two trials in community addiction treatment programs (n = 168 and n = 286), one trial was conducted in a residential facility for female criminal offenders (n = 105), and the most recent trial evaluated a rolling group version of MBRP in an outpatient treatment setting (n = 86).
Results: Results from the randomized clinical trials have found MBRP to be more efficacious than community treatment-as-usual and relapse prevention in the reduction of heavy drinking days and drug use days (Cohen's d range from 0.27 to 0.41).
Discussion: The current results highlight efficacious adaptations of mindfulness-based cognitive behavioral treatment to diverse clinical populations and health care systems in the management of alcohol use disorder.

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AROMATHERAPY IN THE COMPLEX TREATMENT OF EMOTIONAL DISORDERS IN THE STRUCTURE OF ALCOHOL ABSTINENCE SYNDROME

A.A. Ismatov, S.N. Lukmonov
Department of Psychiatry and Narcology, Tashkent Medical Academy, Uzbekistan

Purpose: Determine the preferences of essential oil and their correlations with psychoemotional state.
Materials and Methods: During the participation of 28 women who were being treated in women's ward of city psychiatric narcological hospital. Age ranges from 18 to 60 years. All patients were diagnosed with alcohol dependence, alcohol withdrawal syndrome.
Results: Based on the results of the HADS scale, it turned out that the normal level of anxiety was in 70% of those surveyed; 75% of the women tested did not show signs of depression. Differences between preferences of subjects depending on the level of anxiety/depression on the HADS scale are not revealed. As a result of research. (50% of cases, women choose sandalwood in 50% of cases, in fourth place – fir (70% of votes), in fifth place, as the most unpleasant, is leader of basil (57%). The most pleasant is orange, 2nd place – ylang/sandal, 3rd place – sandal/ylang, 4th place – fir, least pleasant – basil.
Conclusions: The data obtained with aroma diagnostic approach reveal such characteristic psychoemotional features of women, blocks in alcohol withdrawal state, as emotional instability, the need for relaxation, poor awareness of their spiritual and psychological problems.

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HOW TO INCREASE TREATMENT COVERAGE FOR ALCOHOL DEPENDENT PATIENTS – SPECIAL POPULATIONS IN POLAND

M.J. Turczynowicz-Kosmowski[1], W.E. Kosmowski[2]
[1]Faculty of Law, University of Warsaw, Poland and [2]Department of Psychiatry CM Bydgoszcz, Nicolaus Copernicus University, Poland

In the treatment of alcohol addicts, harm reduction plays an important role, especially by rapid diagnostics of health problems and therapy adapted to their severity. According to legal regulations in Poland, forced treatment is possible after experts' opinion – one psychiatrist and one psychologist or addiction therapist. Two premises are needed: clinical (diagnose of alcohol dependence) and behavioral (at least one of the following: demoralization of juveniles, family dysfunction, repeated disturbance of the peace, work avoidance). There are no age restrictions. It is regulated by the Act on Upbringing in Sobriety. The effectiveness of this treatment is lower than in the case of treatment with patient's consent. It results largely from insufficient therapy availability. In 2000, over 24.5 thousand petitions for forced addiction treatment were submitted to the court; in 2012 there were 40,159 petitions. The number of persons obliged to the treatment increased from 35 thousand in 2000 to almost 55 thousand in 2012. The second path includes addiction treatment for inmates, in accordance with the Executive Penal Code. There are 33 special therapeutic units in Poland focused on alcohol dependence treatment. In addition, in some cases it is possible to change detention into obligation to ambulatory addiction treatment.

MONDAY, SEPTEMBER 10 2:50 PM–4:20 PM
ISBRA-WHO WORKSHOP
HOW TO INCREASE TREATMENT COVERAGE FOR ALCOHOL USE DISORDERS
FACILITATOR: KARL F. MANN

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TREATMENT OF PATIENTS WITH MULTIPLE SUBSTANCE USE DISORDERS

M. Delic
Center for Treatment of Drug Addiction, University Psychiatric Hospital Ljubljana, Slovenia

People with substance use disorders are heterogeneous, with wide variations across groups in terms of substances used, their resources and strengths. There are different modalities of treatment and different interventions we use. Very often persons with opioid or cocaine addiction use are addicted also to alcohol and benzodiazepines. Alcohol is commonly combined with both prescription and illicit drugs in an effort to achieve a "better" or "stronger" high, or in an effort to counteract the effects of certain substances. Treatments of drugs and alcohol addiction are usually divided in Slovenia, also alcohol is very embedded and tolerated in people's life. All these factors are considered in creation of treatment programs we have in Slovenia in which we integrated psycho and pharmacotherapy. The purpose of this presentation is to describe program in which we address multiple substance use disorders (opioids, cocaine, benzodiazepines and alcohol). Since withdrawal from multiple substances is more complicated than withdrawal from one substance, inpatient medical detox is generally recommended. The accent is on addressing motivation, teaching coping skills, changing reinforcement contingencies, fostering management of painful affects, improving interpersonal functioning and enhancing social supports, and fostering compliance and retention in pharmacotherapy.

SUNDAY, SEPTEMBER 9 1:30 PM–5:15 PM
THE 13TH INTERNATIONAL SYMPOSIUM ON ALPD AND CIRRHOSIS
SESSION 1 – GUT DYSBIOSIS AND ALCOHOLIC LIVER DISEASE (ALD)

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GUT DYSBIOSIS, NUCLEAR TRANSGLUTAMINASE AND HEPATOCYTE DEATH

S. Kojima
Liver Cancer Prevention Research Unit, RIKEN Center for Integrative Medical Sciences (IMS), Japan

Accumulation of a crosslinking enzyme transglutaminase (TG)2 in the nucleus induces apoptosis in hepatic cells treated with alcohol/free fatty acids (Gastro 2009; JCP 2012) and MYCN(+) liver cancer stem cells treated with acyclic retinoid (Mol Cancer 2011; PNAS 2018) via crosslinking and silencing Sp1 thus decreasing expression of c-Met or MYCN.
The liver acts as the first barrier to the spread of fungi and bacteria present in intestine. In ASH and NASH patients, these fungi and bacteria invade gastrointestinal mucosa to reach the liver. Co-incubation of human hepatic cells or mouse primary hepatocytes derived from wild-type but not $TG2^{-/-}$ mice with pathogenic *Candida* species and *E. coli*, but not *Saccharomyces cerevisiae*, induced hepatic cell death by enhancing nuclear TG2 via ROS, as detected by a fluorescent probe and ESR. Both *N*-acetyl cysteine (a ROS scavenger) and phenosafranin (an inhibitor of nuclear localization of TG2) suppressed nuclear TG activity and inhibited apoptosis, while deletion of *C. glabrata nox-1* resulted in a failure to induce the same phenomena. A similar induction of hepatic ROS and TG activities was observed in *C. albicans*-infected mice.
These results address an association of ROS-producing fungi/bacteria with enhanced nuclear TG2 in hepatic cells leading to their apoptosis.

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GUT DYSBIOSIS AND ALCOHOLIC LIVER DISEASE (ALD)

B. Schnabl
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The intestinal microbiota and the human body have a symbiotic relationship. A disruption of this delicate homeostasis between host and microbes can lead to disease. Chronic liver disease is associated with an increase in microbial numbers and changes in the bacterial and fungal composition. We have recently demonstrated that chronic alcohol consumption is associated with altered intestinal fungi (mycobiota) and translocation of fungal products. The contribution of dysbiosis to alcoholic liver disease goes beyond a dysfunction of the intestinal barrier. Microbial metabolites are equally important for the progression of liver disease. For example, changes in bile acid profiles, lower bacterial synthesis of butyrate and saturated long-chain fatty acids contribute to ethanol-induced liver disease. Restoration of intestinal homeostasis and eubiosis is an effective strategy for attenuation of alcohol-related liver disease. Recent preclinical studies emphasized the importance of intestinal inflammation for the onset of gut barrier disruption and microbial translocation for alcoholic liver disease. In conclusion, the gut microbiota represents an excellent target to prevent the onset and progression of liver disease.

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AKKERMANSIA MUCINIPHILA AND ALCOHOLIC LIVER DISEASE

H. Tilg
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Akkermansia muciniphila is one of the most abundant members of the human gut microbiota (1–5% of all intestinal microbes). The abundance of A.muciniphila is decreased during obesity and diabetes. It has recently also been demonstrated that a purified membrane protein from A.muciniphila improves metabolic dysfunction in mice. Several food extracts (e.g. an arctic berry extract) which improve metabolic liver disease increase intestinal concentrations of A.muciniphila.
We recently investigated the role of A.muciniphila in alcoholic liver disease (ALD). Humans with severe alcoholic hepatitis show a massive decrease in the concentration of fecal A.muciniphila. Ethanol feeding in mice also resulted in a dramatic loss of A.muciniphila. Interestingly, oral feeding of A.-muciniphila restored this decrease potently. The administration of A.muciniphila to mice exposed to ethanol (acute and chronic model) improved hepatic steatosis, liver injury and neutrophilic liver infiltrations. This was the case both in a preventive and therapeutic setting. Mechanistically, administration of A.muciniphila enhanced mucus thickness and tight junction expression. Intestinal concentrations of A.muciniphila have recently also been demonstrated to affect efficiacy of checkpoint inhibitors in various malignancies. To conclude, ethanol-induced depletion of A.muciniphila might contribute to ALD. Supplementation of this bacterium could evolve as new therapeutic principle in liver diseases.

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THE ROLES AND MECHANISMS OF CELLULAR SENESCENCE IN OBESITY-ASSOCIATED LIVER CANCER

E. Hara
Department of Molecular Microbiology, Research Institute for Microbial Diseases, Osaka University, Japan

Multiple epidemiological studies have revealed that obesity is a major risk factor for not only diabetes and cardiovascular diseases but also cancer. Effective strategies for obesity prevention are therefore needed for cancer prevention. However, since the prevalence of excess bodyweight in most developed countries has been increasing markedly over the past several decades, alternative approaches are also required to conquer obesity-associated cancer. Although several phenomena have been proposed to explain how obesity increases cancer risk, the exact molecular mechanisms underlying these cancer have remained largely obscure. Recently, we have traced the association between obesity and increased cancer risk to microbiota communities that provoke cellular senescence. The analyses also revealed the role of cellular senescence in obesity-associated cancer. In this symposium, I will provide an overview of our recent work on cellular senescence in obesity-associated cancer and discuss the next steps, focusing on the potential clinical implications of these findings.

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CIRCADIAN CLOCK AND DYSBIOSIS IN ALD

A. Keshavarzian, R. Voigt, G. Swanson, P. Engen, M. Sheik, A. Naqib, S. Green, C. Forsyth
Rush University, USA

Several human epidemiological studies have now demonstrated that excessive alcohol consumption is required but not sufficient to cause end organ damage including alcoholic liver disease (ALD) since only 20% of patients with alcohol use disorders (AUD) develop ALD. Multiple animal experimental studies have shown that gut-derived inflammation is the required cofactor for ALD and recent human and animal studies demonstrated that abnormal intestinal microbiota ("dysbiosis") is the most likely trigger for this inflammatory cascade. The question then is why only subset of those with AUD develop dysbiosis. We hypothesized that disruption of circadian rhythm is one of the key factors that makes gut microbiota more susceptible to alcohol effect leading to severe enough dysbiosis to disrupt intestinal barrier integrity and trigger sustained inflammatory cascade that is required for ALD. The hypothesis is based on: (1) alcohol can disrupt circadian rhythms, (2) shift workers with disrupted circadian rhythms are at risk of developing ALD and NALD and (3) circadian disruption is extremely common in western societies and is a pro-inflammatory state. In this presentation, we will provide evidence from our animal and human studies that support our hypothesis and demonstrate that: (1) circadian misalignment in both rodent and human is associated with low butyrate producing dysbiotic microbiota community, disruption of intestinal barrier function and systemic inflammation, (2) disrupted circadian exacerbates alcohol-induced dysbiosis, gut leakiness to LPS and ASH and (3) the deleterious impacts of circadian misalignment on alcohol-induced gut leakiness appears to be due to low butyrate and low butyrate promotion of epigenetic changes in tight junctional proteins.
Supported by RO-1 grant from NIAAA.

SUNDAY, SEPTEMBER 10 8:30 AM–12:05 PM

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SESSION 2 – ALCOHOL, INFLAMMATION AND ORGAN CROSSTALK

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ROS GENERATION VIA ENDOCYTOSIS OF TLR4-NOX2 IN MACROPHAGES

W.-i. Jeong
Graduate School of Medical Science and Engineering, KAIST, Korea

Reactive oxygen species (ROS) contribute to the development of non-alcoholic fatty liver disease (NAFLD). ROS generation by infiltrating macrophages involves multiple mechanisms, including Toll-like receptor 4 (TLR4)-mediated NADPH oxidase (NOX) activation. Here, we show that palmitate-stimulated $CD11b^{+}F4/80^{low}$ hepatic infiltrating macrophages, but not $CD11b^{+}F4/80^{high}$ Kupffer cells, generate NOX2-mediated ROS via dynamin-mediated endocytosis of TLR4-MD2 complex, independently from MyD88 and TRIF. We demonstrate that differently from LPS-mediated dimerization of the TLR4-MD2 complex, palmitate binds a monomeric TLR4-MD2 complex that triggers endocytosis, ROS generation and increases pro-interleukin-1β expression in macrophages. Palmitate-induced ROS generation in human $CD68^{low}CD14^{high}$ macrophages is strongly suppressed by inhibition of dynamin. Furthermore, NOX2-deficient mice are protected against high-fat diet-induced hepatic steatosis and insulin resistance. Therefore, endocytosis of TLR4 and NOX2 in macrophages might be a novel therapeutic target for non-alcoholic fatty liver disease.

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EXTRACELLUAR VESICLE MIRNAS IN ALCOHOLIC STEATOHEPATITIS

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Extracellular vesicles (EVs) have been growingly shown to play important roles in cell-to-cell communication and as biomarkers. We recently reported that hepatocyte-derived EVs (Hep-EVs) are increased in circulation in a murine model and in patients with mild alcoholic steatohepatitis (Hepatology 2017). Here the study was extended to characterize EVs released by hepatocytes isolated from a murine model of neutrophilic alcoholic hepatitis (AH) with advanced fibrosis and to determine the microRNA composition of these EVs via miR-seq for their potential roles in modulating hepatic stellate cells (HSC) phenotype. We found that Hep-EVs and circulating EVs were significantly increased in AH mice. The miR-seq analysis detected differentially expressed miRNAs in Hep-EVs from AH mice (AH-Hep-EVs). Some up-regulated miRNAs (miR-126 etc) are known to target IκBα genes and contribute to liver fibrogenesis. Treatment of mouse primary HSCs with AH-Hep-EVs up-regulated bona fide HSC activation markers and more importantly, some of 344 genes uniquely and differentially regulated in HSCs from AH model which are also predicted targets of identified miRNAs (miR-25 etc). These results support the notion that Hep-EVs contribute to HSC activation and liver fibrosis in AH via delivery of a specific miRNA cargo to facilitate a unique transcriptome profile in activated HSCs.

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STERILE INFLAMMATION IN ASH AND NASH

W.Z. Mehal
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Sterile Inflammation (SI) occurs after tissue injury, and the liver is notable for having a high amplitude of SI resulting in the clinical syndromes of alcoholic and non-alcoholic hepatitis (ASH and NASH). There is great interest in the factors that initiate SI, the pathways that control amplitude and result in its termination. We have been examining the role of specific initiating signals such as oxidized mitochondrial DNA and regulating factors such as pyruvate kinase M2 (PKM2).
Oxidized mitochondrial DNA has significant pro-inflammatory activities via activation of TLR9 and cGAS pathways, and frequently exists in the setting of increased ROS. We have been identifying the relative importance of ROS and oxidized mitochondrial DNA in SI, and clarifying the contribution of the cGAS pathway.
PKM2 is a multifunctional protein that is best known as a cytosolic kinase and results in the production of pyruvate. It has additional functions as a transcription regulator for HIF-1a and other loci. We have identified that PKM2 has an important role in regulating SI in the liver in ASH and NASH. This has implications for therapy as the transcriptional regulation of PKM2 can be manipulated to reduce liver inflammation.

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ALCOHOL, INFLAMMATION, AND ORGAN CROSS-TALK

L.E. Nagy
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Chronic ethanol exposure results in inflammation in adipose tissue; this response is associated with activation of complement as well as the development of alcoholic liver disease (ALD). Adipose communicates with other organs, including liver, via the release of soluble mediators, such as adipokines and cytokines, characterized as the “adipose secretome”. Here we investigated the role of the anaphylatoxin receptors C3aR and C5aR in the development of adipose tissue inflammation and regulation of the adipose secretome in murine ALD (mALD). Ethanol feeding increased the expression of adipokines, chemokines and leukocyte markers in gonadal adipose tissue from WT and *C3aR*−/−, but not *C5aR*−/− mice. Bone marrow chimeras, generated with WT and *C5aR*−/− mice, revealed C5aR expression on adipocytes contributed to ethanol-induced adipose inflammation. Chronic ethanol feeding regulated both the quantity and distribution of adipokines secreted from adipocytes. Interestingly, the cargo of adipocyte-derived extracellular vesicles (EVs) was distinct from the soluble secretome. C5aR modulated the impact of chronic ethanol on the content of the adipose secretome, as well as influencing the cargo of an extensive array of adipokines from adipocyte-derived EVs. Taken together, our data demonstrate that C5aR contributes to ethanol-mediated changes in the adipose secretome, likely contributing to intra-organ injury in ALD.

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ALCOHOL-INDUCED LIVER-LUNG INTERACTIONS

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Both Alcoholic Liver Disease (ALD) and alcohol-related susceptibility to acute lung injury are estimated to account for the highest morbidity and mortality related to chronic alcohol abuse and, thus, represent a focus of intense investigation. In general, alcohol-induced derangements to both organs are considered to be independent and are often evaluated separately. However, the liver and lung share many general responses to damage, and specific responses to alcohol exposure. For example, both organs possess resident macrophages that play key roles in mediating the immune/inflammatory response. Additionally, alcohol-induced damage to both organs appears to involve oxidative stress that favors tissue injury. Another mechanism that appears to be shared between the organs is that inflammatory injury to both organs is enhanced by alcohol exposure. Lastly, altered extracellular matrix (ECM) deposition appears to be a key step in disease progression in both organs. Indeed, recent studies suggest that early subtle changes in the ECM may predispose the target organ to an inflammatory insult. This presentation will review the parallel mechanisms of liver and lung injury in response to alcohol consumption, as well as also explore the potential that these mechanisms are interdependent, as part of a liver-lung axis.

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PROTEOSTASIS: AN IMPORTANT REGULATOR OF INFLAMMATION IN ALD

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The importance of a multitude of pathways crucial in maintaining cellular protein homeostasis such as heat shock response, ER or unfolded protein response and autophagy in alcoholic organ injury have been recently emerging. Understanding effects of alcohol on these pathways is critical to develop new therapeutic strategies. During cellular stress, the molecular chaperone machinery prevents protein aggregation or misfolding and facilitates protein folding to maintain cellular proteostasis. We propose that studying the role of chaperones in alcohol mediated innate immune cell activation during liver injury will uncover novel cellular targets and therapies. Many signaling kinases and adapters in macrophages including activation of NLRP3 inflammasome, a multimeric protein complex, that serves as a scaffold to cleave pro-caspase-1 and induce IL-1β and IL-18 is identified in alcoholic liver disease (ALD). Stress-mediated chaperone heat shock protein 90 (HSP90) facilitates NLRP3 inflammasome activation in innate immune cells. Our data reveal that HSP90 is required for NLRP3 inflammasome activity in alcoholic liver, specifically in macrophages/Kupffer cells and its therapeutic targeting reduces active IL-1β in ALD. In addition, induction of HSP70 may also serve to directly inhibit liver macrophage activation. Our studies will demonstrate clinical relevance of HSP90 inhibition in preventing inflammation in ALD.

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IL-17 LINKS LIVER INFLAMMATION TO ALCOHOL DEPENDENCE

T. Kisseleva
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Chronic alcohol abuse has a detrimental effect on the brain and liver. There is no effective treatment for these patients and the mechanism underlying alcohol addiction and consequent alcohol-induced damage of the liver/brain axis remains unresolved. We compared experimental models of alcoholic liver disease (ALD) and alcohol dependence in mice and demonstrated that genetic ablation of IL17 Receptor A (IL17ra$^{-/-}$), or pharmacological blockade of IL17 signaling effectively suppressed the increased voluntary alcohol drinking in alcohol-dependent mice, and blocked alcohol-induced hepatocellular and neurological damage. Our data suggest that IL17A is a critical common mediator of excessive alcohol consumption and alcohol-induced liver/brain injury, and targeting IL17A may provide a novel strategy for treatment of alcohol-induced pathology.

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ROLE OF AUTOPHAGY IN ALCOHOL-INDUCED ADIPOSE ATROPHY AND LIVER INJURY

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Increasing evidence implicates the role of adipose-liver axis in in the pathogenesis of alcoholic liver disease (ALD). However, the mechanisms of how adipose tissue is affected by alcohol and contributes to ALD are largely unknown. We found that chronic-plus-binge alcohol led to smaller adipocytes and decreased adipose tissue mass without obvious inflammation. Mechanistically, we found that chronic plus binge alcohol inhibited mTOR/Akt signaling pathways and enhanced autophagic flux in epididymal adipose tissue. Adipose-specific autophagy-related gene 5 (Atg5) knockout (A-Atg5 KO) mice were resistant to alcohol-induced adipose tissue atrophy. Moreover, A-Atg5 KO mice had increased browning in subcutaneous white adipose tissue likely due to impaired autophagic removal of mitochondria (mitophagy). In addition, we found autophagy is required for the differentiation of adipocyte in vitro but ethanol and acetaldehyde did not affect the differentiation of adipocytes in vitro. A-Atg5 KO mice also had increased basal levels of adiponectin and FGF21 although there were only mildly further increased after ethanol. As a result, A-Atg5 KO mice were more resistant to alcohol-induced oxidative stress and liver injury, though they still developed alcohol-induced liver steatosis.

SUNDAY, SEPTEMBER 10 1:15 PM–5:05 PM

THE 13TH INTERNATIONAL SYMPOSIUM ON ALPD AND CIRRHOSIS

SESSION 3 – ALCOHOL, METABOLIC REPROGRAMMING, AND MALIGNANCIES

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HEPATIC STEATOSIS AND IMPAIRED GLUCOSE HOMEOSTASIS

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We previously reported activating factor 3 (*ATF3*) gene is associated with the induction of type 2 diabetes (T2D) and alcohol consumption-induced metabolic dysfunction. Hepatic steatosis induced by chronic ethanol consumption or obesity may contribute to impaired glucose tolerance and T2D; however, the precise mechanisms and target molecules that are involved remain unclear. We aimed to explore the exact functional role of ATF3 as a mechanistic link between hepatic steatosis and T2D. Zucker diabetic fatty (ZDF) rats were utilized for animal experiments. An *in vivo*-jetPEI siRNA delivery system against ATF3 was used for loss-of-function experiments. We analyzed the baseline cross-sectional data derived from the hepatic steatosis registry ($n = 322$).
ATF3 was highly expressed in the livers of ZDF rats and human hepatic steatotic liver. Insulin resistance and steatosis were associated with increased ATF3 expression and decreased fatty acid oxidation via mitochondrial dysfunction and were attenuated by *in vivo ATF3* silencing. Knockdown of *ATF3* ameliorated glucose intolerance, impaired insulin action, and inflammatory responses in ZDF rats. In patients with steatosis, a significant positive correlation was observed between hepatic ATF3 expression and surrogate markers of T2D, and mitochondrial dysfunction. Therefore, ATF3 may serve as a potential therapeutic target for hepatic steatosis and T2D.

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MICRORNA IN ALCOHOL INDUCED LIVER INJURY

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We generated hepatocyte miR-21 (Hep-KO)-deficient mice to elucidate its role in alcoholic liver disease (ALD). Hep-KO mice fed the ethanol diet had increased hepatic triglyceride (TG) but decreased plasma TG levels, which was associated with increased lipogenesis but decreased VLDL secretion. Interestingly, inflammation was attenuated in Hep-KO, as evident by the decreased serum AST and ALT levels, and reduced expression of key hepatic pro-inflammatory genes. At the cellular level, the activation of P38 and JNK were suppressed in Hep-KO. We identified DUSP16, a gene known as a phosphatase of P38 and JNK, as a miR-21 downstream target. DUSP16 protein was down-regulated in patients with alcoholic liver cirrhosis, where miR-21, P-P38 and P-JNK levels were elevated. We further demonstrated that miR-21 was secreted from hepatocytes in exosomes to mediate the inflammatory response of Kupffer cells. Taken together, hepatocyte miR-21-deficiency promotes alcoholic steatosis, but ameliorates liver injury and inflammation through the miR-21/DUSP16/P38 pathway. Our work provides novel insights into the understanding of the molecular mechanism of non-coding RNAs as key regulators in alcoholic liver disease.

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CELL FATE AND METABOLIC REPROGRAMMING OF TUMOR-INITIATING STEM-LIKE CELLS

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Background & Aims: Tumor-initiating stem-like cells (TICs) are defective in maintaining asymmetric cell division and responsible for tumor recurrence. Stem cell markers such as Nanog have been implicated in various cancer, but whether they are functionally contributing to cancer pathogenesis has remained unclear. Novel NOTCH/NUMB-interacting protein, TBC1D15, is overexpressed and contributes to p53 degradation in TICs. Aims are to identify NANOG- or TBC1D15-mediated oncogenic mechanisms and to test tumorigenic roles.
Methods: We determined novel targets of NANOG in tumor-initiating cells (TICs) from patient and mouse models of hepatocellular carcinoma (HCC) using genome-wide NANOG-binding site analysis (ChIP-seq) and how *Nanog* is regulated at the transcriptional to promote oncogenesis and self-renewal in TICs. TBC1D15 interacting proteins were searched by large-scale immunoaffinity purification and LC-MS analysis. We examined HCC development in alcohol Western diet (AWD)-fed HCV NS5A Tg mice with hepatocyte-specific TBC1D15 deficiency or hepatocyte-specific expression of non-phosphorylatable NUMB mutations (non-p-NUMB).
Results: Silencing NANOG inhibits tumor development in HCC mouse models and genesis of TICs. NANOG binds genes of oxidative phosphorylation and β-oxidation in mitochondria. Silencing NANOG promotes oxidative phosphorylation and β-oxidation, indicating that NANOG is a suppressor of mitochondria-mediated energy production. We identified NuMA1, RANGAP1 and NOTCH1-4 as TBC1D15-interacting proteins. TBC1D15-NuMA1 association impaired NuMA1-LAN interaction which is essential for an asymmetric division machinery, thereby promoting TIC self-renewal. TBC1D15-NOTCH1 interaction activated and stabilized NOTCH1 and NOTCH1 Intracellular Domain (N1ICD) which in turn upregulated transcription of *Nanog* essential for TICs.
Conclusions: These results suggest that NANOG-mediated metabolic reprogramming through suppression of mitochondria function in both experimental and clinical HCC downstream of TLR4/NANOG generates TICs and drives liver tumorigenesis. TBC1D15 and p-NUMB are required for liver tumor development *in vivo*.

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LIPIDOMIC ABNORMALITIES IN ASH

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Alcoholic hepatitis (AH) has high mortality despite steroid therapy. Lipid abnormalities play an important role in the pathophysiology of alcoholic hepatitis. In our study cohort of human subjects with alcoholic hepatitis (moderate and severe based on MELD score) when compared with heavy drinking and healthy nonalcoholic controls, several plasma lipidomic changes were observed. One of the key findings of our work is that the ratio of 16:1 n7/16:0 increased in a step wise manner from healthy nonalcoholic controls (mean $\pm$ SEM, 0.13 $\pm$ 0.03) vs. heavy drinking controls (0.17 $\pm$ 0.03) vs. moderate alcoholic hepatitis (0.37 $\pm$ 0.04) vs. severe alcoholic hepatitis (0.39 $\pm$ 0.03) ($p < 0.0001$ by ANOVA for multiple comparisons). Also, the ratio of 18:1 n9/18:0 increased incrementally from healthy controls to heavy drinking controls to moderate alcoholic hepatitis to severe alcoholic hepatitis (2.36 $\pm$ 0.17 vs. 2.46 $\pm$ 0.22 vs. 3.07 $\pm$ 0.23 vs. 3.56 $\pm$ 0.19 respectively, $p < 0.0001$). The hepatic lipidome was characterized in Tsukamoto mouse model of binge drinking and compared to the western diet alone. One of the main findings was significantly increased total cholesterol esters and diacylglycerols in alcohol binge model. In contrast, total phosphatidylcholine was significantly decreased in alcohol binge model.

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ROLE OF CYTOGLOBIN IN STELLATE CELL ACTIVATION, LIVER FIBROSIS, AND CANCER DEVELOPMENT

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Cytoglobin (CYGB) belongs to the globin family and is expressed in hepatic stellate cells (HSCs). In addition to its gas-binding ability, we have been demonstrated that CYGB deficiency induced spontaneous fibrosis and cancer development in aged mouse liver and augmented their manifestation in mice treated with DEN- or CDAA-diet. On the other hand, HSC-specific overexpression of CYGB-mCherry protected mice from TAA-triggered liver fibrosis. These results obtained by *in vivo* studied confirmed that CYGB is an important molecule for maintenance of HSCs in a quiescent status. While we have been searching for molecules that triggered CYGB induction in human HSCs, we noticed that FGF2 is a key factor in inducing the alteration in both CYGB and αSMA expression in human HSCs. FGF2 initiated the phosphorylation of both JNK and c-JUN. C-JUN overexpression up- and down-regulated CYGB and αSMA expression, respectively. In ChIP analyses, phospho-c-JUN bound its consensus motif located -218 to -222 bases from the transcription initiation site in the *CYGB* promoter upon FGF2 stimulation. In contrast, TGFβ1 antagonized the effect of FGF2. In conclusion, CYGB is likely a critical molecule relevant to the maintenance of quiescent phenotype of human HSCs.

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TREATMENT OF LIVER FIBROSIS AND CIRRHOSIS

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Following chronic liver injury of any etiology, there is progressive fibrosis. To date, removing the causative agent is the only effective therapy to stop or even reverse liver fibrosis. Therefore, the development of effective antifibrotic therapies represents a challenge for modern hepatology. In the past decade, dramatic advances have been made in the understanding of the cellular and molecular mechanisms underlying liver fibrogenesis, which have identified new targets for therapy.

The first line of therapy is to protect the hepatocyte from injury, and therefore block progressive inflammation and fibrosis. The best studied hepatoprotective agents are the FXR agonists. These have advanced from bile acid derived FXR agonists such as OCA with several side effects to non-bile acid FXR agonists with fewer side effects. Other hepatoprotective drugs include inhibitors of ASK1, a MAPKKK that induces apoptosis and JNK inhibitors.

Inhibitors of inflammation may also block downstream fibrosis. Several chemokines, cytokines, and interleukins have been targeted. These include CCR2 (a major chemokine receoptor for macrophage in the liver), CCR5 (a major chemokine receptor for hepatic stellate cells), and IL-17, a key mediator of the innate immunity in the liver. Reactive oxygen species which are downstream products of injury may also contribute to inflammation and fibrosis. In particular, the role of NOX1 and NOX4 has been demonstrated in liver fibrosis and small molecular inhibitors have been tested.

The identification of activated hepatic stellate cells (HSCs) as the major fibrogenic cell type in the injured liver, as well as the recognition of key cytokines involved in this process, have facilitated the design of promising new antifibrotic therapies. These therapies are aimed at inhibiting the accumulation of activated HSCs at the sites of liver injury and preventing the deposition of extracellular matrix. Although many of these approaches are effective in experimental models of liver fibrosis, their efficacy and safety in humans are still unknown.

A number of antifibrogenic agents are effective in cultures of activated HSCs and in experimental models of liver fibrosis. Importantly, clinical trials evaluating the efficacy and safety of some of these agents are underway. The most promising therapies include antioxidant drugs, cytokine modulators, and antagonists of vasoconstrictor substances. Moreover, several natural products show antifibrotic activity in experimental fibrosis. Future research should be focused on the pathogenesis of fibrosis in different types of liver diseases as well as on the development of drug carriers to specifically deliver antifibrotic compounds to the activated HSCs.

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PROMOTION OF PANCREATIC CANCER DEVELOPMENT BY ALCOHOL AND WESTERN DIET FEEDING

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Pancreatic ductal adenocarcinoma (PDAC) is an aggressive tumor with metastatic capacity. Environmental factors, such as cigarette smoking, chronic pancreatitis, heavy alcohol drinking, and obesity, are also know to increase a risk of PDAC. In the present study, we tested whether the combination of these environmental risk factors induces advanced pancreatic tumors in *Pdx1*^{Cre}; LSL-*Kras*^{G12D} mice. Treatment with all of these factors induced advanced pancreatic cancer development including invasive PDAC. Among these risk factors, we found that a combination of alcohol feeding with Western diet induces aggressive tumor in the pancreas and its metastasis to the liver.