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TUESDAY, SEPTEMBER 11
1. ALCOHOL

P1-1-1

EFFICACY OF GABAPENTIN IN THE TREATMENT OF ALCOHOL DEPENDENCE: A DOUBLE-BLINDED, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

R. Kalayasiri[1,2], P. Chompookham[2], W. Rukngan[2], S. Nilaban[2], S. Suwanmajo[2], P. Yoosom[2]
[1]Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Thailand and [2]Princess Mother National Institute on Drug Abuse Treatment, Thailand

Rationale: Pharmacological treatments for alcohol use disorder show a modest effect, and they are unavailable in certain countries.
Objectives: To investigate the effects of gabapentin on alcohol drinking in a Thai alcohol-dependent population.
Methods: One hundred twelve individuals with alcohol dependence were randomly assigned in equal numbers to either of two groups: gabapentin treatment o-r placebo. Thirty-four patients (30.3%) completed the study protocol, i.e., oral treatment with at least 300 mg of gabapentin per day or placebo, administered once a day for twelve weeks. The alcohol drinking pattern was assessed by means of the timeline followback method. The drinking behaviours of the two groups were compared by means of the Poisson repeated measures model.
Results: Twenty subjects (35.7%) from the gabapentin group and 14 subjects (25.0%) from the placebo group completed the study protocol. The participants in the gabapentin group did not differ significantly from those in the placebo group with respect to demographics or baseline alcohol drinking behaviour. After follow-up, the gabapentin group showed a lower percentage of heavy drinking days per week than the placebo group ($p < 0.005$).
Conclusions: Gabapentin may be used to reduce the frequency of heavy drinking in individuals with alcohol use disorder.

P1-1-2

MATERNAL ALCOHOL BINGE IS ASSOCIATED WITH NEUROINFLAMMATION AND AFFECTS COGNITIVE AND MOTIVATIONAL RELATED BEHAVIOURS IN OFFSPRING MICE

O. Valverde[1], L. Cantacorps[1], S. Montagud-Romero[1], S. Alfonso-Loeche[2], C. Guerri[2]
[1]Department of Experimental and Health Sciences, GReNeC-NeuroBio., University Pompeu Fabra, Spain and [2]Molecular and Cellular Pathology of Alcohol, Principe Felipe Research Center, Spain

Perinatal alcohol exposure caused by maternal alcohol intake during gestation and lactation periods can have detrimental effects on the brain development and behaviour of offspring. However, little is known about the long-term effects of maternal alcohol binge drinking on brain function. To address this issue, we used pregnant C57BL/6 female mice with time-limited access to a 20%v/v alcohol solution as a procedure to model alcohol binge drinking during gestation and lactational periods. Adult male offspring were assessed for cognitive functions, motor coordination, emotional behaviour and rewarding effects of alcohol in the conditioned place preference paradigm. Early alcohol exposure induced motor coordination impairments in the rotarod test. Y-maze performance was impaired in early alcohol-exposed mice. Moreover, increased anxiety-like behaviour and attenuated alcohol-induced rewarding effects were observed in adult male offspring. Behavioural effects were associated with an upregulation of pro-inflammatory signalling, such as Toll-like receptor 4, nuclear factor-kappa B p65, and others in both the prefrontal cortex and hippocampus of mice exposed to alcohol. Our results demonstrate that maternal binge-like alcohol drinking causes long-lasting effects on motor, cognitive and emotional-related behaviours associated with neuroinflammation and that such effects may underlie the persistent cognitive and behavioural impairments observed in foetal alcohol spectrum disorders.

P1-1-3

MOOD DISORDERS AND ALCOHOL CONSUMPTION IN PRE-CLINICAL AND EPIDEMIOLOGICAL STUDIES

P. Ruiz[1,2], A. Calliari[1], A. Pilatti[2], P. Genovese[1], R. Pautassi[2]
[1]Universidad de la República, Uruguay and [2]Universidad Nacional de Córdoba, Argentina

Mood disorders and alcohol consumption co-occur and emerge during adolescence, yet there is controversy as to how they relate to each other, and their neurobiological substrates. We analyzed these phenomena via pre-clinical and epidemiological studies. We induced depressive- and mania-like states in adolescent rats by administering reserpine or amphetamine drugs. The effectiveness of these models was tested via measurements of dopamine in the insula, and by behavioral tests of exploratory behavior (i.e., open field). The main results were that females, but not males, with experimentally-induced depression exhibited heightened ethanol intake during late adolescence; whereas treatment with amphetamine, increased ethanol intake in males, but not in females, rats. These results indicate that depression and mania, in females and males respectively, can trigger the initiation of voluntary ethanol drinking in adolescence. We also conducted an online survey in Uruguayan youth ($n = 1527$, 27% men, mean age $= 23.5 \pm 3.5$ years) that measured alcohol use and consequences, and psychological discomfort. We observed a significant association between alcohol use and psychological discomfort, which were fairly similar across sex. The results support the hypothesis postulating mood variations, with correlated alterations in insular dopamine levels, as a predisposing factor for problematic alcohol consumption.

P1-1-4

STAR-RELATED LIPID TRANSFER PROTEIN 10 AS NOVEL KEY PLAYER IN ETHANOL-INDUCED ERBB2 BREAST CANCER PROGRESSION

A. Floris[1,2], S. Orru[2], K. Ramani[1], M. Biancolella[3], C. Cossu[1], M.L. Tomasi[1]
[1]Cedars-Sinai Medical Center, USA, [2]University of Cagliari, Italy and [3]University of Rome Tor Vergata, Italy

Propose: Alcohol abuse induces ErbB2 Receptor Tyrosine Kinase 2 (ErbB2) oncogene in breast cancer (BR). StAR-related lipid transfer protein 10 (StarD10), a lipid transporter of phosphatidylcholine and phosphatidylethanolamine, essential for lipid metabolism and membrane fluidity, is highly expressed in 35% of ErbB2-positive BR. Our aim is to investigate the role of StarD10 and ErbB2 cross-talk in BR under ethanol administration and elucidate the molecular mechanisms.
Methods: MCF-7 and SKBR-3 cell lines were used to analyze mRNA (Real-Time PCR), protein levels (Western Blotting), StarD10 promoter activity (reporter assay), cell proliferation (MTT) and phosphatidylcholine (enzyme-coupled).
Results: Ethanol-treated cells exhibited increased StarD10 and ErbB2 expression. StarD10 and ErbB2 positively regulate each other's expression. Overexpression of ErbB2 downstream (p65, c-MYC, c-FOS, c-JUN) induced StarD10 promoter activity. However, Stard10 silencing and overexpression promoted cell growth and migration. In addition, ethanol-treated cell media showed high level of secreted phosphatidylcholine, while StarD10 silencing completely prevented it. In contrast, StarD10 overexpression promoted phosphatidylcholine secretion and induced it further in co-treatment with ethanol. This finding could explain how StarD10 potentially controls the cell membrane fluidity and influences ErbB2 function.
Conclusions: This is the first report demonstrating that ethanol modulates in dynamic manner ErbB2 role through StarD10 involvement in BR.

P1-1-5

EFHD2/SWIPROSIN-1 IS A CONSERVED RESILIENCE FACTOR AGAINST ALCOHOL DRINKING ESCALATION

C.P. Müller[1], M. Reichel[1], T. Jia[2], E.B. Quinlan[2], A. Schambony[3], T. Bäuerle[4], V. Eulenburg[5], A. Lourdusamy[6], G. Schumann[2], D. Mielenz[7]
[1]Department of Psychiatry and Psychotherapy, University Clinic, Friedrich-Alexander-University of Erlangen-Nuremberg, Germany, [2]MRC SGDP Centre, Institute of Psychiatry, Kings College London, De Crespigny Park, London, UK, [3]Biology Department, Developmental Biology, Friedrich-Alexander University Erlangen-Nuremberg, 91058 Erlangen, Germany, [4]Institute of Radiology, University Medical Center Erlangen, Palmsanlage 5, 90154 Erlangen, Germany, [5]Institute of Biochemistry, Friedrich-Alexander-University of Erlangen-Nuremberg, 91054 Erlangen, Germany, [6]Division of Child Health, Obstetrics and Gynaecology, School of Medicine, University of Nottingham, NG7 2UH, UK and [7]Division of Molecular Immunology, Department of Internal Medicine III, Nikolaus-Fiebiger-Center, University Clinic, Friedrich-Alexander-University of Erlangen-Nuremberg, Germany

Alcohol is a widely used drug around the globe. A relatively small proportion of the regular consumers, however, develop alcohol addiction. Resilience factors that protect from the transition are not understood. Here we report recent findings on the role of EFhd2/Swiprosin-1 in the control of alcohol addiction-associated behaviours. We observed that mice lacking EFhd2 drink more alcohol than controls and spontaneously escalate their consumption. EFhd2 knock out (KO) mice showed a sensation-seeking/low anxiety phenotype. The lack of EFhd2 reduced extracellular dopamine levels in the brain, but enhanced responses to alcohol. A reversal of the behavioural phenotype with β-carboline normalized alcohol preference in EFhd2 KO mice. These findings were confirmed in a human sample with a positive association of an EFHD2 SNP with lifetime drinking and a negative association with anxiety in healthy adolescents. We found that EFhd2 regulates the expression of genes involved in brain development. Magnetic resonance imaging (MRI) in mice showed that a lack of EFhd2 reduces cortical volume in adults, but enhances dendrite and spine number of neurons. Human MRI confirmed the negative association between lifetime drinking and superior frontal gyrus volume. These findings suggest EFhd2 as a conserved resilience factor against alcohol consumption and its escalation.

P1-1-6

BUILDING NEW PERSPECTIVE AND INTERNATIONAL PARTNERSHIP IN ACADEMIC DEGREE TRAINING AND EDUCATION STUDY PROGRAMS IN ALCOHOL AND OTHER DRUG ADDICTIONS: THE INTERNATIONAL CONSORTIUM OF UNIVERSITIES FOR DRUG DEMAND REDUCTION

T. Zima[1], M. Miovský[2], A. Vondrová[2]
[1]Charles University, Czech Republic and [2]Department of Addictology, 1st Faculty of Medicine, Charles University, Czech Republic

The International Consortium of Universities for Drug Demand Reduction (ICUDDR) is newly established body (2016) and it is a global consortium of universities which offer graduate and postgraduate study programs specifically focusing on the transfer and adaptation of science-based knowledge regarding the prevention and treatment of alcohol and other substance use disorders. The Consortium provides a collaborative forum to support and share curricula and experiences in the teaching and training of this knowledge as well as to promote and encourage the recruitment of persons interested in the research, prevention and treatment of alcohol and other substance use disorders and public health. The ICUDDR (www.icuddr.com) provides an opportunity for universities and institutions of higher learning to share their expertise as well as to support instructors/faculty, trainers, and students in their learning and adoption of the science of substance use disorders. Two international internet-based surveys have recently examined the scope of academic education programs in addiction studies. The Charles University became a coordinating centre for Europe and has develop down academic degree programs on BC, MA and PHD levels but also has started adaptation of the first international curricula for prevention (UPC) and for treatment (UTC).

P1-1-7

MTORC2 IN THE DORSOMEDIAL STRIATUM OF MICE CONTRIBUTES TO ALCOHOL-DEPENDENT F-ACTIN POLYMERIZATION, STRUCTURAL MODIFICATIONS, AND CONSUMPTION

S. Laguesse[1,2], N. Morisot[1], K. Phamluong[1], D. Ron[1]
[1]Department of Neurology, University of California, San Francisco, CA 94143, USA and [2]GIGA-Neurosciences, University of Liege, Liege, Belgium

Actin cytoskeleton is the major component of dendritic spines and plays an essential role in structural and functional synaptic plasticity. The mammalian target of rapamycin (mTOR) is a serine and threonine kinase which associates with Rictor, mSIN1 and Deptor to form the mTOR complex 2 (mTORC2). mTORC2 is an important regulator of actin polymerization that has been involved in learning and memory. Here, we report that excessive alcohol intake increases F-actin assembly in the dorsomedial striatum (DMS) of mice, thereby altering dendritic spine morphology in a mechanism that requires mTORC2. Specifically, we found that excessive alcohol consumption increases mTORC2 activity in the DMS, and that knockdown of Rictor reduces actin polymerization. We further showed that alcohol intake increases the spine head size of DMS medium spiny neurons and the proportion of mushroom-shaped spines, and that Rictor knockdown attenuates the alcohol-dependent alterations in spine morphology. Finally, we show that silencing Rictor in the DMS reduces alcohol consumption, whereas intra-DMS infusion of the mTORC2 activator, A-443654, increases alcohol intake. Together, our results suggest that mTORC2 in the DMS facilitates the formation of F-actin, which in turn induces changes in dendritic spine structure to promote excessive alcohol intake.

P1-1-8

ANXIETY SENSITIVITY IN ASSOCIATION WITH ALCOHOL-RELATED BEHAVIORS AMONG COLLEGE STUDENTS: THE ROLE OF NEGATIVE URGENCY

L. Garey[1], B.Y. Kauffman[1], D.J. Paulus[1], C. Jardin[1], A.G. Viana[1], C. Neighbors[1], M.J. Zvolensky[1,2]
[1]Department of Psychology, University of Houston, USA and [2]Department of Behavioral Sciences, University of Texas MD Anderson Cancer Center, USA

Extant work has documented the relationship between anxiety sensitivity (AS) and problematic alcohol-related behaviors. However, little research has evaluated underlying mechanisms that may explain their association. The present study tested the hypothesis that AS would exert an indirect effect on alcohol-related behaviors through negative urgency among a sample of 507 college students (74.4% female; $M_{age} = 22.07$; $SD = 3.83$) who reported at least one heavy episodic drinking (HED) event in the previous month and at least 1 lifetime sexual partner. Alcohol-related behaviors included sex-related alcohol negative consequences, negative consequences of alcohol use, and alcohol-related protective behavioral strategies. Results indicated that AS indirectly related to sex-related alcohol negative consequences, negative consequences of alcohol use, and alcohol-related protective behavioral strategies through negative urgency. These findings remained significant after controlling for gender, age, Greek life membership, number of lifetime sexual partners, negative affectivity, and typical drinking in the past month. Findings provided novel empirical evidence that, among college students, AS may be a risk factor for alcohol-related behaviors indirectly through negative urgency. Overall, the present investigation extends the growing body of literature aimed to explicate the relationship between AS and alcohol-related behaviors and may aid in intervention approaches among college students.

P1-1-9

MEDICAL GUIDELINES FOR THE USE OF THIAMINE IN ALCOHOL USE DISORDER: NO LACK OF CLINICAL EFFICACY, BUT LACK OF RECOMMENDATIONS?

N. Pruckner, J. Baumgartner, B. Hinterbuchinger, B. Vyssoki
Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria

Introduction: Patients with alcohol use disorder (AUD) frequently suffer from cognitive deficits ranging from mild symptoms to most severe forms. Wernicke encephalopathy (WE), caused by thiamine deficiency, is a potentially fatal neurological syndrome. It frequently presents in patients with alcohol dependency and, if left untreated, can progress to Korsakoff syndrome. Due to oftentimes indistinct clinical presentation, WE remains undiagnosed in up to 80% of cases.
Methods: We conducted a systematic review of the current treatment guidelines for AUD in order to identify recommendations for the use of thiamine. Two different keyword combinations were entered in PubMed and Scopus, additional guidelines were searched screening the online sites of the respective agencies or societies. In total, 11 guidelines were included.
Results: Thiamine was mentioned in all of the reviewed publications. Specifications on application modalities and indications varied considerably. While the majority of reviewed guidelines recommended parenteral thiamine only for patients at high risk for WE, some gave no information regarding the application form or dosage. Furthermore, hardly any evidence-based recommendations exist on a more general use of thiamine as a preventative intervention in individuals with AUD.
Further research is of utmost importance to raise awareness for this obviously undervalued problem.

P1-1-11

ASTROCYTE-DERIVED EXOSOMES AS INFLAMMATORY MEDIATORS INDUCED BY ETHANOL: ROLE OF TLR4

F. Ibáñez[1], M. Pascual[1,2], J. Montesinos[1], J. Ureña[1], C. Guerri[1]
[1]Department of Molecular and Cellular Pathology of Alcohol, Principe Felipe Research Center, Valencia, Spain and [2]Department of Physiology, School of Medicine and Dentistry, University of Valencia, Valencia, Spain

Ethanol activates glial cells through Toll-like receptor 4 (TLR4) responses triggering neuroinflammation. Recent evidences indicate the participation of exosomes, tiny cytoplasmic vesicles (30–100 nm), in the intercellular signaling and in the regulation and amplification of neuroinflammation. Here we evaluate the involvement of the exosomes secreted by astroglial cells in ethanol-induced inflammatory response, and the potential role of TLR4 in this process. We use exosomes isolated from the extracellular medium of primary culture astrocytes, from WT and TLR4-KO mice, treated with or without ethanol (50 mM) during 24 h. Using flow cytometry and nanoparticle tracking analysis system to measure particles in suspension, as well as exosomal markers (tetraspanins), we observed that the total number of secreted nanovesicles was higher in ethanol-treated WT astrocyte than in untreated cells. We further noted that exosomes from ethanol-treated WT astrocytes contains higher levels of different proteins (TLR4, p65, R-IL-1β, caspase-1, NLRP3) and changes in several inflammatory-related miRNA (146a, 200a, 200b) than non-treated WT cells. No changes were observed in the amount of isolated exosomes between untreated and ethanol-treated TLR4-KO cells. These results suggest that astrocyte-derived exosomes could act as cellular transmitters, amplifying the neuroinflammatory response induced by ethanol through TLR4 activation.

P1-1-12

CURRENT STATUS OF ALCOHOLIC HEPATITIS IN JAPAN (2011–2014) AND EFFECTS OF STEROID THERAPY ON ITS PROGNOSIS

Y. Horie[1], M. Kikuchi[2]
[1]Shonan Keiiku Hospital, Japan and [2]National Hospital Organization Tokyo Medical Center, Japan

Background and aims: Using a new scoring system for alcoholic hepatitis (AH), the Japan Alcoholic Hepatitis Score (JAS), ability of the score to predict outcome was confirmed in order to identify therapeutic interventions such as steroid that can improve prognosis.'
Methods: Questionnaires were sent to 1,496 medical institutions asking for information on patients with AH during 2011 to 2014.
Results: The full demographic data of 148 patients with severe AH were analyzed. Eighty-three were alive and 65 were dead. A level of total bilirubin (TB), and prothrombin time (PT-INR) at day 5 were higher in the severe AH patients who died. Patients whose TB levels over 10 mg/dL had a higher mortality rate, while steroid administration improved it.
Conclusions: These results suggest that, irrespective of severity, steroid therapy should be carried out if TB levels are over 10 mg/dL or those at day 5 do not show full recovery.
Keywords: alcoholic hepatitis, Japan Alcoholic Hepatitis Score, corticosteroids, bilirubin, gastrointestinal bleeding.

P1-1-13

REAL-TIME NEGATIVE AFFECT, CENTRAL AUTONOMIC DYSREGULATION, AND RELAPSE IN ALCOHOL USE DISORDER TREATMENT SEEKERS

D. Eddie[1], D. Chaffee[1], M. Barr[2], P. Fielding[3], J.F. Kelly[1]
[1]Recovery Research Institute, Massachusetts General Hospital, Harvard Medical School, USA, [2]Harvard University, USA and [3]Tufts University, USA

There is growing laboratory-based evidence that individuals with alcohol use disorder (AUD) experience central autonomic network dysregulation, and that this dysregulation may play a key role in AUD relapse, yet to date, central autonomic functioning has never been studied in real time as individuals in early recovery from AUD interact with their environment. Moreover, though high levels of negative affect are known to increase AUD relapse risk, negative affect has typically been studied as though it were a static phenomenon using individuals' aggregated, retrospective self-reports. Most existing research has not taken advantage of newer real-time psychological assessment methods that can study dynamic psychological processes such as affect as individuals navigate their environment. The present study is, for the first time, combining ambulatory electrocardiogram (ECG) monitoring with ecological momentary assessment of affect to better understand the psychophysiological and affective determinants of relapse in individuals receiving outpatient treatment for AUD. Findings are reported here on associations between in situ heart rate variability, a reliable biomarker of central autonomic regulation derived from the ECG waveform, in situ negative affect, and 90-day follow-up alcohol use among 50 AUD treatment seekers.

P1-1-14

ROLE OF MIRNAS IN THE ETHANOL-INDUCED NEUROINFLAMMATION AND TLR4 RESPONSE IN MICE CEREBRAL CORTEX: DEEP SEQUENCING AND MIRNAS PROFILE

C.M. Cuesta, J. Ureña-Peralta, S. Alfonso-Loeches, C. Guerri
Research Center Prince Felipe, Cell Pathology Laboratory, Spain

MicroRNAs emerge as important regulators of gene expression and modulators of inflammatory responses in neurodegenerative diseases and neurological disorders. Alcohol abuse can induce brain damage and neurodegeneration and recent evidences shown the participation of the immune receptors toll-like (TLRs) in the neuroinflammation and brain damage associated with alcohol-abuse. We evaluated the role of miRNAs as potential modulators of the neuroinflammation associated with alcohol abuse and the influence of TLR4 response in these effects. Using mice cerebral cortex and next-generation sequencing along with bioinformatics analysis, we identified miRNAs that were differentially expressed in ethanol-treated vs. untreated WT and TLR4-KO mice. We observed a differentially expression of miR-183 Cluster (miR-96/-182/-183) and miR-200a and miR-200b that were downregulated while mirR-125b and miR-146a were up-regulated in ethanol-treated WT vs. untreated mice. These miRNAs modulate different targets genes related to voltage-gated sodium channel, neuron hyperexcitability (Nav1.3, TPRV1, PP1-γ and BDNF) as well as genes associated to innate immune TLR4 signalling response and inflammation. Interestingly, these ethanol-effects were mostly abolished in TLR4-KO mice. In brief, our results show the relationship between alcohol intake and miRNAs expression opening a new therapeutics targets to prevent the deleterious effects of alcohol in brain.

P1-1-15

RESTORING TIMING OF ORBITOFRONTAL NEURONS TO DECREASE PERSEVERATIVE RESPONDING IN PRENATAL ALCOHOL EXPOSED MICE IN A TOUCHSCREEN-BASED VISUAL REVERSAL LEARNING TASK

J.A. Kenton[1], K. Marquardt[1], J.L. Brigman[1,2]
[1]Department of Neurosciences, University of New Mexico School of Medicine, USA and
[2]New Mexico Alcohol Research Center, UNM Health Sciences Center, USA

Prenatal alcohol exposure (PAE) leads to deficits in executive function that persist into adulthood. Previously, we have shown that moderate PAE (BAC: ~90 mg/dL) in mice impairs behavioral flexibility by increasing perseverative responding on a touchscreen-based visual reversal learning task. In vivo electrophysiology recordings during behavior showed decreased inter-trial phase consistency during early reversal in the orbitofrontal cortex (OFC) after unexpected rewards in PAE mice. Here, we 1) used optogenetics to stimulate pyramidal neurons in the OFC following unexpected rewards to restore phase alignment and reduce perseveration in PAE mice and 2) examined the effect of PAE on populations of inhibitory interneurons. PAE and saccharine control (SAC) mice were trained, microinfused with channelrhodopsin- or EYFP-expressing adenovirus directly into the OFC, and implanted with recording optrodes targeting the OFC and dorsal striatum. PAE and SAC mice were given a reminder session followed by reversal. During a highly perseverative period, PAE and SAC mice received 465 nm, 5mW, 10 Hz, 5 ms pulses for 1 sec following a correct choice. Targeted stimulation during early reversal reduced perseveration in $ChR2^+$ PAE mice compared to $ChR2^+$ SAC and EYFP controls. Additionally, the number of GABAergic interneurons in the OFC of PAE mice was significantly reduced compared to controls.

P1-1-16

CHEMOGENETIC MANIPULATION OF THE BASOLATERAL AMYGDALA – NUCLEUS ACCUMBENS CIRCUITRY IN A MODEL OF ALCOHOL ADDICTION VULNERABILITY

S.E. Ewin, A.D. Baldassaro, A.M. Chappell, E.S. Carter, J.L. Weiner
Wake Forest School of Medicine, USA

Our lab has established a rodent model of adolescent social isolation (aSI) which engenders robust and enduring increases in behaviors linked to alcohol addiction vulnerability. We have shown that the basolateral amygdala (BLA), a brain region heavily implicated in the pathophysiology of addiction, is hyper-excitable following aSI. The BLA sends glutamatergic projections to other addiction-related brain regions, including the nucleus accumbens (NAc). Despite the well-known role of the BLA and NAc in mediating addiction-related behaviors, little is known about the specific role of the BLA-NAc circuit in these behaviors or if increases in NAc excitability contribute to the addiction vulnerable phenotype promoted by aSI. Our first studies employed an unbiased approach, examining the effects of aSI on NAc excitability. We found that aSI led to a robust increase in NAc excitatory synaptic activity. Additionally, using a chemogenetic approach, we demonstrated, for the first time, that silencing the BLA-NAc excitatory projection selectively decreases appetitive, but not consummatory behaviors in an operant ethanol self-administration procedure. Further work is being done to determine if the BLA-NAc projection is impacted following aSI and whether adaptive changes in this circuit contribute to the escalation in ethanol drinking associated with this model of alcohol addiction vulnerability.

P1-1-17

ETHANOL WITHDRAWAL PRODUCES OPPOSING SYNAPTIC ALTERATIONS OF PRELIMBIC AND INFRALIMBIC TERMINALS IN THE RAT BASOLATERAL AMYGDALA

M.M. Mcginnis, N.J. Alexander, B.A. Mccool
Department of Physiology and Pharmacology, Wake Forest School of Medicine, USA

The basolateral amygdala (BLA) is a crucial component of the neural circuitry that regulates emotional behaviors including fear and anxiety. These functions are supported in part by synaptic inputs from upstream brain regions. Here we use optogenetics and electrophysiology to reveal the impact of chronic intermittent ethanol (CIE) exposure on BLA glutamatergic circuits formed by projections from the prelimbic (PrL) and infralimbic (IL) cortices. Following viral expression of channelrhodopsin, adult male Sprague Dawley rats were exposed to CIE or air in vapor chambers for 7 consecutive days. Anxiety-like behavior was measured using the elevated zero maze 24 h into withdrawal and then rats were sacrificed for electrophysiology studies. Optogenetically stimulated paired-pulse ratios were recorded as a measure of presynaptic glutamate function. Our data shows that rats exposed to CIE exhibit increased anxiety-like behavior during withdrawal, indicating that our paradigm results in a dependence-like behavioral phenotype. Interestingly, we found that withdrawal from 7 days of CIE strengthens PrL and weakens IL synapses. The current findings are particularly exciting when viewed in the context of the opposing roles of PL and IL in conditioned behaviors, suggesting that ethanol exposure promotes maladaptive behaviors by differentially altering specific neural circuits.

P1-1-18

GENETIC LOCI FOR ALCOHOL-RELATED LIFE EVENTS AND SUBSTANCE-INDUCED AFFECTIVE SYMPTOMS IN AN AMERICAN INDIAN AND A EUROPEAN AMERICAN POPULATION

Q. Peng[1], C. Bizon[2], I.R. Gizer[3], K.C. Wilhelmsen[4], C.L. Ehlers[1]
[1]Department of Neuroscience, The Scripps Research Institute, La Jolla, CA, USA, [2]Renaissance Computing Institute, University of North Carolina, Chapel Hill, NC, USA, [3]Department of Psychological Sciences, University of Missouri, Columbia, MO, USA and [4]Department of Genetics and Neurology, University of North Carolina, Chapel Hill, NC, USA

Traditional GWAS have identified a limited number of genetic risk or protective variants for alcohol use disorders (AUD) and related phenotypes. We conducted association and gene-based analyses using low coverage whole genome sequence (LCWGS) in two independent cohorts: 742 American Indians (AI) and 1,711 European Americans (EA). Two phenotypes were evaluated: 1) a metric based on the occurrence of 36 alcohol-related-life-events reflecting the severity of AUD, 2) two alcohol-induced affective symptoms accompanying severe AUDs. We identified three new loci for alcohol-related-life-events with converging evidence from both cohorts: NAF1-FSTL5, rare variants in PDE4C and KCNK2. PRKG2 and rare variants in EBI3 (IL-27B) were uniquely associated with alcohol-induced affective symptoms in AI. A ncRNA on 12q24.32 was uniquely associated with alcohol-induced depression in EA. The top GWAS findings were primarily rare/low-frequency variants in AI, and common variants in EA. Adrenal gland was the most enriched in tissue-specific gene expression analysis for alcohol-related-life-events in AI, and nucleus accumbens was the most enriched for alcohol-induced affective symptoms. Prefrontal cortex was the most enriched in EA for both traits. These studies suggest that LCWGS can identify novel, especially uncommon, variants associated with severe AUD phenotypes although the findings may be population specific.

P1-1-19

AN AMYLIN ANALOGUE ATTENUATES OPERANT ALCOHOL SELF-ADMINISTRATION AND RELAPSE-LIKE DRINKING IN VARIOUS ANIMAL MODELS OF ALCOHOL USE DISORDER

A.L. Kalafateli[1], D. Vallöf[1], G. Colombo[2], I. Lorrai[2], P. Maccioni[2], E. Jerlhag[1]
[1]Department of Pharmacology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden and [2]Neuroscience Institute, Section of Cagliari, National Research Council of Italy, Monserrato (CA), Italy

Alcohol use disorder (AUD) is a serious cause of mortality and morbidity, however limited efficacy of existing pharmacotherapy requires further investigation of potential neurochemical alcohol intervention targets. Alcohol activates areas of the mesolimbic dopamine system, which consists of dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Reward induced by food and addictive drugs involve common mechanisms suggesting that gut-brain hormones like amylin, which control appetite and energy balance, could be involved in reward regulation. Our recent findings have identified salmon calcitonin (sCT), an amylin receptor agonist and analogue of endogenous amylin, as a potential regulator of alcohol reward and intake. We show that repeated sCT administration attenuated alcohol intake as well as food intake in Wistar rats. Additionally, acute sCT administration reduced operant alcohol self-administration (under the fixed ratio 4 schedule of reinforcement) in selectively bred Sardinian alcohol-preferring rats, while it did not alter operant self-administration (under the progressive ratio schedule of reinforcement) of a highly palatable chocolate-flavoured beverage in Wistar rats. Moreover, acute administration of sCT prevented relapse-like drinking in the “alcohol deprivation effect” model in Wistar alcohol-experienced rats. Collectively, our data suggest that amylin signalling may contribute to the development of AUD.

P1-1-20

THE EFFECT OF ETHANOL ON VICTIMS BY MURDER

R. Katada, S. Nakagawa, K. Nakama, Y. Miyashita, H. Fujimoto, K. Higashisaka, K. Sugimoto, K. Harada, H. Matsumoto
Department of Legal Medicine, Faculty of Medicine, Osaka University, Japan

Drunkenness state often brings about disputes including fighting. Ethanol has also a variety of pathophysiological effects for disease. Therefore, it is indicated that ethanol affects prognosis of traumatic organ injury by accident and assault. However, the examination about ethanol and drug intake situation in murder case and outbreak situation has not been done. In this study, we examined drug intake, outbreak situation and influence of ethanol in murder case. The autopsy cases are in Osaka University legal medicine from 2013 to 2017. We defined the murder case in this study as the estimated example from document of corpse examination certificate. Among the cases, the ratio of blood ethanol concentration was 0% (higher than 1.5 mg/mL), 3.1% (1.0–1.5), 6.3% (0.5–1.0), 71.8% (lower than 0.5), 18.8% (unknown). For the cause of death in high ethanol concentration, it was violence execution, suffocation etc. The ratio that showed positive in drug test was 0%. About the case outbreak day, there was the most Saturday and Monday. From these findings, there were few cases indicating high ethanol concentration in murder case. There were not many victims who were in condition to have drunk, but, was shown to often occur on the weekend in murder case.

P1-1-21

BLOOD ETHANOL CONCENTRATION PROFILES OF MALE AND FEMALE JAPANESE QUAIL

S.E. Eaton, M.A. Saunders, J.E. Jagielo-Miller, M.A. Prendergast, C.K. Akins
Psychology, University of Kentucky, USA

Cues have been explored in quail because they are a visual species, and may be an ideal model for studying the association of visual cues related to alcohol consumption and alcohol use disorder (AUD). Because minimal research has examined blood ethanol concentrations (BECs) in quail, and this knowledge is critical to develop a model of AUD, we aimed to document BECs and metabolism rates in quail. Quail were gavaged with 3 g/kg of a 20% ethanol solution, blood was then collected at specific time points and analyzed for BECs. Male quail absorbed the ethanol quickly and had relatively high BECs within the first 30 min, however, females had lower BECs. This difference was not apparent at 60 min following gavage. Peak levels occurred in both male and female quail at approximately 60 min following gavage. BECs in quail remained high for the remaining 180 min, thus indicating that quail have a slow clearance of ethanol from their system. This could be due to physiological differences, the crop may store some ethanol for later release. With an understanding of the rate of onset and metabolism of ethanol, researchers can explore the relationship between discrete visual cues and BEC’s in quail.

P1-1-22

A LONG-TERM EXTENSION STUDY FOR THE PHASE 3 STUDY OF NALMEFENE IN PATIENTS WITH ALCOHOL DEPENDENCE IN JAPAN

H. Miyata[1], I. Nakamura[2], M. Takahashi[3], Y. Murai[3], K. Tsuneyoshi[4], D. Meulien[5], S. Higuchi[6]
[1]Department of Psychiatry, Jikei University School of Medicine, Japan, [2]Department of Medical Affairs, Otsuka Pharmaceutical Co., Ltd., Japan, [3]Department of Clinical Management, Clinical Development Headquarters, Otsuka Pharmaceutical Co., Ltd., Japan, [4]Department of Biometrics, Clinical Development Headquarters, Otsuka Pharmaceutical Co., Ltd., Japan, [5]Clinical Research and Development – Neurology, H. Lundbeck SAS, France and [6]National Hospital Organization, Kurihama Medical and Addiction Center, Japan

The present study aimed to examine the long-term safety and efficacy of nalmefene for alcohol dependence in a 1- year study in Japanese patients who completed the previous 24-week double-blind placebo controlled study. This extension study consisted of a 24-week open-label treatment period, followed by a 4-week run-out double-blind, placebo-controlled period and a 4-week posttreatment observation period. Patients who completed the previous study, were eligible to enter this extension study, where they were treated with nalmefene 20 mg as needed, followed by the run-out period where they were randomized 1:1 to receive nalmefene 20 mg or placebo.
Reported here are patients who received nalmefene 20 mg throughout the entire 48-week treatment period. Overall, nalmefene 20 mg was well tolerated; the main treatment emergent adverse events reported in ≥5 percent of patients (137 pts) included nasopharyngitis, nausea, somnolence, dizziness, malaise, and vomiting. No deaths were reported during the 48-week treatment period. The number of heavy drinking days and total alcohol consumption decreased from baseline to 48 weeks (22.54 ± 6.70 vs. 8.23 ± 9.59 days per month and 94.10 ± 34.43 vs. 43.75 ± 30.71 g per day, respectively) during the study. In conclusion, long-term treatment with nalmefene in Japanese patients with alcohol dependence is safe and efficacious.

P1-1-23

THE DIFFERENCES IN DECISION-MAKING AMONG ALCOHOL USE DISORDER PATIENTS AND HEALTHY CONTROLS USING CAMBRIDGE GAMBLING TASK

S.J. Chung[1], J.Y. Lee[1], A. Choi[1], M.K. Park[1], E.H. Kim[1], D.H. Lee[1], J.S. Choi[1,2]
[1]Department of Psychiatry, SMG-SNU Boramae Medical Center, Seoul, Korea and [2]Department of Psychiatry and Behavioral Science, Seoul National University College of Medicine, Seoul, Korea

Objectives: This study aimed to identify the differences in decision making abilities among alcohol use disorder patients (AUD) and healthy controls (HC) using Cambridge gambling task (CGT). Additionally, the study investigated the relationship between clinical variables and CGT variables.
Methods: 67 adults (41 were HC and 26 were diagnosed with AUD) completed CGT and self-reported questionnaires including Behavioral Activation System and Behavioral Inhibition System (BAS/BIS), Barratt Impulsiveness scale version 11 (BIS-11), Connor-Davidson Resilience Scale (CD-RISC), Beck Depression Inventory (BDI), Beck Anxiety Inventory(BAI), Aggression Questionnaire (AQ) and Rosenberg's Self-Esteem Scale (RSES).
Results: After controlling for age, there were significant differences between groups with respect to overall proportion bet ($F(1, 64) = 5.184$, $p < 0.05$) and risk taking ($F(1, 64) = 4.948$, $p<0.05$) in each descending mode on the CGT. There were some significant correlations between CGT variables and clinical variables in total participants, but no significant correlations in AUD group.
Conclusion: These results indicate AUD group showed greater impairment in self-control during decision making and are more likely to engage in risky behaviors compared to HC group. Our study suggests these features may be trait marker of AUD as distinct from clinical traits and there is a need to address self-control when discussing treatment of patients with AUD since these can be risk factors for AUD.

P1-1-24

INFLUENCE OF CHRONIC ETHANOL CONSUMPTION ON THE PATHOGENESIS OF ENDOTOXIN SHOCK

K. Yuui, R. Kudo, S. Kasuda, K. Hatake
Department of Legal Medicine, Nara Medical University, Japan

To clarify the effects of ethanol on vasculature, the maintenance of vessel contraction and relaxation in chronic ethanol-fed rats was investigated with a focus on the relaxation of superior mesenteric arteries (SMAs) occurring in endotoxin shock. Vascular rings were isolated from rat SMAs to measure isometric tension and IL-1β was added when peak contraction was achieved.
In both the control and chronic ethanol-fed groups, transient contraction via IL-1β was suppressed by a thromboxane A2 (TXA2) receptor antagonist and indomethacin, a cyclooxygenase inhibitor. Transient contraction in chronic ethanol-fed rats was further increased compared to that in the control group.
On the other hand, IL-1β induced gradual relaxation in the control group, which was inhibited by the addition of inducible nitric oxide synthase (iNOS) inhibitors. However, IL-1β-induced relaxation was not observed in the SMAs of ethanol-fed rats.
In conclusion, vessel relaxation occurring upon IL-1β exposure was found to be mediated by the iNOS/NO pathway, and vessels showed transient contraction via TXA2 at a stage prior to abrupt relaxation. Furthermore, because chronic ethanol intake enhanced transient vessel contraction upon IL-1β exposure and suppressed subsequent relaxation, ethanol may have a protective effect on vessels in endotoxin shock.

P1-1-25

CHRONIC ETHANOL CONSUMPTION ENHANCES ENDOTHELIUM-DEPENDENT RELAXATION IN THE RAT SUPERIOR MESENTERIC ARTERIES

R. Kudo, K. Yuui, S. Kasuda, K. Hatake
Department of Legal Medicine, Nara Medical University, Japan

We have previously shown that chronic ethanol consumption enhances acetylcholine (Ach)-induced endothelium-dependent relaxation (EDR) in the superior mesenteric arteries (SMA). However, the detailed mechanism underlying this effect remains unclear. The present study aimed to investigate the role of the inducible EDHF (iEDHF) pathway in increased EDR after chronic ethanol intake. Ach-induced EDR was significantly higher in ethanol-fed rats than in the control rats. In the presence of both apamin and charybdotoxin, which inhibit cEDHF and iEDHF, the increased Ach-induced EDR in ethanol-fed rats was attenuated. Additionally, treatment with iEDHF inhibitors quinacrine, miconazole, PD-146176, and AUDA, also attenuated the increased Ach-induced EDR in ethanol-fed rats. Furthermore, the protein expression of arachidonate 15-lipoxygenase (ALOX15) was greater in the SMAs of ethanol-fed rats than in the control rats whereas soluble epoxide hydrolase was not altered. These results suggest that the iEDHF pathway is involved in the increased Ach-induced EDR in ethanol-fed rats. Additionally, activation of the ALOX15 protein may also participate in the increased SMA relaxation.
Thus, chronic ethanol consumption was found to enhance iEDHF-mediated EDR through activation of the ALOX15 protein.

P1-1-26

RELATIONSHIP BETWEEN ALCOHOL SENSITIVITY AND ORAL ACETALDEHYDE LEVEL AFTER AN ALCOHOL MOUTHWASHING

A. Himemiya-Hakucho, T. Tanaka, S. Yamaji, J. Liu, T. Fujimiya
Department of Legal Medicine, Graduate School of Medicine, Yamaguchi University, Japan

Background and aim: Acetaldehyde could be produced in the oral cavity after local alcohol exposure. We evaluated the relationship between alcohol sensitivity and pharmacokinetics of acetaldehyde and ethanol in the oral cavity after an alcohol mouthwashing.
Methods: At first fifty-five subjects divided into Flusher (F) or Non-flusher (NF) groups based on ethanol patch test washed their mouths with 5% v/v alcohol for 30 s, then breath and/or saliva was collected more 10 times during 20 min. Acetaldehyde and ethanol concentrations were measured by gas chromatography.
Results: Breath acetaldehyde in the F group remained constantly higher than those in the NF group throughout the 20 min; C_{max} (ppb) were 808 $\pm$ 70 for the NF group, 1,715 $\pm$ 223 for the F group ($p = 0.001$); AUC (ppb·min) were 3,528 $\pm$ 1,399 for the NF group, 8,637 $\pm$ 1,293 for the F group ($p = 0.002$). Whereas, there were no significant changes in breath ethanol, ethanol and acetaldehyde in saliva between the both groups.
Conclusions: The results suggested that high concentration of oral acetaldehyde could be shown by only local ethanol exposure even without alcohol ingestion in flushers and might contribute to the increased risk of head and neck cancer.

P1-1-29

ALCOHOL AND INJURIES IN THE ACCIDENT AND EMERGENCY ROOM OF MAHARAJ NAKORN CHIANG MAI HOSPITAL AND NAKORNPING HOSPITAL

K. Thaikla[1], S. Chariyalertsak[1,2], N. Chotirosniramit[3], I. Ngampasutadol[4]
[1]Research Institute for Health Sciences, Chiang Mai University, Thailand, [2]Faculty of Public Health, Chiang Mai University, Thailand, [3]Faculty of Medicine, Chiang Mai University, Thailand and [4]Nakornping Hospital, Thailand

Emergency room is the best contexts for studying on the result of alcohol drinking towards injury. The purpose of this study was to examine the alcohol related injury and to what extent alcohol consumption increases the risk of injury.
Method: This study uses Case Crossover Design to collect the data from April 2016 to February 2017. The inclusion criteria for the subjects were patients presenting to the emergency room within 6 h of their injury, were 18 years or older. The breath samples were collected by the ALCO-SENSOR III breathalyzer, and the face-to-face interview questionnaire.
Result: 1,060 injured patients, the most patients were male 57.1%; 32.0% aged 18–24 years. 16.4% drank alcohol before the incidents 6 h. 14.3% had alcohol detected by breath with the average 226.9 mg% blood alcohol content, which was 5 times exceeding the amount legally permitted of less than 50 mg%. Within 6 hafter alcohol consumption, the risk of the severe injury was 2.5 times (95% CI 1.5–4.3) and the risk of the traffic injury was 4.4 times (95% CI 2.8–7.2)
Conclusion: These findings have important public health consequences. Alcohol drinking 6 h prior to the incident results in more risk for injury.

P1-1-30

NEUROADAPTATIONS IN THE PREFRONTAL CORTEX AND HIPPOCAMPUS AFTER ALCOHOL RELAPSE

Y. Takashima[1], M. Pavlich[2], C.D. Mandyam[1,2]
[1]Anesthesiology/University of California, San Diego, CA, USA and [2]VA San Diego Healthcare System, USA

Alcohol use disorder (AUD) is a chronic relapsing disorder producing significant public health issues worldwide. AUD also plays a significant causal role in numerous types of cardiovascular and pulmonary diseases which results in harm to the well-being and health of people. The process of developing AUD does not occur in a day, but over a series of repeated cycles of intoxication, withdrawal from alcohol, and re-exposure to alcohol. Our investigation determined the effects of moderate to severe AUD on the functional plasticity of pyramidal neurons in the prefrontal cortex (PFC) and granule cell neurons (GCNs) in the hippocampus, brain regions involved in the craving stage – thought be a critical element driving propensity for relapse.
Whole-cell patch-clamp recordings were performed in acute brain slices from rats that experienced ethanol (EtOH) via chronic intermittent ethanol vapor inhalation (CIE) followed by protracted abstinence (PA; CIE-PA), CIE-PA followed by one day of CIE (Relapse[R]; CIE-R), and aged-matched EtOH naïve controls. Our results demonstrate that re-exposure to EtOH after PA leads to distinct alterations in neuronal excitability and synaptic transmission of pyramidal neurons and GCNs that may contribute to altered synaptic connectivity and activity in the PFC and hippocampus and enhance propensity for relapse.

P1-1-31

INACTIVATION OF IMMUNE CELLS IN ALCOHOL-INDUCED OSTEOPENIA

M. Naruo[1,2,3], Y. Negishi[4], M. Katsuyama[1], T. Haseba[1,5], K. Okazaki[3], Y. Ono[1], T. Okuda[1]
[1]Dept. of Legal Med., Nippon Medical School, Japan, [2]Dept. of Orthop. Surg., Tomei Atsugi Hospital, Japan, [3]Dept. of Orthop. Surg., Tokyo Women's Medical University, Japan, [4]Dept. of Microbiol. Immunol., Nippon Medical School, Japan and [5]Dept. of Legal Med., Kanagawa Dental Univ., Japan

Introduction: Excessive alcohol intake can induce osteopenia; however, the immunological mechanism underlying alcohol-induced osteopenia is still unclear. Here, we investigated the immune cells in the bone treated with alcohol.
Methods: Femurs and tibias were obtained from 13-week-old female C57BL/6 mice treated with alcohol/control for 4 weeks. After eliminating the bone marrow, the bones were cut into small pieces and incubated with collagenase D. Subsequently, the bones were smashed using pestle and mortar, and the cells in the Haversian and Volkmann's canal and the loosely adhered cells were collected. These cells were stained by fluorescent-labeled monoclonal antibodies, and the number of macrophages, dendritic cells, $CD8^+$ T cells, $CD4^+$ T cells, NK cells, invariant natural killer T (iNKT) cells, and co-stimulatory molecules on these cells were analyzed using flow-cytometry.
Results: No statistical differences were observed in the proportion of bone immune cells between the controls and alcohol-treated mice. However, the CD69 expression on the $CD8^+$ T, $CD4^+$ T, NK, and iNKT cells was suppressed in the alcohol-treated mice.
Conclusions: Chronic alcohol intake inactivates the immune cells in the bone due to the suppression of CD69 expression on them. We suggest this may be crucial for alcohol-induced osteopenia.

P1-1-32

EFFECTS OF DRINKING CONDITIONS ON ACETALDEHYDE AND ETHANOL CONCENTRATION IN BREATH AND SALIVA IN HEALTHY JAPANESE MEN WITH DIFFERENT ADH1B AND ALDH2 GENOTYPE: RESEARCH OF SHOCHU, A JAPANESE TRADITIONAL SPIRITS

S. Kushio[1], A. Iwami[1], A. Yokoyama[2], T. Kairiku[1], Y. Kajiwara[1], H. Takashita[1], K. Kinoshita[3]
[1]Research & Development Laboratory, SANWA SHURUI Co., Ltd., Japan, [2]National Hospital Organization Kurihama Medical and Addiction Center, Japan and [3]School of Pharmaceutical Sciences, Mukogawa Women's University, Japan

Traditionally, Shochu, a Japanese distilled alcohol beverage is consumed by many ways of drinking such as straight, on the rock, Mizu Wari (diluted with water) and Oyu Wari (diluted with hot water). It is reported that Shochu contains very high concentration of acetaldehyde, however, we can lower the amount of acetaldehyde efficiently by using a specific refinement. It is not clear whether the initial acetaldehyde content in alcohol beverages influences alcohol metabolism or not, therefore there's still room for discussing the role of acetaldehyde outside ethanol metabolism.
ADH1B genotype exists as ADH1B*1/*1 (less active), ADH1B*1/*2 (active) and ADH1B*2/*2 (more active) and ALDH2 genotype exists as ALDH2*1/*1 (active), ALDH2*1/*2 (inactive) and ALDH2*2/*2 (completely inactive). Japanese genetically tend to have higher ADH1B activity and lower ALDH2 activity. In this study, we investigated the effects of initial acetaldehyde concentration in alcohol beverages on the saliva acetaldehyde levels by comparing two different kinds of Shochu. We also demonstrated the effects of ingested temperature and alcohol concentration on the acetaldehyde and ethanol levels in saliva and breath in healthy Japanese men with different ADH1B and ALDH2 genotype.

P1-1-33

PHARMACOGENETIC STUDY OF BACLOFEN ON GABBR1 AND GABBR2 GENES IN ALCOHOL USE DISORDER

N. Ramoz[1,2], P. Gorwood[1,2,3]
[1]INSERM U894, Center of Psychiatry and Neuroscience, France, [2]Université Paris Descartes, Université Sorbonne Paris Cité, France and [3]Hôpital Sainte Anne, Clinique des Maladies Mentales et de l'Encéphale CMME, Paris, France

Alcohol use disorder (AUD) is a major health problem resulting from several factors. Thus, 50% of the involved factors are related to heritability. These genetic factors are implicated at different levels (temperament at risk, initial tolerance, secondary complications. . .) and in the ability to respond to various treatments to maintain abstinence, which is called pharmacogenetics. Baclofen is the only GABA-B agonist used in AUD. The heterogeneity of the therapeutic response to baclofen in AUD is likely and due to the presence of positive and negative studies. Clinical experience shows that the effective dose is highly variable from one subject to another (20 to 300 mg/day). Our goal is to study the pharmacogenetic association of the target molecules (GABAB) of the baclofen in AUD.
Pharmacogenetic study of baclofen was performed on a sample of 188 subjects from the ALPADIR cohort (randomized, double-blind trial, evaluating the efficacy of XylkaR at a target dose of 180 mg daily versus placebo in maintenance of abstinence from alcohol-dependent patients). We genotyped 8 markers in the gamma-aminobutyric acid (GABA) B receptor 1 and 2 genes (GABBR1 & GABBR2). Results will be presented.
This research work was supported by the Ethypharm laboratory (INSERM transfer contract 131042A10).

P1-1-34

DYNORPHIN/KAPPA OPIOID RECEPTOR ACTIVITY WITHIN THE CENTRAL AMYGDALA AND BNST CONTRIBUTES TO BINGE-LIKE ETHANOL CONSUMPTION IN MICE

H.L. Haun[1], M.M. Kolesinska[2], M.L. Lopez[1], W.C. Griffin[1], H.C. Becker[1]
[1]Medical University of South Carolina, USA and [2]College of Charleston, USA

Binge alcohol (ethanol) consumption is the most common form of excessive drinking and can be modeled in rodents with the Drinking in the Dark (DID) paradigm. Recently, we have demonstrated involvement of the dynorphin/kappa opioid receptor (DYN/KOR) system in regulating excessive ethanol consumption in this binge model. However, the discrete brain regions and circuitry that mediate the influence of DYN/KOR activity on binge drinking have not been fully investigated. Since there is dense expression of DYN-containing (DYN+) neurons and KOR within the extended amygdala, this macrostructure is a prime target for mediating these effects. In the current studies, we found that microinjection of the KOR agonist, U50, 488 (0.2 μg/side) into BNST of male C57BL/6J mice significantly increased binge-like ethanol consumption by 71% compared to vehicle ($p<0.05$). In contrast, intra-BNST microinjection of the KOR antagonist, norBNI (2.5 μg/side) significantly decreased ethanol intake by 78% ($p<0.05$). The central amygdala (CeA) contains a high density of DYN+ neurons that project to BNST (CeA-BNST-DYN+) which may contribute to excessive drinking. Chemogenetic inhibition of the CeA-BNST-DYN+ circuit in male prodynorphin-IRES-Cre mice resulted in a 56% reduction in binge-like ethanol intake ($p<0.05$). Together, these data implicate the extended amygdala DYN/KOR system in modulating binge ethanol consumption.

P1-1-35

DIFFERENTIAL EFFECTS ON ACUTE SALIVARY CYTOKINE RESPONSE FOLLOWING ALCOHOL CONSUMPTION AND ALCOHOL HANGOVER: PRELIMINARY RESULTS FROM TWO INDEPENDENT STUDIES

A.J. Van De Loo[1,2], K. Knipping[3], M. Mackus[1], A.D. Kraneveld[1,2], J. Garssen[1,3], A. Scholey[4], G. Bruce[5], J.C. Verster[1,2,5]
[1]Division of Pharmacology, Utrecht University, Utrecht, The Netherlands, [2]Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, The Netherlands, [3]Nutricia Research, Utrecht, The Netherlands, [4]Centre for Human Psychopharmacology, Swinburne University, Melbourne, Australia and [5]Psychology, Social Work, Health Behaviour and Addictions, University of the West of Scotland, Paisley, UK

Background: Previous research has reported changes in blood cytokine concentrations both after consumption of alcohol, and during the alcohol hangover phase. The aim of the current two studies was to further elucidate how alcohol and alcohol hangover influences salivary cytokine concentration in healthy participants.
Methods: In study 1 ($N = 15$) participants consumed alcohol on the test day and placebo on the control day. Saliva was collected every hour for 8 h. In study 2 ($N = 35$), saliva was collected the morning following an evening of alcohol consumption (mean of 8.48 +/-1.39 h after stopping with drinking) and on an alcohol-free control day. In both studies cytokine concentrations that could be reliably assessed (IL-1β, IL-8, TNF-α in both studies, and IL-6, IL-10 in study 2 only) were compared between both test days.
Results: Directly after consuming alcohol (study 1) significant increases in pro-inflammatory cytokines (IL-1β, Il-8) were found on multiple timepoints ($p<0.05$). During the hangover phase (study 2) both pro-inflammatory (IL-6, TNF-α) and anti-inflammatory (IL-10) cytokine concentrations were significantly increased ($p<0.05$).
Discussion: The increase in both pro- and anti-inflammatory saliva cytokine concentrations confirm that alcohol consumption affects the immune system, both acutely and during the hangover phase.

P1-1-36

CHEMOGENETIC MANIPULATION OF THE INSULA ALTERS ALCOHOL CONSUMPTION IN RATS

M. Haaranen, A. Schäfer, A. Kuhlefelt, P. Hyytiä
University of Helsinki, Finland

The anterior insula (AI) and its connections are associated with processing of multisensory information and goal-directed decision making. Recent data suggest that they also control voluntary alcohol consumption in rats and humans. To further elucidate AI's role in the regulation of alcohol consumption we used chemogenetic tools for manipulating AI. An excitatory G-protein coupled designer receptor exclusively activated by designer drugs (Gq-DREADD, AAV8-hSyn1-hM3D (Gq)-mCherry) was expressed bilaterally in AI. Neuronal activation by clozapine-N-oxide (CNO, 10 mg/kg) decreased alcohol consumption in alcohol-preferring AA (Alko Alcohol) rats allowed to drink 10% alcohol for 2 h q.a.d. To characterise the effects of AI activation on efferent connections, we expressed the Gq-DREADD unilaterally, followed by CNO activation and quantification for the neuronal activation marker c-Fos expressing puncta in AI-connected brain regions, compared with the contralateral c-Fos expression. To characterise further the role of the output connections, we injected Cre-dependent DREADDs bilaterally into the AI while applying a retro-Cre to the AI terminal areas in order to achieve pathway-specific DREADD expression, followed by CNO DREADD activation. Collectively, these experiments show that the AI with its rich connectivity modulates alcohol reinforcement and consumption and could thus be a future therapeutic target.

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P1-1-37

INHIBITION OF PLATELET AGGREGATION BY ETHANOL IN WHOLE BLOOD UNDER A SHEAR STRESS CONDITION

K. Ekawa, M. Marumo, I. Wakabayashi
Department of Environmental and Preventative Medicine, Hyogo College of Medicine, Japan

Purpose: Blood coagulability is lowered by alcohol drinking. The effects of ethanol on platelet aggregation were investigated using a total thrombus-formation analysis system (T-TAS), which is a recently developed instrument that makes it possible to evaluate platelet aggregation under a physiological condition with shear stress.
Methods: Whole blood and washed platelet suspension were used for measurements of platelet aggregation by using the T-TAS and light transmission method, respectively. In the measurement using the T-TAS, shear stress of 1500s-1 was loaded to whole blood and the times needed to generate 10 kPa (T10), 30 kPa (T30) and 50 kPa (T50) in chips containing the blood, which depend on thrombus formation, were measured.
Results: In light transmission method, ethanol at 0.5%–2% inhibited thrombin-stimulated platelet aggregation in a concentration-dependent manner. In the measurement using the T-TAS, T10 and T30 were increased by ethanol at 0.125%–2% in a concentration-dependent manner, while T50 was inhibited by 2% ethanol but not by ethanol at lower concentrations.
Conclusions: The inhibitory effect of ethanol on platelet aggregation is sensitively detected by using the T-TAS. Ethanol at its physiological concentrations is thought to inhibit platelet thrombus formation at its early stage.

P1-1-38

PRENATAL EXPOSURE TO ALCOHOL AND OTHER SUBSTANCES INCREASES THE RISK OF CHILD MALTREATMENT AND ITS EFFECTS ON ADOLESCENT BEHAVIOR

C.L. Petrenko, J. Warmingham, M. Alto, T. Adams, J. Manly
Mt. Hope Family Center, University of Rochester, USA

Prenatal exposures to alcohol and other substances (PEAS) are associated with mental health problems across the lifespan. Many people with PEAS also experience other adversities that affect outcomes, such as maltreatment. This study tested the relationship of PEAS and adolescent mental health within the context of the intergenerational transmission of child maltreatment. The diverse sample of 162 adolescent girls (ages 13—15) and their biological mothers resided in low-income neighborhoods in a middle-sized U.S. city. Over half of mothers (64%) and teens (54%) each reported experiencing maltreatment as children. Latent class analysis of maternal-reported prenatal exposures indicated a class characterized by heavy binge drinking and other substance exposure (PEAS class) and a class with low to no exposures. Nearly all mothers in the PEAS class had experienced maltreatment in their own childhood. Structural equation modeling results indicated that adolescent maltreatment experiences mediated the pathway between PEAS and child mental health problems, particularly for adolescent externalizing behavior. This indicates that PEAS increases risk for childhood maltreatment, which acts as a mechanism by which PEAS increases risk for adolescent mental health symptoms. This study highlights the importance of studying PEAS in the context of intergenerational risk and resilience factors.

P1-1-39

CONSTRUCTION OF ALCOHOLISM RECOVERY MEASURE HAREA (HAKUHOU ALCOHOL RECOVERY EVALUATION AXIS)

Y. Kindaichi, M. Saitou, M. Okabe, A. Kasai, S. Yamazaki
Hakuhou Clinic, Japan

Background: Recovery from alcohol dependence has been defined as not only continued sobriety but a process of multi-dimensional change such as improvement of individual condition in physical, psychological, and social aspects (AA, ASAM, BFI, CSAT). This study aims to construct a new evaluation measure: Hakuhou Alcohol Recovery Evaluation Axis (HAREA), which objectively evaluates recovery from alcohol dependence.
Methods: To determine recovery measures, we collected recovery images from 27 medical professionals (doctors, nurses, psychiatric social workers, clinical psychologists, and occupational therapists: average experience, 14.4 years) who treat alcoholism in Japan and 64 patients who actually experienced recovery, and constructed a questionnaire from these images. To evaluate objectively and precisely, inter-evaluator consistency was calculated. To examine the validity of evaluation measures, we performed logistic analysis on subjects of alcoholics with sobriety days of three years or more as an external criterion. To examine latent factors for predicting recovery, we performed an exploratory factor analysis.
Results: Four types of 119 questions were constructed; (1) basic factors for recovery, (2) social factors, (3) bonding factors (fellowship / self-help group), and (4) resilient factors.
Conclusion: A new alcoholism recovery measure, HAREA, was constructed for patients who need sobriety. We plan to confirm its validity at overseas sites.

P1-1-40

ANALYSIS OF THE ROLE OF EPIGENETICS IN GENETIC DIFFERENCES IN RESPONSE TO PRENATAL ALCOHOL EXPOSURE: EVALUATION OF BXD MICE

K. Hamre[1], C. Tan[2], D. Goldowitz[2]
[1]Dept. of Anat. & Neurobiol., Univ. of Tennessee Health Science Center, USA and [2]Dept. of Pathol. & Laboratory Medicine, Univ. of British Columbia, Canada

Previously, we evaluated the level of ethanol-induced cell death following prenatal exposure across BXD mouse strains and demonstrated that there were significant genotypic differences. We hypothesized that epigenetics may have a strong role in this strain-specific susceptibility and the purpose of the present study was to identify what epigenetic mechanisms may underlie these differences. There could be 1) strain-specific differences irrespective of treatment, 2) differences between ethanol-treated and controls (ethanol effect), or 3) an interaction between the two. Tissue from ethanol-exposed (embryonic day 9, given 5.8 g/kg via gavage) and control (isocaloric maltose-dextrin) embryos across strains were compared. Expression of H3K4, H327, and H3 was examined via immunocytochemistry and quantified on Image-J. Results were molecule specific: Strains that exhibit high cell death show higher staining intensity of H3 compared to their respective controls and to strains with low cell death. For H3K4, there were differences in the controls between strains with high and low cell death. These results support the hypothesis that epigenetic treatment can mediate strain differences in susceptibility to prenatal ethanol exposure. Further, multiple epigenetic pathways are involved in this process in a complex manner with some differences basal between strains and some ethanol-induced.

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P1-1-41

ANALYSIS OF ETHYL GLUCOSIDE IN URINE BY GAS CHROMATOGRAPHY/MASS SPECTROMETRY AS A MARKER OF DRINKING ALCOHOL

K. Hara, B. Waters, N. Ikematsu, M. Kashiwagi, A. Matsusue, M. Takayama, S.-I. Kubo
Department of Forensic Medicine, Faculty of Medicine, Fukuoka University, Japan

In our drug screening test by GC-MS, we frequently detect ethylglucoside (EG), which is present in large amounts in sake from urine. We are very interested in investigating the relationship between EG detection in human urine and alcohol drinking. As a primary study, we investigated a quantitative method of EG by GC-MS using autopsy specimen, and volunteer urine. The extraction from urine was performed by an acetonitrile extraction. Apparatus: a Shimadzu QP-2010 Ultra. Column: A tandem capillary column consisting of two short connected Rtx-200 columns. GC-oven temperature program: initially 80°C for 1.5 min, then to 200°C at 70/min, and to 320°C at 50°C/min. EG and octylglucoside (IS) could be chromatographed at the baseline level. The calibration curve was linear from 20 to 200 ug/mL. There was no correlation between EG and ethanol. From the samples from volunteers, it was confirmed that EG was excreted in urine long after the drinking of beer. Therefore, even if ethanol in urine is low, the presence of EG could possibly indicate beer or sake drinking. Urinary EG analysis can be used for proof of alcohol drinking. This analytical method can also be used for drug screening.

P1-1-42

A STUDY ON THE EFFECTS OF ALCOHOL OR ACETALDEHYDE CONCENTRATION ON DIFFERENT ALCOHOL METABOLIZING ENZYME GENOTYPES

Y.J. Lee[1], K.J. Park[1], M.-G. Yoo[1], H.-K. Kim[2], S.-G. Kim[2], S.I. Park[1], H.-J. Lee[1]
[1]Division of Endocrine and Metabolic Diseases, National Institute of Health, Korea and [2]Department of Psychiatry, Pusan National University Yangsan Hospital, Korea

Excessive alcohol consumption is a major public health problem in East Asian country. Alcohol use lead to a cascade of problems including increased chances of risky behavior and wide range of negative health consequences from alcoholic liver disease to upper gastric and liver cancer. To investigate genetically susceptible factors to alcohol metabolizing, we selected about 300 candidate SNPs for genes involved in alcohol metabolism in GWAS catalog, and then performed genotyping-by-sequencing in the Korean population (n = 104). In this study, we identified the variations in ADH5 and Park-1 genes, which are directly associated with blood alcohol or acetaldehyde concentration. Namely, blood alcohol concentration was significantly different according to ADH5 genotype and Park-1 genotype, and blood acetaldehyde concentration was significantly different according each genotype. In addition, we suggest that chromosome 12 locus might have direct or indirect effects on alcohol metabolism. These results indicate that ADH5 and Park-1 genes show highly significant association between alcohol metabolizing enzyme genotypes and the blood alcohol or acetaldehyde concentration in the Korean population.

P1-1-43

PRENATAL STRESS INDUCES EXCESSIVE ALCOHOL CONSUMPTION AND ANXIETY-LIKE BEHAVIORS IN ADULT OFFSPRING

E. Dong[1], S.C. Pandey[1,2]
[1]Department of Psychiatry, University of Illinois at Chicago, Chicago IL, USA and [2]Jesse Brown VA Medical Center, Chicago IL, USA

The etiology of anxiety comorbid with alcohol use disorder (AUD) remains to be elucidated. Epidemiologic evidence suggests that individuals during their prenatal development may be especially vulnerable to the effects of environmental factors such as stress that predisposes them to psychiatric disorders including AUD later in life. To explore the cause of the comorbidity, we examined anxiety-like and alcohol drinking behaviors in adult offspring of prenatally stressed dam (PS-rat) using well-characterized paradigms-elevated plus maze (EPM), light/dark box (LDB) and two-bottle free-choice. It was found that both male and female PS-rat showed higher alcohol consumption when pharmacologically relevant concentrations of 3–12% ethanol were offered. The drinking behavior of PS-rat is characterized by increasing intake of alcohol solution and decreasing water intake but there were no significant differences between two groups in total fluid intake. This suggests that prenatal stress induces higher alcohol preference in adult offspring as compared with control non-stress adult offspring. Taken together, this study provides evidence that PS-rat has construct validity as a relevant animal model with epigenetic etiology underlying anxiety and AUD comorbidity endophenotypic profile.

P1-1-44

EARLY POSTNATAL ETHANOL EXPOSURE AFFECTS MIDLINE THALAMUS AND BEHAVIORS DEPENDENT ON PREFRONTAL-THALAMO-HIPPOCAMPAL CIRCUIT IN ADULT RAT

Z.H. Gursky, A.Y. Klintsova
Department of Psychological & Brain Sciences, University of Delaware, USA

One consequence of prenatal alcohol exposure is altered brain development, indicated by human psychological and neuroimaging studies. Mechanistic research in rodent models of fetal alcohol spectrum disorders (FASD) support this notion, implicating both timing and dose as critical factors determining the extent of damage. Individuals with FASD can express behavioral disruptions as impaired executive functions, corresponding to alterations in neuroanatomy of hippocampus (HPC) and prefrontal cortex (PFC). Recent animal research indicates that executive functions are dependent on intact function of the circuit comprised of the HPC and medial PFC via the thalamus (specifically, nucleus reuniens; Re). In the current study, we demonstrate that Long Evans rats exposed to ethanol (5.25 g/kg/day, intragastric intubation) on postnatal days 4 through 9 display nucleus-specific damage to the midline thalamus and selective behavioral deficits convergent with the neuroanatomical alterations observed. Neuroanatomical alterations included loss of neurons and total cell number in Re (as assessed in female rodents by unbiased stereological methods) but not adjacent thalamic nuclei. Behavioral alterations included impaired spatial memory (assessed in male rodents with an object-in-place paradigm) and rule switching (assessed with an operant behavioral flexibility task). These findings suggest that mPFC-Re-HPC circuit structure and function are impaired in FASD.

P1-1-45

MATERNAL ALCOHOL AND OTHER SUBSTANCE USE DURING CONCEPTION AND PREGNANCY: A LATENT CLASS ANALYSIS APPROACH

J.M. Warmingham, T.R. Adams, M. Alto, C.L. Petrenko, J.T. Manly
Mt. Hope Family Center, University of Rochester, USA

Prenatal alcohol exposure is a known teratogen that affects fetal development. Research on alcohol and drug use indicates that alcohol use often co-occurs with other substance use, but little research has investigated patterns of prenatal polysubstance use. In this study, 167 biological mothers of adolescent girls were recruited from a low-income area of a Northeastern U.S. city. Mothers reported their alcohol, marijuana, tobacco, and cocaine use during conception and pregnancy, as well as their childhood history of maltreatment. Latent class analysis was used to ascertain best fitting profiles of prenatal alcohol and other substance use. A two-class solution was selected for both conception and pregnancy. During conception, 19% of mothers endorsed high alcohol bingeing and also had elevated use of marijuana, tobacco, and cocaine use, and the remaining 81% endorsed low substance use. During pregnancy, there was a group of mothers (9%) who endorsed alcohol and other drug use. Maternal history of maltreatment was used as a covariate in class solution estimation and marginally predicted membership in the polysubstance use group during pregnancy ($\beta = .021$, $p = .08$). This is a novel investigation that preliminarily considers contextual risk factors for prenatal alcohol and other substance exposure in a low income sample.

P1-1-46

ALCOHOL, IN VIVO, CHANGES CSF CHEMISTRY TO INCREASE NEUROACTIVE AMINO ACIDS

S. Worrall[1], G. Simmons[3], P. Mills[3], J. Rainger[3], H. Keates[3], M. Plan[2], P.F. Nixon[1]
[1]Biochemistry and Molecular Biology, University of Queensland, Australia, [2]Australian Institute for Bioengineering & Nanotechnology, University of Queensland, Australia and [3]School of Veterinary Science, University of Queensland, Australia

The effects of alcohol on the brain are much less when alcohol is applied ex vivo to pieces of brain than when it is administered in vivo, suggesting that some substance(s) other than ethanol may mediate those effects. Here we report that slow infusion of ethanol to achieve blood alcohol concentrations of 40–50 mM in anaesthetised weanling piglets increased the cerebrospinal fluid (CSF) concentrations of all common amino acids except serine. The increases exceeded 8-fold for glycine and glutamate, sufficient to achieve neuroactive concentrations if this CSF were at appropriate synapses. CSF was sampled at the cisterna magna and the piglets were alcohol-naïve.
The source of the excess CSF amino acids is open to investigation, but we have previously hypothesized that the accumulation of NADH resulting from the activity of alcohol dehydrogenase would so interfere in energy metabolism that, in cells lacking glutamate decarboxylase, glutamate would accumulate. In the brain, these cells include glutamatergic neurons and the cells of the choroid plexus epithelium. Excess NADH would also interfere in the metabolism of other amino acids including glycine.

P1-1-47

GLUTATHIONE DEFICIENCY-ELICITED REPROGRAMMING OF ACETYL-COA METABOLIC FLUX PROTECTS AGAINST ALCOHOL-INDUCED STEATOSIS

Y. Chen[1], S. Manna[2], S. Golla[2], K.W. Krausz[2], Y. Cai[2], R.G. Millian[3], D.C. Thompson[4], F.J. Gonzalez[2], V. Vasiliou[1]
[1]Department of Environmental Health Sciences, Yale University, USA, [2]Laboratory of Metabolism, National Cancer Institute, USA, [3]Bioinformatics Support Program, Yale School of Medicine, USA and [4]Department of Clinical Pharmacology, University of Colorado, USA

Depletion of glutathione (GSH) is considered a critical pathogenic event promoting alcohol-induced lipotoxicity. We recently show that systemic GSH deficit in mice harboring a global deletion of the glutamate-cysteine ligase modifier subunit gene (Gclm) confers protection against alcohol-induced steatosis. While several molecular pathways have been linked to the observed hepatic protection, including NRF2 and AMPK pathways, the precise mechanisms are yet to be defined. To gain insights into the molecular mechanisms underpinning the protective effects caused by loss of GCLM, we have combined global and targeted metabolic profiling of hepatic polar metabolites with liver microarray analysis. These inter-omics analyses revealed both low GSH- and alcohol-driven changes in cellular pathways involving amino acids, nucleic acids, carbohydrate and fatty acid metabolism. Notably, in the livers of alcohol-treated Gclm-null mice, the major net effect of these changes was that acetyl-CoA flux diverged from lipogenesis to alterative metabolic pathways, including amino sugar biosynthesis, N-acetylation of glutamate, and bioenergenesis. This study indicates that fine-tuning of hepatic GSH homeostasis may evoke reprogramming of metabolic flux to cope with alcohol-induced cellular stress.

P1-1-48

GAMMA GLUTAMYLTRANSFERASE MEASUREMENT IN DRIED SERUM SPOTS

R. Quraishi, D. Singh, A. Ambekar, R. Jain, R. Rao
National Drug Dependence Treatment Center, All India Institute of Medical Sciences, New Delhi, India

Serum gamma-glutamyltransferase (GGT) is an alcohol use biomarker tested regularly in clinical setting including epidemiological studies. Filter paper is a proven matrix to transport and store samples from epidemiological studies. This study was aimed to develop an efficient method to measure GGT from dried serum spots.

Standard and quality controls were spotted (20 μL) on to filter paper (Wattmann 3 mm). The spots were dried and stored at 2–8°C. Assay was carried out by cutting the spot into small pieces and extracted in 250 μL buffer reagent R1 (Randox laboratories). After brief vortexing (twice) the sample were centrifuged at 2,500 rpm for 5 min. GGT activity was measured in the elute using chemistry analyzer (Beckman Coulter).

Clinical validation was carried out in samples collected from alcohol dependent patients ($n = 123$) spanning the GGT range 10 to 4,075 U/L. The GGT values mean (SD) in serum and dried serum were 271.5 (494.0) and 268.5 (473.6) IU respectively. The two methods correlated well with values ICC 0.99 and r 0.95. Inter and intra assay CV of direct and dried serum were 4.86, 5.15 and 4.11, 4.63 respectively. To conclude, dried serum method has the potential to measure GGT efficiently in a clinical setting.

P1-1-49

THE RELATIONSHIP BETWEEN RESILIENCE AND SOCIAL ASPECTS OF PATIENTS WITH ALCOHOL USE DISORDER: A CROSS-SECTIONAL STUDY

A. Yamashita[1], S.-I. Yoshioka[2]
[1]Department of Nursing, Faculty of Human Health Sciences, Niimi College, Japan and [2]School of Health Sciences, Tottori University Faculty of Medicine, Japan

Aim: Resilience has been described as intrinsic healing potential that can aid patients with alcohol use disorder (AUD) during recovery. The purpose of this study was to clarify the relationship between resilience and social aspects in AUD patients participating in a self-help group.

Methods: February to April 2015, a total of 48 AUD patients were surveyed using a self-administered questionnaire. The questionnaires concentrated on three categories of interest: lifestyle, sociodemographic characteristics, and resilience. For data analysis, the patients were categorized into two groups (high and low score groups) based on median resilience scores, and the chi-square test was used to compare scores between groups.

Results: The results of this analysis revealed that the median score of the target groups' innate and acquired resilience was 37.0 and 30.0, respectively. Comparison between the high ($n = 27$) and low ($n = 21$) innate resilience groups revealed a tendency to have someone to consult with ($p < 0.1$). Comparison between the high ($n = 28$) and low ($n = 20$) acquired resilience groups revealed no significant differences.

Conclusion: Our results suggest the need to increase the availability of confidants and create an environment promoting recovery and a sense of security in AUD patients.

P1-1-50

MECHANISMS UNDERLYING THE INHIBITION OF ORBITOFRONTAL CORTEX NEURON FIRING BY ETHANOL

J.J. Woodward, S. Nimitvilai
Neuroscience, Medical Univ. of South Carolina, USA

The orbitofrontal cortex (OFC) is critical for behaviors including risk assessment and decision making in the face of competing outcomes. Dysfunction of the OFC either by injury, stroke or drugs may predispose individuals to engage in harmful actions such as heavy drinking. Studies from this laboratory showed that ethanol inhibits OFC neuron firing via activation of strychnine-sensitive glycine receptors, however, the processes underlying this effect are unknown. In this study, we tested the hypothesis that the ethanol-induced inhibition of OFC neuron firing is dopamine-receptor dependent and requires functional astrocytes. Acute application of ethanol (66 mM) to neurons in the lateral OFC of adult C57 male mice inhibited current-evoked spiking by nearly 50%. This inhibition was not affected by the D2 antagonist sulpiride but was blocked by the D1/D5 receptor antagonist SCH23390. As dopamine, acting via D5 receptors, has been shown to induce astrocytic glycine release, we treated OFC slices with fluorocitrate to inactivate this process. Under these conditions, the inhibitory effect of ethanol on OFC neurons spiking was significantly blunted. These findings suggest that ethanol induces the release of dopamine from the OFC slice activating D1/D5 receptors on astrocytes to release glycine, possibly via reversal of the GlyT1 transporter.

P1-1-51

CONCURRENT USE OF ALCOHOL WITH OTHER SUBSTANCES: RESULTS FROM NESARC-III

T.D. Saha, S. Patricia Chou
National Institutes of Health, USA

Introduction: Little is known about the sociodemographic profiles, intensity of drinking, severity of alcohol use disorder (AUD), and psychopathology among individuals with specific patterns of concurrent alcohol, nicotine and drug use.

Methods: Data were from the National Epidemiologic Survey on Alcohol and Related Conditions-III. We examined sociodemographic correlates and psychopathology among individuals with specific patterns of concurrent use of alcohol, nicotine and drug relative to alcohol use only, using multinomial logistic regression. We also examined whether concurrent alcohol, nicotine and drug use increased the intensity of drinking and severity of AUD.

Results: The majority (62.0%) of past-year drinkers used only alcohol. Generally, individuals with concurrent use of alcohol, nicotine and drugs were more likely to be men, younger, never/previously married, with lower education and income. Concurrent use of alcohol, nicotine and drugs was generally more likely to experience psychopathology than the alcohol use only. Intensity of drinking and severity of AUD was greater among the concurrent use groups relative to the alcohol use only group.

Conclusions: Research on consequences and treatment outcome of concurrent use of alcohol and other substances is warranted to inform the development of more effective prevention/intervention programs.

P1-1-52

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 (PHASE 3 TRIAL)

S. Higuchi[1], I. Nakamura[2], M. Takahashi[3], Y. Murai[3], K. Tsuneyoshi[4], D. Meulien[5], H. Miyata[6]
[1]National Hospital Organization Kurihama Medical and Addiction Center, Japan, [2]Department of Medical Affairs, Otsuka Pharmaceutical Co., Ltd., Shinagawa Grand Central Tower, 2-16-4 Konan, Minato-ku, Tokyo 108-8241, Japan, [3]Department of Clinical Management, Clinical Development Headquarters, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan, [4]Department of Biometrics, Clinical Development Headquarters, Otsuka Pharmaceutical Co., Ltd., Osaka, Japan, [5]Clinical Research and Development – Neurology, H. Lundbeck SAS, Paris La Défense Cedex, France and [6]Department of Psychiatry, Jikei University School of Medicine, Tokyo, 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 percent confidence interval [CI]: −6.05, −2.62; $p < 0.0001$) and nalmefene 10 mg (difference: −4.18 days per month, 95 percent 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 percent 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 mg and 10 mg were effective in reducing alcohol consumption and were well tolerated in alcohol-dependent patients with high or very high DRL.

P1-1-53

PPAR-GAMMA ACTIVATION BY PIOGLITAZONE REDUCES ALCOHOL DRINKING AND STRESS-INDUCED REINSTATEMENT OF ALCOHOL SEEKING THROUGH MODULATION OF THE MESOLIMBIC DOPAMINE TRANSMISSION IN ALCOHOL-PREFERRING RATS

N. Cannella, Y. Fotio, A. Borruto, M. Petrella, F. Benvenuti, V. Lunerti, R. Ciccocioppo
School of Pharmacy, University of Camerino, Italy

The peroxisome proliferator-activated receptor gamma (PPARgamma) is an isoform of the PPARs family, involved in adipogenesis and glucose metabolism. PPARgamma is expressed in the ventral tegmental area (VTA) dopaminergic neurons and in other mesolimbic areas, which suggest a potential role of this receptor in the regulation of reward processing and motivated behavior in drug addiction. Indeed, evidences demonstrated that oral administration of pioglitazone, a selective PPARgamma agonist, suppresses alcohol drinking and yohimbine-induced reinstatement of alcohol seeking in marchigian sardinian alcohol-preferring (msP) rats. However, the brain circuitry underlying these effects are not yet elucidated.
To this end, we tested the effect of pioglitazone microinjections in the VTA, rostro-medial tegmental nucleus (RMTg), central amygdala (CeA) and nucleus accumbens shell (NAcSh) on alcohol intake in both two-bottle choice and operant self-administration paradigms, and on yohimbine stress-induced reinstatement of alcohol seeking. PPARg activation in the RMTg, but not in the other probed nuclei, reduced alcohol intake in both drinking paradigms. Reinstatement of alcohol seeking induced by the pharmacological stressor yohimbine was blocked by pre-treatment with pioglitazone in the RMTg and CeA. Our results extend previous findings on the effects of PPARgamma on alcohol-seeking behavior and confirm the potential of pioglitazone as treatment for alcoholism.

P1-1-54

EMOTIONAL SELF-REGULATION AND ALCOHOL CONSUMPTION IN SPANISH YOUNG PEOPLE

J. Castro-Calvo[1,2], C. Giménez-García[1], R. Ballester-Arnal[1], M.D. Gil-Llario[3]
[1]Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I de Castellón, Spain, [2]Addictive and Compulsive Behaviours Lab (ACB-lab), Institute for Health and Behaviour, University of Luxembourg, Esch-sur-Alzette, Luxembourg and [3]Departamento de Psicología Evolutiva y de la Educación, Universitat de València, Spain

Background and aim: Deficits in Emotion-Regulation Skills are associated with Alcohol Use Disorders. Motivational variable may facilitate this connection, particularly among young people at risk. Spanish young people have revealed a riskier pattern of alcohol consumption. This study examines differences on motivations for alcohol consumption, particularly about emotional self-regulation, based on the level of emotional discomfort (depression and anxiety).
Methods: 600 young people from Spain (30% men) aged between 18 and 24 years old filled an online ad hoc questionnaire about lifestyles and patterns of alcohol consumption (frequency of consumption, drunkenness, motivations and interference suffered by alcohol), as well as depression and anxiety (discomfort experience).
Results: Depressed and anxious young people showed more alcohol consumption to regulate their discomfort, particularly for calming down ($p<.018$), escaping from problems ($p<.001$), or being self-confident ($p<.017$), among others. In general, there are statistical significant relations between these regulating strategies and depression and anxiety and, particularly, between depression mood and looking for euphoria.
Conclusions: Young people who suffer emotional discomfort, at subclinical level, reveal more alcohol consumption for regulating their depressed mood and anxiety. Probably, this will increase their risk for suffering clinical disorders. Therefore, preventive plans would include this aspect to be effective.

P1-1-55

RELATIONSHIPS AMONG EXPECTANCIES, DRINKING MOTIVATION AND PROBLEM DRINKING AMONG JAPANESE ADULTS: THE ROLE OF EXPECTANCIES FOR NEGATIVE MOOD REGULATION

T. Hamamura[1,2]
[1]Division of Clinical Psychology, Department of Integrated Educational Sciences, The University of Tokyo, Japan and [2]Japan Society for the Promotion of Science, Japan

Previous studies suggest that emotion regulation plays an important role in predicting alcohol use and abuse. Expectancies for negative mood regulation appear to be associated with alcohol consumption, but results have been inconsistent. Expectancies for negative mood regulation refer to beliefs about improving negative mood (Catanzaro & Mearns, 1990, 2016). The current study aimed to investigate whether expectancies for negative mood regulation would better explain problematic drinking compared to other cognitive variables such as drinking motivation and expectancies for drinking outcome. This study recruited 2,052 Japanese adults who have reported problematic drinking via a research marketing company. After agreeing to participate in the study, participants completed self-reported measures of alcohol-related problems, expectancies for negative mood regulation, drinking motivation, alcohol outcome expectancies, and perceived stress. Results indicated that the average age was 48.1 years, and women reported significantly higher drinking problems that men did. Multiple regression analyses revealed that expectancies for negative mood regulation explained the variance of alcohol-related problem above and beyond the variance explained by drinking motivation, expectancies for drinking outcome, and perceived stress. Findings suggest that beliefs about alleviating negative mood are an important cognitive variable in understanding problem drinking among Japanese adults.

TUESDAY, SEPTEMBER 11
2. NICOTINE

P1-2-1

ROLE OF NOCICEPTIN/ORPHANIN FQ SYSTEM IN NICOTINE CONSUMPTION AND SEEKING
N. Cannella, A. Domi, M. Petrella, V. Lunerti, F. Benvenuti, F. Casarola, R. Ciccocioppo
School of Pharmacy, University of Camerino, Italy

Nicotine dependence represents the primary cause of preventable mortality in the world. Several studies evidenced the implication of nociceptin/orphanin FQ (N/OFQ) system in the regulation of addiction-related phenomena. Here, we evaluated the role of N/OFQ system on nicotine reinforcement. We set out with a pharmacological approach demonstrating that the N/OFQ receptor (NOP) antagonist LY2817412, but not the agonist Ro646198, reduced nicotine self-administration. Next, we compared wild-type and NOP knock-out (-/-) rats. NOP-/- rats self-administered less nicotine, showed less motivation for the substance and less propensity to cue-induced reinstatement after 21 days of abstinence respect to wild-type. Accordingly, LY2817412 reduced nicotine self-administration and cue-induced reinstatement on wild-type but not on NOP-/- rats. Next, we hypothesized that N/OFQ system exerts its role at least partially by modulating the capability of nicotine to modulate the firing of dopaminergic neurons in the ventral tegmental area (VTA). To test this hypothesis, we performed ex vivo electrophysiological experiments which showed that NOP receptor blockade reduced nicotine-induced depolarization of VTA dopamine neurons. All these findings support a role for the N/OFQ system as mediator of nicotine reinforcement.

P1-2-2

EARLY DETECTION OF PERIPHERAL ARTERY ISCHEMIA IN HEALTHY MALE SMOKERS BY AN ANKLE BRACHIAL INDEX AFTER EXERCISE: SASAYAMA STUDY
Y. Kubota[1], A. Higashiyama[2], M. Marumo[1], M. Konishi[3], Y. Yamashita[3], T. Okamura[4], Y. Miyamoto[2], I. Wakabayashi[1]
[1]Hyogo College of Medicine, Japan, [2]National Cerebral and Cardiovascular Center, Japan, [3]Sasayama City Office, Japan and [4]Keio University, Japan

Cigarette smoking is a major risk factor for peripheral artery disease (PAD). We investigated the relationship between smoking and the risk of non-normal (≦0.99) ankle-brachial index (ABI) at rest and after ankle plantar flexion exercise in healthy male community-dwellers. A cross-sectional study was performed in 228 Japanese men aged 40–64 years without a history of cardiovascular diseases. Participants were divided into never-, ex- and current-smokers. The multivariate-adjusted odds ratios (OR) for non-normal ABI of ex- and current-smokers in relation to never-smokers were estimated after adjusting for age and other confounding factors. At rest, the prevalence of non-normal ABI did not significantly differ by smoking status. The prevalence of non-normal ABI increased significantly by exercise from 1.8 to 11.5% in ex-smokers and from 3.8 to 17.0% in current-smokers, while the prevalence was not affected by exercise in never-smokers (4.8% at rest and 3.2% after exercise). The multivariate-adjusted OR for non-normal ABI after ankle plantar flexion exercise, in relation to never-smokers, was 3.85 (95% CI: 0.79–18.9) for ex-smokers and 6.97 (95% CI: 1.32–36.7) for current-smokers. In conclusion, measuring ABI after ankle plantar lexion exercise is useful for early detection of subclinical patients with PAD in male smokers.

P1-2-3

MECAMYLAMINE REVERSAL OF THE SYNERGISTIC ENHANCEMENT OF ETHANOL STIMULATION BY NICOTINE
E. Cuellar[1], T.J. Phillips[1,2,3]
[1]Department of Behavioral Neuroscience, Oregon Health & Science University, USA, [2]VA Portland Health Care System, USA and [3]Portland Alcohol Research Center, USA

In a rodent model of sensitivity to the stimulant effects of alcohol (ethanol), nicotine given with ethanol synergistically enhances the stimulant response. Combined stimulant/euphoric effects of these drugs could encourage their co-abuse. We examined the role of nicotinic acetylcholine receptors (nAChR) by administering the non-specific nAChR antagonist, mecamylamine, 10 min prior to treatment with saline, ethanol or ethanol+nicotine. A low 1 g/kg dose of ethanol was used to avoid a ceiling effect in ethanol+nicotine-treated mice. Data were collected in automated monitors on 3 days: after saline treatment only on days 1 and 2 and after drug treatments (or saline in the control group) on day 3. Distance traveled was non-significantly elevated in the ethanol group and significantly increased in the ethanol+nicotine group. A lower dose of mecamylamine reduced activity levels of the nicotine+ethanol group to levels similar to the ethanol group; a higher dose blocked the stimulant effects of both ethanol and ethanol+nicotine. Thus, nAChR involvement in nicotine-induced enhancement of ethanol stimulation can be discerned at a lower antagonist dose than their involvement in ethanol-induced stimulation. Receptor subtypes and brain circuitry will be future directions.
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P1-2-4

ELECTRONIC SMOKERS IN INDONESIA: A NEW ADDICTION
C.H. Lusikooy[1,2], K. Siste[2]
[1]Drug Dependence Hospital, Indonesia and [2]Departement of Psychiatry, Medical Faculty, Universitas Indonesia, Indonesia

Despite tobacco control efforts, the rising use of electronic cigarettes (e-cigarettes) in Indonesia is sparking concern among policy makers. The lack of information on e-cigarettes present a new challenge to public health, as it may fuel nicotine addiction or serve as an alternative to cease tobacco use. The debate is widespread, yet early troublesome evidence shows how popular e-cigarette use is despite unknown health consequences, particularly among Indonesian youth and current adult tobacco smokers as a result of appealing and aggressive advertising. With specific attention among youth, teenagers <14 years who have used e-cigarettes are at increased risk to use other smokable tobacco products in later adolescence, projecting to 1 in 5 Indonesian youth suffering from nicotine addiction by the age of 16–19 (18% prevalence). Whilst among adults, many e-cigarette users are driven by factors other than smoking cessation (i.e. oral fixation, hobby elements, social belonging), that projects into 0.3% prevalence of current users. In the absence of data on toxicity and addiction incidences, the trend calls for empirical evidence on the trajectory of e-cigarette use as a method to prevent and reduce nicotine exposure and addiction altogether.

TUESDAY, SEPTEMBER 11
3. OTHER DRUG

P1-3-1

PREVALENCE AND CORRELATES OF ADVERSE CHILDHOOD EXPERIENCES (ACES) AMONG METHAMPHETAMINE USERS IN JAPANESE PRISON

M. Yamaki[1], Y. Takeshita[1], M. Takahashi[2], A. Kondo[3], T. Shimane[3]
[1]Research and Training Institute Ministry of Justice Japan, Japan, [2]Tokyo Juvenile Classification Home, Japan and [3]National Center of Neurology and Psychiatry, Japan

A great deal of research revealed that adverse childhood experiences (ACEs) increased risk of negative health outcomes later in adulthood. However, little is known about ACEs among incarcerated substance users. The purpose of the current research is to estimate the prevalence of ACEs by gender in a sample of Japanese methamphetamine users. A total of 699 inmates, who were admitted into prison due to Stimulants Control Act violation, completed anonymous self-report questionnaire. Approximately 75% of the participants experienced at least one ACE, and females reported significantly higher number of adversities than males. The most common ACE was parental death or separation, followed by psychological abuse. Our findings suggest the importance of early prevention and intervention for child maltreatment, and also have an implication for the recommendation of gender-responsive, trauma-focused intervention especially for female inmates. Future directions for research and treatment will be discussed.

P1-3-2

WHAT MAKES PRESCRIBING DRUGS HAS IT CHALLENGES? A CASE SERIES AT CIPTO MANGUNKUSUMO HOSPITAL

D. Satyasari[1], K.S. Kurniasanti[2]
[1]Resident in Psychiatry Department, University of Indonesia/Cipto Mangunkusumo Hospital, Indonesia and [2]Psychiatrist in Psychiatry Department, University of Indonesia/Cipto Mangunkusumo Hospital, Indonesia

Background: Prescribing drugs like benzodiazepines has challenges itself, especially in patients with a history of substance dependence. This study will describe enablers and obstacles in prescribing benzodiazepines in patients with history of dependency.
Methods: A case series of adult patients with a history of substance use and currently still using benzodiazepines at outpatient psychiatric unit in Cipto Mangunkusumo Hospital, gathered between September 2017 and March 2018.
Result: There were six patients, aged around 40 years old observed in this study. They were diagnosed and treated for schizophrenia spectrums. All patients has a history of using substances. Currently, they use benzodiazepines to help them sleeping and cope with problems, uncomfortable feelings because antipsychotics, antidepressants, mood stabilizers don't assist them to sleep well. Half the patients had ambivalences regarding their goals to be abstinence from benzodiazepines, yet some tried to negotiate in the process. It was related with a sense of different perspectives of treatment goal by patient and therapist.
Conclusion: In patient with schizophrenia spectrums with history of dependence, it has some challenges to prescribe benzodiazepines. They are having ambivalences regarding their goals to be abstinence from benzodiazepine. It's important to explore patient's needs, treatment goals, and encourage them to achieve it.

P1-3-3

THE ASSOCIATION BETWEEN DEPRESSIVE SYMPTOMS AND LOWER URINARY TRACT SYMPTOMS AMONG KETAMINE ABUSERS IN TAIWAN

H.-T. Wei[1,2], S.-C. Chang[1], M.-H. Chen[3], P.-Y. Jau[1], K.-C. Yu[1], M.-Y. Yen[2], Y.-H. Yeh[1], C.-H. Hsu[1]
[1]Branch of Linsen, Chinese Medicine and Kunming, Taipei City Hospital, Taiwan, [2]Kunming Prevention and Control Center, Taipei City Hospital, Taiwan and [3]Taipei Veterans General Hospital, Taiwan

Background: Ketamine abuse is a substantial public health crisis in Taiwan. Long term ketamine use may lead to psychological and physical hazards.
Method: Participants were enrolled from the compulsory ketamine use relapse prevention lectures for ketamine abusers seized by the police. The lectures were held by the Taipei City Government according to Law for the Control of Narcotics. Self-reported questionnaires included profile of ketamine use, International Prostate Symptom Score (IPSS), and Beck Depression Inventory (BDI-II) were delivered with informed consents under the approval of the Taipei City Hospital Institutional Review Board.
Result: 346 (Male/Female: 248/98) participants were enrolled with a mean age of 28.66 $\pm$ 6.20 and history of 56.75 $\pm$ 48.04 months of ketamine use. The mean IPSS score was 6.11 $\pm$ 6.77 while 105 (30.4%) participant revealed moderate to severe lower urinary tract symptoms. The mean BDI-II score is 15.45 $\pm$ 10.39 while 115 (33.2%) participants revealed moderate to severe depression. A positive correlation between IPSS and BDI-II was noted (Correlation coefficient: 0.321, $p < 0.001$, adjusted for age, sex, daily amount of ketamine use, and duration of ketamine use)
Conclusion: Urinary tract symptoms are significantly correlated to depressive symptoms and both may result in great health hazards. Therefore, further prevention and intervention programs should be developed.

P1-3-4

CLASSIFICATION OF COGNITIVE RESPONSE PATTERNS OF FAMILY MEMBERS OF DRUG USERS

Y. Tsuji[1,2], S. Aoki[3,4], Y. Sakano[5]
[1]Graduate School of Psychological Science, Health Sciences University of Hokkaido, Japan, [2]Research Fellow of Japan Society for the Promotion of Science, Japan, [3]Center for Medical Education and Career Development, Fukushima Medical University, Japan, [4]Department of Neuropsychiatry, Fukushima Medical University, Japan and [5]School of Psychological Science, Health Sciences University of Hokkaido, Japan

Introduction: Various cognitive response patterns occur in families related to drug use. It is important to understand cognitive response patterns in order to provide adequate psychosocial supports. The purpose of this investigation is to classify cognitive response patterns of families.
Methods: Participants were 7 families of drug users, and 11 healthcare professionals on drug problems. They were requested to receive an interview or to answer the questionnaire asking cognitive responses related to drug problems. Collected items were classified by KJ method by three clinical psychologists.
Result: 60 items were collected, and classified into 13 categories. 1) sense of guilty, 2) responsibility, 3) dissatisfaction with the current situation, 4) suspicion of drug use, 5) hopelessness, 6) pessimism on the future of the families, 7) denial, 8) interference on the other families, 9) pessimism on the future of the drug users, 10) conflict with related others, 11) disturbance in work, 12) isolation, and 13) fear of being arrested.
Discussion: As a result of KJ method, cognitive response patterns of families can be classified in terms of family themselves, drug users, and social context. To provide adequate psychosocial supports, it is necessary to understand the state of families multidimensionally, considering cognitive response patterns classified in this investigations.

P1-3-5

BENZODIAZEPINE USE AMONG PATIENTS WITH BUPRENORPHINE-NALOXONE MAINTENANCE TREATMENT IN DRUG DEPENDENCE HOSPITAL, JAKARTA

I.I. Aritonang[1,2], K. Siste[2]
[1]Drug Dependence Hospital, Indonesia and [2]Department of Psychiatry, Medical Faculty, Universitas Indonesia, Indonesia

Buprenorphine-Naloxone (buprenorphine) maintenance treatment helps people reduce or stop their abuse of opioids and has been shown to be effective in reducing the negative health effects and deaths associated with opioid addiction and dependency. Benzodiazepine use is common among patients prescribed buprenorphine for opioid dependence, either under a health care professional's direction or illicitly, to self-medicate or to increase the effects of opioids. The prevalence of benzodiazepine misuse among clients in Opioid Substitution Treatment (OST) ranges from 45% in France to 70% in Germany. The frequency of benzodiazepine misuse among those undergoing OST is reported to increase with the length of treatment. Fatal overdoses from mixing benzodiazepines with buprenorphine, especially through concurrent intravenous administration, are a major safety concern. Many clinicians believe that benzodiazepine prescriptions should be avoided because benzodiazepines hinder development of psychological coping strategies, can be misused and can contribute to relapse.
This study is aimed to identify the characteristics of benzodiazepine use among patients with buprenorphine-naloxone maintenance treatment in Drug Dependence Hospital, Jakarta. The results will help clinicians to develop strategies to manage use of prescribed or illicit benzodiazepines at initiation of buprenorphine treatment, or if it emerges as a concern during treatment.

P1-3-6

IN VIVO IMAGING FOR THE EFFECT OF COCAINE

Y. Zhu[1], N. Ito[1], T. Nagai[1], K. Kuroda[2], K. Kaibuchi[2], T. Nabeshima[3], K. Yamada[1]
[1]Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Japan, [2]Department of Cell Pharmacology, Nagoya University Graduate School of Medicine, Japan and [3]Advanced Diagnostic System Research Laboratory Fujita Health University, Graduate School of Health Sciences & Aino University, Japan

Background: Cocaine indirectly stimulates dopamine D1 receptors which is a G protein-coupled receptor and consequently activates cAMP response element (CRE) binding protein. In this study, we developed a simple in vivo imaging system to measure the effects of CNS-acting drugs.
Method: We transfected HEK293 with adeno-associated virus (AAV) plasmid which contains CRE promoter and luciferase gene (pAAV-cre-luc2p). The transfection was confirmed by expression of luciferase protein after forskolin stimulation. We injected the AAV particle into the striatum of mice and administrated saline or cocaine to these mice and performed immunohistochemistry at 6 h after administration. Besides, luciferase activity was measured by in vivo imaging system after the cocaine administration.
Result: Forskolin treatment increased the expression of luciferase 3 and 6 h after the treatment in HEK293 cell, and the expression of luciferase was 5 times higher in the treated group 6 h after stimulation than the control group. Similarly, in vivo imaging analysis also revealed that cocaine treatment increased luciferase activity compared to control group 6 h after the treatment.
Conclusion: This system we developed is useful for imaging and screening of CNS-acting drugs in preclinical study.

P1-3-8

INTENSIVE FAMILY INTERVENTION IS POSITIVE FOR BETTER PROGNOSIS AMONG A 19-YEAR-OLD MALE WITH AMPHETAMINE USE DISORDER: A CASE REPORT

C.H. Hsiao[1], G.-Y. Lai[1], C.-H. Li[1], M.-C. Yuan[1], H.-T. Wei[1,2]
[1]Kunming Prevention and Control Center, Taipei City Hospital, Taiwan and [2]Branch of Linsen, Chinese Medicine and Kunming, Taipei City Hospital, Taiwan

We report a 19-year-old male with history of amphetamine use disorder for two years. The client was referred to the substance use disorder treatment clinic by the juvenile court. In the starting six months of follow-up, the patient suffered from severe familial conflicts especially conflicts with father. Active drug use and psychotic and mood symptoms induced by amphetamine were noted. Therefore, we invited his father to join the clinic while intensive family intervention was performed. After a few months, his family changed the attitude of treating the patient and also joined the recovery program actively with the client. Gradual improvements were noted under intensive outpatient follow-ups. Individual counseling were also performed along with family therapy. Case managing, regular urine drug testing and relapse prevention techniques were also performed. A distinct outcome was noted and he remained abstinent from amphetamine for the following six months. This case demonstrated that family engagement and intensive family education is positive toward the prognosis of clients with amphetamine use disorder.

P1-3-9

COHORT STUDY AND DEVELOPMENT OF COMMUNITY-BASED SUPPORT FOR DRUG USERS ON PROBATION IN JAPAN, VOICE BRIDGES PROJECT

A. Takano[1], Y. Kumakura[2], E. Ban[3], T. Usami[3], T. Matsumoto[3]
[1]Department of Psychiatric Nursing, Yokohama City University, Japan, [2]Department of Mental Health, The University of Tokyo, Japan and [3]Department of Drug Dependence Research, National Center of Neurology and Psychiatry, Japan

A zero-tolerance drug policy in Japan has limited community-based support for drug users. In 2016, the Japanese government started a new probation system and drug users who previously would have been incarcerated for several years were discharged from jail earlier and received community-based support during the probation period. The aim of this study is to assess prognosis such as relapse or quality of life among drug users on probation. Additionally, we intend to promote the relationship between institutions providing community-based support. The study cohort includes people who have just started probation and volunteered to participate in the study. Over three years, participants are asked questions about drug use, work, participation in programs related to drug problems, and other items by public community mental health center staff through face-to-face or telephone interviews. The study is ongoing and 87 people are participating from seven public mental health centers as of April 2018. Most participants were male, methamphetamine users, arrested more than twice, and had a moderate degree of drug dependence. Recruitment is ongoing and initial outcomes will be evaluated at the end of the year.

P1-3-10

RISK FACTORS FOR LONG-TERM PRESCRIPTION OF BENZODIAZEPINE: COHORT STUDY USING A LARGE HEALTH INSURANCE CLAIM DATABASE IN JAPAN

A. Takano[1], S. Ono[2], H. Yamana[3], H. Matsui[4], T. Matsumoto[5], H. Yasunaga[4], N. Kawakami[6]
[1]Department of Psychiatric Nursing, Yokohama City University, Japan, [2]Department of Biostatistics & Bioinformatics, The University of Tokyo, Japan, [3]Department of Health Services Research, The University of Tokyo, Japan, [4]Department of Clinical Epidemiology and Health Economics, The University of Tokyo, Japan, [5]Department of Drug Dependence Research, National Center of Neurology and Psychiatry, Japan and [6]Department of Mental Health, The University of Tokyo, Japan

Aim: The long-term use of benzodiazepines and benzodiazepine-related hypnotics (BZDs) has raised concerns about dependence and tolerance. However, risk factors for long-term prescription remain uncertain. The aim of this study was to identify risk factors associated with long-term prescription of BZDs.
Methods: Using a large health insurance database in Japan (Japan Medical Data Center, Tokyo, Japan), we identified outpatients aged 18 to 65 years who newly started oral BZDs between October 2012 and April 2015. We defined long-term BZD use as a consecutive prescription of any BZD for eight months, and where withdrawal symptoms reportedly increase. Multivariable logistic regression analysis was performed to assess the association between potential predictors at initial prescription and the long-term prescription.
Results: Of the 71,955 new users identified, 6,462 (9.0%) were prescribed BZDs for at least eight months. Older age, cancer, psychiatric diseases, and use of hypnotics were significantly associated with the long-term BZD prescription. The half-life of BZDs was not associated with the long-term prescription.
Conclusion: Several risk factors for long-term prescription of BZDs were identified. Further strategies are needed to reduce long-term prescription of BZDs, especially among patients with risk factors.

TUESDAY, September 11
4. Behavioral Addiction

P1-4-1

BUILDING BRIDGES BETWEEN SUBSTANCE AND BEHAVIORAL ADDICTIONS: ALCOHOL CONSUMPTION AND THEIR PREDICTIVE POWER OVER INTERNET AND CYBERSEX USE AND ABUSE IN ADOLESCENTS

J. Castro-Calvo[1,2], C. Giménez-García[1], J. Billieux[2], M.D. Gil-Llario[3], R. Ballester-Arnal[1]
[1]Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I de Castellón, Spain, [2]Addictive and Compulsive Behaviours Lab (ACB-lab), Institute for Health and Behaviour, University of Luxembourg, Esch-sur-Alzette, Luxembourg and [3]Departamento de Psicología Evolutiva y de la Educación, Universitat de València, Spain

Several studies reported an increased risk of behavioral addictions associated with hazardous or addictive use of psychoactive substances. The aim of this study is to analyze the predictive power of alcohol consumption over internet and cybersex addictive use and related harm. 312 adolescents (47.4% men) between 14–16 years old completed an ad hoc scale assessing alcohol consumption (yes/no). Internet and cybersex addictive use and related harm were measured through the number of hours online (in general/for sexual purposes) and the scores in 2 scales (Internet Addiction Test, IAT; Internet Sex Screening Test, ISST). The number of hours online (in general/for sexual purposes) were significant higher (d of .61 and .24 respectively) for those who reported having drunk alcohol. Scores on the IAT and ISST were also higher (d of .53 and .27). Regressions including alcohol consumption as independent variable predicted 7.4% of time online (β=.27; p<.001) and 6.7% of internet addiction symptoms (β=.27; p<.001), but only 1.2% of time online for sexual purposes and 1.7% of cybersex addiction symptoms. Thus, Internet and cybersex addictive use and related harm is increased among those adolescents who have used alcohol. However, the overlap between these conditions in terms of predictive power is only reliable in Internet addiction.

P1-4-2

THE RELATIONSHIP BETWEEN SMARTPHONE ADDICTION AND SYMPTOMS OF DEPRESSION, ANXIETY, AND ATTENTION-DEFICIT/HYPERACTIVITY IN SOUTH KOREAN ADOLESCENTS

S.-G. Kim
Department of Psychiatry, Chosun University of Medicine, Korea

Background and aims: This study aimed to investigate the prevalence of smartphone addiction and its association with depression, anxiety, and Attention-Deficit Hyperactivity Disorder (ADHD) symptoms in a large sample of Korean adolescents.
Methods: A total of 4,512 (2034 males and 2,478 females) middle and high school students in South Korea were included in this study. Subjects were asked to complete a self-reported questionnaire, including measures of the Korean Smartphone Addiction Scale (SAS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Conners-Wells' Adolescent Self-Report Scale (CASS). Smartphone addiction and non-addiction group is classified according to diagnostic criteria of SAS score.
Results: 338 subjects (7.5%) were categorized to the addiction group. Total SAS score was positively correlated with total CASS score, BDI score, BAI score, female sex, smoking, and alcohol use. Using multivariate logistic regression analyses, the odds ratio of ADHD group compared to the non-ADHD group for smartphone addiction was 6.43, the highest among all variables (95% CI: 4.60–9.00).
Conclusion: Our findings indicate that ADHD may be a significant risk factor for developing smartphone addiction. The neurobiological substrates subserving smartphone addiction may provide insights on to both shared and discrete mechanisms with other brain-based disorders.

P1-4-3

WHAT HAS BEEN CHANGED WITH GROUP THERAPY FOR GAMBLING DISORDER?

A. Iriki, D. Nakabayashi, M. Kurahashi, S. Tanaka, T. Taka, I. Tachi, H. Kinoshita, T. Sasada
Osaka Psychiatric Medical Center, Japan

In DSM 5, among behavioral addiction, only gambling disorder became a category of dependency, which is the same as alcoholism and drug addiction. The prevalence of gambling disorder is about 3–5% in Japan. More than 3–5 million japanese have a gambling problem. In addition, Japan has 60% of the world's gaming machines. Nevertheless, there were few ways to treat the gambling problem in Japan. Little is known about effective treatment for gambling disorder. There is no effective medication for gambling. In October 2014, our hospital, Osaka Psychiatric Medical Center, became an addiction treatment center. We created an original textbook based on cognitive behavioral therapy, named GAMP (Gambling Addiction Meeting Program). From August 2016, we carried out group therapy sessions for outpatients once a month. What has been changed with GAMP? Our doctor's response to the gambler has changed. We now have the specialized program for gambling disorder. So, We can respond to the needs of patients and their families proudly. Medical staff, patients and their family, everyone has been feeling a sense of accomplishment. And these improved continuation rate of gambler's treatment.

P1-4-4

PERCEPTION OF PSYCHIATRIC RESIDENTS IN INDONESIA ON INTERNET ADDICTION

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

Recently, internet addiction has already taken its first few victims in Indonesia. However, many physicians seem not to have a thorough knowledge about it. Psychiatric residents who have been exposed to various psychiatric disorders are expected to take a lead. This study aims to assess the readiness of psychiatric residents in managing internet addiction from their knowledge, attitude, and perception on internet addiction.
A web-based survey assessing knowledge, attitude, and perception related to internet addiction was administered to psychiatric residents of a certain education center.
A total of 52 residents completed the questionnaire. About 60% of the respondent said that they have not had adequate knowledge on internet addiction, hence not confident in dealing with the diagnosis and management. Among 8 scales measured by the questionnaire (emotional representation, demoralization, illness coherence, consequences, chronic timeline, patient control, timeline cyclical, and treatment control), residents seemed to have lowest mean score of 1.882 (SD 0.374) in demoralization scale and highest mean score of 4.139 (SD 0.538) in consequences scale.
A new curriculum on internet addiction, or other behavioral addiction, needs to be developed to improve the residents' perception on this topic.

Keywords: internet addiction, medical education, psychiatric resident:

P1-4-5

AMPHETAMINE PRIMES ENHANCED MOTIVATION TOWARD UNCERTAIN CHOICES IN RATS WITH GENETIC ALCOHOL PREFERENCE

V. Oinio[1,2], M. Sundström[1], P. Bäckström[2], J. Uhari-Väänänen[1,2], K. Kiianmaa[2], A. Raasmaja[1], P. Piepponen[1]
[1]University of Helsinki, Finland and [2]National Institute for Health and Welfare, Finland

Comorbidity with gambling disorder and alcohol use disorder is well documented. The purpose of this study was to examine the influence of genetic alcohol drinking tendency on reward-guided decision making behavior of rats and the impact of dopamine releaser D-amphetamine on this behavior. In this study, Alko alcohol (AA) and Wistar rats went through long periods of operant lever pressing training where the task was to choose the most profitable out of two options. The lever choices were guided by different-sized sucrose rewards, and the probability of gaining the larger reward was slowly changed to a level where choosing the smaller reward would be the most profitable in the long run. After training, rats were injected (s.c.) with dopamine releaser D-amphetamine to study the impact of rapid dopamine release on this learned decision making behavior. Administration of D-amphetamine promoted unprofitable decision making of AA rats more robustly when compared to Wistar rats. These results indicate that conditioning to the lever pressing in uncertain environments is more pronounced in AA than in Wistar rats and indicate that the reinforcing effects of a gambling-like environment act as a stronger conditioning factor for rats that exhibit a genetic tendency for high alcohol drinking.

TUESDAY, SEPTEMBER 11
5. ALCOHOL-INDUCED ORGAN DAMAGE

P1-5-1

ALCOHOL INHIBITS CIRCADIAN NUCLEAR TRAFFICKING AND INCREASES PROTEIN-PROTEIN INTERACTION

B.T. Davis, R. Zuwala, M. Shaikh, C. Forsyth, A. Keshavarzian
Rush University Medical Center, Department of Internal Medicine, USA

In a subset of alcoholics, alcohol increases intestinal permeability a critical factor to the development of Alcoholic Liver Disease (ALD). Susceptibility to permeability has been linked to circadian disruption. We've shown that IP 1) is increased with the alcohol induction of circadian protein PER2 and 2) blocked by inhibiting oxidative stress (OS) or 3) blocked with siRNA knockdown of PER2 or CYP2E1 in-vitro. OS also inhibits the nuclear trafficking of PER2. PER2 is an inhibitor of intestinal regulator protein PPARg. We aim to elucidate the influence of alcohol on PER2 trafficking and PER2-PPARg protein-protein interaction (PPI), which could negatively affect permeability. Permeability, protein expression, location and binding were assessed in-vitro using transepithelial electrical resistance, Western Blot, and Immunohistochemistry, and Immunoprecipitation. Immunohistochemical protein expression and location C57BL/6J mice Caco-2 monolayers showed increased expression and binding of PER2 and PPARg and permeability. Permeability was mitigated with a PPARg agonist in-vitro. Alcohol also induced changes in expression and trafficking of PER2 in the colonic tissues of mice. Alcohol may alter PER2 and PPARg behaviors which indicates a role for the dynamic transport of circadian proteins in the maintenance of the intestinal barrier.

P1-5-2

COMORBIDITY OF ADULT ADHD AND ALCOHOL INDUCED DEPRESSION: AUGMENTATION WITH METHYLPHENIDATE

S. Kandrakonda[1], S.S. Penugonda[2], S.K. Ch[3]
[1]MaxCure Corporate Hospitals, India, [2]Assistant Professor of Pharmacology, India and [3]Associate Professor of Psychiatry, India

Objective: Adjunctive use of methylphenidate, a central stimulant, has been considered as a potential therapeutic choice for patients with ADHD, bipolar depression, and depression secondary to substance use.
Method: Fifty six ($N = 56$) Adult ADHD subjects with alcohol induced depression participated in a four week prospective cross-sectional study comparing treatment response in two treatment groups: Group I- SSRI ($N = 28$), Group II- SSRI plus methylphenidate ($N = 28$). The primary outcome measure was change in depression severity. Remission was defined as a score of 6 or less on the Hamilton Depression Rating Scale (HRDS). Secondary outcomes included measures of anxiety, apathy, quality of life (CGI) and cognition.
Results: Daily doses ranged from 10 mg to 20 mg for SSRI (Citalopram, mean = 15 mg) and from 5 mg to 40 mg for methylphenidate (mean = 16 mg). All groups showed significant improvement in depression severity and in cognitive performance. However, the improvement in depression severity (Chi-square= 6.31, $p < 0.04$) and Clinical Global Impressions improvement score (Chi-square = 4.21, $p < 0.02$) was more prominent in the SSRI plus methylphenidate Adult ADHD Group II compared with the Group I.
Conclusion: Combination of antidepressants and methylphenidate seems to be an effective new option for the treatment of alcohol induced depressions comorbid with Adult ADHD.

P1-5-3

GLYCINE/SARCOSINE RATIO AS NOVEL BIOMARKER FOR ALCOHOL-INDUCED LIVER FIBROSIS UNDER SUMOYLATION CONTROL

M.L. Tomasi[1], C. Cossu[1,2], K. Ramani[1]
[1]Cedars-Sinai Medical Center, USA and [2]University of Sassari, Italy

Propose: Alcohol-induced liver fibrosis (ALD) is characterized by excessive deposition of extracellular matrix (ECM) components in response to chronic abuse. Sarcosine is generated by glycine-*N*-methyl-transferase (GNMT) and converted back into glycine via sarcosine-dehydrogenase (SARDH). GNMT is silenced in human ALD, while promotes oxidative stress in knockout mice. SUMOylation is a post-translational modification that controls numerous cellular processes. Alcohol-fed mouse liver SUMO-proteomic data reveled that GNMT and SARDH are SUMOylated Our aim is to examine whether dysregulated SUMOylation influence GNMT and SARDH enzymatic activity in ALD and elucidate the molecular mechanism(s).
Methods: hepatocytes (HEP), Kupffer (KCs) and stellate cells (HSCs) from in vivo ethanol-fed mouse models were used to measure mRNA, proteins and enzymatic levels.
Results: Ethanol promoted SUMOylation machinery only in HSCs and HEP resulting in increased GNMT SUMOylation and total levels, specifically in HSCs. In contrast, SARDH SUMOylation fell despite an increase in its total level. Ethanol increased glycine and lowered sarcosine levels in mouse plasma. Co-culture model (HEP, HSCs, KCs), show increased oxidative stress as well as glycine/sarcosine ratio in HSCs but not in HEP and KCs, while SUMO silencing abolished it.
Conclusions: Oxidative stress-induced SUMOylation regulates HSCs activation and may influence transmethylation targeting GNMT and SARDH.

P1-5-4

ADIPOSE-SPECIFIC LIPIN-1 OVEREXPRESSION INDUCES FERROPTOSIS AND AGGRAVATES EXPERIMENTAL ALCOHOLIC STEATOHEPATITIS IN MICE

Z. Zhou[1], M. Daniels[1], N. Kainrad[1], G. Bonavita[1], T.J. Ye[1,2], M. You[1]
[1]Department of Pharmaceutical Sciences, Northeast Ohio Medical University, USA and [2]Department of Biology, Shanghai University of Traditional Chinese Medicine, China

Lipin-1 regulates lipid metabolism and inflammation by functioning as a mammalian Mg^{2+} dependent phosphatidate phosphatase and as a transcriptional regulatory protein. Ethanol-mediated inhibition of adipose lipin-1 gene expression was associated with alcoholic fatty liver in mice. We investigated adipose-specific lipin-1 in the development and progression of alcoholic steatohepatitis using mice overexpressing lipin-1 in adipose (LPIN1-Tg). LPIN1-Tg and wild-type (WT) mice were pair-fed with ethanol using a chronic-plus-binge ethanol feeding protocol. In comparison with ethanol-fed WT mice, chronic-plus-ethanol-fed LPIN1-Tg mice showed rapid onset and progression of steatosis, inflammation, hepatobiliary damage and fibrogenic responses. Mechanistically, adipose-specific lipin-1 overexpression caused prominent iron overload in the liver and adipose in response to ethanol challenge. The iron overload in ethanol-fed LPIN1-Tg mice was associated with reduced glutathione contents, decreased nicotinamide adenine dinucleotide phosphate levels and enhanced liver lipid peroxidation, which are biomarkers of ferroptosis. In conclusion, adipose-specific lipin-1 overexpression triggered hepatic ferroptosis, a novel form of iron-dependent cell death, and subsequently exacerbated ferroptotic liver damage in ethanol-fed mice. Our study identified ferroptosis as a mechanism in mediating the detrimental effects of adipose-specific lipin-1 overexpression in mice under chronic-plus-binge ethanol exposure. Modifying adipose lipin-1-ferroptosis signaling may represent a therapeutic approach for treating human alcoholic steatohepatitis.

P1-5-5

MITONEET LIGAND-1 ALLEVIATES EXPERIMENTAL ALCOHOLIC STEATOHEPATITIS IN MICE THROUGH MITIGATION OF FERROPTOSIS

M. Daniels[1], Z. Zhou[1], G. Bonavita[1], T.J. Ye[1,2], M. You[1]
[1]Department of Pharmaceutical Sciences, Northeast Ohio Medical University, USA and [2]Department of Biology, Shanghai University of Traditional Chinese Medicine, China

MitoNEET, a redox-sensitive protein anchored in the outer mitochondrial membrane and hosted a [2Fe-2S] cluster, is a target of thiazolidinediones (TZDs) and regulates lipid metabolism, iron homeostasis and inflammation. MitoNEET ligand-1 (NL-1) is a specific mitoNEET ligand with minimal PPARγ activity. mitoNEET contributes to alcoholic steatohepatitis in mice. This study explored mechanisms of NL-1 in ethanol-induced liver damage. Utilizing a chronic-plus-binge alcohol feeding protocol, four mouse groups were pair-fed with or without ethanol. Two mouse groups were given 3 mg.kg body wt(-1).day(-1) with or without ethanol in their diets for 10-days. NL-1 treated-mice resisted ethanol-induced liver injury as revealed by reduced steatosis, normalized serum levels of alanine aminotransferase, aspartate aminotransferase, and attenuated serum alkaline phosphatase levels. NL-1 treatment completely ameliorated ethanol-induced aberrant iron homeostasis by diminishing accumulation of hepatic iron and attenuating serum ferritin levels. Concordance with normalized hepatic iron, NL-1 administration enhanced hepatic glutathione (GSH) and nicotinamide adenine dinucleotide phosphate (NADPH) and diminished liver lipid peroxidation, which are three biomarkers of ferroptosis. Conclusion
NL-1 prevented excessive hepatic iron and attenuated ferroptotic liver damage in ethanol-fed mice. The NL-1 protection against ethanol-induced liver damage is mediated through mitigating of mitoNEET-related ferroptosis. NL-1 may potentially treat human alcoholic steatohepatitis.

P1-5-6

THE SIGNIFICANCE OF DETERMINING PROINFLAMMATORY CYTOKINES (TNF-ALPHA, IL-6, IL-17, IL-33) IN ALCOHOL ADDICTS WITH COGNITIVE DEFICIT

V. Banjac[1], N.Z. Radulovic[1], V. Banjac[2]
[1]Clinic of Psychiatry, University Clinical Center of the Republic of Srpska, Bosnia and Herzegovina and [2]Medical Faculty of Banjaluka, Bosnia and Herzegovina

Introduction: There is an emerging body of evidence that there is a link between alcohol and neuroinflammation. Alcohol intoxication, withdrawal and chronic use impacts the immune system, causing release of pro-inflammatory cytokines, which can precipitate inflammatory tissue injury leading to end organ failure. Brain cytokine disturbances may impact neurological function, mood and cognition. Alcoholics experience a number of cognitive deficiencies.
Aim: The aim is to determine the correlation between the change in the level of proinflammatory cytokines (TNF-alpha, IL-6, IL-17, IL-33) in serum and the level of cognitive impairment in alcohol addicts.
Method: The research would be designed as a clinical research. The whole sample of participants will be divided into two groups. Experimental group will be comprised of patients – alcohol addicts who are in abstinence at least a month. The control group will be comprised of healthy subjects. Psychiatric assessment scales (MoCa test and The Addenbrooke's Cognitive Examination) will be used to evaluate cognition. Serum cytokine levels will be measured using ELISA technique.
Expected results: The research should indicate a more frequent occurrence of cognitive deficit in alcohol addicts and its association with the level of proinflammatory cytokines in serum.
Keywords: alcoholism, cognitive deficit, proinflammatory cytokines:

P1-5-7

HEPATIC GLUTAMATE PROMOTES ALCOHOLIC FATTY LIVER THROUGH THE MGLUR5-MEDIATED ENDOCANNABINOID PRODUCTION IN STELLATE CELLS

W.-M. Choi[1], M.-H. Kim[1], R. Cinar[2], H.-H. Kim[1], Y.-R. Shim[1], J.-H. Lee[1], B. Gao[3], W. Kim[4], G. Kunos[2], W.-I. Jeong[1]

[1]Laboratory of Liver Research, Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Korea, [2]Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, USA, [3]Laboratory of Liver Diseases, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, USA and [4]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Korea

Paracrine activation of hepatic cannabinoid receptor 1 by hepatic stellate cell (HSC)-derived 2-arachidonoylglycerol (2-AG) is one of the critical mechanisms mediating alcoholic steatosis by stimulating de novo lipogenesis in hepatocytes. However, the precise mechanism of 2-AG production in HSCs is unknown. We found that chronic ethanol consumption significantly increased glutamate levels in blood and liver of ethanol-fed mice compared to controls. System x_c^-, which exports glutamate and imports cystine for glutathione synthesis, was upregulated through the antioxidant transcription factor Nrf2. Chronic ethanol consumption induced cysteine deficiency by impairing transsulfuration pathway, resulting in the glutamate excretion for cystine (immediately reduced to cysteine) via system x_c^- in hepatocytes. Intriguingly, comparing with other hepatic cells, the metabotropic glutamate receptor 5 (mGluR5) was highly expressed in HSCs and 2-AG production in HSCs was remarkably increased by mGluR5 activation. Consistently, genetic or pharmacologic inhibition of mGluR5 or system x_c^- significantly attenuated alcoholic steatosis in ethanol-fed mice, followed by suppression of 2-AG production and de novo lipogenesis. Taken together, our findings demonstrate that increased excretion of hepatic glutamate by system x_c^- as a lipogenic mediator promotes alcoholic steatosis through mGluR5-mediated 2-AG production in HSCs, which could be a potential therapeutic target for alcoholic liver disease.

P1-5-8

CX_3CR1 TRANSDIFFERENTIATES F4/80 LOW MONOCYTES INTO PRO-INFLAMMATORY F4/80 HIGH MACROPHAGES IN ALCOHOLIC LIVER DISEASE

M.-H. Kim[1], Y.-S. Lee[2], H.-S. Yi[3], S.Y. Kim[1], H.-H. Kim[1], J.H. Kim[2], J.E. Yeon[2], K.S. Byun[2], J.-S. Byun[4], W.-I. Jeong[1]

[1]Lab. of Liver Research, Graduate School of Medical Science and Engineering, KAIST, Daejeon 34141, Korea, [2]Department of Internal Medicine, Korea University College of Medicine, Seoul 08308, Korea, [3]Research Center for Endocrine and Metabolic Diseases, Chungnam National University School of Medicine, Daejeon 34952, Korea and [4]Department of Oral Medicine, School of Dentistry, Kyungpook National University, Daegu 41940, Korea

The expression of chemokine receptor CX_3CR1 is related to migration and signaling in cells of the monocyte-macrophage lineage. However, the precise roles of CX_3CR1 are unknown in alcoholic liver disease. Here, we showed that mouse F4/80^{low}CX_3CR1^{low} monocytes were transdifferentiated into F4/80^{high}CX_3CR1^{high} macrophages with abundant cytoplasm as Kupffer cells. Similarly, human CD16$^-$$CX_3CR1^{low}$ monocytes transformed into CD16$^+$$CX_3CR1^{high}$ macrophages via co-culturing with HUVECs. In addition, siRNA-induced CX_3CL1 suppression of HUVECs attenuated expression of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and CX_3CR1, whereas recombinant CX_3CL1 treatment reversed this expression in co-cultured monocytes, suggesting CX_3CR1-mediated inflammatory signaling in macrophages. Similarly, hepatic CX_3CR1^+F4/80^{high} macrophages of $CX_3CR1^{+/GFP}$ mice showed higher expression of IL-1β and TNF-α than CX_3CR1^-F4/80^{high} macrophages of $CX_3CR_1^{GFP/GFP}$ mice. More interestingly, in alcoholic liver injury, despite similar frequencies of hepatic F4/80^{high} macrophages, $CX_3CR_1^{GFP/GFP}$ mice showed reduced hepatic fat accumulation, liver injury, and inflammatory responses than $CX_3CR1^{+/GFP}$ mice. In conclusion, up-regulation of CX_3CR1 expression by endothelial cells contributes to transdifferentiation of F4/80^{low} monocytes into F4/80^{high} macrophages and switch to pro-inflammatory phenotype, subsequently leading to acceleration of alcoholic liver injury. Thus, CX_3CR1 could be a novel therapeutic target for pro-inflammatory macrophages in alcoholic liver injury.

P1-5-9

ALCOHOLIC NEURODEGENERATION INVOLVES TLR7 TO TRAIL DEATH RECEPTOR SIGNALING

L.G. Coleman, J. Zou, L. Qin, F.T. Crews

Pharmacology, University of North Carolina at Chapel Hill, USA

Alcohol abuse is associated with hippocampal and cortical neurodegeneration, which is associated with functional deficits. We recently reported a role for the immune receptor Toll-like Receptor 7 (TLR7) in neurodegeneration through a novel miRNA-TLR7 signaling pathway. We now find that ethanol-TLR7 signaling causes cell death through the TNF-related apoptosis-inducing ligand (TRAIL) Death Receptor (DR) Ligand. In postmortem human alcoholic hippocampus, TRAIL strongly correlated with TLR7 protein ($R = 0.75$, $^{***}p = 0.0001$) with DR4 increased. A novel TLR7 antagonist prevented ethanol-induced cell death and blocked TRAIL in Hippocampal-Entorhinal Slice Culture (HEC). Immunofluorescent labeling in mouse brain found the majority of TRAIL was present in neurons and astrocytes, with microglial depletion having no effect on TRAIL mRNA. Ethanol, in vivo and in vitro (SH-SY5Y neurons and U373MG astrocytes) upregulated TRAIL and its receptors, DR4 and DR5 (1.5–2 fold). Interestingly, neurons and astrocytes secreted TRAIL in response to ethanol, suggesting autocrine-paracrine signaling. The TLR7 antagonist blocked ethanol-induction of TRAIL in HEC and SH-SY5Y neurons, and prevented ethanol-induced TRAIL secretion from neurons. Further, the TRAIL-neutralizing antibody prevented TLR7-mediated cell death in HEC. Thus, ethanol induces TLR7-mediated cell death via activation of TRAIL signaling. Thus, TRAIL represents a novel target for the alcohol associated neurodegeneration.

P1-5-10

NEUROIMMUNE AND EPIGENETIC MECHANISMS UNDERLYING THE ADOLESCENT BINGE ETHANOL-INDUCED LOSS OF BASAL FOREBRAIN CHOLINERGIC NEURONS: RESTORATION WITH ANTI-INFLAMMATORY DRUGS AND VOLUNTARY EXERCISE

R.P. Vetreno[1], S.C. Pandey[2], F.T. Crews[1]

[1]University of North Carolina at Chapel Hill, USA and [2]University of Illinois at Chicago, USA

Binge drinking and alcohol abuse are common during adolescence. Using a preclinical rodent model of adolescent intermittent ethanol (AIE), we find reductions of basal forebrain cholinergic neurons that persist from late adolescence (P55) into adulthood (P220), an effect we observed in the human alcoholic brain. In Experiment 1, we found that both wheel running from P24 to P80 and the anti-inflammatory drug indomethacin prevented AIE-induced loss of cholinergic neuron markers (i.e., ChAT, TrkA, and p75^{NTR}) as well as the increase of phosphorylated NF-κB p65 (pNF-kB p65) in the adult basal forebrain. In Experiment 2, wheel running from P56 (24 hr after the conclusion of AIE) to P95 restored the AIE-induced cholinergic neuropathology as well as the increase of pNF-kB p65 in the adult (P95) basal forebrain. Further, ChIP analysis revealed that wheel running reversed the AIE-induced dimethylation of H3K9 on both the ChAT and TrkA genes as well as DNA methylation on the ChAT promoter CpG Island. Exercise also recovered the AIE-induced behavioral flexibility impairments on the Morris water maze in adulthood. These data suggest that AIE treatment causes a phenotypic loss of cholinergic neurons and not neurodegeneration highlighting the potential for the development of therapeutics.

P1-5-11

INHIBITION OF SOLUBLE EPOXIDE HYDROLASE ACTIVITY ATTENUATED ETHANOL-ASSOCIATED LIVER INJURY IN MICE

Jeffrey.B. Warner, S.G. Dastidar, D.R. Warner, Y.L. Song, C.J. Mcclain, I.O. Kirpich
University of Louisville, USA

Introduction: Epoxygenated metabolites of polyunsaturated fatty acids (EpFAs) are known as beneficial, anti-inflammatory lipid mediators. Soluble epoxide hydrolase (sEH) rapidly converts EpFAs to their corresponding diols, dihydroxy-FAs, whose properties are not well understood. Alterations in epoxy- and dihydroxy-FAs have been implicated in the pathogenesis of numerous pathologies, including liver disease of different origins. In the present study we tested the hypothesis that inhibition of sEH will attenuate ethanol-induced liver injury in mice.
Methods: Mice were subjected to chronic or acute-on-chronic ethanol administration. The sEH inhibitor, t-TUCB, was administered along with food. Liver steatosis, inflammation, and injury were evaluated.
Results: Compared to controls, mice receiving t-TUCB had significantly reduced ethanol-induced increase in plasma ALT activity (a marker of liver injury) in both chronic and acute-on-chronic ethanol feeding models. sEH inhibition resulted in reduction of ER stress (as demonstrated by decreased Xbp1 splicing and CHOP expression) and a decrease in neutrophil infiltration and down-regulation of the expression of the pro-inflammatory gene Cxcl1 in the liver.
Conclusions: Collectively, these data demonstrated that sEH inhibition attenuated ethanol-induced liver injury via decreasing ER stress and inflammation. Further studies are required to elucidate the specific mechanisms by which each lipid mediates ethanol-induced liver injury.

P1-5-12

ISOZYME-SPECIFIC IDENTIFICATION AND CHARACTERIZATION OF SUBSTRATES CROSSLINKED BY TRANSGLUTAMINASES IN LIVER FIBROSIS

H. Tatsukawa, H. Nakagawa, K. Hitomi
Graduate School of Pharmaceutical Sciences, Nagoya University, Japan

The transglutaminase (TG) family comprises eight isozymes that catalyze the crosslinking reaction between glutamine and lysine residues and contribute to the fibrotic diseases via stabilization of ECM and the activation of TGF-β in several tissues. However, despite a growing body of evidence implicating TG2 as a key enzyme in fibrosis, the causative role of TG2 and the involvement of the other isozymes have not yet been fully elucidated. Therefore, here we clarified the distributions of TG isozymes and their in situ activities and identified the isozyme-specific possible substrates for both TG1 and TG2 using their substrate peptides in mouse fibrotic liver. In total, 43 and 42 possible substrates were identified for TG1 and TG2, respectively. These included keratin 18, a biomarker for hepatic injury, which was accumulated in the fibrotic liver and showed the partly similar distribution with TG1 activity. Our findings suggest that the activity of each TG was independently activated in a different area of the liver tissue during fibrotic induction, and played a potential role in the functional modification of substrates such as keratin 18, which are relevant to liver fibrosis progression.

P1-5-13

ALCOHOL EXPOSURE IS ASSOCIATED WITH ALTERED PHOSPHOLIPID METABOLISM IN HUMAN PLACENTAL TISSUE

O.K. Kärkkäinen[1], J. Repo[2], A. Lehikoinen[3], M. Lehtonen[2,4], S. Auriola[2,4], S. Heinonen[5], K. Hanhineva[1], K. Vähäkangas[2]
[1]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Finland, [2]School of Pharmacy, University of Eastern Finland, Finland, [3]Department of Pediatrics, University of Eastern Finland, Finland, [4]LC-MS Metabolomics Center, Biocenter Kuopio, Finland and [5]Department of Obstetrics and Gynecology, University of Helsinki, Finland

We evaluated alcohol exposure associated changes in the metabolic profile of human placental tissue both in vivo and in vitro to examine molecular mechanisms of alcohol caused pathological changes. We did mass spectrometry based metabolomics analysis to placental samples. In vivo placental samples were collected from both alcohol exposed and control pregnancies ($n = 6$ / group). We used parallel villous samples from non-exposed pregnancies ($n = 7$) for the in vitro experiments, where the samples were exposed to alcohol (2‰) or vehicle for 24 h. Phospholipid metabolism was significantly altered in the alcohol exposed in vivo placentas when compared to the controls. Especially levels of phosphatidylethanolamines (PEs), lysoPEs and plasmalogen-PEs were increased in the placental samples from alcohol-exposed pregnancies. Alcohol also affected phospholipid metabolism after in vitro exposure of villous samples. However, excluding palmitate containing phosphatidylcholines, the direction of change in many metabolites was opposite in in vivo and in vitro samples. This could be due to difference in dose and duration of exposure, or environmental exposures like smoking. In conclusion, in human placenta, alcohol exposure was associated with changes in the levels of phospholipids vital for cellular metabolism, signaling and membrane structure.

P1-5-14

PSYCHIATRIC FORENSIC OPINION ON THE ABILITY TO MAKE A LAST WILL BY A PERSON WITH ALCOHOL-RELATED DISORDERS AND CONCOMITANT SOMATIC DISEASES – A CASE STUDY

W.E. Kosmowski
Department of Psychiatry CM Bydgoszcz, Nicolaus Copernicus University, Poland

Giving psychiatric opinions on testators with alcohol-related disorders and concomitant diseases is a difficult juridical problem. It requires considering the influence of the general state of health on the mental state. Hospital records rarely include a full description of patient's mental state. Witness testimonies are generally contradictory, which makes it difficult to give an opinion. This analysis includes opinions of two teams of experts and hospital records. According to the first team, the patient was not able to make a declaration of will, but according to the second team – he was. The testator died five days after admission and during hospitalization he allegedly made a declaration of will. He suffered from pneumonia after influenzae, alcohol dependence, acute renal failure, alcoholic hepatitis and acute respiratory failure. Before admission, the patient drank alcohol for three months. Despite the pharmacological treatment and oxygen therapy, patient's condition deteriorated. Witnesses' descriptions that the patient spoke freely while making a declaration of will are not possible from the medical point of view. The second team of experts made two mistakes: they neglected the impact of the general health on patient's mental state and his ability to express a will and a logical error (petitio principii).

TUESDAY, SEPTEMBER 11
6. ISBRA-WHO WORKSHOP

P1-6-1

EVALUATION OF THE ACQUIRED ANDROGEN DEFICIENCY IN PATIENTS WITH ALCOHOL DEPENDENCE AND ITS RELATIONSHIP TO THE SEVERITY (PRESENCE) OF SEXUAL DYSFUNCTIONS

M.N. Hikmatov, K.S. Ikromov, S.N. Lukmonov, F.S. Rakhimdjanova
Department of Phychiatry and Narcology, Tashkent Medical Academy, Uzbekistan

Objective: To evaluate the acquired androgen deficiency in patients with alcohol dependence and to determine its relationship to the presence of sexual dysfunctions.
Material of the study. As a material for the study, 42 patients served whose average age was 43.1 ± 10.2 years. All of them were treated on the basis of Department of Psychiatry and Narcology of TMA about alcohol dependence (F10.2) and complained of violations of sexual functions.
Methods of research. To assess the severity of various manifestations, a questionnaire was used that allows one to suspect an androgen deficiency, "AMS – Aging Males' Symptoms" questionnaire developed by L. A. J. Heinemann et al. [1999].
Results: We found that among the manifestations of androgen deficiency in patients with alcohol dependence, somatic manifestations were leading (16.15 ± 5.8 points) in the form of a general decrease in working capacity, reduced activity. The dominant manifestations are somatovegetative disorders; Psychological symptoms and sexual disorders themselves are associated with alcohol problems.
Conclusions: Thus, the obtained data indicate that patients suffering from alcohol dependence develop earlier manifestations of androgen deficiency. Proceeding from this, it is necessary to continue studying the mechanisms of development of androgen deficiency not only in patients with alcoholism.

P1-6-2

INTELLECTUAL PRESERVATION OF PATIENTS OF DIFFERENT ETHNICITY WITH PSYCHOTIC FORMS OF ALCOHOLISM

K.S. Ikromov, M.N. Himkmatov, S.N. Lukmonov, F.S. Rakhimdjanova
Department of Psychiatry and Narcology, Tashkent Medical Academy, Uzbekistan

Purpose: Study the characteristics of cognitive activity of patients with alcoholic psychoses of Uzbek and Russian nationality.
Material and methods: 155 patients with alcoholism (F10.2) and alcoholic psychoses (F10.4) registered in City Narcological Dispensary (Taskent city) were subjected to clinical and psychological examination, of which 91 people of Uzbek nationality and 64 people of Russian nationality permanently residing in Tashkent.
Results of the study: Ethnocultural features of intellectual activity of persons with alcohol dependence are reflected in the level of abstract thinking. Patients with alcoholic psychoses (AP) significantly more often ($p = 0.005$) experience difficulties in constructing a realistic and meaningful associative connection. Violations in magnetic sphere are represented by inertia and weakening of short-time operative memory, which indicates a lack of mobility of mental processes. The revealed signs of lowering level of generalizations, graphic phenomena-indicators of organic brain damage are more pronounced in patients with alcoholic psychoses, regardless of their ethnicity.
Conclusions: Diagnostics of violations of intellectual safety in alcohol dependence in relation to patients of other cultures is necessary to expand the ethno-cultural competence of narcologists involved in rehabilitation of patients, including the appointment of anti-haemorrhage therapy in the process of formation and stabilization of remission.

P1-6-4

PREVALENCE OF SUBSTANCE USE IN SCHOOL GOING CHILDREN

M. Nayak[1], S. Sharma[2], A. Bhardwaj[3]
[1]NSCB Medical College, Jabalpur, India, [2]NIMHANS, Banglore, India and [3]NHS, Nottingham, UK

Objective: The present study was planned to find out the prevalence of substance use in school going children.
Method: This was a cross sectional school based study which included children from higher secondary schools of Mathura city in October- January, 2017. Students of class IX to XII were chosen from randomly selected four schools. 1,527 students and their class teachers were included in the study. Evaluation was done on Drug Abuse Screening Test (DAST) and Child Behavior Checklist (CBCL).
Results: Majority of the students were in age group of 16–18. 168 (11.2%) students were abusing nicotine, alcohol or mixed. 71 (4.66%) were found to use tobacco, 38 (2.49%) use alcohol and 59 (3.87%) used mixed drugs. While comparing CBCL & DAST score significant difference were found in conduct disorder ($p < 0.010$) and mania like symptoms ($p < 0.042$).
Conclusion: The prevalence of substance use in overall study population was 11.2%.

P1-6-5

ROLE OF SOCIOECONOMIC POSITION (SEP) IN THE ASSOCIATION OF ALCOHOL USE AND PERIODONTAL HEALTH

R. Sankaranarayanan[1], T. Saxlin[1,2,4], M. Knuuttila[4,5], P. Ylöstalo[4,5], L. Suominen[1,2,3]
[1]Institute of Dentistry, University of Eastern Finland, Kuopio, Finland, [2]Oral and Maxillofacial Department, Kuopio University Hospital, Kuopio, Finland, [3]Public Health Evaluation and Projection Unit, National Institute for Health and Welfare (THL), Helsinki, Finland, [4]Institute of Dentistry, University of Oulu, Oulu, Finland and [5]Medical Research Centre Oulu, Oulu University Hospital, University of Oulu, Finland

Aims: To investigate the association of different alcoholic beverages/serum gamma-glutamyltransferase level (GGT) with periodontal pockets and additionally, whether this association differs by socioeconomic position (SEP).
Methods: This study included 4,294 dentate, non-diabetic adults aged 30–65 years who underwent periodontal examination during the Health 2000 Survey in Finland. The outcome was the number of teeth with deepened (4 mm or deeper) periodontal pockets recorded during the clinical oral examination. The exposure was the frequency of intake of different alcoholic beverages (wine, beer, spirits/other strong alcohol) during the last 12 months assessed by a self-report questionnaire, and the serum GGT levels. Zero-inflated negative binomial regression models were used to examine the associations.
Results: We found no consistent association between intake of different alcoholic beverages/GGT levels with deepened periodontal pockets in the total study population or among the non-smokers. However, highly educated non-smokers, who had frequent spirit intake, were less likely to have teeth with deepened pockets compared to non-drinkers. Less educated non-smokers, on the other hand, who had frequent spirit intake, had a higher likelihood of having teeth with deepened pockets compared to non-drinkers.
Conclusions: The association of beverage-specific alcohol intake (specifically frequency of spirit intake) with deepened periodontal pockets varied by SEP.

WEDNESDAY, SEPTEMBER 12
1. ALCOHOL

P2-1-1

SUBJECT REACTIVITY IN VETERANS WITH ALCOHOL USE DISORDER DURING SCREENING FOR CLINICAL TRIAL ENTRY: EFFECTS ON ALCOHOL USE

F.N. Fong[1], D.L. Pennington[1,2], N. Bautista[1], H.D. Pothier[1], L.S. Muquit[1], M. Cano[1], B. Lasher[1], E. Herbst[1,2], S.L. Batki[1,2]
[1]San Francisco Veterans Affairs Health Care System, USA and [2]University of California, San Francisco, USA

We measured changes in alcohol use in Veterans with alcohol use disorder (AUD) during screening for entry into randomized clinical trials (RCTs). We hypothesized that subject reactivity to screening procedures would lead to reductions in use.
We conducted moderation analyses (Hayes Process Model 1) in 140 Veterans (13 female) with AUD and PTSD entering one of two RCTs of topiramate treatment. We examined if concurrent AUD treatment moderated changes in alcohol use (Timeline Follow Back Method) from the 90 days prior to screening to the week after screening was completed, just prior to randomization.
Drinks per week (55.3 $\pm$ 42.4) and heavy drinking days per week (4.0 $\pm$ 2.3) in the 90 days prior to randomization significantly reduced during screening (β=-28.9, β=-2.0, both $p < 0.01$). Concurrent AUD treatment involvement significantly moderated the effect of reducing drinks per week ($p = 0.04$); Veterans involved in AUD treatment had significantly greater reduction in number of drinks per week than those not involved (β=-37.0, $p < 0.01$; β=-17.0, $p < 0.02$, respectively).
Veterans significantly reduced alcohol use amount and frequency during screening for clinical trial entry. Concurrent treatment involvement moderated reactivity effects on alcohol use reduction. Future AUD treatment studies among Veterans should account for screening phase reactivity on clinical trial treatment outcome.

P2-1-2

THE ASSOCIATION BETWEEN HYPERTENSION AND ALCOHOL CONSUMPTION BY ALCOHOL FLUSHING RESPONSE

M. Yoo, K.J. Park, H.B. Jang, H.-J. Kim, Y.J. Lee, S.I. Park, H.-J. Lee
Division of Endocrine and Metabolic Diseases, Korea National Institute of Health (KNIH), Korea

Chronic and heavy alcohol consumption is known to be associated with an increased risk for developing high blood pressure. In Korea, high risk drinking rate has been steadily increasing, similarly, the prevalence of hypertension is on the rise. As widely known, alcohol consumed by ALDH2-deficient individuals result in facial flushing, like many East Asians, which is more susceptible to many diseases, such as a series of cancers and cardiac diseases. Thus, we investigated the association between alcohol consumption and hypertension by alcohol flushing response. In study, we analyzed 1,665 adult men in Korean population, and categorize into five groups in according to drinking amount per day in non-flushing and flushing. The prevalence of hypertension was 35.5% for abstainers, 41.5% and 34.0% for less than 30 g per day alcohol consumption, and 44.7% and 56.3% for more than 30 g per day alcohol consumption in non-flushing and flushing, respectively. In addition, we found that alcohol consumption increased the risk of hypertension, in particular, flushing were higher risk of hypertension than non-flushing in more than 30 g per day alcohol consumption. These results indicate that men with flushing may have a higher risk of hypertension, even if they have same alcohol consumption than those non-flushing.

P2-1-3

THE ROLE OF CLASS I AND III ALCOHOL DEHYDROGENASES (ADHS) IN STRUCTURE OF BOWMAN'S CAPSULES WITH CUBOIDAL EPITHELIUM IN MALE MICE

M. Katsuyama[1], M. Ishizaki[2], T. Haseba[1,3], T. Okuda[1], Y. Sasaki[4], M. Maruyama[5], T. Akimoto[5], T. Oguro[4], M. Naruo[1,6,7], Y. Ohno[1]
[1]Department of Legal Medicine, Nippon Medical School, Japan, [2]Department of Analytic Human Pathology, Nippon Medical School, Japan, [3]Department of Legal Medicine, Kanagawa Dental University, Japan, [4]Division of Morphological and Biomolecular Research, Nippon Medical School, Japan, [5]Division of Laboratory Animal Science, Nippon Medical School, Japan, [6]Department of Orthopedic Surgery, Tomei Atsugi Hospital, Japan and [7]Department of Orthopedic Surgery, Tokyo Women's Medical University, Japan

Aim: Class I alcohol dehydrogenase (ADH1) contributes to the most in alcohol oxidation. In addition, our previous study suggested that Class III alcohol dehydrogenase (ADH3) with high K_m for ethanol, plays important roles in alcohol metabolism in case of chronic alcohol intake or at high blood ethanol concentration. Both of ADHs abundantly localize in the kidney, suggesting their roles in alcohol metabolism. The aim of this study is to investigate how these ADHs relate to alcohol-induced renal morphological changes.
Method: Wild-type (WT), ADH1 and ADH3 knockout male mice ($Adh1^{-/-}$ and $Adh3^{-/-}$) consumed 10% ethanol in drinking water for 1 month. Mice given water were used as controls. The kidneys of morphological changes were evaluated by counting the number of glomeruli having Bowman's capsular with cuboidal epithelium (CE).
Result: In the WT mice, CE were significantly increased in chronic alcohol intake. Furthermore, microvilli were found inside the CE that suggesting the possibility of reabsorption. On the other hand, CE were increased in the $Adh1^{-/-}$ and $Adh3^{-/-}$ mice both intake of alcohol and water.
Conclusion: Chronic alcohol intake induced CE in WT mice but not in $Adh1^{-/-}$ and $Adh3^{-/-}$ mice. Therefore, ADH1 and ADH3 might influence alcohol-induced renal morphological changes.

P2-1-4

ASSOCIATION OF RESTING-STATE AUTONOMIC NERVOUS SYSTEM AND RESPONSE INHIBITION IN ALCOHOL USE DISORDER: A HEART RATE VARIABILITY ANALYSIS

Y. Kim
Department of Psychiatry, SMG-SNU Boramae Medical Center, Korea

Top-down inhibitory dysfunction with cardio-chronotropic control via a vagally mediated pathway is observed in alcohol use disorder (AUD). Low heart rate variability (HRV) is a risk factor for inhibitory dysfunction in the physiological, cognitive, and affective context. We investigated the differences in short-term HRV parameters between AUD and healthy control (HC). The relationship of HRV, symptom severity, alcohol consumption and response inhibition in AUD was evaluated.
35 AUD patient and 41 HC participated in this study. Neurocognitive performance was measured using the Cambridge Neuropsychological Test Automated Battery. The AUDIT-K and amount of alcohol consumption were used to assess symptom severity and the extent of alcohol exposure. In the frequency domain analysis, AUD showed significantly reduced log high frequency HRV and total power than HC. In the time domain analysis, AUD showed significantly reduced SDNN and RMSSD than HC. The HRV total power was significantly correlated with proportion of successful stop in the Stop Signal Test and stroop color word error in AUD. Patients with AUD showed significantly lower resting-state HRV. The relationship with reduced task performance on the prefrontal control in AUD indicated poor self-regulatory system. Low HRV in AUD was state independent, raising its possibility of endophenotype of AUD.

P2-1-5

THE DIFFERENTIAL PSYCHOLOGICAL CHARACTERISTICS OF HANGOVER SENSITIVE AND HANGOVER RESISTANT DRINKERS

J.C. Verster[1,2], A. Merlo[3], M.V.S. Lantman[1], Aurora.J. Van De Loo[1], M. Mackus[1], G. Bruce[3]
[1]Utrecht University, Netherlands, [2]Swinburne University, Australia and [3]University of the West of Scotland, UK

Background: While consuming similar large amounts of alcohol, a minority of drinkers claim to be hangover resistant. The aim of this study was to examine whether hangover sensitive and hangover resistant drinkers differ in psychological characteristics, which may have an impact on the severity of alcohol hangover symptoms.
Methods: An online survey was conducted among Dutch students. Data on their past month heaviest drinking occasion was collected. In addition, they completed the short-form Profiles of Mood States (POMS-SF), the depression anxiety and stress scale (DASS-21), the neuroticism subscale of the Eysenck Personality Questionnaire, and the brief mental resilience scale (BRS). Those who consumed alcohol and reached an estimated breath alcohol concentration of at least 0.11% were included in the statistical analysis.
Results: Compared to hangover resistant drinkers ($N = 893$), hangover sensitive drinkers ($N = 93$) reported significantly ($p < 0.05$) higher levels of stress, and anxiety on the DASS-21, depression anger-hostility, and tension-anxiety on the POMS-SF, and neuroticism on the EPQ. The groups did not significantly differ on mental resilience.
Discussion: Hangover sensitive drinkers experience higher levels of psychological distress when compared to hangover resistant drinkers. The two groups do not, however, differ in their ability to bounce back or cope with stressful life events.

P2-1-6

FROM ANTIDEPRESSANT TO ADDICTION: EFFECTS OF REPEATED ETHANOL EXPOSURE

C. Heaney, K. Raab-Graham
Physiology/Pharmacology, Wake Forest University Health Sciences, USA

Comorbidity of alcohol use disorder (AUD) and major depressive disorder (MDD) in adults ranges from 12–30%, and can be explained by the self-medication hypothesis, which proposes that people turn to alcohol to alleviate their MDD symptoms. Alcohol could initially alleviate the symptoms of MDD, leading to increased alcohol consumption as treatment-seeking behavior, and with prolonged and repeated exposure, AUD develops. We have recently demonstrated that a single administration of ethanol (eth) produces an antidepressant-like behavioral effect, and that this effect is blocked with a 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 of Ro 25-6981 (Ro), an NR2B-specific NMDAR antagonist. Further, a single exposure to both Ro and Eth stimulate new protein synthesis of the metabotropic gamma-aminobutyric acid (GABA) receptor subunit GABABR2, and increased surface expression of these receptors. GABABR markers are decreased in AUD and MDD patient populations and animal models, suggesting a critical role of this receptor in the etiology and treatment of these disorders. Here, we have started to characterize the effect of increasingly chronic ethanol exposure on the rapid antidepressant pathway.

P2-1-7

THE ASSOCIATION BETWEEN BINGE DRINKING PRIOR TO INJURY TIME AND OCCURRENCE OF ALCOHOL-RELATED INJURIES – A CROSS-SECTIONAL STUDY AMONG JAPANESE COLLEGE STUDENTS

G. Saito[1], H. Yoshimoto[2], A. Takayashiki[2], K. Kawaida[3], Y. Takemura[4]
[1]Primary Care and Medical Education, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan, [2]Department of Primary Care and Medical Education, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan, [3]National Defense Medical College, Tokorozawa, Saitama, Japan and [4]Department of Family Medicine, Mie University Graduate School of Medicine, Tsu, Mie, Japan

Introduction: Alcohol-related injuries in college students are one of the major public health problems in the world. We clarified the association between binge drinking prior to injury time and occurrence of alcohol-related injuries among Japanese college students.
Methods: In January 2018, we sampled college and graduate students aged 20 years or older during annual health examinations at a Japanese college. The questionnaire assessed the frequency of alcohol consumption, amount of alcohol consumed per day, binge drinking during the past year, alcohol-related injuries during the past year, aldehyde dehydrogenase 2 (ALDH2), Brief Sensation Seeking Scale (BSSS), club activities and demographic data including age and sex. Logistic regression analysis was conducted on the association between binge drinking prior to injury time and occurrence of alcohol-related injuries.
Results: Of the 1,845 students who underwent health examinations, 1,525 completed the questionnaire. In the logistic regression analysis, binge drinkers (OR 16.2 [3.91–67.4]) had a history of significantly more alcohol-related injuries, even after adjusting for excessive weekly drinking, ALDH2, BSSS, club activities, age, and sex.
Conclusions: Alcohol-related injuries in college students in Japan were strongly associated with binge drinking.

P2-1-8

DISRUPTION OF FOLATE-PRODUCING GUT MICROBIOTA CONTRIBUTES TO ETHANOL-INDUCED FOLATE DEFICIENCY AND TERATOGENESIS

T. Wu, F. Yuan, Y. Li, H. Fan, L. Lu, J. Liu, S.-Y. Chen
Department of Pharmacology and Toxicology, University of Louisville Alcohol Research Center, University of Louisville Health Sciences Center, USA

Maternal consumption of ethanol is known to disrupt folate absorption, distribution, and metabolism, which contributes to ethanol-induced teratogenicity. It has been demonstrated that the folate synthesized by intestinal bacteria can be absorbed and used by the host. To test whether ethanol exposure can disrupt folate-producing gut microbiota and contribute to ethanol-induced teratogenesis, female C57/BL6 mice were fed with a liquid diet containing 5.2% ethanol for 8 weeks, and then fed with diet containing ethanol and LGG or tributyrate for 3 additional weeks, followed by an abstinence period during which the females were mated, and then returned to the ethanol-containing diet on GD 7–8. Ethanol exposure significantly decreased the levels of folate-producing bifidobacteria and the folate concentrations in maternal serum, intestinal lumen and mucosa. Prenatal ethanol exposure resulted in growth retardation, craniofacial abnormalities, and ocular defects in mouse embryos. Supplementation with LGG or tributyrate reversed the ethanol-induced reduction in the levels of folate-producing bifidobacteria and the folate concentration, and diminished ethanol-induced growth retardation, craniofacial abnormalities, and ocular defects. These results demonstrate that disruption of gut microbiota contributes to ethanol-induced folate deficiency and teratogenesis and that supplementation of LGG or tributyrate might prevent FASD by restoring the homeostasis of maternal gut microbiota.

P2-1-9

ASSOCIATION BETWEEN ALCOHOL PROBLEM AND STRESS RELATED FACTORS AMONG NUCLEAR EMERGENCY WORKERS FOR LONG PERIOD

H. Hiro[1], A. Hino[1], K. Mafune[1], A. Inoue[2], J. Shigemura[3], M. Yamada[4], T. Okubo[4]
[1]Department of Mental Health, University of Occupational and Environmental Health, Japan, [2]Kitasato University School of Medicine, Japan, [3]National Defense Medical College, Japan and [4]Radiation Effect Research Foundation, Japan

Introduction: Fukushima Daiichi Nuclear Power Plant suffered serious damage by the Great East Japan Earthquake and Tsunami in 2011. This study examined the association between alcohol problem and stress related factors among the nuclear emergency workers 4–6 years after the disaster.
Methods: In total, 3,000 workers completed self-administered questionnaire by mail. Alcohol problem was measured by using AUDIT. Evaluated stress related factors included life events, stress coping, sense of coherence, self-esteem, self-efficacy, resilience, social support, life satisfaction, job satisfaction and stigma-associated stress owing to post-disaster management criticisms. Multiple regression analysis was performed by AUDIT score as an explained valuable and stress related factors as explanation valuables.
Result: AUDIT score was not significantly high in the workers who had worked for long period of time. It was related to the scores of life events, stress coping, sense of coherence and stigma-associated stress.
Discussion: Mitigating stigma-associated stress may be one of the effective measures to prevent the alcohol problems among these workers.

P2-1-10

ASSOCIATION BETWEEN DOPAMINE BETA HYDROXYLASE GENE POLYMORPHISMS AND ALCOHOL DEPENDENCE IN A JAPANESE POPULATION

M. Miyamoto[1], K. Ikeda[2], D. Nishizawa[2], K. Suzuki[1], S. Narita[3], E. Yoshihara[1], K. Iwahashi[1,2,4]
[1]Laboratory of Physiology (Project of Neurophysiology), Course of Environmental Health Science, Graduate School of Environmental Health, Azabu University, Kanagawa, Japan, [2]Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan, [3]Physiological Examination Center, Tohoku University Hospital, Miyagi, Japan and [4]Health Administration Center, Azabu University, Kanagawa, Japan

Since dopamine is a major neurotransmitter involved in the brain's reward system, which is a target of psychoactive substances including alcohol, dopamine beta hydroxylase (DBH) in regulating the dopamine signal may play an important role in the pathogenesis of alcohol dependence. In this study, we examined whether the functional polymorphisms of -1021C/T (rs1611115) and 444G/A (rs1108580) in DBH gene are related to alcohol dependence. Furthermore, in order to investigate DBH gene polymorphism in more detail, we also compared the polymorphism in DBH gene between patients with alcohol dependence and control subjects of aldehyde dehydrogenase 2 (ALDH2; rs671)*1/*1 genotypes.
The subjects of this study comprised 64 patients with alcohol dependence and 75 unrelated healthy people. The DBH genotypes were determined by PCR-RFLP.
No significant differences in the DBH polymorphisms and haplotypes were found between alcohol dependence and control subjects. In addition, there was not also significantly different between patients with alcohol dependence and control subjects of ALDH2*1/*1 genotypes.
The present study suggests that the polymorphisms of -1021C/T and 444G/A in the DBH gene are not risk factors for alcohol dependence in a Japanese population. Further large-scale studies including other dopamine-related polymorphisms in other populations in Japan are needed.

P2-1-11

TOWARDS THE ESTABLISHMENT OF AN ALCOHOLISM REHABILITATION PROGRAM (ARP) INCLUDING MEASURES FOR THE PREVENTION OF LOCOMOTOR DISABILITY

C. Iwahara[1], S. Sakate[2], Y. Tanaka[1,3], S. Kamiya[1], Y. Mizukami[2], K. Masuko[4,5]
[1]National Hospital Organization Kurihama Medical and Addiction Center, Japan, [2]Sagami Women's University, Japan, [3]National Hospital Organization Disaster Medical Center, Japan, [4]Sanno Medical Center, Japan and [5]International University of Health and Welfare, Japan

Background: Excessive ethanol drinking can exacerbate low muscle strength and low bone mineral density. Female alcoholics, whose numbers have been increasing in Japan, are at particular risk because of the occurrence of menopause and comorbid eating disorders. To establish an alcohol rehabilitation program (ARP) that includes measures for preventing locomotor disabilities, we attempted to assess the nutritional and locomotive statuses of female alcoholics.
Methods: Female Japanese alcoholics (mean age, 43.4 $\pm$ 5.8) hospitalized for ARP were enrolled. Body mass index (BMI), body composition, muscle strength, and nutritional intake were assessed.
Results: On average, the patients had insufficient dietary intakes and physical activity levels before admission. On admission, the majority of the patients were lean and insufficiently nourished, and their muscle masses and their muscle strengths were relatively low. Abstinence during the ARP improved their nutrition, but awareness of the importance of locomotive function did not reach sufficient levels.
Conclusion: This patient group is considered to have a high risk of future locomotor disabilities, in which a failure of body image could play a crucial role, at least in part.
We propose that ARP should include preventive interventions and education focusing on the importance of locomotive function.

P2-1-12

INTEGRATED CUE-REACTIVITY AND EYE-TRACKING PARADIGM TO ASSESS SELECTIVE BEHAVIORAL RESPONSE AND SELECTIVE ATTENTION TO SIMULTANEOUS ALCOHOL AND SMOKING CUES

C. Haass-Koffler, R. Souza, J. Wilmott, V. Long, K. Goodyear, E. Aston, M. Magill, J.-H. Song, R. Swift
Brown University, USA

More than 80% of individuals with an alcohol use disorder (AUD) are also smokers. The primary aim of this study was to develop a paradigm that integrated a cue-reactivity (CR) with an eye-tracking (ET) to measure selective behavioral response and selective visual attention. To provide an additional tool to measure craving, we also explored correlation of CR-ER data with substance craving. This was a pilot human laboratory study (n = 32) with moderate-heavy drinking smokers who completed both a CR and an ET.
Both in the CR and ET, time spent interacting with alcohol/cigarette was higher than water ($p < 0.001$) but there was no difference between the two substances (p's>0.05). In the integrated CR-ET, time spent interacting with alcohol correlated to total time fixating on alcohol ($p < 0.05$) and time spent interacting with the cigarette trends with time fixating on the cigarette ($p = 0.06$). The time interacting with alcohol was correlated with cravings for alcohol and cigarettes (p's < 0.05). In participants grouped by self-reported preferred substance, alcohol cravings were higher regarding the substance (p's < 0.05).
The integrated CR-ET paradigm is an useful measure to relate behavior and attention and capture the difference in craving between groups so that tailored interventions may be developed in the future.

P2-1-13

INVOLVEMENT OF MICRORNA IN ETHANOL-INDUCED CARDIOTOXICITY

K. Noritake, T. Aki, K. Uemura
Department of Forensic Medicine, Tokyo Medical and Dental University, Japan

Background and aims: We have previously demonstrated that disruption of the actin cytoskeleton and inactivation of an anti-apoptotic transcriptional co-activator Yes-associated protein (YAP) are involved in ethanol cytotoxicity on cardiomyocytes. MicroRNAs (miRNAs) are known to play a critical role in the control of cardiomyocyte proliferation and regeneration by YAP regulation. Here, we investigated functional roles of miRNA in the ethanol-induced cardiocytotoxicity.
Methods and results: To identify miRNAs involved in ethanol-induced cardiotoxicity, we used miRNA microarrays and found that expression of miR-133a, which is the most abundant and cardiac-specific miRNA, was decreased in HL-1 murine atrial cardiomyocytes after exposure to ethanol. Using quantitative RT-PCR, we found that miR-133a expression was decreased in a time-dependent manner during exposure to 2% ethanol. In addition, mRNA levels of Hcn2 and cyclin D2, which are miR-133 targets and involved in cardiac arrhythmia (electrical remodeling), were increased in ethanol-exposed cells. In contrast, mRNA levels of CTGF, an anti-apoptotic growth factor and a target of YAP and miR-133a, was decreased in ethanol-exposed cells.
Conclusion: Our data show that miRNAs should be crucially involved in the cytotoxicity of ethanol on HL-1 cardiomyocytes.

P2-1-14

IN A WORKPLACE, WHAT KINDS OF EMPLOYEES SHOULD BE INCLUDED IN AN ALCOHOL BRIEF INTERVENTION? BASED ON A CONTINUOUS SURVEY OF THE STATE OF ALCOHOL CONSUMPTION BY EMPLOYEES USING AUDIT

T. Yuzuriha[1], H. Tanaka[2], T. Muto[1]
[1]National Hospital Organization Hizen Psychiatric Center, Japan and [2]Nippon Steel & Sumitomo Metal Corporation Kashima Works, Japan

We conducted an AUDIT survey of the employees of a workplace once a year over three years. The analysis of 2,338 male employees resulted in an average AUDIT score of 6.0 in both the first and third year results. The results of the first year's survey revealed AUDIT scores ranging from 8 to 14 points for 580 employees, and 15 or more points for 158 employees. Even among those who did not receive an Alcohol Brief Intervention during this period, some naturally improved, as 40% of those who scored 8 points or more in the first year scored below 8 points in the third year; similarly, 63% of those who scored 15 points or more in the first year scored less than 15 points two years later. Additionally, the results of both the first and third year surveys indicated that those who continued to be problem drinkers with AUDIT scores of 8 points or more were significantly older than those who improved their scores in the third year survey to below 8 points. Moreover, among those who showed improvement with regard to their drinking problem, a significantly large number self-evaluated the quantity they consumed as large or slightly large.

P2-1-15

EFFECT OF THE FAAH-INHIBITOR PF-04457845 ON ESCALATED ALCOHOL SELF-ADMINISTRATION AND ANXIETY-LIKE BEHAVIOUR FOLLOWING SOCIAL DEFEAT- AND WITNESS STRESS IN RATS

R. Barchiesi, G. Augier, E. Augier, E. Domi, M. Heilig, E. Barbier
Center for Social and Affective Neuroscience, IKE, Linköping University, Sweden

Comorbidity of alcohol use- and anxiety disorders is a major cause of disability and a challenge for mental health services. Here, we used a model of social defeat stress (SDS) in male Wistar rats to assess the impact on alcohol- and anxiety related behaviours. To disentangle the psychological component from the combined psychological and physical stress in the defeated animal, a second animal was made to witness the SDS. Both SDS and witness stress induced similar long term phenotypes, with animals displaying an escalated alcohol consumption in operant self-administration and with a high number of animals expressing an increased anxiety-like behaviour, ten days after the last social defeat. It is well established that the endocannabinoid system is important in buffering stress and we therefore hypothesised that targeting this system can rescue our stress-induced phenotypes. We are now investigating whether the specific, irreversible fatty acid amide hydroxylase (FAAH) inhibitor PF-04457845 is able to prevent the escalated alcohol self-administration and mitigate the increased anxiety-like behaviour observed in our socially defeated and witness rats. Upregulating the endocannabinoid anandamide through inhibition of FAAH offers an increased therapeutical potential with fewer side effects compared to treatments that directly target the cannabinoid receptor 1.

P2-1-16

ACCURATE MASS MALDI-TOF/TOF LIPID IMAGING OF HUMAN BRAIN TISSUE

C.C. Smith[1], M.B. O'Rourke[2], M. Padula[3], S.M. De La Monte[4], D.L. Sheedy[1], J.J. Kril[1], G.T. Sutherland[1]
[1]Discipline of Pathology, Sydney Medical School, The University of Sydney, Australia, [2]Sydney Mass Spectrometry, Charles Perkins Centre, The University of Sydney, Australia, [3]Proteomics Core Facility, University of Technology Sydney, Australia and [4]Liver Research Centre, Division of Gasteroenterology and Department of Medicine, Alpert Medical School of Brown University, USA

Loss of lipid-rich white matter is the major pathological finding in alcohol-related brain disease but there is sparse knowledge on the specific lipid species involved. Matrix Assisted Laser Desorption/Ionisation-Imaging Mass Spectrometry (MALDI-IMS) is an evolving method using a MALDI-TOF/TOF instrument that allows for the visualization of a range of biomolecules, including lipids, in tissues. The key step for lipid identification is accurate mass determination, however this normally requires additional instrumentation such as liquid chromatography-mass spectrometry or fourier transform cyclotron resonance as a complementary platform. Here, we describe a protocol that includes red phosphorus as an on-tissue calibrant in the low mass range, that allows accurate mapping of lipid species in tissue using MALDI-IMS as a stand-alone platform. This study demonstrates the utility of this protocol by showing differences in the abundance of lipids in post-mortem human brain tissue of controls and chronic alcoholics from the NSW Brain Tissue Resource Centre.

P2-1-17

GENDER DIFFERENCES IN THE ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND ALCOHOLIC BEVERAGE PREFERENCE AMONG JAPANESE YOUTH AGES 18 TO 22

Y. Miyoshi[1], S. Katsuno[2], N. Nishioka[3]
[1]School of Medicine, Gifu University, Japan, [2]Professor Emeritus, Gifu Pharmaceutical University, Japan and [3]Graduate School of Education, Hyogo University of Teacher Education, Japan

Purpose: To ascertain gender differences in the association between alcohol consumption over one's lifetime, during the past year, or during the past 30 days and alcoholic beverage preferences among Japanese youth based on the JYPAD survey.
Methods: Data were obtained from 1,015 respondents among randomly selected youth age 18 to 22 who lived in the Kanto region of Japan and who completed a self-administered questionnaire as part of the JYPAD conducted in 2016. The sample was analyzed using cross analysis of the statistical program SPSS.
Results: In the order of preference, 287 females who drank alcohol during the past 30 days drank "cocktails"(65.2%), "plum wine/fruit liqueur" (58.5%),"shochu (white liquor) highballs" (53.3%), "beer/low-malt beer" (26.5%), "wine"(14.3%), "sake" (13.2%), "shochu" (9.8%), or "whiskey" (9.8%), and 285 males who drank alcohol during the past 30 days drank "beer/low-malt beer" (49.1%), "shochu highballs" (42.5%), "plum wine/fruit liqueur" (34.4%), "cocktails" (33.7%), "sake" (24.6%), "whiskey" (21.1%), "shochu" (14.0%), or "wine" (13.7%).
Conclusions: This study found marked gender differences in preferences for the six types of alcoholic beverages among Japanese youth, regardless of the period when alcohol was consumed. Females preferred "cocktails", "plum wine/fruit liqueur", or "shochu highballs", and males preferred "beer/low-malt beer", "sake", or "whiskey".

P2-1-18

MUSCLE MASS AND MUSCLE STRENGTH IN FEMALE ALCOHOLICS AT THE TIME OF ADMISSION TO AN ALCOHOLISM REHABILITATION PROGRAM (ARP)

S. Sakate[1], C. Iwahara[2], Y. Tanaka[2,3], S. Kamiya[2], Y. Mizukami[1], K. Masuko[4,5]
[1]Sagami Women's University, Japan, [2]National Hospital Organization Kurihama Medical and Addiction Center, Japan, [3]National Hospital Organization Disaster Medical Center, Japan, [4]Sanno Medical Center, Japan and [5]International University of Health and Welfare, Japan

We aimed to clarify the characteristics of body composition and muscle strength in female alcoholics at the time of admission to an Alcoholism Rehabilitation Program (ARP). This study included seven female alcoholics (mean age, 43.4 ± 5.8). We excluded patients who had severe intercurrent physical or mental illnesses. Their body composition and muscle strength were measured using bioelectrical impedance analysis and grip strength, respectively. Among the seven patients, three patients (42.9%) were below 18.5 with a BMI, and one (14.3%) was 25 or higher. Their body fat percentage was 29.0 ± 0.3%, and two patients had a body fat percentage of greater than 30%. The total body muscle mass was 33.1 ± 2.6 kg, and the values of six patients fell below those of age- and gender-matched Japanese people. Grip strength was 20.4 ± 6.4 kg, and the values of all patients fell below those of age- and gender-matched Japanese people. Grip strength in three patients was below 18 kg, which is even compatible with the range of sarcopenia as defined for elderly by the Asian Working Group for Sarcopenia. Our study suggested that female alcoholics are more likely to develop conditions that lead to a state of frailty in the future.

P2-1-19

ALCOHOL USE IN PREGNANT VS. NON-PREGNANT WOMEN LIVING WITH HIV IN UGANDA AND SOUTH AFRICA

L.T. Matthews[1,2], G.A. Raggio[3], C. Psaros[3], R. Fatch[4], G. Goodman[3], J. Magidson[5], G. Amanyire[6], A. Cross[7], J.A. Hahn[4], J.E. Haberer[1,2]
[1]Center for Global Health, Massachusetts General Hospital, USA, [2]Department of Medicine, Harvard Medical School, USA, [3]Department of Psychiatry, Massachusetts General Hospital, USA, [4]Department of Medicine, UCSF School of Medicine, USA, [5]Department of Psychology, University of Maryland, USA, [6]Makerere University Joint AIDS Program, Uganda and [7]Desmond Tutu HIV Foundation, University of Cape Town, South Africa

Background: Alcohol misuse is common among individuals with HIV and may increase during stressful periods, such as pregnancy. Pregnant women living with HIV (WLWH) also report high rates of depression and stigma, which may influence substance use. No study has examined objective alcohol consumption and under-reporting among pregnant WLWH in sub-Saharan Africa, where HIV and alcohol misuse rates are high.
Methods: Participants were WLWH recruited from outpatient clinics in Uganda and South Africa. Women provided self-report data (alcohol use, depression, stigma) and blood samples to measure objective alcohol intake (phosphatidylethanol [PEth]). Alcohol use (positive by self-report or PEth) and under-reporting (detectable PEth when alcohol use was not reported) were compared between pregnant and non-pregnant participants. Pregnancy was evaluated as a moderator of the associations between alcohol use, depression, and stigma.
Results: Among pregnant women ($n = 163$), 40% were using alcohol (vs. 44% non-pregnant, $p>0.05$), and 16% under-reported (vs. 13% non-pregnant, $p>0.05$). Pregnancy did not significantly moderate the correlation between alcohol use and depression ($p>0.05$).
Conclusion: Alcohol use was common among pregnant WLWH, and underreporting was more common compared to non-pregnant participants. Alcohol use screening and counseling should be integrated with pregnancy care.
Keywords: HIV, Alcohol, Pregnancy, WLWH, Depression, Stigma, Phosphatidylethanol:

P2-1-20

ENGINEERING GUT BACTERIA TO MODULATE ALCOHOL CONSUMPTION AND INVESTIGATE GUT-BRAIN MECHANISMS

E. Grantham[1], M. Blevins[2], Y. Blednov[1], J. Brodbelt[2], B. Davies[3], R. Adron Harris[1]
[1]Waggoner Center for Alcohol and Addiction Research, University of Texas – Austin, Austin, TX, USA, [2]Department of Chemistry, University of Texas – Austin, USA and [3]Institute for Cellular and Molecular Biology, University of Texas – Austin, Austin, TX, USA

The discovery of more efficacious treatments for alcohol use disorder (AUD) remains a challenging goal in the field of alcohol research. One promising approach is based on research on the gut-brain axis. This line of communication provides a potential mechanism for targeting alcohol behaviors. We investigated how genetically engineered gut bacteria may alter excessive alcohol consumption and preference in a mouse model. Small lipids produced in the gut, such as n-acylethanolamines (NAEs), are implicated in the rewarding aspects of drugs and act on a specific nuclear hormone receptor (peroxisome proliferator activated receptor-α, PPARα). We previously showed that PPARα agonists decrease alcohol consumption and alter other related behaviors in mice. Here we present a potential mechanism for targeting PPARα through gut bacteria engineered to enhance NAE production. We show that bacteria can be engineered to increase production of NAEs and colonize the mammalian gut. Although NAEs are promising therapeutic molecules, it appears that administration of a probiotic strain of *E. coli* itself alters consumption and preference for alcohol in a mouse model. Future experiments will focus on mechanisms by which probiotic bacteria can influence behavior as well as improvements in the production of NAEs to target PPARα.

P2-1-21

PLASMA FOLLICLE STIMULATING HORMONE LEVEL IS NEGATIVELY CORRELATED WITH NEGATIVE CRAVING FOR ALCOHOL IN ALCOHOL-DEPENDENT MALES

K.M. Victor[1], A.M. Ho[1], J.R. Geske[2], S.J. Winham[2]
[1]Department of Psychiatry and Psychology, Mayo Clinic, USA and [2]Department of Health Sciences Research, Mayo Clinic, USA

Sex differences in the susceptibility to alcoholism-related phenotypes are well-known, but the underlying mechanisms remained elusive. We investigated the association of plasma sex-related hormone/protein levels with alcohol dependence and alcohol craving in 29 DSM-IV-TR alcohol dependent males and 29 age-and-race matched non-alcoholic male controls. The propensity to drink during specific emotional situations was assessed by the Inventory of Drug-Taking Situations (IDTS). The levels of sex hormones (estradiol, estrone, progesterone and testosterone) as well as follicle stimulating hormone (FSH), luteinizing hormone, and sex hormone binding protein were measured by LC/MS/MS and automated immunoassays. Conditional logistic regression analyses were conducted to examine the association between sex-related hormone/protein levels and risk for alcohol dependence and alcohol craving scales, accounting for the matching variables. We observed that FSH level was significantly higher in AD subjects than controls ($p_{corrected} = 0.035$). We further detected a significant inverse correlation between FSH and IDTS negative craving subscale (Spearman's rho = -.540; $p = 0.021$) in AD subjects. These results indicate that plasma FSH level is associated with alcohol dependence and FSH level is correlated with the propensity to drink in negative emotional situations. Future studies are needed to replicate these findings and explore whether these associations also apply to females.

P2-1-22

DIET OF FEMALE ALCOHOLICS BEFORE AND AFTER ADMISSION TO AN ALCOHOLISM REHABILITATION PROGRAM (ARP)

Y. Mizukami[1], Y. Tanaka[2], S. Kamiya[3], S. Sakate[1], C. Iwahara[3], K. Masuko[4,5]
[1]Sagami Women's University, Japan, [2]National Hospital Organization Disaster Medical Center, Japan, [3]National Hospital Organization Kurihama Medical and Addiction Center, Japan and [4]Sanno Medical Center, Japan, [5]International University of Health and Welfare, Japan

Many female alcoholics have comorbid eating disorders, and their nutritional status can potentially be different from those of male alcoholics. In this study, we conducted a diet survey on the nutritional state of female alcoholics before and during hospitalization and examined changes in their diet. Seven females (age, mean ± standard deviation: 43.4 ± 5.8 years) participated in an Alcoholism Rehabilitation Program (ARP). A self-administered questionnaire designed to assess their diet before hospitalization was conducted at the time of admission. Registered dietitians computed in-hospital nutritional intake from meal size in the first week after admission. Four patients who were classified as underweight at the time of admission, had eaten once or twice daily before hospitalization. Answers to "How has your diet changed?" after being admitted to the hospital were "My appetite is increasing" ($n = 4$), and "I have lost my appetite" ($n = 2$). Participants suffered from undernutrition because they had often skipped meals and eaten unbalanced diets before being admitted to our hospital. Approximately 40% of the participants had history of laxative abuse and vomiting. Therefore, we consider that nutritional management in female alcoholics is necessary after admission because some of them continued to have decreased nutritional intake after admission.

P2-1-23

VOLUMETRIC ALTERATIONS IN THE NUCLEUS ACCUMBENS OF YOUNG BINGE DRINKERS: A STRUCTURAL MAGNETIC RESONANCE IMAGING STUDY

A. Crego, E. López-Caneda, S. Sousa, A. Sampaio
CIPsi, University of Minho, Portugal

Background: Binge drinking (BD) is defined as a pattern of high alcohol intake in a short time followed by periods of abstinence. This behaviour is very common during adolescence and early adulthood, a developmental stage characterized by the maturation of the prefrontal and striatal networks, important circuits related to the capacity to control and reinforce behaviours. The basal ganglia, specifically the nucleus accumbens (NAc) and the caudate nucleus (CN), are part of these frontostriatal circuits involved in reward processes underlying addictive behaviours. The main goal of this study was to investigate the presence of morphological alterations in the NAc and the CN in a sample of young binge drinkers (BDs).
Methods: Twenty college BDs and 15 age-matched abstainers (18–23 years-old) underwent a structural magnetic resonance imaging (MRI) acquisition. The NAc and the CN were manually segmented using the Slicer 3D software.
Findings: Results revealed a significant volumetric increase in the NAc of BDs compared to the control group.
Conclusions: These findings are in line with results of previous MRI studies with automatic segmentation methods in young BDs (Howell et al., 2013) and they are suggestive of anomalous (delayed) maturation of striatal regions as a result of repeated bingeing episodes.

P2-1-24

THE EXPERIENCE OF TREATMENTS PROVIDED TO ALCOHOLICS IN GENERAL HOSPITALS IN TOKYO AND ITS VICINITY

K. Ito[1], R. Tanaka[2], H. Maesato[3]
[1]Faculty of Nursing Toho University, Japan, [2]Tokyo Healthcare University, Japan and [3]National Hospital Organization Kurihama Medical and Addiction Center, Japan

Although it is estimated that the number of alcoholics in Japan exceeds 1 million people (Higuchi, 2013), only 50,000 patients consult a medical institution, while many others leave their alcoholism unattended despite the need for treatment. The number of people with untreated alcoholism who are repeatedly hospitalized in general hospitals for the treatment of somatic diseases is considerable. It is, however, presumed that specialist treatments for alcoholism are difficult to perform in these institutions.
The purpose of this study is to clarify the treatment and support for patients with alcoholism in general hospitals in Tokyo and its vicinity.
Semi-structured interviews were conducted with eight healthcare professionals (2 physicians, 4 nurses, and 2 psychiatric social workers) who have had experience with handling alcoholic patients in the psychiatric wards of general hospitals in Tokyo and its vicinity.
All the interviews were tape-recorded, transcribed, and examined for the main categories and themes. These themes were identified and coded using thematic analysis and constant comparison of the data.
Based on these results, the paper will discuss the roles and limitations of general hospitals in metropolitan Tokyo with regards to the treatment of alcoholism.

P2-1-25

BENEFIT FROM ADEQUATE CLINICAL EVALUATION OF ALCOHOL DEPENDENCE IN FORENSIC PSYCHIATRY

N.Z. Radulovic, V. Banjac
Clinic of Psychiatry, University Clinical Center of the Republic of Srpska, Bosnia and Herzegovina

Introduction: The basis of domestic violence is aggressive behaviour. That requires an adequate clinical assessment for the prevention, treatment and rehabilitation of violent behaviour.
Aim: The aim is to determine what are the risk factors for criminogenic behaviour in alcohol addicts.
Method: The research was carried out among alcohol addicts with and without data on domestic violence. Psychiatric assessment scales (MMPI 202 and Barratt's Impulsivity Scale) were used for this purpose. The SPSS software system version 20 was deployed in processing statistical data.
Results: MMPI test showed that there is a statistically significant difference between the perpetrator and non-perpetrator group when it comes to personality traits. This finding confirmed the hypothesis that alcohol dependents, who committed domestic violence, are characterized by inflexibility and impulsivity. Based on this is possible to make predictions of future criminogenic behaviour. Barratt's Impulsivity Scale confirmed a statistically significant difference between a perpetrator and non-perpetrator group when it comes to the level of cognitive impulsivity.
Conclusion: Barratt's Impulsivity Scale proved to be very good in the prediction of future criminal behaviour. Individualization of the treatment is important to prevent the risk of repeated domestic violence.

P2-1-26

NICOTINE INCREASES ALCOHOL SELF-ADMINISTRATION VIA MU OPIOID RECEPTOR ACTIVITY IN THE VENTRAL TEGMENTAL AREA

E. Domi[1], A. Hansson[2], M. Paetz[2], E. Barbier[1], E. Augier[1], G. Augier[1], D. Gehlert[3], M. Heilig[1]
[1]Center for Social and Affective Neuroscience, IKE, Linkoping University, Linkoping 581 83, Sweden, [2]Institute of Psychopharmacology, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim 68159, Germany and [3]Cerecor Inc., Baltimore 21202, MD, USA

Alcohol and nicotine are the most commonly co-abused drugs, with a large majority of alcoholics diagnosed with a comorbid addiction to nicotine. The endogenous opioid system is involved in the rewarding properties of both alcohol and nicotine. We previously found that CERC-501, a highly selective KOR antagonist reduced escalated alcohol self-administration induced by the intermittent access to alcohol 20%. In here we tested the effect of CERC-501 on escalation of alcohol drinking induced by nicotine. Chronic nicotine elicited a robust and specific escalation of alcohol drinking without affecting saccharin self- administration and locomotion. CERC-501 did not suppress nicotine-induced increased alcohol self-administration in opposite to naltrexone which blocked escalated drinking. Our in situ hybridization data showed a different pattern of expression and functional activation of MORs in alcohol escalation induced by nicotine, while KORs expression and activity was not affected by the combination of the two drugs. Specifically, our data showed an increased expression and a decreased function of MORs in the ventral tegmental area of alcohol-escalated rats. Together our results suggest that targeting mu rather than k-opioid receptors may represent a promising pharmacotherapeutic approach for the treatment of alcohol use disorders where alcohol consumption is driven by nicotine.

P2-1-27

FREE-CHOICE ALCOHOL DRINKING LEADS TO QUININE-RESISTANT ALCOHOL INTAKE AND REVERSED BY INTRA-DLS D1-ANTAGONIST

C.A. Houck, L.A. Millie, N.J. Grahame
Indiana University-Purdue University Indianapolis, USA

Drinking despite aversive consequences is a criterion of alcohol use disorder. Previous studies have shown the development of quinine-resistant alcohol drinking, but used animals that achieved relatively low blood alcohol levels. Selectively bred crossed High Alcohol Preferring (cHAP) mice average over 250 mg/dL. Compulsive drinking is hypothesized to be D1-receptor mediated via the dorsolateral striatum (DLS). We hypothesized that 5 weeks of free-choice EtOH would lead to quinine resistance and intra-DLS infusion of a D1-antagonist, SCH23390 would attenuate quinine-resistant alcohol drinking.
cHAP mice had five weeks (5W), two weeks (2W), or zero weeks (0W) of EtOH and water two-bottle choice. We then adulterated the EtOH with quinine, and both 5W and 2W groups drank more quinine-adulterated EtOH than the 0W mice. A second group of cHAPs were cannulated bilaterally in the DLS and had a 2W drinking history. SCH23390 reduced quinine-adulterated alcohol intake, but did not affect unadulterated alcohol drinking.
These findings show that a history of free-choice EtOH drinking induces quinine resistance faster in cHAP mice compared to prior models. This acquired quinine resistance is attenuated by acute administration of a D1-antagonist in the DLS, suggesting that an alcohol history induces compulsivity and that dopamine contributes to this behavior.

P2-1-28

SUPPRESSION OF MEMORIES IN THE THINK/NO-THINK ALCOHOL TASK: AN EVENT-RELATED POTENTIAL STUDY

E. López-Caneda[1], A. Crego[1], A.D. Campos[2], A. González-Villar[3], A. Sampaio[1]
[1]Psychological Neuroscience Lab, Research Center in Psychology, University of Minho, Portugal, [2]Human Cognition Lab, Research Center in Psychology, School of Psychology, University of Minho, Portugal and [3]Department of Clinical Psychology and Psychobiology, University of Santiago de Compostela, Spain

Background: The Think/No-Think (TNT) task has proved to be a suitable paradigm for measuring memory inhibition (MI), i.e., the ability to suppress unwanted or contextually-relevant thoughts. In the present study, we developed the Think/No-Think Alcohol (TNTA) task, a new paradigm specially designed for examining MI in alcohol-related contexts.
Methods: Twenty-five healthy females (18–32 years) participated in the study. The TNTA task consists of 36 alcohol/non-alcohol pictures paired with 36 neutral images. Participants were asked to memorize each of these pairs. Subsequently, brain activity was measured by event-related potentials (ERPs) while subjects had to think or suppress the previously learned pictures. Finally, recall of pictures was assessed.
Results: Recall of No-Think pictures was significantly reduced in comparison with Think pictures. Furthermore, there was lower recall of Alcohol No-Think compared to Non-Alcohol Think pictures. ERP analysis revealed larger amplitudes within the 400–600 ms time window for Think compared to No-Think condition in the left centro-parietal region.
Conclusions: Our results replicate findings typically reported in the TNT paradigm, namely reduced recall and decreased left parietal positivity for No-Think items. Thus, the TNTA task seems to be a proper paradigm for measuring MI in alcohol-related contexts, which might have important applications in alcohol research.

P2-1-29

EFFECT OF EXPERIMENTER- VERSUS SELF-ADMINISTERED DELTA-9-TETRAHYDROCANNABINOL ON ALCOHOL DRINKING IN MICE SELECTIVELY-BRED FOR HIGH (HAP2) AND LOW (LAP2) ALCOHOL PREFERENCE

M.P. Smoker[1], S.L. Boehm[1,2]
[1]Psychology, Indiana University – Purdue University Indianapolis, USA and [2]Indiana Alcohol Research Center, Indiana University – Purdue University Indianapolis, USA

Alcohol and cannabis are frequently co-abused, and while CB1 receptor agonism via synthetic cannabinoids enhances alcohol self-administration, the effect of THC has been largely unexamined. An initial experiment examined the impact of both the acute administration of and prior exposure to THC on binge-like drinking in HAP2 female and male mice. Initially, acute THC significantly decreased alcohol intake and locomotor activity. However, mice recovered from the effect on drinking, but not locomotion, on subsequent days. Complicating interpretation was that mice also sensitized to repeated injection. Prior exposure to THC significantly decreased alcohol intake in female mice on their first opportunity to drink, possibly due to having previously perceived THC-induced changes in subjective state as aversive. However, prior exposure did not substantially impact the initial effects of acute THC on drinking or locomotion. Given the impact of injection on behavior, current work is examining the effect of self-administered THC on drinking in HAP2 and LAP2 mice using a newly-developed edible THC model. Although these mouse lines differ in alcohol drinking, they consume edible THC to a similar degree at doses producing behavioral effects in C57BL/6J mice. The impact of edible THC consumption prior to alcohol drinking is currently being examined.

P2-1-30

SOCIO-DEMOGRAPHIC AND INDIVIDUAL PSYCHOLOGICAL FEATURES OF RUSSIAN WOMEN AT RISK OF ALCOHOL-EXPOSED PREGNANCY

A.K. Kulieva[1,2], E.A. Burina[1]
[1]Saint-Petersburg State University, Russia and [2]Saint-Petersburg Psychological Association, Russia

According to statistics, in Russia alcohol consumption level exceeds WHO standards. Excessive alcohol use by women of childbearing age leads to a high risk of alcohol-exposed pregnancy (AEP). Individual social and psychological features of women at AEP risk were studied. The study involved 80 women aged 18–44: 40 – control group, 40 – experimental group (brief intervention was conducted to prevent AEP). The study used the methods of personality questionnaire BIG 5, subjective control level and motivational induction method. According to the results of subjective control study, the differences between the groups were found only in the factor «Internality of achievements» (in the experimental group: M = 5.60; SD = 0.709; in the control group: M = 5.25; SD = 0.870; $t(78) = -1.973$, $p<0.1$). According to BIG 5 personality test, women of both groups were extroverted, organized, ready for cooperation, emotionally stable and had personal resources. A negative correlation was found between the alcohol consumption frequency and extroversion ($r(80) = -0.274$, $p<0.05$). A study of motivational induction showed that the motivation of women in both groups was generally directed toward self-development, self-realization, and social interaction. Women at risk of AEP were mostly non-working with higher education, often having 1 child, divorced or unmarried, having an abortion history, smoking and non-physically active.

P2-1-31

THE RISK OF FETAL ALCOHOL SYNDROME IN PREGNANT WOMEN AND WOMEN PLANNING PREGNANCY

E.A. Burina[1], A.K. Kulieva[1,2], A.Y. Marianian[3,4]
[1]Saint-Petersburg State University, Russia, [2]Saint-Petersburg Psychological Association, Russia, [3]Irkutsk State Medical Academy of Postgraduate Education, Russia and [4]Scientific Center of Family Health and Human Reproduction Problems, Russia

Fetal Alcohol Syndrome (FAS) is an incurable disease that occurs as a result of alcohol use by women during pregnancy. According to statistics, Russia is one of the countries with a high level of alcohol consumption. 280 non-pregnant women aged 18–44 participated in the study: 140 represented control group, 140 – experimental group (brief motivational intervention performed to prevent FAS). Follow-up interviews were conducted in 3, 6 and 12 months after the baseline. During the research, 21 women (10 experimental and 11 control) became pregnant. Thus, the study results of knowledge, attitudes, behavior in dynamics in pregnant women showed that in 12 months pregnant women demonstrate positive changes in knowledge level and attitudes nature. The actual alcohol consumption by pregnant women of both groups was significantly less and less than that of non-pregnant women. Changes in the alcohol use in experimental group were more significant than in control. The planning pregnancy subgroup included 32 women: 20 experimental, 12 control. The study results of alcohol-exposed pregnancy risk in women planning pregnancy showed that in 12 months this risk declined more significantly than in the entire sample. Changes in real alcohol use are more significant in pregnant women in the experimental group.

P2-1-32

THE EFFECTIVENESS OF BRIEF INTERVENTION AS FETAL ALCOHOL SYNDROME PREVENTION

E.A. Burina[1], G.L. Isurina[1], A.K. Kulieva[1,2]
[1]Saint-Petersburg State University, Russia and [2]Saint-Petersburg Psychological Association, Russia

According to 2016 statistics, the level of alcohol consumption in Russia is 12.8 liters per year, which exceeds the norm of 8 liters, making FAS risk particularly relevant. To reduce FAS risk a brief intervention based on motivational interview was used. The study involved 280 non-pregnant women aged 18–44. All women were given materials about FAS and the effects of alcohol on the fetus. The experimental group ($N = 140$) also underwent dual-focused brief intervention. As part of the intervention, the participants were informed of the effect of alcohol on the fetus and suggested developing behavior aimed at either using contraceptive methods or refusing to drink alcohol. After 3, 6 and 12 months, follow-up interviews were conducted to measure the changes in knowledge and attitudes of women about alcohol and their actual behavior – alcohol and contraception. At the beginning of the study, all 280 women were at risk of FAS. At the end of the study, 147 (52.5%) women of childbearing age (76 participants in the experimental and 71 participants in the control group) were not at alcohol-exposed pregnancy risk, while the time slice demonstrated that changes occurred in the experimental group faster. Thus, brief intervention proved effective in preventing FAS.

P2-1-34

EFFECTS OF ALCOHOL HANGOVER ON MOOD AND COGNITIVE MULTI-TASKING: A SEMI-NATURALISTIC LABORATORY STUDY

S. Benson[1], E. Ayre[1], J. Verster[1,2], A. Scholey[1]
[1]Centre for Human Psychopharmacology, Swinburne University, Australia and [2]Division of Pharmacology, Utrecht University, Netherlands

The majority of research assessing cognitive performance during a hangover has been laboratory studies using controlled doses. While this methodology offers many benefits, it does not mimic naturalistic settings and may not capture the effects seen in 'real-life'. This study will use a naturalistic study design to determine the effects of hangover on cognitive performance and mood.
Participants completed testing procedures during a screening visit and two conditions: i) with a hangover and ii) without a hangover (counterbalanced). During each testing visit, participants complete the PURPLE Multi-Tasking Framework (PMTF), Bond-Lader Visual Analogue Scale, Profile of Mood States and NASA Task Loading Index.
Preliminary analyses of 16 participants revealed that participants were significantly less alert ($F(1, 15) = 31.48$, $p<.001$) and content ($F(1, 15) = 14.24$, $p.002$), and significantly more anxious ($F(1, 15) = 7.07$, $p = .018$) and mentally fatigued (($F(1, 15) = 27.15$, $p<.001$) during the hangover visit. Participants accuracy ($t(15) = 2.33$, $p = .034$) and reaction time ($t(14) = 2.66$, $p = .018$) in the Stroop task were significantly impaired during the hangover condition. Participants reported the PMFT to be significantly demanding and require more effort during the hangover condition.
Preliminary analysis revealed impairments to mood and performance during the hangover condition. Participants indicated greater difficulty and need for more resources to complete cognitive tasks during the hangover visit.

P2-1-35

EFFECTS OF ALCOHOL HANGOVER ON COGNITIVE PERFORMANCE: A FIELD AND ONLINE MIXED METHODOLOGY STUDY

A. Scholey[1], S. Benson[1], J. Kaufman[1], E. Ayre[1], C. Allen[2], J. Verster[3], G. Devilly[4]
[1]Centre for Human Psychopharmacology, Swinburne University, Australia, [2]Queensland Olice Service Academy, Australia, [3]Division of Pharmacology, Utrecht University, Netherlands and [4]Griffith University, Australia

Studies into the cognitive effects of hangover have reported mixed effects, though generally they have found deficits in executive and attentional measures. The current study used BAC and self-reported drinking behaviour during a night out and related these to hangover severity and cognitive function measured over the internet in the same subjects the following morning.
Volunteers were interviewed and breathalysed as they left an entertainment district of an Australian state capital. They were provided with a unique identifier and invited to log onto a website the following morning. The website included questions regarding demographic and morphometric data, an online version of the Alcohol Hangover Severity Scale and an online analogue of the Trail Making Test B of executive function and working memory.
$N = 108$ completed the next morning measures. Hangover severity was significantly correlated with previous night's BAC ($r = 0.228$, $p = 0.019$). Time to complete the Trails test was significantly correlated with hangover severity ($r = 0.245$, $p = 0.012$), previous night's BAC ($r = 0.197$, $p = 0.041$) and time spent dinking ($r = 0.376$, $p<0.001$).
These findings confirm that hangover negatively affects cognitive functioning and that poorer attentional/working memory performance correlates with hangover severity. The results also support the utility of using online measures in this kind of study.

P2-1-36

APPLICATION OF CPT TO SUBSTANCE USE DISORDERS EXPERIENCED TRAUMA IN JAPAN: TWO CASE REPORTS

Y. Takagishi[1,2], S. Tanaka[2,3], M. Ito[2], M. Horikoshi[2]
[1]Department of Psychology, Surugadai University, Japan, [2]National Center for Cognitive Behavioral Therapy and Research, National Center of Neurology and Psychiatry, Japan and [3]Self-Defense Forces Central Hospital, Japan

Background: There are many people in substance use disorders (SUD) who have experienced and suffered from symptoms due to trauma. Cognitive Processing Therapy (CPT) is a type of cognitive-behavioral therapy found to be effective for treating post-traumatic stress disorder (PTSD).
Purpose: This case report describes an example of applying CPT to SUD with partial PTSD and evaluate CPT on reduction of PTSD symptoms and control of substance use.
Case description: We report two cases of SUD/partial PTSD, both sexually assaulted women. Case 1 was a 50's woman who had a history of alcohol use disorder. Case 2 was a 20's woman who had been abusing analgesics.
Outcomes: Case 1 completed all treatment content, showing reduction in PTSD symptoms and good control of substance use. Case 2 joined up to seven sessions and offered to drop out of treatment because she felt uncomfortable talking about trauma. In case 2, there was no meaningful reduction in PTSD symptoms and substance use could not be well controlled.
Discussion: In two cases, it was shown that CPT may work effectively for SUD patients with partial PTSD, and in some case introduction may be difficult. The factors of the difference were discussed.

P2-1-37

PSYCHOLOGICAL OR PHYSIOLOGICAL STRESS-INDUCED ALCOHOL CONSUMPTION IN MICE LACKING OPIOID RECEPTORS

Y. Moriya[1,2], Y. Kasahara[2], F.S. Hall[3], K. Ikeda[1], G.R. Uhl[4], I. Sora[2,5]
[1]Department of Psychiatry and Behavioral Science, Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Japan, [2]Department of Biological Psychiatry, Tohoku University Graduate School of Medicine, Sendai, Japan, [3]Department of Pharmacology and Experimental Therapeutics, University of Toledo College of Pharmacy and Pharmaceutical Sciences, Toledo, USA, [4]Research Service, New Mexico VA Healthcare System, Albuquerque, NM, USA and [5]Department of Psychiatry, Kobe University, Graduate School of Medicine, Kobe, Japan

Objective: Adverse life experiences are associated with an increased risk of developing alcohol use disorders (AUD). One factor that has not been adequately examined in previous studies of the genetic contributions to AUD is sex, which is a substantial shortcoming in the field given that there are significant influences of sex on alcohol consumption patterns and alcoholism in humans and in animal models. Genetic factors, such as allelic variation in opioid receptor system genes, have a substantial influence on alcohol consumption, but only a limited set of such genetic influences on behavioral activity associated with forced drinking have been examined.
Methods: The effects of restraint stress on ethanol intake were assessed using a two-bottle home-cage consumption procedure (8% v/v ethanol vs. water) in male and female WT and mu-opioid receptor (MOP) KO mice. Furthermore, WT and MOP KO mice were studied during forced ethanol drinking, continuous access to ethanol for twelve days, after which all mice were tested for locomotor activity in an open field apparatus.
Results: Male and female show opposite behaviors in terms of alcohol intake.
Conclusion: The study shows that disturbances of MOP influences the behavioral consequences of ethanol consumption following stress in a sex-dependent manner.

P2-1-38

COMPARISON OF ETHANOL AND METHANOL EFFECTS ON HUMAN PLATELET AGGREGATION

M. Marumo, K. Ekawa, I. Wakabayashi
Department of Environmental and Preventive Medicine, Hyogo College of Medicine, Japan

Objective: The purpose of this study was to determine whether and how in vitro effects of ethanol and methanol on platelet aggregation are different.
Methods: Aggregation of and Ca^{2+} entry into human washed platelets were measured by light transmission method and spectrofluorometry, respectively.
Results: Platelet aggregation induced by thrombin, thapsigargin, or 1-oleoyl-2-acetyl-sn-glycerol (OAG) was inhibited by ethanol (0.5–2%). Ethanol (0.5–2%) inhibited Ca^{2+} entry induced by thapsigargin or OAG but not that induced by thrombin. Thrombin-induced platelet aggregation was significantly augmented by methanol at 0.5–2%. Methanol at 2% but not that at lower concentrations significantly attenuated thapsigargin-induced platelet aggregation. Methanol (0.5–2%) did not significantly affect platelet aggregation induced by OAG and Ca^{2+} entry into platelets induced by thrombin, thapsigargin or OAG.
Conclusions: In vitro effects of ethanol and methanol on Ca^{2+} entry into and subsequent aggregation of platelets are different as follows. Ethanol inhibits platelet aggregation induced by thrombin, thapsigargin or OAG, while methanol has diverse effects on platelet aggregation, depending on the aggregation stimuli. Ethanol inhibits Ca^{2+} entry induced by thapsigargin or OAG but not that by thrombin, while methanol does not affect Ca^{2+} entry induced by each of the three stimulants.

P2-1-39

PREDICTION OF ALCOHOL CONSUMPTION USING IMPLICIT ASSOCIATION TEST TO JAPANESE ALCOHOL DRINKERS

Y. Ogai[1,2], N. Morita[1], T. Saito[1], K. Ikeda[2]
[1]Faculty of Medicine, University of Tsukuba, Japan and [2]Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Japan

The aim of the present study was to examine whether an implicit attitude to alcohol drinking for Japanese alcohol drinkers predict their alcohol consumption within a week after measurement.
The participants were 70 adult alcohol drinkers with informed consent. At baseline online survey, alcohol-pleasure Implicit Association Test (IAT) and self-rating scales including severity of their alcohol dependence with Alcohol Use Disorder Identification Test (AUDIT), relapse risk of alcohol with Alcohol Relapse Risk Scale (ARRS), subjective craving for alcohol with Visual Analogue Scale (VAS) were administered. A follow-up online survey was conducted after one week to measure their alcohol consumption.
As a result of correlation analysis, significant correlation between IAT-D score and amount of alcohol drinking within a week was found (.270). The AUDIT total score, the ARRS total score, and craving to alcohol with VAS scale were also significantly correlated with their alcohol consumption respectively (.353, .514, .589).
These results indicated that implicit attitude for alcohol preference could predict their alcohol consumption, although their prediction power was smaller than self-rating scale. This was considered by the influence of using general sample in this study who don't need to stop drinking alcohol.

P2-1-40

THE OPRM1-A118G SNP IN MODULATION OF TRV130-INDUCED REWARD-RELATED BEHAVIOR

A. Thorsell, L. Holm, M. Heilig
CSAN, IKE, Linköping University, Sweden

The OPRM1-A118G SNP leads to an amino acid change in exon 1 from an asparagine for an aspartic acid (N40D) and affects at a putative N-glycosylation site. The SNP contributes to a phenotype with increased alcohol-intake and reward, as well as an increased treatment response to mu-opioid receptor (MOR) antagonists such as naltrexone. Here, we evaluate the contribution of the A118G SNP to reward-related behavior for the biased MOR agonist, TRV130, using "humanized" mice carrying the human exon 1 of the OPRM1-gene either as the major 118A allele (118AA) or with the 118G SNP (118GG).
Reward-related behavior was evaluated using the conditioned place preference paradigm. Three doses of TRV130 were first evaluated using C57Bl/6J: 0.3, 1.0 and 3.0 mg/kg bodyweight. The 1.0 mg/kg dose was then used for further testing.
Treatment with TRV130 1.0 mg/kg robustly induced CPP in both 118AA and 118GG carriers. In the 118GG carriers the CPP-score was significantly increased compared to the 118AA (79 +/- 3% vs. 68 +/- 2%) indicating a higher reward-value in the 118GG carriers.
In summary, as for alcohol, the A118G SNP seemingly contributes to the reward-value of the MOR biased agonist TRV130.

P2-1-41

THE MU-OPIOID-RECEPTOR BIASED AGONIST TRV130 MODULATES REWARD-RELATED BEHAVIOR IN A BETA-ARRESTIN DEPENDENT MANNER

L. Holm, A. Thorsell, M. Heilig
CSAN, IKE, Linköping University, Sweden

The mu-opioid receptor (MOR) is a G-protein-coupled receptor signalling through both G-proteins as well as β-arrestins, and ligands for the receptor may be biased towards either the G-protein or β-arrestin-mediated pathways. TRV130 is a G-protein pathway biased agonist to the MOR, that produces a potent antinociceptive effect in mice without inducing severe constipation or respiratory dysfunction. Here, we examined reward-related behavior for TRV130 in a classic conditioned place preference (CPP) paradigm using beta-arrestin 2 knockout mice (wt, het, and ko).
The CPP model used was a two-chamber set-up (Med Associates Inc. ST Albans, VT, USA). Following pre-test, conditioning was done in daily 30 min sessions alternating TRV130 and vehicle for 8 days (4 TRV130 (1.0 mg/kg) and 4 vehicle sessions). The test-session was preceded by a vehicle injection and run for 30 min.
TRV130 (1.0 mg/kg) induced CPP in wt BARR-mice (CPP-score 68.3 +/- 1.9%), while both the het BARR and the ko BARR showed blunted CPP (score 62.2 +/- 2.2 and 58.7 +/- 1.2, respectively).
Data presented here indicate that TRV130 induces reward-related behavior via a beta-arrestin dependent mechanism.

P2-1-42

ATTENUATION OF ANXIETY AND CRAVING USING NEUROSTEROIDS AMONG INDIVIDUALS WITH ALCOHOL USE DISORDER AND COMORBID PTSD

E. Ralevski, J. Serrita Jane, J. Newcomb, I. Petrakis
Department of Psychiatry, Yale University School of Medicine, USA

Purpose: The role of stress in AUD and PTSD is well established. Neurosteroids like progesterone through its metabolite allopregnanolone are central in the regulation of the HPA axis and the stress response. The goal of this study is to determine whether pretreatment with progesterone will attenuate trauma-induced alcohol craving and trauma-induced anxiety in patients with AUD and PTSD.
Methods: This is an ongoing, double-blind, randomized, between subject, placebo-controlled study designed to compare pretreatment with progesterone (3 days of 200 mg. bid) to placebo. On a single test day trauma and neutral cues consisting of personalized 5 min. scripts are presented in random order.
Results: Progesterone when compared to placebo significantly reduced trauma-induced craving ($p<0.05$). The same was true for anxiety and other negative emotions like fear and anger that were also significantly reduced after pretreatment with progesterone when compared to placebo.
Conclusions: The preliminary findings from our data show that progesterone is superior to placebo in reducing trauma-induced craving and negative emotions, a finding that may have a role in treatment of AUD and PTSD. Future work will focus on the direct action of allopregnanolone (a recently awarded R21 grant to the PI) on stress induced craving in AUD.

P2-1-43

ROLE OF ASTROCYTE CALCIUM SIGNALING IN EXCESSIVE ALCOHOL CONSUMPTION IN MICE

E.K. Erickson[1,2], S.P. Farris[2], Y.A. Blednov[2], R.D. Mayfield[2], R.A. Harris[2]
[1]Institute for Cellular and Molecular Biology, University of Texas at Austin, Austin, TX, USA and [2]Waggoner Center for Alcoholism and Addiction Research, University of Texas at Austin, Austin, TX, USA

Astrocytes have recently been identified as active contributors to information processing in the brain. While many studies have shown that astrocyte phenotype is altered by alcohol exposure, it is unknown how alcohol dependence affects the astrocyte transcriptome. To identify astrocyte-specific gene expression changes in response to a mouse model of alcohol dependence (chronic intermittent ethanol vapor exposure), we used an astrocyte isolation technique followed by RNA-sequencing. Weighted gene co-expression network analysis (WGCNA) revealed a gene network in astrocytes negatively associated with alcohol dependence involving synaptic regulation and downstream signaling. Highly connected genes within this network were linked with astrocyte-specific synaptic functions including neurotransmitter uptake, calcium signaling, and gliotransmitter release. To identify the role of astrocyte calcium signaling in alcohol drinking behavior, we used astrocyte-specific designer receptors exclusively activated by designer drugs (DREADDs) to activate PFC astrocytes in a mouse model of excessive alcohol consumption (every-other-day drinking). Astrocyte calcium activation led to an increase in alcohol consumption and preference. These data highlight the need to isolate specific cell types to understand their contribution to alcohol-related gene expression changes, and point to a potential role for alcohol-induced changes in astrocyte calcium regulation in the development of behaviors related to alcohol use disorder.

P2-1-44

THE ASSOCIATION OF ALCOHOL DRINKING AND ADOLESCENCE VIOLENCE BEHAVIOR IN THAILAND

W. Wongin[1,2], S. Paileeklee[1]
[1]Department of Community Medicine, Faculty of Medicine, Khon Kaen University, Thailand and [2]Suratthani Province Health Office, Thailand

Objectives: To investigate the association of alcohol drinking with adolescence violence behavior in Thailand
Methods: A case-control study was conducted in adolescent aged 15–19 in 6 regional area. Cases were 240 adolescent with history of violence behavior in Department of Juvenile Observation and Protection detention facilities. Controls were 960 students without violence behavior in Secondary school. Data were collected using self-administered questionnaire, then were analyzed to obtain frequency, percentage, OR and AOR.
Results: Almost all cases were boy (93.8%), age 18 and 19 years old (37.1% and 25.8%). Most of the control were girl (73.5%), aged 15 and 16 years old (32.4% and 29.2%). Most of adolescent reported that ever involved in quarrel and fighting in case (70.0%), and 53.8% ever involved in quarrel and fighting resulting in injuries and medical treatment. Whilst, 4.8% of controls ever involved in quarrel and fighting. Among case and control 85.8% and 22.6% drinking alcohol. Alcohol drinking were significantly increasing risk of violence behavior (OR 20.76, 95% CI; 13.98–30.81). Multiple logistic regression reported that alcohol drinking increasing risk of violence behavior. (AOR 21.54, 95% CI; 14.07–33.00).
Conclusion: The study revealed that alcohol drinking contributing very high risk of adolescence violence behavior.

P2-1-45

WEARABLE TECHNOLOGY (MI BAND AND YU BAND) A BOON FOR ALCOHOLIC PATIENTS IN NEW DELHI, INDIA

V. Sharma, S. Sharma
University College of Medical Sciences, India

Objective: To develop methods for analyzes and monitor of data in alcohol use disorder patients via wearable technology (MI Band and Yu Band). To study effects of daily life routine activities on body activities data by wearable devices that can obtain real-time alcohol use disorder data, processes them and provides assistance based on pre-determined specifications in alcoholic patients.
Method: Total of 48 PD patients were taken as subject with an equal ratio of male and female and age group between 20 to 45 years in New Delhi, India. Wearable monitoring devices like MI band and Yu Band were put on the wrist of alcoholic patients for 30 days and a questionnaire was filled out by each patient.
Result: Present results shown that both wearable device (MI band and Yu Band) reading showed there was a normal heart rate, more calorie burnt with better control of sugar control and average good sleep count in more physically workout, include walking in alcoholic patients compared to less physically workout alcoholic patients, identified by professional physiotherapists
Conclusion: By using, these wearable devices ensured their health awareness with more concerned towards exercising and demonstrate the benefit of such a context-aware system and motivate further studies.

P2-1-46

HOW DOES ANXIETY SENSITIVITY RELATED TO THE GROWTH CURVE OF ALCOHOL USE FOLLOWING CBT FOR SMOKING?

D. Paulus[1], A. Rogers[1], A.M. Raines[2], N. Schmidt[3], M. Zvolensky[1]
[1]University of Houston, USA, [2]Southeast Louisiana Veterans Health Care System, USA and [3]Florida State University, USA

Smoking is associated with increased alcohol consumption and the use of alcohol is associated with smoking lapses. Nontargeted alcohol use can reduce following smoking treatment. Yet, little is known regarding psychological constructs underlying alcohol use. Anxiety sensitivity, a transdiagnostic risk factor associated with alcohol use, smoking, and mental health problems. The current study sought to examine individuals with greater anxiety sensitivity have less reductions in alcohol use in the 12-month follow-up period following cognitive-behavioral smoking cessation treatment. Data was available from 180 treatment seeking smokers (M_{age} = 38.52, SD = 14.00, 46.8% male). Results indicated that alcohol use severity did indeed decline significantly over time (B = -0.13, SE = 0.03, p<0.001). Additionally greater anxiety sensitivity was associated with slower decline in alcohol use severity over the 12-month period (B = −0.01, SE = 0.003, p = 0.012). The current study offers novel evidence into the role of anxiety sensitivity in relation to alcohol use during a quit attempt. Assessing and targeting anxiety sensitivity may provide one avenue towards improved smoking cessation outcomes as well as reduced use of alcohol.

P2-1-47

ETHANOL DEPENDENCE AND WITHDRAWAL DYSREGULATE SUBSTANCE P/NEUROKININ 1 RECEPTOR SIGNALING IN THE CENTRAL NUCLEUS OF THE AMYGDALA

S. Khom[1], T. Steinkellner[2], K.C. Rice[3], T.S. Hnasko[2], M. Roberto[1]
[1]Department of Neuroscience, The Scripps Research Institute, USA, [2]Department of Neurosciences, UCSD, USA and [3]Drug Design and Synthesis Section, Chemical Biology Research Branch, NIDA and NIAAA, USA

Substance P (SP)/neurokinin 1 (NK-1) receptor signaling plays a critical role in stress-elicited ethanol seeking and ethanol consumption (Schank and Heilig, 2017). The underlying cellular mechanisms, however, are poorly understood. Here, we investigated the effects of SP and the NK-1 receptor antagonist L822429 on GABAergic neurotransmission in the medial subdivision of the central amygdala (CeA) of ethanol-naïve, ethanol-dependent and ethanol-withdrawn (2-weeks-withdrawal) rats. In naïve rats, SP significantly increases frequency and amplitudes of spontaneous inhibitory postsynaptic currents (sIPSCs) indicating enhanced GABA release and changes in postsynaptic $GABA_A$ receptor function, while the antagonist L822429 decreases sIPSCs frequency suggesting basal SP release in the CeA. In addition, SP and ethanol display additive effects on GABA release suggesting independent intracellular signaling pathways, while NK-1 receptor antagonism blocks acute ethanol effects. Most notably, SP and L822429 effects on sIPSCs are significantly more pronounced in ethanol-dependent and ethanol-withdrawn animals suggesting that both ethanol dependence and subsequent ethanol withdrawal increase sensitivity to SP/NK-1 receptor signaling, albeit ethanol dependence significantly decreases NK-1 receptor and SP expression in the CeA. Collectively, our data show that ethanol-dependence induces a profound and long-lasting dysregulation of the SP/NK-1-system in the CeA, a brain region critical in the development of alcohol dependence.

P2-1-48

CHRONIC ALCOHOL-INDUCED LIVER INJURY IN HEPATIC ALCOHOL DEHYDROGENASE DEFICIENT DEER MICE: A DOSE-DEPENDENT STUDY

S. Amer, K.K. Bhopale, J. Wang, G.S. Shakeel Ansari, B.S. Kaphalia
Department of Pathology, University of Texas Medical Branch, Glaveston, TX 77555, USA

Alcoholic liver disease (ALD) is a serious health problem with significant morbidity and mortality. Initial events leading to pathogenesis of ALD are not well defined due to a lack of suitable animal model. Therefore, we conducted a dose-dependent study in hepatic alcohol dehydrogenase deficient (ADH^-) deer mice fed 1, 2 or 3.5% ethanol in the liquid diet daily for 2 months. Hepatic lipids, liver injury markers including oxidative stress, endoplasmic reticulum (ER) stress and AMP activated kinase (AMPK) signaling in the liver tissue were examined. Ingested alcohol was found to be rapidly metabolized by both strains fed 1 or 2% ethanol as compared to 3.5% ethanol. However, the blood alcohol levels were significantly higher in ADH^- vs. ADH^+ mice fed 3.5% ethanol. Hepatic lipid including steatosis were significantly increased in the livers of ADH^- mice fed 3.5% ethanol. Surprisingly, no significant oxidative stress was found in both strains fed ethanol. On the other hand, an induced expression of hepatic CYP2E1 decreased with increasing ethanol dose in ADH^- mice as opposed to increasing trend in ADH^+ mice. Overall, ethanol metabolism under hepatic ADH inhibition appears to be a key factor in ethanol-induced liver injury. Supported by funds from NIAAA/NIH.

P2-1-49

CRITICAL ROLE FOR THE ANTERIOR INSULAR CORTEX IN THE PROPENSITY TO RELAPSE FOLLOWING PUNISHMENT-IMPOSED ABSTINENCE TO ALCOHOL SEEKING

E.J. Campbell[1,2], J. Flanagan[1,2], N.J. Marchant[3], A.J. Lawrence[1,2]
[1]The Florey Institute of Neuroscience and Mental Health, Australia, [2]Florey Department of Neuroscience and Mental Health, University of Melbourne, Australia and [3]Department of Anatomy and Neurosciences, VU University Medical Center, Amsterdam, Netherlands

In humans, individual variation in the expression of particular traits contributes to the onset of neuropsychiatric disease states, including drug addiction. One defining feature of addiction is 'persistent drug use despite negative consequences', however, this only occurs in a distinct minority of drug users. Here, we model compulsive alcohol use in rats by punishing the drug-reinforced operant response. First, we train rats to self-administer alcohol in one environment, then punish their alcohol-reinforced lever responses in a different environment using contingent foot shock punishment. Finally, we test rats for alcohol seeking in either the alcohol-associated environment or the punishment-associated environment following short or prolonged abstinence. We show individual variation in alcohol seeking behaviour in the punishment-associated environment after prolonged abstinence. Interestingly, this increased propensity to relapse was associated with neural activation in the anterior insular cortex and functional inactivation of this region prevented relapse in the punishment context following prolonged abstinence.

P2-1-50

BETA-ENDORPHIN MEDIATES SEX DIFFERENCES IN THE CAUSES AND CONSEQUENCES OF BINGE DRINKING

E.M. Rhinehart[1], T.B. Nentwig[2], D.E. Wilson[1], J.E. Grisel[2]
[1]Department of Biology, Susquehanna University, Selinsgrove, PA, USA and [2]Department of Psychology, Bucknell University, Lewisburg, PA, USA

The sexually dimorphic effects of alcohol are clinically well-characterized; however, the underlying mechanisms for sexual dimorphisms in the effects of alcohol remain unclear. Both beta-endorphin (BE) and GABAergic signaling are critical for the physiological and behavioral effects of alcohol. Therefore, we sought to determine whether genetic manipulation of B-E expression would impact the behavioral effects of alcohol and patterns of GABAaR subunit expression in the brain. Adult male and female control (B6) and B-E deficient (KO) mice were assessed for binge drinking and loss of righting reflex (LORR) and male B6 and KO mice were assessed for GABAaR subunit expression via qRT-PCR in the hippocampus, amygdala, hypothalamus and bed nucleus of the stria terminalis (BNST). Male KO mice exhibited enhanced LORR, whereas female KO mice were more likely to exhibit binge-like drinking behavior, and these differences were minimized by gonadectomy. In Alcohol naive adult male mice, B-E deficiency caused significant alterations in central patterns of GABAaR subunit expression. Therefore, B-E has sexually dimorphic effects on alcohol intake as well as the sedative effects of EtOH. In addition, differences in central GABAaR subunit expression in B-E deficient mice provide a potential mechanism for studying individual differences in the response to alcohol.

P2-1-51

THE ASSOCIATION BETWEEN ALCOHOL USE DISORDERS AND HEALTH-RELATED QUALITY OF LIFE AMONG THAI ADULT POPULATION USING THE 2013–2014 NATIONAL HEALTH EXAMINATION SURVEY DATA

J. Nontarak[1], S. Assanangkornchai[2]
[1]Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Thailand and [2]National Health Examination Survey, Health Systems Research Institute, Thailand

Introduction: Harmful use of alcohol could be related to poorer quality of life, particularly when there is a comorbidity. This study aimed to determine the relationship between health-related quality of life and alcohol use disorder with or without comorbidity.
Methods: Data from the fifth National Health Examination Survey (NHES V) in 20013-14 were analyzed. Alcohol use patterns were categorized based on Alcohol Use Identification Test (AUDIT) scores into four levels: non-low risk, hazardous, harmful and probably dependent drinker. Health-related quality of life (HRQoL) was measured by the EuroQol 5-Dimension (EQ-5D) and categorized into good (>0.8) and low to moderate (<-0.8) QoL.
Results: Males were more likely to be classified into hazardous-to-dependent drinking groups (38.8% vs. 11.5%) and in the good category of the HRQoL (59% vs. 50.5%). Mean QoL scores were 0.88, 0.84, 0.83 and 0.78 for non-drinkers, hazardous-harmful, dependent drinkers and drinkers with chronic disease comorbidity. Hazardous-dependent drinkers and those with chronic disease comorbidity were 1.2 (95% CI: 1.0–1.4) and 3.4 (95% CI: 2.4–4.7) as likely to have low quality of life, compared to non-drinkers.
Conclusion: Alcohol use disorder was found to lower the quality of life, especially when such drinkers had a comorbid disease, independently to socio-demographic factors.

P2-1-52

REHABILITATION MODEL FOR POLYDRUGS ABUSE WITH MENTAL DISORDER IN MARZOEKI MAHDI MENTAL HOSPITAL, INDONESIA

Prasetiyawan, K. Siste
Department of Psychiatry, Medical Faculty, Universitas Indonesia, Indonesia

Mr. JR, 38 years old, drank alcohol since he was 8 years old. His father used to throw alcohol party in his house. When he was 11 years old, he started using "putaw" (heroin) by injection, drinking alcohol, and sometimes using amphetamine & cannabis. Ten years ago he tried to stop using putaw after being overdosed three times, caught by the police two times, and suffered from HIV/AIDS (now he is under ARV treatment). He received methadone for 5 years, but at the same time he drank "ciu" (traditional alcohol) in high dose leading to alcohol dependency. Four years ago, he entered rehabilitation center and started to reduce his alcohol dependence from 8 to hold a bottle a day. Last year, he was arrested and left the rehabilitation center, which led him to depression. Three months later, he abused Subuxone by injection.
In December 2017, he stayed in Marzoeki Mahdi Mental Hospital for IPWL program (an Indonesian government program for drug problems). He received Therapeutic Community program, Cognitive Behavior Therapy, and pharmacotherapy. He succeeded three months rehabilitation program without drugs and alcohol. Now, he is still in the IPWL program with good compliance.

P2-1-53

PREVALENCE OF BINGE DRINKING AND ASSOCIATION WITH SUBSTANCE USE: A CROSS-SECTIONAL NATIONWIDE GENERAL POPULATION SURVEY IN JAPAN

T. Shimane[1], D. Qiu[1], K. Wada[1,2]
[1]Department of Drug Dependence Research, National Institute of Mental Health, National Center of Neurology and Psychiatry, Japan and [2]Department of Addiction Treatment Research, Saitama Prefectural Psychiatric Hospital, Japan

Objective: To measure the association between binge drinking prevalence and substance use among the Japanese general population.
Methods: Data were retrieved from a cross-sectional Japan-wide general population survey on drug use. A two-stage stratified random sampling method was implemented to select 5,000 individuals aged 15–64 years. In total, 2,905 (response rate: 58.1%) completed a self-administered anonymous questionnaire, from September to October 2017. We adopted the United States' Substance Abuse and Mental Health Services Administration's definition of binge drinking; i.e., five or more alcoholic drinks for males or four or more alcoholic drinks for females on the same occasion on at least 1 day in the past month.
Results: The overall prevalence of binge drinking was 36.9% (49.1% and 25.4% among males and females, respectively). Binge drinking occurred at frequencies of 1–2 days (18.2%), 20–29 days (11.9%), 3–5 days (11.4%), and 30 days (11.3%). Frequent binge drinkers were likely to have experienced substance use, including cannabis ($p<0.001$), methamphetamine ($p = 0.007$), 3,4-Methylenedioxymethamphetamine ($p = 0.016$), and inhalants ($p = 0.005$).
Conclusions: This is the first report on the prevalence of binge drinking among the entire Japanese population. We found that a frequent binge drinking episode might increase the risk of illicit drug use.

P2-1-54

ZINC ACETATE AS PERSPECTIVE COMPOUND FOR DEVELOPMENT OF PHARMACEUTICALS, WHICH ARE EFFECTIVE AGAINST ALCOHOLIC BRAIN DAMAGE

O.I. Kharchenko[1], G.M. Shayakhmetova[2], L.I. Ostapchenko[1]
[1]Division of Medicine, ESC Institute of Biology and Medicine of National Taras Shevchenko University, Ukraine and [2]Department of Toxicology, SI "Institute of Pharmacology and Toxicology NAMS of Ukraine", Ukraine

Alcohol-induced modulation of Zn transporters results in decreased Zn levels in brain Aim of study is estimation of zinc acetate effects on brain cells membranes phospholipids at different periods of ethanol intoxication. Wistar rats were divided into 3 groups: 1 – control; 2 – ethanol (per os 40%, 2 mL/100 g/day, 21 days); 3 -ethanol+zinc acetate (200 mg/kg). Contents of Zn, phospholipids were measured in brain on 4^{th}, 7^{th}, 11^{th}, 16^{th} and 21^{st} days of experiment. Zn content in brain of alcoholized rats did not differ significantly from the control parameters in the early stages of experiment (4^{th} and 7^{th} days) with abrupt decrease (almost twice) on 11^{th}, 16^{th} and 21^{st} days. Progressive decrease in phosphatidylserine and phosphatidylethanolamine contents was noticed. More than 2 folds fall in phosphatidylcholine and phosphatidylinositol contents observed on 11^{th} and 7^{th} days. Lysophosphatidylcholine content increased 2 folds throughout study. Following zinc acetate administration gradual increase in Zn level was recorded. That resulted in increase of phosphatidylcholine content (11^{th} and 21^{st} days – 1.3 and 1.5 folds); other phospholipids contents reached control values at these periods. Thus modulation of Zn metabolism could be potential tool in the treatment of alcohol-associated abnormalities of lipids metabolism in brain.

WEDNESDAY, SEPTEMBER 12
3. OTHER DRUG

P2-3-1

METHAMPHETAMINE USERS IN JAPANESE PRISONS: COMORBID HAZARDOUS ALCOHOL CONSUMPTION

T. Shimane[1], M. Tani[2], M. Yamaki[2], M. Kobayashi[2], A. Kondo[1], M. Takahashi[3]
[1]Department of Drug Dependence Research, National Institute of Mental Health, National Center of Neurology and Psychiatry, Japan, [2]Research and Training Institute Ministry of Justice, Japan and [3]Tokyo Juvenile Classification Home, Japan

Objective: Alcohol consumption can arouse cravings among stimulant users; it often acts as a trigger of relapse. This study assessed hazardous alcohol consumption among methamphetamine users in Japanese prisons.
Methods: Data were drawn from an anonymous survey for inmates in all Japanese prisons who were incarcerated owing to violation of the Stimulants Control Act. From July to November 2017, 699 newly entered inmates (462 males, 237 females) completed a self-administered questionnaire. Hazardous alcohol consumption was assessed with the Alcohol Use Disorders Identification Test (AUDIT) and classified into four groups according to total score: zone I, 0–7; zone II, 8–15; zone III, 16–19; zone IV, 20–40.
Results: The average AUDIT score was 6.8 for males, 6.5 for females, and 6.7 for all participants. With a cutoff point of 8 or above, 33.6% of prisoners had hazardous alcohol consumption. Risk levels of alcohol consumption were classified as zone I, 58.8%; zone II, 22.2%; zone III, 5.4%; zone IV, 6.0%; and unknown, 7.6%.
Conclusions: We found potential risk of alcohol dependence among methamphetamine users in prison. Relapse prevention for such users should include alcohol consumption and related triggers.

P2-3-2

TRANSCRIPTOME PROFILING ON THE STRIATUM OF CYNOMOLGUS MONKEYS AFTER CHRONIC ADMINISTRATION OF COCAINE AND HEROIN

M.R. Choi[1], Y.-B. Jin[2], S.H. Bang[1], Y. Lee[2], H.-N. Kim[2], K.S. Son[1], C.-N. Im[1], K.-T. Chang[2], S.-R. Lee[2], D.-J. Kim[1]
[1]Department of Psychiatry, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea and [2]National Primate Research Center (NPRC), Korea Research Institute of Bioscience and Biotechnology (KRIBB), Cheongju, Korea

Cocaine and heroin cause not only severe public health problems including anxiety, depression and hallucinations but also the impairments of neural plasticity and cognitive function in the brain including striatum. This study aimed to identify the genes differentially expressed in the striatum of cynomolgus monkeys in response to cocaine and heroin. After chronic administration of cocaine and heroin in the monkeys, we performed large-scale transcriptome profiling in the striatum using RNA-Seq technology and analyzed functional annotation. Of 4,319 transcripts satisfying with fold change 1.5 among three groups (cocaine, heroin and control), 547 transcripts were more than 1.5-fold up-/downregulated in cocaine-treated group, while 1,238 transcripts were more than 1.5-fold up-/downregulated in heroin-treated group compared to control group. On the other hand, 3,432 transcripts exhibited the differential expression between cocaine- and heroin-treated groups. Based on the results of functional annotation analysis, genes associated with endocytosis and long-term potentiation were differentially expressed between cocaine-treated and control groups, while genes associated with calcium signaling and Wnt signaling pathways were differentially expressed between heroin-treated and control groups. Our results give the insights into their correlated molecular mechanisms as well as genes up-/downregulated in the striatum by chronic administration of cocaine and heroin.

P2-3-3

AN OPERANT TASK FOR TESTING RISKY DECISION-MAKING IN MICE

T. Wang[1,2], K. Fukumoto[1], H. Mizoguchi[1], K. Yamada[2]
[1]Research Center for Next-Generation Drug Development, Research Institute of Environmental Medicine, Nagoya University, Japan and [2]Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Japan

In real-life situations, individuals are making decisions by reconciling risk and benefits of each potential option. Patients suffering from addiction and other psychiatric disorders are likely to have an impairment in decision-making, which is apparently detected by the standardized behavior tasks (e.g. Iowa gambling task). Moreover, clinical studies have reported that dopamine therapy may result in the development of impaired decision-making in patients with dopaminergic dysfunction such as Parkinson's disease. In the present study, we aimed to establish and optimize the animal model of impaired decision-making for the development of new therapeutic strategy in these disorders.
To access risky decision-making in mice models for translational research, mice were subjected to an operant two-choice task, in which each mouse has to learn to choose one of two options, a safe option associated with a relatively low risk but small reward and a risky option with a relatively high risk but larger reward. In the task, naïve mice exhibited different preference of risky option in a reward amount- and probability- dependent manner. Thus, this method may provide a quantitative way to access risky decision-making in mice. In ongoing experiments, we attempt to evaluate the effect of dopaminergic modulation on risky decision-making.

P2-3-4

ACUTE METHAMPHETAMINE ADMINISTRATION IMPAIRS COGNITIVE FUNCTION IN A TOUCHSCREEN-BASED VISUAL DISCRIMINATION TASK IN C57BL/6 MICE

J. Liao, B. Wulaer, T. Nagai, K. Yamada
Nagoya University Graduate School of Medicine, Japan

Methamphetamine (METH) is a highly addictive drug and its abuse causes not only personal but also serious social and medical problems. In recent years, touchscreen-based cognitive tasks have been developed for mice and rats to provide a better translational approach across species for further understanding the cognitive impairments observed in various neuropsychiatric disorders and for testing potential pharmacological interventions. In this study, we investigated the effect of METH on performance of C57BL/6 mice in a touchscreen-based visual discrimination task. Mice were initially trained to discriminate a pairwise stimuli simultaneously displayed on the screen to obtain reward. On the testing day, mice were injected with either saline or METH (1 mg/kg, i.p.) 30 min before the test. METH-treated group showed a marked decrease in correct response rate as well as response latency as compared with saline-treated control group. We demonstrated that acute METH treatment induces cognitive dysfunction by using the translatable visual discrimination task.

P2-3-5

CHANGES THE EXPRESSION OF BRAIN-ENRICHMENT MICRORNAS IN METHAMPHETAMINE DEPENDENCE IN MICE

K. Mizuo, S. Watanabe
Department of Legal Medicine, Sapporo Medical University, Japan

The psychomotor stimulants such as methamphetamine produces a strong rewarding and lead to extensive abuse with sociological and psychiatric problems. However, little is known about the mechanisms underlying methamphetamine dependence. Recent studies demonstrated that microRNA (miR) have important role in the regulation of several physiological functions. In the present study, we investigated the expression of miRs in methamphetamine-induced rewarding effect. The rewarding effect was evaluated by conditioned place preference. The mice were killed by decapitation and the limbic forebrain (containing nucleus accumbens) was dissected. RT-PCR analysis for detection of miRs in the brain was performed. We observed that the expression of miR-124 was significantly increased in limbic forebrain of methamphetamine-dependent mice. It has been reported that miR-124 plays a critical role in the regulation of synaptic activities. These findings suggest that the increase in the expression of miR-124 may change the synaptic activities, resulting in the development of methamphetamine-induced rewarding effect. We previously reported that the expression of miR-124 was significantly increased in limbic forebrain following chronic treatment of ethanol. Taken together, our findings suggest the possibility that the miR-124 is a common miR in the regulation of dependence of abused drugs.

P2-3-6

THE ASSESSMENT OF TRADITIONAL CHINESE MEDICINE CONSTITUTIONS ACCOMPANIED BY PSYCHOLOGICAL CONDITIONS OF ADULT MALES WITH KETAMINE ABUSE IN TAIWAN

P.-Y. Jau[1], S.-C. Chang[1], H.-T. Wei[1,2], C.-H. Hsu[1]
[1]Branch of Linsen, Chinese Medicine and Kunming, Taipei City Hospital, Taiwan and [2]Kunming Prevention and Control Center, Taipei City Hospital, Taiwan

People with ketamine abuse often have psychological symptoms in their daily life. Such symptoms including insomnia, depression, hostility, anxiety, interpersonal sensitivity, and others could be evaluated by 5-item Brief Symptom Rating Scale (5-BSRS). In traditional Chinese medicine (TCM) theory, psychological conditions may have interactions with physical conditions. We want to evaluate the differences of TCM constitutions between two groups of male ketamine abusers that psychological conditions need consultants (six points and above) or not (five points and under), and further provide possible treatments in clinical TCM. Also we wonder if pain VAS scores among male ketamine abusers relate to psychological conditions. The result shows that male ketamine abusers who need consultants are at most different in TCM constitutions of qi-deficiency and phlegm-dampness, and secondly different in TCM constitutions of qi-stagnation. In addition, male ketamine abusers with worse psychological conditions show more VAS scores. We suggest that TCM doctors in Taiwan may treat adult male ketamine abusers with worse psychological conditions on benefiting qi, eliminating dampness, regulating the flow of qi and stopping the pain.

P2-3-7

EXAMINING PROFESSIONAL ROLES BEHIND BARS WHEN WORKING WITH PEOPLE WITH MENTAL ILLNESS AND/OR SUBSTANCE USE DISORDERS

H. Toi
Department of Human Care and Support, Toyo University, Japan

A growing need for treatment and services exists in the criminal justice system, especially for people with mental illness and/or substance use disorders. However, few studies have examined mental health professional's roles in prisons when working with this population. A survey of mental health professionals, especially social workers, was conducted in state prisons in the Northeast region of the United States. One hundred and twenty participants completed the survey. Principal components analysis identified the four-component model for professional roles, composed of 22 items. It accounted for 59% of the variance, with good internal consistency (Cronbach's $\alpha = .90$). These factors were named as: reentry planning role (7 items, $\alpha = .89$); clinical role (6 items, $\alpha = .88$); advocacy and mediating role (5 items, $\alpha = .70$); and professional development role (4 items, $\alpha = .59$). These findings suggest four different dimensions of professional roles that are essential in working with people who have mental illness and/or substance use disorders in prison. The results indicated that participants assume a broad range of professional roles in a multidisciplinary team in prison. Further examination of professional roles using a confirmatory factor analysis may help advance research and practice for this population.

P2-3-8

PREVALENCE OF ILLICIT SUBSTANCES USE AMONG SECONDARY SCHOOL STUDENT IN THAILAND, 2015

S. Paileeklee[1], K. Thaikla[2], S. Charoenratana[3], S. Dithisawatwet[4], N. Tantirangsee[5]
[1]Department of Community Medicine, Faculty of Medicine, Khon Kaen University, Thailand, [2]Research Institute for Health Sciences, Chiang Mai University, Thailand, [3]Social Research Institute, Chulalongkorn University, Thailand, [4]Office of Disease Prevention and Control Region 8, UdonThani, Thailand and [5]Songkhla Rajanagarindra Psychiatric Hospital, Thailand

Substance use is one of social problems among teenagers. This paper aimed to report prevalence of illicit substance use among secondary school student in Thailand.
National school survey was conducted in secondary school, academic year 2015. Multi-stages sampling was applied and data were collected using self-administered questionnaire in 196 schools, from 40 provinces.
Of all 38,535 students, 54.5% were female. The students with life-time experience of any illicit substance use and in past 12 months were 5.5% and 2.4%. Among those ever experienced, 70% experienced only single type, whilst 7.2% had experienced all. Boy had higher prevalence than girl, and prevalence increased regarding school years. The vocational school student had highest prevalence of both life-time and past year. The most common substances used were Cannabis, Kratom (Mitragyna speciosa (Korth.) and Methamphetamines in both boy and girl. The first age of experience to inhalants was earlier than other substances, and boy exposed to substance earlier than girls. Among those use illicit substance in past 12 month, proportion of maintain substance use in past 30 days were 48.3%-68.4%.
Substance used among school student is needed for comprehensive prevention measures. Effective screening and cares should be launched for student with illicit substance use.

WEDNESDAY, SEPTEMBER 12
4. BEHAVIORAL ADDICTION

P2-4-1

THE RELATIONSHIP BETWEEN SMARTPHONE ADDICTION PREDISPOSITION AND IMPULSIVITY AMONG KOREAN SMARTPHONE USERS

H.-S. Jo[1], E. Na[2], D.-J. Kim[1]
[1]Department of Psychiatry, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea and [2]Addiction Treatment Center, Department of Psychiatry, Maeumsarang Hospital, Wanju, Korea

The smartphone ownership rate has been growing steeply worldwide, and smartphone overuse causes various adverse effects. Previous studies suggest that adolescents are vulnerable to addiction because they lack the ability to control impulsivity. However, only a few studies have investigated psychological factors related to smartphone addiction predisposition (SAP) among adolescents. We investigated the prevalence of SAP in adolescents and adults and associations between impulsivity and SAP. A total of 7,003 participants answered the entire set of questionnaires. Participants completed self-report questionnaires regarding demographic characteristics, level of SAP, and trait impulsivity. They were divided into three groups based on age: adolescent-group, early-adulthood-group, and adulthood-group. SAP was assessed with the Smartphone Addiction Proneness Scale, and impulsivity was assessed with Dickman's Impulsivity Inventory (DII). The adolescent-group had the highest percentage of SAP. Dysfunctional DII score was highest in the adolescent-group, and there was a significant difference between the adolescent-group and the other two groups. Moreover, the higher the level of SAP, the greater the dysfunctional impulsivity score. Result suggests that adolescents are vulnerable to SAP, which is similar to substance other types of addiction. In addition, impulsivity may be one of the factors contributing to this vulnerability, as it does to other addictions.

P2-4-2

DIFFICULTIES AND SUPPORTS FOR FAMILY MEMBERS OF PEOPLE WITH GAMBLING DISORDER

N. Morita[1], K. Arai[2], N. Tanaka[3], Y. Kawaguchi[4]
[1]Faculty of Medicine, University of Tsukuba, Japan, [2]Faculty of Health Sciences, Division of Nursing Sciences, Tokyo Metropolitan University, Japan, [3]The Society Concerned about the Gambling Addiction, Japan and [4]Faculty of Child Development and Education, Uekusa Gakuen University, Japan

This research investigated difficulties of family members of people with gambling problems and their utilization of support services regarding these problems. Subjects were 224 family members who attended counseling offered by a private organization for recovery from gambling addiction. Most were in their 50s and 60s, and were wives and mothers of gamblers. The main kinds of gambles included pachinko/slot machines (92.0%) and horse race (18.8%). Frequent gambling problems which family members experienced were economic difficulties (lifelong 86.1%; now 33.1%), family rifts/marital separation/divorce (43.7%; 23.1%), depression (43.5%; 7.5%), and verbal violence (42.3%; 8.8%). Of the family members, 80% had gamblers' debt and 16.5% of them paid more than 10,000,000 yen. Among subjects, 44.2% consulted support facilities within four years of discovering gambling problems, but it took more than 10 years for 26.8% of them to seek help from such facilities. Multiple logistic model revealed significant factors of number of problems related to gambling, including "the time period since detection of gambling problems until consultation" (OR: 5.2) for more than four lifelong problems. These findings imply that we should help family to consult to support facilities for members with gambling disorders earlier to reduce problems caused by the disorder.

P2-4-3

ALCOHOL-DRINKING AND EATING BEHAVIORS ASSOCIATED WITH ACTIVE GHRELINERGIC AND SEROTONINERGIC NEURONS IN THE LATERAL HYPOTHALAMUS AND AMYGDALA OF BRAIN REWARDING SYSTEM

N. Miyagi[1], R. Kuramoto[1], A. Mori[1], K. Murata[2], A. Namera[2], M. Nagao[2], K. Yoshimoto[1,2]
[1]Department of Food and Biotechnology, Hiroshima Institute of Technology, Japan and [2]Department of Forensic Medicine, Hiroshima University, Japan

Ghrelin acts on growth hormone secretagogue receptor 1A, GHS-R1A. Plasma ghrelin levels decreased following the EtOH treatment in 1- and 3-month-old short-term, 1-day, alcohol vapor-exposed, STA, mice. EtOH administration increased plasma ghrelin levels in 1- and 3-month-old long-term, 20-day, alcohol vapor-exposed, LTA, mice. In vivo ghrelin release in the lateral hypothalamus, LH, increased in STA and LTA mice after the i.p. administration of EtOH. EtOH increased in vivo dopamine, DA, but not serotonin, 5-HT, release in the LH of STA mice, and increased in vivo DA and 5-HT release in the LH of LTA mice. GHS-R1A mRNA expression and GHS-R1A protein levels in the LH were increased in LTA mice. The injections of ghrelin, inactivated ghrelin, Des-asyl-ghrelin, and GHSR-antagonist, D-lys3- GHRP-6, into the central nucleus of amygdala, cAMY, on the DA and 5-HT releases of the ACC were investigated. The injection of ghrelin into the cAMY increased the release of ACC DA and increased 5-HT release later. These results support the neurobiological correlation between the development of drinking behavior and activation of ghrelinergic and serotonergic neurons in the LH. The development of eating behavior and habitual alcohol drinking behavior showed common neurocircuitries in the brain rewarding system.

P2-4-4

NETWORK PROPERTY OF GAMBLING DISORDER

K. Tsurumi[1,2], N. Oishi[3], T. Murai[1], H. Takahashi[1]
[1]Department of Psychiatry, Kyoto University Graduate School of Medicine, Japan, [2]Department of Psychiatry, University of Cambridge, UK and [3]Medical Innovation Center, Kyoto University Graduate School of Medicine, Japan

Resting-state functional connectivity (rsFC) between large-scale brain networks such as salience network (SN), default mode network (DMN), and central executive network (CEN) are intensively explored partly because of their involvement with cognitive functions such as cognition and self-monitoring for SN, self-referential process or memory for DMN, and information processing or decision making for CEN.
Gambling disorder (GD) patients are known to have difficulty in self-monitoring and in adjusting their behavior based on past events. These difficulties might arise from network dysfunction such as SN and DMN.
In our previous study, we explored rsFC between insula, because its anterior part comprises of SN, and DMN.
However, internodal connectivity among SN and DMN nodes are unclear.
We incorporated 6 min resting state fMRI data of 23 GD patients and 27 matched healthy control (HC) subjects and analyzed the data to explore rsFC between component nodes of SN and DMN using FSL software and conn toolbox of SPM software.
GD patients showed reduced rsFC between a node of dorsal DMN and that of anterior SN, between two nodes within posterior SN compared to HC subjects.
These alterations might reflect the pathophysiology of GD.

P2-4-5

GLIAL CELL LINE-DERIVED NEUROTROPHIC FACTOR (GDNF) PLASMA LEVELS IN INTERNET GAMING DISORDER PATIENTS

J.-E. Jeong
Seoul St. Mary's Hospital, Korea

Objective: Glial cell line-derived neurotrophic factor (GDNF) has been reported to be involved in negatively regulating the actions of addictive disorders. The objective of this study was to investigate alterations of plasma levels of GDNF in Internet gaming disorder (IGD) and to assess the relationship between GDNF levels and the severity of IGD indices.
Method: Nineteen male patients with IGD and 19 healthy sex-matched control subjects were evaluated for alterations of GDNF levels and associations between GDNF levels and clinical characteristics of Internet gaming including the Young's Internet Addiction Test (Y-IAT).
Results: The mean GDNF levels were significantly decreased in patients with IGD (106.44 $\pm$ 126.58 pg/mL) compared to healthy controls (210.85 $\pm$ 190.11 pg/mL, $p = .028$). GDNF levels were not significantly associated with weekday and weekend average Internet gaming usage hours, elapsed time after the last game, and Y-IAT total scores. However, a negatively correlated trend was shown between GDNF levels and Y-IAT salience sub-factor scores ($r = -.354$, $p = .055$).
Conclusion: These findings support the assumed role of GDNF in the regulation of IGD and dopaminergic neurotransmission. In addition, these results also suggest the possibility that plasma GDNF levels may serve as a biomarker in IGD.

P2-4-6

BRAIN ACTIVATION PATTERNS ASSOCIATED WITH CUE REACTIVITY AND CRAVING IN INTERNET GAMING DISORDER: AN FMRI STUDY

J.-E. Jeong
Seoul St. Mary's Hospital, Korea

Objective: This study aimed to investigate the brain activation pattern associated with cue reactivity and craving in Internet gaming disorder (IGD).
Methods: The sample included 23 healthy control (HC) males (30.04 $\pm$ 5.17 years) and 25 males with IGD (30.27 $\pm$ 5.27 years) were selected. Before the fMRI scanning, the Internet gaming video was presented for 1 min. The gaming craving was measured, using the 10 point visual analog scale. We used a block design (gaming, mosaic, and landscapes).
Results: The participants with IGD recorded higher craving scores than with HC. The IGD group revealed more activation on right dorsolateral prefrontal cortex (DLPFC), left occipital lobe, bilateral caudate nucleus, and right medial prefrontal cortex (mPFC) under gaming pictures (relative to mosaic pictures) compared to HC. Brain activity within left ventrolateral prefrontal cortex (VLPFC) and anterior part of left prefrontal cortex was decreased in IGD group compared to HC under gaming pictures (relative to landscapes pictures).
Conclusion: The IGD group showed more activation in DLPFC, caudate, and left occipital cortex, related to craving and visual information. On the other hand, IGD showed deactivation in VLPFC, which may plays a role in emotion regulation.

P2-4-7

A LITERATURE REVIEW OF RECOVERY TERMS IN SELF-HELP GROUPS FOR GAMBLING ADDICTION IN JAPAN

T. Kiryu, Y. Tanabe, T. Matsushita
Nursing Course, School of Medicine, Yokohama City University, Japan

It is said that 4.8% adults have gambling addiction in Japan. Given that the prevalence of gambling addiction is 1.5% in foreign countries, the prevalence rate tends to be high in Japan. Nonetheless, the condition of underdeveloped treatment for gambling addiction has continued over a long period of time in Japan. However, the measures for gambling addiction in Japan were expanded in 2016, and it is expected that future support for gambling addicts will be increased. Conventionally, the most basic support system for addicts is self-help groups (SHGs) where people with the same problem gather together.
The purpose of this research was to review the literature on recovery from gambling addiction through SHGs in Japan and to study effective recovery. The "Japan Medical Abstracts Society" database was used for the literature search.
There were 39 papers on treatment of and recovery from gambling addiction from 2013–2018, of which nine were on SHG recovery. The literature on this has shown an increasing trend in recent years. It has been suggested that recovery requires recognizing that one has gambling addiction, being receptive to others' opinions, accepting the self as the first step, and continuing to participate in SHGs.

P2-4-8

PREDICTING INTERNET GAMING ADDICTION USING BRAIN BIOMARKERS

C.-H. Park, J.W. Chun, H. Cho, D.J. Kim
Catholic University of Korea, Korea

There are increasing attempts to capture addiction using objective biomarkers. Here we examined whether Internet gaming addiction (IGA) could be detected with predictive models based on neuroimaging-derived brain biomarkers. For 93 individuals playing Internet-based games, including 45 individual diagnosed with IGA and 48 individuals diagnosed as not having IGA, 60 features of gray matter (GM) function, 60 features of GM structure, 60 features of GM connectivity, 40 features of white matter (WM) structure, and 60 features of WM connectivity were extracted from brain MRI data. We employed a machine learning method, specifically linear discriminant analysis, to construct predictive models on the basis of the brain features. The accuracy of the predictive models varied from 65% to 80% depending on the type of brain features. Among the five types of brain features, connectivity-related features, including gray matter connectivity and white matter connectivity, were shown to be better for predictions, with relatively higher predictive accuracy. Furthermore, the combinations of all brain features provided prediction accuracy up to 92%. We suggest that neuroimaging-derived brain features can be used as biomarkers for the diagnosis of IGC with high degree of accuracy.

TUESDAY, SEPTEMBER 12
6. ISBRA-WHO WORKSHOP

P2-5-1

Synergy of Ethanol and Atherogenic Diet Consumption Accelerates the Process of Atherosclerosis Via the Shift of Aortic Oxidative Stress and Anti-Oxidative Stress Balance In Hyperlipidemia Mice

Jinyao Liu[1], Yuzo Furuta[2], Ayako Himemiya-Hakucho[1]:
[1]Department of Legal Medicine, Graduate School of Medicine, Yamaguchi University, Japan: [2]Advanced Academic-Doctor Promotion Course, Graduate School of Medicine, Yamaguchi University, Japan

The synergy of ethanol and atherogenic diet (AD) consumption on the process of atherosclerosis was investigated in apolipoprotein E/low-density lipoprotein receptor double knockout mice (KO). Adult male KO fed AD and C57BL/6j wild type mice fed a standard chow diet were randomly divided into with and without ethanol treatment, and bred for 4 months. Ethanol and AD consumption induced the increase in max IMT and the hypoechoic plaque formation of the abdominal aorta, increase in mean Oil-Red-O content of the 4 aortic sections, increase in the ratio of 8-OHdG and metallothionein (MT) immunofluorescent staining positive areas in aorta, and the suppress in AD-induced up-regulated Mt1 and Mt2 mRNA expressions. 8-OHdG were expressed in the nuclei of CD31 and α-SMA positive cells. Up-regulated aortic Nos3 and aortic platelet derived growth factors' mRNA expressions were only shown in KO mice fed ethanol and AD. AD-induced the significant up-regulated mRNA expression of upstream stimulatory factor 1 was suppressed in KO mice fed ethanol and AD. The synergy of ethanol and AD consumption may promote the shift of aortic oxidative stress and anti-oxidative stress balance toward oxidative stress predominance and reduced anti-oxidative stress leading to the development of atherosclerosis in KO mice with hyperlipidemia.

P2-5-2

DEVELOPMENT OF A PERIPHERALLY RESTRICTED ARYL UREA BASED CB1 RECEPTOR ANTAGONIST FOR ALCOHOLIC STEATOSIS

R. Maitra, G. Amato, A. Manke, R. Snyder, S. Runyon
Center for Drug Discovery, RTI International, USA

Type 1 human cannabinoid receptor (hCB1) antagonists are useful for treating alcoholic liver diseases and other important indications. However, inhibition of hCB1 receptors in the central nervous system (CNS) can produce serious adverse effects. We have produced potent and selective aryl and heteroaryl substituted analogues of otenabant (CP-945,598) with limited brain penetration. An aryl urea inverse agonist from this series of compounds (RTI-1092769) has favorable properties for continued development. This compound is potent (Ki = 22 nM) and >1000-fold selective for hCB1 over hCB2, has good stability in human liver microsomes, and low P450 induction potential. Additionally, this compound failed to reverse cannabinoid induced hypothermia. Pharmacokinetic studies in rodents confirmed oral absorption, long half-life and very low brain penetration. Finally, the CB1 inverse agonist was tested in a mouse model of alcoholic liver steatosis induced by feeding a Lieber DeCarli liquid diet containing alcohol for 4 weeks. This peripherally selective inverse agonist blocked liver steatosis upon oral dosing for the last 2-weeks. In conclusion, an advanced candidate targeting hCB1 receptors in the liver and other peripheral tissues has been identified for further development (This work was made possible by R01AA023256 from NIAAA to RM).

P2-5-3

ALCOHOL DRINKING PATTERNS AND LIVER CIRRHOSIS: FINDINGS FROM THE CHINA KADOORIE BIOBANK

P.K. Im[1], Iona.Y. Millwood[1], L. Yang[1], Y. Guo[2], Z. Bian[2], L. Li[3], Z. Chen[1]
[1]Nuffield Department of Population Health, University of Oxford, 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: There is limited research addressing the roles of alcohol drinking patterns on liver cirrhosis in Chinese populations.
Methods: We analyzed data from the nationwide China Kadoorie Biobank cohort of 512,713 adults aged 30–79 years recruited during 2004–2008. Information on alcohol drinking patterns was collected by baseline questionnaire, with incidence of liver cirrhosis (n = 2,666) collected through death and disease registries and health insurance records to 2017. Cox regression yielded adjusted hazard ratios (HR) relating alcohol consumption to liver cirrhosis.
Results: One third of men drank alcohol weekly at baseline, among whom a dose-response relationship between alcohol consumption and liver cirrhosis was observed (p-trend<0.0001). After excluding participants with prior chronic liver diseases, weekly drinkers who consumed >420 g of alcohol/week were associated with a nearly four-fold risk of liver cirrhosis (HR = 3.76, 95%CI: 3.25–4.35), compared with those who consumed <140 g/week. Participants who reported heavy drinking episodes (i.e. >60 g/session) and daily drinking had increased risk of liver cirrhosis compared with those who did not. Men who usually drank with meals had a lower risk of liver cirrhosis (0.69 [0.55—0.88]) compared with those drinking outside of meals, after adjusting for total weekly consumption.
Conclusions: The impacts of alcohol consumption on liver cirrhosis varied by drinking patterns.

P2-5-4

DECREASED HEPATIC EPOXY/DIHYDROXY FATTY ACID RATIOS IN PATIENTS WITH ALCOHOLIC HEPATITIS: POTENTIAL MECHANISM AND/OR BIOMARKER OF A PROGRESSIVE LIVER DISEASE

D.R. Warner, C.J. Mcclain, I.A. Kirpich
Department of Medicine, University of Louisville, USA

Alcoholic hepatitis (AH) is one of the most severe forms of alcoholic liver disease (ALD) with short-term mortality as high as 20 to 30%. However, the pathogenesis of AH is not well understood and there is no effective therapy. Oxylipins, including epoxy- and dihydroxy-fatty acids (Ep-FAs and dihydroxy-FAs, respectively), are important signaling molecules involved in the regulation of various biological processes, including inflammation. Experimental evidence suggests that Ep-FAs are beneficial, anti-inflammatory lipid mediators, while the properties of dihydroxy-FAs are not well understood. In the present study, we examined oxylipin profiles in liver samples from AH patients and individuals without ALD (control group). Epoxy-metabolites of omega-6 (linoleic and arachidonic) and omega-3 (DHA and EPA) fatty acids were significantly lower in AH as compared to control liver samples. Interestingly, hepatic levels of dihydroxy-FAs were also increased in control individuals, however Ep-FAs/dihydroxy-FAs ratios were significantly higher in controls compared to AH patients. The ratios of Ep-FAs/dihydroxy-FAs oxylipins, including 9,10-EpOME/DiHOME, 12,13-EpOME/DiHOME, and 11,12-EpETrE/DiHETrE were 18, 14 and 9 fold higher in controls compared to AH patients, respectively. These data suggest that Ep-FAs and dihydroxy-FAs may play a significant role in AH pathogenesis, although further studies are needed to identify the mechanisms underlying their function.

P2-5-5

ENDOGENOUS DECREASE IN N-6/N-3 PUFA RATIO MODULATES GUT MICROBIAL DYSBIOSIS AND CONTRIBUTES TO IMPROVEMENT OF LIVER INJURY CAUSED BY ETHANOL AND LPS ADMINISTRATION IN MICE

D. Warner[1], S.G. Dastidar[1], Y. Song[1], J. Warner[1], J. Whitlock[2], E. Li[2], G. Wang[2], C. Mcclain[1], I. Kirpich[1]
[1]University of Louisville, Louisville, KY, USA and [2]University of Florida, Gainesville, FL, USA

Alterations in the gut-liver axis, including microbial dysbiosis, are important factors contributing to the pathogenesis of alcoholic liver disease (ALD). Alcohol, dietary and endogenous lipids may impact microbial community structure and function. We examined how modulation of the tissue n-6/n-3 PUFA ratio affected the gut microbiome and subsequent liver injury caused by ethanol and LPS challenge. Wild-type (WT) and fat-1 transgenic mice (which endogenously convert n-6 to n-3 PUFAs) fed an ethanol diet for 6 weeks revealed elevated ALT levels that were further increased by LPS; however, the magnitude of this effect was less in fat-1 mice. Fecal microbiome analysis revealed several Lachnospiraceae, Ruminococcaeae, and Bacteroidales OTUs that were differentially enriched in fat-1 compared to WT mice following ethanol challenge. In addition, Porphyromonadaceae: Barnesiella was enriched in fat-1 but not WT mice in response to ethanol + LPS challenge. Ethanol alone or in combination with LPS caused a reduction in Lactobacillus (although not significant) in WT but not in fat-1 mice. Our findings revealed novel interactions between host tissue n-6 and n-3 PUFAs and gut microbiota in the context of ALD, and suggested the potential beneficial effects of dietary n-3 PUFAs via modulation of gut microbiome in the management of ALD.

P2-5-6

CONSEQUENCES OF CHRONIC ALCOHOL CONSUMPTION ON TESTIS CELL MACROMOLECULES

G.M. Shayakhmetova, L.B. Bondarenko, V.M. Kovalenko
Department of Toxicology, SI “Institute of Pharmacology and Toxicology NAMS of Ukraine”, Ukraine

There is good evidence for impairment of spermatogenesis and reductions in testosterone level in chronic alcoholics. Mechanisms for these effects have not been yet clear. Present work reports influence of chronic alcoholism on rats’ testes free amino acids contents, levels of CYP3A2 mRNA expression and DNA fragmentation, contents of different cholesterol fractions and proteins SH-groups. Wistar male rats were divided into two groups: I – control (intact animals), II – chronic alcoholism (15% ethanol self-administration, 150 days). Following long-term alcohol consumption testicular free amino acid content significantly changed. Most profound changes were registered for contents of lysine (−53%) and methionine (+133%). Intensity of DNA fragmentation in alcohol-treated rats testes were considerably increased, on the contrary CYP3A2 mRNA expression in testes cells were inhibited, testicular contents of total and etherified cholesterol increased 25% and 45% respectively, proteins SH-groups decreased 13%. Multidirectional changes of testicular dehydrogenases activities were detected. Thereby, we have obtained complex estimation of chronic alcoholism effects in male gonads, especially on amino acids, proteins, ATP and NADPH metabolisms. Our results demonstrated changes in testes on level of proteome and genome. We suggest that such metabolic disorders in male gonads could have negative implication into cellular regulation of spermatogenesis.

P2-5-9

ROLE OF MATRIX RIGIDITY ON HEPATOCYTES AND LIVER SINUSOIDAL ENDOTHELIAL CELLS IN ALCOHOL INDUCED HEPATIC FIBROGENESIS

S.S. Kidambi[1], V. Natarajan[1], S. Thulaisingam[1], E. Harris[2], C. Casey[3]
[1]Dept. of Chemical Engineering, University of Nebraska-Lincoln, USA, [2]Dept. of Biochemistry, University of Nebraska-Lincoln, USA and [3]Dept. of Internal Medicine, Division of Gastroenterology-Hepatology, UNMC, USA

Cascade of events occurs including activation of hepatic stellate cells that trigger the release of chemokines and inflammatory stimulants, and extensive remodeling of ECM that leads to liver stiffening. Our study focuses on the role of matrix stiffness and how it regulates the cellular function of hepatocytes and liver sinusoidal endothelial cells (LSECs) during alcohol exposure. We have demonstrated, using mechanically tunable substrate, that fibrotic levels of matrix stiffness 1) decreased hepatocyte-specific functions, 2) downregulated key drug transporter genes, and 3) downregulated epithelial cell phenotype markers. Additionally, we have demonstrated that LSECs cultured on different levels of stiffness result in rapid capillarization and loss in hyaluronic acid endocytosis that mimics the fibrosis response observed in vivo. Our preliminary data also demonstrates that the cells isolated from ethanol fed rats have increased hepatic-specific functions when cultured on soft environment that recreates the healthy liver environment. This study blends liver biology, mechanobiology, and materials design to develop quantitative and mechanistic insights into the role of liver stiffness and alcohol liver disease.

P2-5-10

EFFECT OF L-CARNITINE ON CHANGE OF MITOCHONDRIAL MORPHOLOGY OF LIVER AND MUSCLE IN CHRONIC ALCOHOL INTAKE

K. Shiraishi[1], K. Tsuruya[1], Y. Arase[1], S. Hirose[1], T. Kagawa[1], T. Mine[1], N. Fukunishi[2]
[1]Department of Internal Medicine, Gastroenterology, School of Medicine, Tokai University, Japan and [2]Teaching and Research Support Center, Tokai University School of Medicine, Japan

Liver mitochondria that produce ROS mainly occurs in alcohol metabolism, but few have examined the effect of L-carnitine on morphological abnormalities of mitochondria. The mitochondria of liver and skeletal muscle of kinetic energy supply center were examined. (Method) Male ICR mouse 4 weeks old was raised for 4 weeks. Liver liquid diet 7% ethanol group (E), control liquid diet (Cont), L-carnitine combination group (Cont+L) and chronic drinking (E+L) were set. L-Carnitine is 0.18 mg / 30 g BW – 0.1 mL forced PO a day. Mitochondria of liver and lower limb muscle was observed using transmission electron microscope. (Results) Liver mitochondrial observation: Cont+L compared with Cont: no change, E group: swelling, increased, E+L: swelling and increase. Skeletal muscle mitochondria observation: Cont+L: increased compared to Cont, E: swelling and decreasing, E+L: size and number increasing. (Inclusion) Morphological abnormality and increase of mitochondria occur in the liver, and morphological abnormality cannot be improved with L-Carnitine combination. It was shown that administration of L-Carnitine increases size and number of mitochondria of muscle when chronic alcohol is ingested. L-Carnitine is important for maintaining the function of skeletal muscle in chronic alcohol intake.

P2-5-11

ALCOHOL DEHYDROGENASE ACTIVITY IN BLOOD: ALTERATIONS IN PATIENTS WITH ALCOHOLIC LIVER DISEASE

A.J. Engstler[1,*], K. Staufer[2,*], F. Jung[1], V. Winkler[1], A. Baumann[1], A. Brandt[1], I. Bergheim[1]
[1]Department of Nutritional Sciences, Molecular Nutritional Science, University of Vienna, Austria and [2]Department of Surgery, Div. Transplantation, Medical University Vienne, Austria

Results of older studies suggest that activity of alcohol dehydrogenase (ADH) in liver of patients with alcoholic liver disease (ALD) is markedly lower than in healthy controls. In recent years it has been shown that ADH-activity can also be determined in blood samples and that this may be indicative of ADH-activity in tissues, but also tumors. However, if ADH-activity is altered in blood of patients with ALD has not yet been clarified.
Twenty-four patients with biopsy-proven ALD (age: 28–83 years; m/f: 20/4) and 16 controls (age: 26–61 years, m/f: 9/7) being at least 48 h abstinent at the time of blood collection were enrolled in the study. An enzyme assay was used to measure ADH-activity in serum, which was normalized to ADH-1 protein determined by western blot. A correlation analysis with markers of glucose and lipid metabolism and liver damage as well as fasting ethanol levels was performed.
Relative ADH-activity in serum was significantly lower in patients with ALD than in controls. Furthermore relative ADH-activity was significantly negative associated with markers of liver damage and insulin resistance and fasting ethanol levels.
Taken together our data suggest that ADH-activity in blood of patients with ALD is lower than in healthy controls.
*Contributed equally.

P2-5-12

TRIBUTYRIN ATTENUATES ALCOHOL-INDUCED CHEMOKINE UP-REGULATION VIA EPIGENETIC MECHANISMS: RELEVANCE TO HEPATIC INFLAMMATION AND INJURY IN ALD

S. Ghare[1,2,3], H. Donde[1,2,3], B.T. Charpentier[1], M.V. Vadhanam[1,2,3], S. Joshi-Barve[1,2,3], L. Gobejishvili[1,2,3], C. Mcclain[1,2,3,4], S. Barve[1,2,3]
[1]University of Louisville Alcohol Research Center, USA, [2]Hepatobiology & Toxicology Center, USA, [3]University of Louisville, USA and [4]Robley Rex Veterans Affairs Medical Center, Louisville, KY, USA

Alcohol-mediated up-regulation of chemo-attractant chemokines (CCL2 and CXCL2) and hepatic leukocyte infiltration are major drivers of the hepatic inflammation and injury in alcoholic liver disease (ALD). The understanding of epigenetic mechanisms regulating chemokine expression remains largely undetermined. The present study investigates the role of alcohol-induced epigenetic mechanisms involving promoter histone modifications in the regulation of CC- and CXC- chemokines and progression of ALD.
The data showed that chronic alcohol feeding caused a temporal increase in hepatic CCL2 and CXCL2 mRNA levels. Promoter histone analysis by chromatin immunoprecipitation (ChIP) assay revealed that correspondent to mRNA expression, alcohol significantly increased transcriptionally permissive histone H3 lysine 9 acetylation (H3K9Ac) levels along with enhanced recruitment of transcription factor NFkB-p65 at the chemokine promoters. Further, the effect of tributyrin, a butyrate prodrug that can inhibit histone deacetylase (HDAC) activity was assessed. Notably, administration of tributyrin protected both early and late stage induction of these chemokines in response to alcohol and resultant neutrophil infiltration in the liver. The present work demonstrates that Tb/butyrate may be useful in preventing the alcohol-induced epigenetic mechanisms and associated pathologic hepatic changes, and may prove to be a useful therapy for the prevention/treatment of ALD.

P2-5-13

AN ATTEMPT TO STUDY THE EFFECTS OF ALCOHOL ALONG WITH SMOKING

S. Sinha
Department of Zoology, Nehru Gram Bharati University, India

The present study pertains to discover the effects of alcohol along with smoking in the adults. We collected the information from the hospitals in the district of Allahabad who were admitted for the treatment of alcoholism and smoking. After taking prior consent with the doctors and close family members we found that the subjects who took alcohol along with smoking were more prone to the loss of consciousness, decision making and ability to think during the time of influence of alcohol along with smoking in comparison to the alcohol and smoking alone. It was also found to be a major cause in infertility, pregnancy problems. There was also a strong risk of liver cancer in cigarette smoking drinkers. Hence there is a dire need to avoid smoking along with intake of alcohol.

P2-5-14

RETINOIC ACID DEFICIENCY INDUCES FASD-LIKE CRANIOFACIAL AND NEURODEVELOPMENTAL MALFORMATIONS: A NEW MOLECULAR ETIOLOGY OF FASD

G.G. Hicks[1], B. Petrelli[1], A. Ozturk[1], M. Pind[1], A. Fainsod[2]
[1]Regenerative Medicine and Department of Biochemistry & Medical Genetics, University of Manitoba, Canada and [2]Department of Developmental Biology and Cancer Research, Hebrew University of Jerusalem, Israel

Prenatal alcohol exposure (PAE) resulting in FASD is the most common cause of neurodevelopmental impairments in the western world. PAE overwhelms the enzymes that would normally convert retinol (Vitamin A) to retinoic acid (RA). We hypothesize that PAE reduces RA levels during critical developmental stages in early gastrulation and this aberration drives the later craniofacial malformations associated with FASD. To biochemically mimic the alcohol-induced RA deficiency in vivo, we genetically engineered a mouse expressing Cyp26A1 from the endogenous Goosecoid (Gsc) promoter to degrade endogenous RA in the organizer at the start of gastrulation. Gsc:Cyp26A1 E8.5 embryos show reduction in RA activity in the frontonasal prominence region and demonstrate body-axis developmental variation in FASD relevant tissues (n = 48). E18.5 embryos were next examined using scanning electron microscopy to demonstrate mutant embryos have sentinel FASD craniofacial malformations (n = 66). Gsc:Cyp26A1 mice also develop craniofacial malocclusions at significantly higher rates than WT littermates (12.5% vs. 0.04%; n = 208 and 3711, respectively). Taken together, our data provide in vivo evidence that strongly supports RA deficiency as a major molecular etiology of craniofacial malformations associated with FASD. The finding suggests Vitamin A supplementation may significantly reduce or prevent FASD outcomes in children with PAE.

TUESDAY, SEPTEMBER 12
6. ISBRA-WHO WORKSHOP

P2-6-3

AMPA RECEPTOR SUBUNIT EXPRESSION AND RECEPTOR BINDING IN PATIENTS WITH ADDICTION

F. Ueno[1,2], T. Suzuki[2,3], S. Nakajima[2], S. Matsushita[1], M. Mimura[2], H. Uchida[2]
National Hospital Organization Kurihama Medical and Addiction Center, Japan, [2]Department of Neuropsychiatry, Keio University School of Medicine, Japan and [3]Department of Neuropsychiatry and Clinical Ethics, University of Yamanashi, Japan

Briefly, while global interest in addiction has become widespread and demand for novel treatment is increasing, effectiveness of currently available treatment options for addiction is still limited. A body of evidence literatures suggests the involvement of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the pathophysiology underpinning addiction. Data from post-mortem studies have provided relevant findings of the pathophysiology of addiction; however, these findings seem mixed. We therefore conducted a systematic review of published postmortem studies that investigated AMPA receptor expression in patients with addiction.
As a result, 11 (17 studies) out of 928 articles were found to be relevant. Seven articles included alcohol use disorders (AUD) and four included heroin/cocaine abusers. The most frequently investigated region was hippocampus (3 studies), amygdala (3 studies), and putamen (3 studies).
In conclusion, hippocampus and amygdala may be associated with the development of addiction through their functions regulating learning and memory, whereas findings in other regions were inconsistent among studies. Moreover, attention to date has been confined to AUD and heroin/cocaine abuse. Human postmortem studies are prone to physiological degenerative changes after death. These limitations emphasize the need of examination of AMPA receptors in living human brains, which have been currently conducting in our PET study.