H2O2: A LINK BETWEEN INFLAMMATION AND IRON METABOLISM

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Hepatitis of any kind is characterized by increased concentrations of reactive oxygen species. H2O2 is the main reactive oxygen intermediate derived from a multitude of cellular metabolic processes as well as from oxidative burst by granulocytes or macrophages. Due to its relatively long half-life time, there is growing evidence that H2O2 also acts as a signaling molecule. Iron metabolism can be influenced by H2O2 by activating the iron regulatory protein 1, which regulates intracellular iron metabolism but also by increasing transferrin receptor 1 that is responsible for cellular iron uptake. Both mechanisms lead to increased cellular iron uptake and decreased levels of circulating serum iron. Hepcidin, the systemic iron regulator, has not been linked to oxidative stress so far. New experiments, however, point out that H2O2 is able to increase hepcidin via STAT3 signaling, thus decreasing iron recycling by macrophages and iron resorption by the duodenum. This is a third mechanism to lower serum iron during increased oxidative stress and preventing toxic reactions between H2O2 and iron.

ROLE OF INNATE IMMUNE SYSTEM IN THE ETHANOL-INDUCED BRAIN DAMAGE, BEHAVIOURAL DYSFUNCTIONS AND ADDICTION

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BINGE DRINKING INDUCES SIGNIFICANT CHANGES IN THE INNATE IMMUNE SYSTEM

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Chronic and intermittent alcohol consumption leads to cognitive impairment in the brain due to the ethanol’s action on specific neurotransmitter systems and intricate signalling pathways. Glial cells actively participate in brain function by nurturing neurons and facilitating neuronal activity as well having an immunological role to protect brain cells from invading pathogens. Dysregulation of this immune function induced by intermittent alcohol abuse may shift the homeostatic balance of inflammatory mediators to a proinflammatory state, activating microglia and inducing neuronal loss thereby inducing behavioural and cognitive impairments. Molecules, which could prevent the microglial activation and cytokine production would downregulate the pro-inflammatory state and help to prevent the decline of cognitive impairment. Studies of a ‘binge drinking’ adolescent female rats identified increased levels of glutamate in the dentate gyrus region of the hippocampus, which were associated with activated microglia. Such microglia will release glutamate when activated as well as a plethora of pro-inflammatory cytokines, e.g. IL-6 and TNFα. Oral administration of a taurine analogue, ethane-β-sulphate to such ‘binge drinking’ rats for a 3-week period stabilized IL-6 within the microglial cell, thereby preventing NFKappaB translocation to the nucleus and cytokine production. Activated microglia were no longer visible after immunohistochemical staining of the dentate gyrus brain region. The innate immune system, which is activated by intermittent alcohol use, can be suppressed by the use of molecules which target specific activators of this system, i.e. NFKappaB.

S06.3 ROLE OF THE TLR4 RESPONSE IN THE NEUROINFLAMMATION, BRAIN DAMAGE AND BEHAVIOURAL DYSFUNCTIONS INDUCED BY CHRONIC ETHANOL CONSUMPTION

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Toll-like receptors (TLRs) play an important role in the innate immune response, and emerging evidence indicates their role in brain injury and neurodegeneration. Our recent results have demonstrated that ethanol is capable of activating glial TLR4 receptors and that the elimination of these receptors in mice protects against ethanol-induced glial activation, induction of inflammatory mediators and apoptosis. However, whether ethanol-induced inflammatory damage causes behavioural and cognitive consequences, and if behavioural alterations are dependent of TLR4 functions are presently unknown. Here we show in mice drinking alcohol for 5 months, followed by a 15-day withdrawal period, that activation of the astroglial and microglial cells in frontal cortex and striatum is maintained and that these events are associated with cognitive and anxiety-related behavioural impairments in wild-type (WT) mice, as demonstrated by testing the animals with object memory recognition, conditioned taste aversion and dark and light box anxiety tasks. Mice lacking TLR4 receptors (TLR4−/−) are protected against ethanol-induced inflammatory damage, and behavioural associated effects. We further assess the possibility of the epigenetic modifications participating in short- or long-term behavioural effects associated with neuroinflammatory damage. We show that chronic alcohol treatment decreases H4 histone acetylation and histone acetyltransferases activity in frontal cortex, striatum and hippocampus of WT mice. Alterations in chromatin structure were not observed in TLR4−/− mice. These results provide the first evidence of the role that TLR4 functions play in the behavioural consequences of alcohol-induced inflammatory damage and suggest that the epigenetic modifications mediated by TLR4 could contribute to short- or long-term alcohol-induced behavioural or cognitive dysfunctions.

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S06.4

INDUCTION OF INNATE IMMUNE GENES BY ETHANOL CREATES THE NEUROBIOLOGY OF ADDICTION

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Addiction evolves through progressively reduced behavioral control and cognitive flexibility with increasing negative emotion and craving. Recent discoveries indicating neuroimmune signaling contribute to addiction and co-morbid depression. Low threshold microglia undergoes progressive stages of innate immune activation involving astrocytes and neurons with repeated drug abuse, stress and immune signals. Increased brain NF-κB transcription of proinflammatory chemokines, cytokines, oxidases, proteases, TLR and other genes create loops amplifying NF-κB transcription and neuroimmune gene expression. Human post-mortem alcoholic brain has increased microglial markers, chemokine-MCP1, TLR receptors and endogenous TLR agonists. Ethanol activates persistent neuroimmune signaling through the formation of loops of NF-kB transcription in glia contributing to a hyperglutamatergic state. Chronic ethanol treatment induces reversal learning deficits coincident with frontal cortical damage mimicking human drug addict deficits in behavioral flexibility. Increasing limbic negative emotion and depression-like behavior are reflected in hippocampal neurogenesis. Chronic ethanol inhibits neurogenesis coincident with depression-like behavior with both reversed by anti-depressants. Antidepressants, naltrexone and anti-inflammatory drugs block ethanol neuroimmune activation, inhibition of neurogenesis and neurotoxicity. The hypothesis that neuroimmune gene induction underlies addiction and affective disorders creates new targets for therapy. This study was supported by NIH and NIAAA.

S07.1
THE IMPACT OF SMOKING AND ALCOHOL ON ACUTE AND CHRONIC PANCREATITIS IN THE WESTERN WORLD

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Pancreatitis is the main alcohol-related disease of the pancreas. Development of acute and chronic pancreatitis has been attributed to effects on exocrine secretion, oxidative stress, apoptosis, inflammatory response and intracellular signalling. To date, epidemiological studies give the best evidence for the impact of smoking on the disease. Present data suggest that coexposure to alcohol and nicotine may impose a strong hazard to the pancreas, with increasing experimental evidence that the same or similar mechanisms may act synergistically. The synergistic role of alcohol and tobacco smoke exposure may be enhanced by a specific genetic background leading to accumulation of toxic metabolites and thereby increasing individual susceptibility to pancreatitis through a variety of mechanisms. This includes known pancreatitis-predisposing mutations as well as drug metabolizing genes and genes with rather broad functions.

S07.2
THE IMPACT OF SMOKING ON THE COURSE OF ALCOHOL DEPENDENCE

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Introduction. Tobacco dependence is one of the most potent predictors of progression from first drink to alcohol dependence. In line, 70-80 of alcohol-dependent subjects are smokers. Therefore, we investigated, whether smoking is related to specific clinical characteristics and the course of alcohol dependence.

Material and methods. We investigated more than 1000 alcohol-dependent subjects consecutively admitted to an inpatient abstention program. All were Caucasian of German descent and met the ICD-10 and DSM-IV criteria of alcohol dependence. We analysed specific characteristics, such as age at onset, family history and time to first relapse considering attention-deficit hyperactivity disorder (ADHD) and antisocial personality disorder (ASPD) as additional variables.

Results. A comorbidity of alcohol and tobacco dependence was significantly associated with increased frequency of ADHD, ASDP, Cloninger’s type 2 alcoholism and a family history positive for alcohol and/or tobacco dependence. Comorbid subjects had a younger age at onset of alcohol dependence. Moreover, there was a higher frequency of unemployment, criminal offences and suicidality. Relapse rates will be presented.

Discussion/conclusion. Alcohol-dependent subjects with tobacco dependence showed an increased frequency of clinical characteristics, usually related to a more severe course of the illness.

S07.3
SMOKING CESSATION IN ALCOHOL-DEPENDENT PATIENTS: RESULTS FROM A RANDOMIZED, CONTROLLED TRIAL

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Introduction. Tobacco smoking is a serious additional hazard for mortality especially in alcohol-dependent persons who usually smoke three times more often, have a higher severity of nicotine dependence and have more difficulties in quitting compared with non-alcoholics.

Methods. Totally 103 inpatients in a qualified alcohol detoxification program took part in a smoking cessation study aiming to stop or reduce their tobacco consumption by >50%. Patients were randomly allocated to the intervention group (cognitive-behavioural sessions of smoking cessation) and a control group (autogenic training).

Results. Comparison of pre- and post-treatment variables revealed significant changes. Both groups showed significant reductions in the number of cigarettes, CO level (breath carbon monoxide) and Fagerström test of nicotine dependence (FTND). However, changes in attitudes regarding the ‘importance to stop smoking’ and the ‘self-efficacy to achieve a smoking stop’ were found primary for the intervention group. Further, sub-group analyses regarding the severity of dependence (nicotine and alcohol) were conducted.

Conclusions. Both treatments appear to be equally effective at reducing smoking behaviour during an alcohol detoxification treatment. However, attitudes regarding the change of smoking behaviour increased in the intervention group only. Further sub-group analyses may help to detect which factors predict a successful outcome.

S07.4
PANCREATIC CANCER: ALCOHOL AND NICOTINE AS RISK FACTORS

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Pancreatic cancer (PC) is one of the most lethal malignancies with a 5-year survival rate <5%. Tobacco smoking is the most prominent avoidable risk factor for PC increasing the PC risk by a factor of 2. Up to 20% of all PC cases can be attributed to smoking. Pipe-smoking, passive smoking and smokeless tobacco use showed no increased risk for PC. Recent studies have shown that the individual susceptibility for PC in smokers is modified by the genetically determined profile of enzymes metabolizing tobacco carcinogens. Alcohol is the leading cause of chronic pancreatitis which is associated with 13-fold increased risk for PC. Early studies could not demonstrate a direct association of PC with alcohol consumption, which can be partly explained by a small number of cases, confounding risk factors or limited information about the alcohol intake. In a recent meta-analysis alcohol drinking (>3 drinks/day) increased the risk for pancreatic carcinogenesis moderately (OR: 1.22; 95% CI, 1.12–1.34; Tramacere et al. 2009). The underlying pathomechanisms are still incompletely delineated. Aetetaldehyde and reactive oxygen species—mediated by oxidative metabolism of alcohol in the pancreas—play a prominent role in pancreatic injury, inflammation and carcinogenesis. The role of fatty acid ethyl esters (FAEE)—resulting from non-oxidative alcohol metabolism in the pancreas—is less clearly defined. Combined drinking and smoking appear to have a synergistic effect on the development of pancreatic cancer. More studies are required to define the specific PC risk in relation to beverage type and drinking pattern. Due to limited treatment options of pancreatic cancer, life-style changes with a reduction in risk factors such as alcohol and nicotine are of utmost importance.