perception, palatability (sucrose intake) or olfactory recognition were found after LPS-pre-treatment. Reduction of TLR signaling and other proinflammatory pathways reduced ethanol intake. Local brain signaling was shown to be important as inhibition of IKKβ – a key element of TLR-pathways – in the nucleus accumbens using local injection of viral CRE in mice with a floxed IKKβ genes.
Conclusions: Taken together, these results provide the most compelling evidence to date for immune signaling in regulation of alcohol consumption and that excessive alcohol consumption activates neuroimmune signaling. This is the basis for our proposal that alcohol consumption and craving is driven by a vicious cycle of neuroimmune activation. Compounds known to inhibit inflammation, microglial activation, and neuroimmune gene expression have shown promising results in reducing alcohol-mediated behaviors in our animal models, indicating that neuroimmune signaling pathways offer unexplored targets in the treatment of alcohol abuse.
Disclosure: Nothing to Disclose.

19.2 Altered Gut-Brain Signaling in an Animal Model of Roux-En-Y Gastric Bypass Surgery: Implications for Alcohol Consumption and Reward

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Background: Roux-en-Y gastric bypass (RYGB) is a very effective surgical method to treat obese patients. Rodent models of obesity have shown that RYGB produced reduced preference and motivation for food and thus may reduce both palatability and rewarding effects of foods. In contrast, concerns have been raised by clinical reports of an increased risk for alcohol use following RYGB surgery. Our recent studies in dietary obese rats corroborated this notion and further investigated the hypothesis that increased alcohol preference and intake is driven by the enhancement in alcohol rewarding effects rather than altered alcohol absorption following RYGB. As a potential underlying mechanism, we investigated involvement of ghrelin and activation of brain reward areas.
Methods: High fat diet-induced obese Sprague Dawley male rats underwent RYGB and were habituated along with their sham-operated (SHAM) obese controls and with lean, normal diet-fed rats (ND) to increasing concentrations of alcohol (2-8%) in a two-bottle choice paradigm (Experiment 1) or a progressive ratio-10 (PR10) schedule of reinforcement operant oral self-administration task (Experiment 2). In addition, the effects of the ghrelin-1a-receptor antagonist D-Lys3-GHRP-6 (50, 100 nmol/kg, IP) were tested on PR10 responding for 4% alcohol. To control for differential alcohol absorption, in a third experiment, rats self-administered alcohol (1%) intravenously (IV). A forth experiment tested whether RYGB also alters motivation to IV self-administer morphine on a fixed ratio-5 (FR-5) and PR-2 schedule. Finally, a fifth experiment examined RYGB effects on the anticipatory responses to palatable versus regular food. Rodents were conditioned to chambers paired with bacon or chow, and then tested for conditioned place preference (CPP) for the bacon-paired chamber, relative to the chow-paired chamber. After CPP, rats were placed in either the bacon- or chow-paired chamber without the food stimulus, and brain-glucose metabolism (BGluM) was measured using positron emission tomography (μPET).
Results: In Experiment 1, RYGB rats drank twice as much alcohol (2-4%) as SHAM and 50% more than ND lean controls. Obese SHAM drank on average significantly less (50%) alcohol than lean ND controls. In Experiment 2, compared to SHAM, RYGB rats made significantly more active spout responses to earn reward, and achieved higher breakpoints on PR-10 task. Pretreatment with a single peripheral injection of D-Lys3-GHRP-6 at either dose was ineffective in altering appetitive or consummatory responses to 4% alcohol in the SHAM. In contrast, RYGB rats demonstrated reduced operant performance to earn alcohol reward on the test day and reduced consummatory responses for two subsequent days following the drug. In Experiment 3, compared to SHAM, RYGB rats made significantly more operant lick responses to earn IV alcohol infusion (+30-50%) on a FR-5 schedule, and achieved higher breakpoints (+25-40%) during a PR-2 task. In Experiment 4, compared to SHAM, RYGB rats completed more cycles on a fixed ratio-2 task to obtain IV infusions of morphine (0.225 mg/kg/infusion) in daily sessions at an accelerated rate starting on Day 6 to reach a two-fold increase by Day 12. Finally, μPET imaging results show that RYGB may lead to changes in brain activity and in particular, brain regions that may underlie changes in reward and taste related behavioral responding.
Conclusions: Our results provide evidence that RYGB increases the rewarding effects of alcohol and that ghrelin receptor is involved in the mechanism. The findings of the IV self-administration study indicate that the enhanced alcohol reward after surgery is not just due to changes in alcohol absorption but may reflect direct effects in the sensitivity to alcohol's rewarding effects in the brain. Furthermore, the greater cue-induced activation of the reward system together with increased morphine self-administration suggests an augmented risk of compulsive drug use after RYGB. Future research is warranted to determine underlying mechanisms and identify individual risk factors preoperatively.
Disclosure: Nothing to Disclose.

19.3 Gut Permeability, Gut Microbiota and Inflammation in Alcoholism: Clinical Data

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Background: Recent data have shown that clinical symptoms of alcohol dependence such as depression and alcohol-craving are related to increases in gut permeability and in inflammation, and that both psychological and biological dimensions at least partially recover after detoxification. These observations suggest that the gut could influence the behavior. However, the nature of the intestinal processes involved in the change in gut permeability and in inflammation and their relation to psychological symptoms are still unknown.

Methods: Two studies were conducted: 1- 13 non-cirrhotic alcohol-dependent (AD) subjects hospitalized for a detoxification program with 15 healthy controls matched for age, sex and BMI. Gut permeability was measured using 51Cr-EDTA. Fecal samples were collected to analyze the gut microbiota composition (using pyrosequencing and qPCR) and metabolomic analysis (GC/MS) was used to assess the gut microbiota function. 2- 63 non-cirrhotic AD subjects were compared to 14 healthy subjects. The inflammatory pathways that were stimulated by gut-derived bacterial products were also analyzed in peripheral blood mononuclear cells (PBMC) at the mRNA level by quantitative PCR, western blotting and DNA binding assays were used for transcription factor analysis. Toll-like receptors activation was assessed by cell cultures. In both studies, psychological symptoms of patients were assessed by self reported questionnaires (depression (BDI), anxiety (STAI) and alcohol craving (OCDS)). The analyses were performed twice, at the first day of alcohol withdrawal and after 18 days of abstinence.
Results: Gut permeability was higher in some AD subjects and was associated with specific alterations in the gut microbiota composition and function. The leaky gut allowed the translocation of gut-derived bacterial toxins such as lipopolysaccharides (LPS) and peptidoglycans (PGN) to the systemic circulation. Correlation analyses revealed that the gut permeability was strongly related to psychological symptoms of alcohol-dependence, at both times of withdrawal. The bacterial toxins simulated their Toll-like receptors in PBMCs and activated specific inflammatory pathways that were found to correlate with alcohol craving. The alcohol withdrawal induced a decrease in gut permeability and in LPS-associated inflammatory pathways. However, 18 days of abstinence did not restore the gut microbiota composition, except in some specific species.
Conclusions: These observations suggest that alterations at the level of the gut microbiota influence the gut permeability and activate specific inflammation pathways that are related to psychological symptoms of alcohol-dependence. Altogether these observations are consistent with a role of inflammation as one mediator of a gut-brain communication in AD patients.
Disclosure: Part 1: I have been consultant or presented conferences for Lundbeck company and Astra Zeneca company, but these activities are totally unrelated to the topic that is exposed in the talk.

19.4 GLP-1 and Ghrelin as New Targets for Alcoholism Treatment? A Translational Overview

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Background: Recent research suggests that the gut-liver-brain axis may play a role in alcohol use disorder (AUD). Two specific pathways for which recent preclinical studies suggest a role in AUD are the glucagon-like peptide-1 (GLP1) and ghrelin. A few preclinical studies suggest that GLP1 receptor (GLP1R) activation attenuates alcohol reinforcing properties; and studies with rodents show that ghrelin administration increases alcohol reward, whereas antagonism of the ghrelin receptor results in reduced alcohol reward and consumption.
Methods: We investigated whether single nucleotide polymorphisms (SNPs) in the GLP1R gene are associated with AUD. Case-control analysis ($n = 908$) was performed in AUD subjects and controls using logistic regression while controlling for self-reported ancestry. The SAGE GWAS sample ($n = 3803$) was used for confirmation purposes. To obtain functional validation, secondary analyses were carried out on data from a human laboratory study of intravenous alcohol self-administration (IV-ASA). As for ghrelin, we conducted a double-blind placebo-controlled proof-of-concept study. Non-treatment seeking heavy drinking alcoholic individuals ($n = 45$) were randomized to receive IV ghrelin 1mcg/kg, 3 mcg/kg or placebo, followed by a cue-reactivity procedure, during which participants were exposed to neutral (juice) and alcohol cues. The primary outcome was the increase in alcohol craving.
Results: As for the set of genetic analyses, 5 GLP1R SNPs were significantly associated with AUD in the case-control study. A trend-level association between a previously reported functional SNP (rs6923761; Ser168Gly) and AUD ($p < .01$) was also observed. In the SAGE samples, the association between 168Ser allele and AUD was further confirmed in males ($p < .05$), but not in females. In the human laboratory experiment, the 168Ser-allele was associated with peak breath alcohol concentrations ($p < .05$) achieved during the IV-ASA. As for the ghrelin IV study, repeated measures of ANCOVA revealed a group effect across ghrelin doses in increasing alcohol craving ($p < .05$). A dose-specific examination revealed a significant effect of ghrelin 3 mcg/kg vs. placebo in increasing alcohol craving ($p < .05$) with a large effect size ($d = .94$). By contrast, no significant ghrelin effect was found in increasing either urge to drink juice or food craving (p: n.s.).
Conclusions: The GLP1 genetic experiments provide novel and convergent findings suggesting that GLP1 signaling may be of importance in AUD, making the GLP1R an attractive target for personalized pharmacotherapy. The IV ghrelin study provides novel pharmacological evidence that ghrelin may play a role in the neurobiology of alcohol craving, thus demonstrating a novel pharmacological target for treatment. Consistent with recent preclinical evidence, our group provides human evidence supporting that GLP1 and ghrelin pathways may represent new intriguing pharmacological targets to treat AUD patients.
Disclosure: Nothing to Disclose.

Panel
20. Neural Circuitry Contributing to Mood, Impulsivity, and Decision Making in Bipolar and Other Inhibitory Disorders: Studies from Imaging and Genetics, to Pharmacology and Model Organisms

20.1 Effect of DAT Genotype on Striatal Function during Response Inhibition to Emotional Stimuli in Bipolar Disorder

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Background: Both neurobiological and genetics research suggest that abnormalities of the brain neurotransmitter