
Methods. We used membrane binding to assayed radioligands and modulators in five brain regions from alcoholics and matched controls (n = 6). Data were analysed by non-linear curve-fitting.

Results. [11C]Flunitrazepam affinity was invariant, [11C]Flumazenil affinity varied regionally, and [11C]Ro15-4513 affinity varied both regionally and between groups. [11C]Flunitrazepam and [11C]Flumazenil receptor densities were higher in several brain regions of alcoholics, whereas [11C]Ro15-4513 density was not. Zolpidem affinity in modulating [11C]Ro15-4513 and [11C]Flumazenil binding was lower in hippocampus and caudate. Regional differences in Hill slope (nH), notably in occipital cortex, precluded a one-site model. Zolpidem modulation of [11C]Flumazenil binding resolved into 2 sites in four regions. Affinity was lower in occipital cortex (52 ± 1 µM) than in other regions (range 9–12 µM), P < 0.01, but variant across alcoholics and controls. Binding capacities varied regionally but not between case–controls. Zolpidem modulation of [11C]Ro15-4513 binding resolved into 2 sites in all areas. In controls, the proportion of binding to the high-affinity site was significantly lower in caudate (29%) than in any other region (49–53%); in alcoholics, the fraction differed between hippocampus (27%) and occipital cortex (71%). Regional profiles of binding capacity differed significantly between alcoholics and controls.

Conclusions. These data reflect local variations in \( \alpha_5 \) and \( \alpha_3 \) GABA_A subunit expression in alcohol misuse.

S26.3 PERSISTENT EFFECTS OF BINGE DRINKING ON ADOLESCENT BRAIN

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Adolescent alcohol binge drinking constitutes a major vulnerability factor to develop alcoholism. However, mechanisms underlying this susceptibility remain unknown. We evaluated the effect of adolescent binge-like ethanol intoxication on vulnerability to alcohol abuse in Sprague-Dawley rats. To model binge-like ethanol intoxication, every 2 days, rats received an ethanol injection (3.0 g/kg) for 2 consecutive days across 14 days either from postnatal day 30 (PN30) to 43 (early adolescence) or from PN45 to PN58 (late adolescence), as first described by the Consuelo Guerri’s group. In young adult animals, we measured free ethanol consumption in the two-bottle choice paradigm, motivation for ethanol in the self-administration paradigm and induced a loss of both ethanol-induced CPP and CTX in young adults. No modification in either sucrose self-administration or amphetamine-induced CPP was observed. IEI exposure during early adolescence also increased basal levels of anxiety-like behaviour. As the nucleus accumbens (Nac) is particularly involved in addictive behaviour, we analysed IEI-induced long-term neuroadaptations in the Nac using c-Fos immunohistochemistry and an array of neurotransmitter-related genes. This vulnerability to ethanol abuse was associated with a lower c-Fos immunoreactivity in the Nac and enduring alterations of the expression of Penk and Scl6a4, 2 neurotransmitter-related genes that have been shown to play critical roles in the behavioural effects of ethanol and alcoholism. This work was supported by the European project AlcoBinge from the INTERREG IV A programme.

S26.4 LONG-TERM COGNITIVE DYSFUNCTIONS IN ADOLESCENT RATS WITH BINGE DRINKING ARE ASSOCIATED WITH NEUROIMMUNE ACTIVATION AND MYELIN DYSFUNCTION

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Adolescence is a critical period for brain development, characterized by neuronal maturation and rearrangement processes, such as myelination and synaptic plasticity. We previously demonstrated that intermittent ethanol administration to adolescent rats increases inflammatory mediators and causes...
The number of rewards and peak and average BrAC were recorded, as well as a progressive ratio (PR) schedule (increasing button presses for infusions). Followed by a 125-min phase where they could push a button for additional self-administration sessions, each consisting of a 25-min priming phase followed by a progressive-ratio. Healthy non-dependent drinkers completed two IV alcohol administration in non-dependent drinkers using two paradigms: free-access and objective (e.g. attention to cues) and physiological (heart rate, salivation) measures of alcohol cue-elicited craving. In this study, administration IV of ghrelin resulted in acute increase in craving (cue-induced urge to drink). Altogether, these data suggest that the ghrelin system may represent a novel pharmacological target to treat patients with alcoholism.

S27

INNOVATIVE TECHNIQUES IN HUMAN LABORATORY ALCOHOL RESEARCH

S27.1

THE COMPUTER-ASSISTED INFUSION SYSTEM (CAIS) FOR EXPERIMENTAL ETHANOL ADMINISTRATION IN HUMANS

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Ingestion of alcohol leads to substantial variability across subjects in the systemic exposure to alcohol, including that of the brain. Using intravenous infusion bypasses these sources of variability and, together with a physiologically based pharmacokinetic (PBPK) model of alcohol distribution and elimination grants much better control over the time course of arterial blood alcohol concentration (aBAC). Infusion rates are adapted once every 30 seconds to follow an aBAC time profile prescribed by the experimenter. Besides improved control over aBAC, other advantages of i.v. alcohol administration over oral ingestion include safety, since aBAC declines immediately after the infusion is stopped and blinding, since alcohol can be administered without the subject’s awareness. Infusion also provides a reliable method for dissociating the response to alcohol administration from demand characteristics such as taste, smell, and familiarity/preference of the source of the alcohol. Initially, these methods were developed to achieve constant aBAC over several hours of experiments testing alcohol effects (“alcohol clamping”). With more refined methods of modeling, infusion was recently developed for self-administration experiments with free access or operant paradigms requiring work to gain access to alcohol. Results of two self-administration studies will be presented. The computer-assisted infusion system (CAIS), i.e. a software platform enabling for all these types of experiments is now made available to interested researchers.

S27.2

CHARACTERIZATION OF OPERANT INTRAVENOUS ALCOHOL SELF-ADMINISTRATION IN HUMANS

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Computer-Assisted Self-infusion of Ethanol (CASE) is a method of intravenous (IV) alcohol administration that allows alcohol self-administration in a laboratory setting, while controlling the breath alcohol concentration (BrAC) using a physiologically-based pharmacokinetic (PBPK) model-based algorithm. The objective of this study was to develop and characterize operant IV alcohol self-administration in non-dependent drinkers using two paradigms: free-access and progressive-ratio. Healthy non-dependent drinkers completed two IV alcohol self-administration sessions, each consisting of a 25-min priming phase followed by a 125-min phase where they could push a button for additional ethanol infusions, using a free-access (FA) schedule (one button press/infusion) and a progressive ratio (PR) schedule (increasing button presses for infusions). The number of rewards and peak and average BrAC were recorded, as well as the total and average number of button presses and button-press rate for the PR group. Regression analyses assessed effects of drinking history, alcohol sensitivity and personality. Results indicated high degree of within-session correlation among self-administration measures for both paradigms, indicating high internal consistency. In the FA paradigm, self-administration measures were significantly associated with drinks/drinking day, alcohol sensitivity, and reward sensitivity. Alcohol urges following priming were associated with self-administration measures for both OB and PR paradigms and rates of self-infusion were associated with subjective response to alcohol and measures of expectancy and impulsivity. Individuals with higher expectancy of negative alcohol effects and with higher impulsivity showed lower responses on both paradigms. These results indicate that IV self-administration measures reflect drinking history and alcohol sensitivity and expectancy effects.

S27.3

STUDYING THE ROLE OF FEEDING-RELATED PATHWAYS IN ALCOHOLISM VIA HUMAN LABORATORY STUDIES

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Feeding-related peptides may play a role in alcohol-related behaviors, including alcohol craving and consumption. We have reported, for example, that anorexigenic peptides such as insulin and thyroid hormones may be associated with alcohol craving and alcohol consumption. More recently, we started investigating the possible role of ghrelin in alcoholism. For example, human studies with alcohol-dependent individuals suggest that higher blood levels of the orexigenic gut-brain peptide ghrelin are associated with higher self-reported alcohol craving. Our most recent longitudinal study indicated a significant difference in baseline ghrelin levels between non-abstinent and abstinent subjects, as well as inverse ghrelin’s patterns between the two groups during the study. Furthermore, there was a positive significant correlation between baseline ghrelin levels and self-reported alcohol craving. More recently, we performed a human laboratory study in non-treatment seeking heavy drinking alcohol-dependent individuals where subjects are randomized to receive an intravenous (IV) administration of ghrelin 1 microg/kg, 3 microg/kg or saline solution (placebo). Then, subjects undertake an alcohol cue-reactivity session to assess cue-induced urge to drink, as well as other subjective (e.g. attention to cues) and physiological (heart rate, salivation) measures of alcohol cue-elicited craving. In this study, administration IV of ghrelin resulted in acute increase in craving (cue-induced urge to drink). Altogether, these data suggest that the ghrelin system may represent a novel pharmacological target to treat patients with alcoholism.

S27.4

SUBJECTIVE RESPONSES TO ALCOHOL IN THE LAB PREDICT NEURAL RESPONSES TO ALCOHOL CUES

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Subjective responses to alcohol represent biomarkers of alcoholism liability and treatment response. This study aimed to integrate the human laboratory with neuroimaging by testing whether subjective responses to alcohol during alcohol administration predict neural responses to alcohol cues in the scanner. Study design included a within-subjects controlled alcohol administration in the laboratory followed by an alcohol taste cues blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) task. Twenty alcohol dependent individuals from the Los Angeles community were recruited (6 females; 90% Caucasian; mean age ± 29.4). Laboratory assessments of subjective alcohol high, liking, wanting (i.e., craving), positive reinforcement, and negative reinforcement during alcohol administration were entered as predictors of neural response to the presentation of alcohol versus control cues in the scanner (whole-brain cluster-corrected at Z > 1.96, p < 0.05). Alcohol craving during alcohol administration was found to predict less neural activity to alcohol cues in regions including the precentral and postcentral gyr, and supplementary motor area. Alcohol high, however, predicted greater neural activity to alcohol cues in regions including the anterior cingulate cortex, angular gyrus, occipital cortex, and superior parietal lobule. Consistent results were observed across the reinforcement factors such that greater positive and negative reinforcement in the lab predicted greater activation during alcohol cue presentation in regions including the precuneus, anterior cingulate cortex, and cuneal cortex. This study provides initial evidence that subjective

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