Aims. Earlier studies have shown that moderate to high doses of alcohol generally have no effect or decrease blood testosterone levels in men. Recently however, it was reported that a low dose of alcohol transiently elevated testosterone levels in healthy men (Sarkola and Eriksson 2003). The aim of the present investigation was to determine the effect of a semi-high dose of alcohol on plasma testosterone levels in men.

Methods. Healthy nonalcoholic Finnish men were recruited. Each subject participated in a random order in two sessions, one including placebo (ginger beer) and one with alcohol mixed with the juice. The alcohol dose was 1.5 g/kg and was consumed within 3 hours starting at 19.00. Blood was collected from the median cubital vein 18.30, 20.00 and 23.00 in the evening, and 10.30, 12.00 and 13.00 next day.

Results. In contrast to earlier findings with corresponding alcohol doses (Ylikahri et al., 1974) an alcohol-mediated testosterone elevation (12%, p = 0.007, Mann-Whitney) was determined by the end of the evening and no significant decrease was observed during the hangover phase.

Conclusions. With a view to earlier findings of testosterone decreases the present finding of a testosterone elevation after a semi-high alcohol dose in men supports the notion of variable effects depending on situational factors. Such a factor could be the degree of fasting, which was pronounced in the earlier studies. Thus, the fed state in the present experiments in combination with lower degree of hangover stress could have changed the subtle balance between the inhibited testosterone catabolism in the liver and the inhibited synthesis in the gonads.

PA2-10
TESTOSTERONE PROMOTES ALCOHOL DRINKING IN AN F2-POPULATION OF THE AA AND ANA RAT LINES
Etelaelahi TJ, Eriksson CJP (Finland)

Aims. A positive relation between endogenous testosterone levels, alcohol-induced testosterone elevations and voluntary alcohol drinking was recently observed in our alcohol-prefering AA and non-prefering ANA rat lines (Apter and Eriksson 2003). In the present study we wanted to get more conclusive evidence for the role of the HPG axis in the promotion of alcohol drinking by using the F2 experimental design.

Methods. Alcohol-prefering AA and alcohol-non-prefering ANA rat lines were crossed-bred to form an F1 population from which the final F2 population (n = 283) was derived by random breeding. All animals were challenged with an alcohol dose (2 g/kg) after which a three weeks voluntary alcohol drinking period took place. After a washout period of one week, half of the animals were cross-bred to form an F1 population from which the final F2 population (Apter and Eriksson 2003). In the present study we wanted to get more conclusive evidence for the role of the HPG axis in the promotion of alcohol drinking by using the F2 experimental design.

Results. Higher endogenous serum testosterone levels (9.3 ± 0.9, mean ± SE) were detected in male rats in the high alcohol consumption group compared with low alcohol consumption (6.1 ± 0.8 nmol/L, p = 0.007, Mann-Whitney). Alcohol intoxication after the drinking period resulted in significantly higher frequency of testosterone elevations in the high drinkers compared with low drinkers (p = 0.046, Chi-square).

Conclusions. The present results provide strong evidence for the role of the HPG axis in the inhibited regulation of voluntary alcohol drinking.

POSTER SESSION PA2
Neuroscience and addiction

PA2-1
SHAPE ANALYSIS OF INSULIN IN ALCOHOL DEPENDENCE
Yonsei University College of Medicine

Aims. Excessive chronic alcohol consumption is associated with significant shrinkage of brain tissue and impairment of associated cognitive functions. In the present study, we have chosen to investigate the effects of chronic alcohol consumption on the insulin. Convergent evidence has supported the anterior-posterior functional organization within the insular cortex: the anterior insular cortex subserves a role as a limbic integrating cortex, while the posterior insular cortex subserves ascending visceral symptoms. Recently, some experimental studies have suggested that the dysfunction of the anterior insular cortex may be involved in substance abuse. We hypothesized that the anterior part of the insula is more vulnerable to the posterior part of the insula to alcohol-related damage and that the shape deformity of anterior insula would correlate with poorer neurocognitive performance.

Methods. Subjects were 20 patients with alcohol dependence and 20 normal healthy subjects. A landmark-based structural and surface shape analysis of the insula was performed using high-spatial resolution magnetic resonance imaging. We investigated the correlation between the shape deformation of the insula and the clinical/neurocognitive characteristics.

Results. The findings demonstrated shape deformations in the inferior, posterior insula, which corresponds to the central dysgranular region, of the left and right insula in alcohol dependent patients compared with normal controls. Furthermore, the inferior shape deformations demonstrated significant correlations with the memory impairment.

Conclusions. Shape analysis of the insula could provide a more sensitive approach than volumetric measures for detecting small volume changes that might be restricted to subregions of the insula.

PA2-2
MORPHOMETRIC CHANGES OF CORPUS CALLOSUM IN CHRONIC ALCOHOLICS—A MAGNETIC RESONANCE IMAGING STUDY
Choi JH, Kim K
Seoul Veterans Hospital

Aims. The purpose of this study determines the difference on corpus callosum between chronic alcoholic patients and controls, and relationship between the severity of ethanol intake and the degree of this atrophy.

Methods. A clinicoradiologic study was carried out in 20 chronic alcoholics and age-matched controls. All subjects were male and right-handed. To estimate alcohol habits for subjects, structured interviews have been made. Measurement of the midsagittal corpus callosum area and thickness (genu, trunkus and splenium), as well as the frontal lobe index (FLI) and the width of the cortical sulci (SWS) on T1- and T2-weighted Magnetic Resonance Images were performed.

Results. Compared to controls, alcoholics had a significantly decreased corpus callosum area and thickness (mainly in genu), and significantly increased FLI and SWS. The callosal area negatively correlated with the cortical atrophies and the area of genu of the corpus callosum negatively correlated with the frontal atrophies. Moreover, the reduction of corpus callosum correlated with the total lifetime dose of ethanol consumed.

Conclusions. In chronic alcoholics, atrophy of the corpus callosum is a common finding and may reflect the severity and pattern of cortical damage. And the degree of callosal atrophy correlated with the severity of ethanol intake as well.

PA2-3
CEREBRAL GLUCOSE METABOLISM MEASURED WITH 18-FDG PET IN ALCOHOLICS AND SUBJECTS AT HIGH-RISK FOR ALCOHOLISM
(Institute of Neuropsychology, University of Munich, Munich, Germany)

Aims. A decrease in the global cerebral glucose metabolism has been repeatedly described among alcohol dependent patients. It is unclear whether these changes result from long-term alcohol use or whether these differences are disease defining traits. Therefore, we measured in vivo cerebral metabolic differences between alcohol dependent patients, first-degree relatives and healthy control persons.

Methods. 10 male alcoholics, 10 subjects at risk for alcoholism (sons of alcoholics) and 18 healthy male controls underwent two 18-FDG PET (180 ± 20 MBq) scans with or without a lorazepam (2 mg) pretreatment. The PET data were analysed using SPM. All subjects were interviewed with the German version of the European Addiction Severity Index (EuropeASI).

Results. Overall cerebral metabolism did not differ between the alcohol dependent patients, their first degree relatives and the normal controls. SPM analyses of the rCGM in the baseline condition revealed a significantly higher metabolic activity in the bilateral caudate nucleus and a significantly lower metabolism in the left insula in detoxified alcoholics compared to controls. However, we did not detect similar differences between the subjects at high risk for alcoholism and the controls.
Conclusions. The results from our study do not confirm the hypothesis of a global metabolic decrease among alcohol dependent patients. A metabolic decrease was found within the bilateral caudate nucleus covering parts of the dorsal striatum. As these findings were limited to alcohol dependent patients, the observed differences might critically rely on long term alcohol use.

PA2-4
NEUROPLASTICITY IN BRAIN REWARD CIRCUITRY FOLLOWING A HISTORY OF ETHANOL DEPENDENCE: A CANDIDATE ANTI-REWARD PROCESS

Hansson AC, Rimondini R, Sommer WH, Heilig M (USA)

Aims. Mitogen-activated and extracellular regulated kinase (MEK) and extracellular signal-regulated protein kinase (ERK) pathways may underlie ethanol-induced neuroplasticity. Here, we used the MEK inhibitor U0126 to probe the role of MEK/ERK signaling for the cellular response to an acute ethanol challenge in rats with or without a history of ethanol dependence.

Methods. A post-dependent state was induced using repeated cycles of alcohol intoxication and withdrawal in Wistar rats. We reasoned that the expression of both c-fos and egfr-1 after acute ethanol challenge, administered in the presence or absence of the MEK1/2 inhibitor U0126, would delineate structures differentially involved in the initial ethanol response in dependent and non-dependent animals, respectively, and would thus serve as a marker for neuroadaptive processes associated with the development of the dependent state. In situ hybridization for c-fos and egfr-1 mRNA was carried out in forebrain structures known to be involved in the mediation of positive and negative drug reinforcement.

Results. Ethanol (1.5 g/kg, i.p.) induced expression of the marker genes c-fos and egfr-1 in brain regions associated both with rewarding and stressful ethanol actions. Under non-dependent conditions, alcohol-induced c-fos expression was generally not affected by MEK inhibition, with the exception of medial amygdala (MeA). In contrast, following a history of dependence, a markedly suppressed c-fos response to acute ethanol was found in orbitofrontal cortex (OFC). The suppressed ethanol response in the OFC and in nucleus accumbens shell (AcSh), key components of circuitry mediating positive drug reinforcement, was returned to normal by pre-treatment with U0126, demonstrating a recruitment of an ERK/MEK mediated inhibitory regulation in the post-dependent state. Conversely, in brain areas involved in stress responses (MeA, paraventricular nucleus, PVN), a MEK/ERK mediated cellular activation by acute ethanol was lost following a history of dependence.

Conclusions. These data reveal highly region-specific neuroadaptations encompassing the MEK/ERK pathway in ethanol dependence. Recruitment of MEK/ERK mediated suppression of the ethanol response in OFC and AcSh may reflect deactivation of ethanol as a reinforcer, while loss of a MEK/ERK mediated response in MeA and PVN may reflect tolerance to its aversive actions. These two neuroadaptations could act in concert to facilitate progression into ethanol dependence.

PA2-5
INFLUENCE OF EMOTIONAL STATE- AND CONTEXT-RELATED CRAVING ON NEURAL CUR-REAIVITY IN ALCOHOL DEPENDENT PATIENTS

Lemетagger T, Klein S, Klein O, Hintz T, Vollmert C, Zimmer A, Mann K, Smolinka MN (Germany)

Objectives. The functional imaging literature on alcohol associated cue-reactivity in alcoholics shows a high heterogeneity of study results. We investigated whether the influence of context- and emotional state-related craving in alcohol dependent patients is able to explain some of these heterogeneous results. In order to do so, we distinguished different types of ‘alcohol temptation’ (craving) in association with brain activity.

Methods. 53 abstinent alcoholics underwent fMRI while watching alcohol associated, abstract and neutral stimuli. Contrasts were created to get evidence on different levels of activation in association with alcohol-stimuli compared to stimuli of neutral and abstract valence. Different context- and emotional state-related craving was assessed by four extracted factors of the Alcohol Abstinence Self Efficacy (AASE) ‘temptation’-scale (reward, relief, testing personal control, psychological and physical needs), whose 20 items were previously subjected to a principle component analysis. Image processing and statistical analysis were performed using SPM 5. The influence of the four factors on neurophysiological cue-reactivity was assessed by using a multiple linear regression analysis (p < 0.005).

Results. We found significant positive associations between ‘reward craving’ and activations in the mesolimbic reward system like the right dorsal striatum and prefrontal regions. A significant negative association was derived between the factor ‘relief craving’ and the activation of regions in the insula as well as frontal and parietal regions. Relevant positive correlations were observed between the ‘testing personal control’ factor and neuronal cue reactivity in the bilateral rostral anterior cingulum, prefrontal cortex and the left hippocampus with insula regions. Finally, craving due to psychological and physical needs was positively associated with activations in the bilateral cerebellum, left gyrus fusiformis and other occipital, temporal and parietal regions.

Conclusions. These results indicate that different contextual and emotional state factors are able to explain some of the heterogeneous study results in neural cue reactive. The dominance of ‘reward craving’, more related to social stimuli, is linked to higher neuronal activity in the mesolimbic reward system. ‘Relief craving’, involving more intra-individual cues like anger and sadness, is associated with deactivations in regions related to drug urges (insula) and visual orientation (parietal and occipital). Craving in relation to ‘test one’s control over drinking’ is associated with an activation of the anterior cingulate, a region involved in the regulation of emotional responses. The left gyrus fusiformis, which plays a role in object recognition, an aspect of visual object processing, is associated with craving due to ‘psychological and physical need’.

PA2-6
BIOGENIC AMINES METABOLISM IN RAT BRAIN FOLLOWING VENTRICULO-CISTERNAL PERFUSION BY ETHANOL

Zimatkine SM, Denisenko AV (Belarus)

Aims. The estimation of changes of biogenic amines metabolism in rat brain following ventriculo-cisternal perfusion by ethanol solution.

Methods. Under the general anesthesia of male Wistar rats were placed into the stereotaxic apparatus and artificial liquor was administered into the lateral ventricle through the needle using the syringe automatic micropump, during 1 hour with a constant speed (12 ml/min). The samples of perfusate released from the large cistern (cisterna magna) of the brain stem through the needle and plastic capillary were collected every 10 min for examination. Then the artificial liquor was replaced for artificial liquor + 100 mM ethanol solution and 10 min samples of perfusate were collected during 2 hours. Then rats were sacrificed and the samples of 6 brain regions were analyzed and compared with the similar brain samples of rats perfused 3 hours with artificial liquor only. Biogenic amines, their precursors and metabolites were analyzed by HPLC with electrochemical detection.

Results. In perfusate released from cisterna magna tryptophan, 5-hydroxytryptophan, serotonin, 5-hydroxyindoleacetic acid, tyrosine, 3,4-dihydroxyphenylalanine, 3,4-dihydroxyphenylacetic acid, homovanillic acid and 3-methoxy-4-hydroxyphenylglycol have been found. In brain samples the same compound as well as dopamine, norepinephrine and 3-methoxytyramine were detected. It was found that ventriculo-cisternal perfusion by ethanol significantly increased the tryptophan, serotonin and tyrosine levels in perfusate. In addition the ventriculo-cisternal perfusion by ethanol during 3 hours significantly increased the tyrosine level in brain cortex and midbrain. DopA in hypothalamus and midbrain, DOPAC in hypothalamus, but decreased the serotonin level in hypothalamus, 5-hydroxyindoleacetic acid in medulla oblongata and dopamine level in striatum.

Conclusions. The determination of biogenic amines, their precursors and metabolites in ventriculo-cisternal perfusate give the possibility to examine the dynamics of biogenic amines metabolism in the brain following ethanol administration.

PA2-7
DIFFERENTIAL EXPRESSION OF CHRI1 AFFECTS STRESS-INDUCED ALCOHOL CONSUMPTION IN MICE?

Molander A, Deusing J, Wurst W, Spanagel R (Germany)

Aims. Dysregulation of the corticotrophin-releasing hormone (CRH) system mediating endocrine and behavioural responses to stress has been attributed to a variety of stress related psychiatric disorders, such as drug abuse and...
alcoholism. Two CRH receptors, CRH1 and CRH2, have been identified. Previous studies (Sillaber et al., 2002, Trentleman et al., 2006; Timpl et al., 1998) show that primarily the CRH1 receptor is associated with alcohol consumption and that global CRH1 knock-out (KO) mice (CRH1−/−) increase their alcohol intake after repeated exposure to stress (Sillaber et al.; 2002). In this study, we investigated the role of centrally expressed CRH1 receptors on alcohol intake, comparing a CNS specific CRH1 KO mouse model (CRH1 Nestin-Cre) to the global CRH1−/− mice and wild-type (wt) controls.

Methods. After a habituation period of approx. 12 weeks to 8% (v/v) ethanol versus water, the voluntary alcohol consumption was measured: 1) before, during and after three days of consecutive exposure to the psychological and severe stressor ‘social defeat stress’, and 2) before, during and after three days of consecutive exposure to the mild and emotional stressor ‘swim stress’. There was a time-period of approx. four weeks in-between the social defeat and the swim stress sessions.

Results. We found no difference in daily ethanol intake between the CRH1−/− mice and their wt controls during baseline measurements and before stress exposure. During social defeat stress the CRH1−/− mice significantly increased their ethanol intake compared to baseline values and compared to the wt controls. The increase lasted 1–2 days after the last day of stress exposure, after which the ethanol intake returned to baseline levels. The (CRH1 Nestin-Cre) KO mice also differed in their basal ethanol intake as compared to the wt mice during baseline measurements. However, during and shortly after (1–2 days) social defeat stress the (CRH1 Nestin-Cre) KO decreased their ethanol intake compared to the wt controls. All mice responded similar to the ‘swim stress’, with a slight increase in ethanol intake, as compared to the baseline values.

Conclusions. These data show an opposing role of CRH1 in CNS and the extrahypothalamic HPA system in terms of stress-induced alcohol intake as compared to the wt mice during baseline measurements. However, during and shortly after social defeat stress the (CRH1 Nestin-Cre) KO mice decreased their ethanol intake compared to the wt controls. The role of the CRH1 will in the near future also be examined in alcohol deprivation as well as withdrawal and anxiety related drinking models.

PA3-1
ALDH2 AND ADH1B POLYMORPHISMS IN JAPANESE FEMALE ALCOHOLICS
Kimura M, Matsushita S, Miyakawa T, Rob T, Yokoyama A, Higuchi S (Japan)

Aims. Polymorphisms of the aldehyde dehydrogenase-2 (ALDH2) and alcohol dehydrogenase-1B (ADH1B) genes are associated with alcohol dependence (AD). Patients who develop AD in spite of as negative genetic risk factors such inactive ALDH2 and the superactive ADH1B are hypothesized to possess other strong environmental or psychological factors that drive individuals to drinking. This study aims to identify the effect of ALDH2 and ADH1B polymorphisms in Japanese female alcoholics and reveal the characteristics of female alcoholics with inactive ALDH2.

Methods. The subjects were 115 Japanese female alcoholics and 438 male alcoholics hospitalized in Kurehama Alcoholism Center. The diagnosis of alcohol dependence and other psychiatric disorders was based on DSM-IV criteria. ALDH2 and ADH1B genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods as previously described.

Results. The frequencies of ALDH2 and ADH1B genotype distributions did not differ between female and male alcoholics. The onset age of female alcoholics with the inactive ALDH2 genotype was significantly lower than that of those with active ALDH2 genotype. The prevalence of psychiatric comorbidities such as eating disorders, panic disorders, and borderline personality disorder was higher in patients with inactive ALDH2 than in those with active ALDH2. Female alcoholics with the superactive ADH1B genotype tended to show earlier onset and higher prevalence of psychiatric comorbidities than those with the normal ADH1B genotype.

Conclusions. There were no sex differences in the distribution of ALDH2 and ADH1B polymorphisms, but female alcoholics with inactive ALDH2 showed earlier onset and higher frequencies of psychiatric comorbidities than those with active ALDH2.

PA3-2
SNP- AND HAPLOTYPE ANALYSIS OF THE TRYPOTPHAN HYDROXYLASE 2 (TPH2) GENE IN ALCOHOL DEPENDENT PATIENTS AND ALCOHOL RELATED SUICIDE
Zill P, Preuss UW, Kollier G, Bondy B, Stryka M (Germany)

Aims. Several lines of evidence indicate that disturbances of the central serotonergic system are involved in the pathophysiology of alcohol dependence and suicidal behavior. Recent studies have indicated that a newly identified second isoform of the tryptophan hydroxylase gene (TPH2) is preferentially involved in the rate limiting synthesis of neuronal serotonin. Genetic variations in the TPH2 gene have been associated with an increased risk for major depression and suicidal behavior.

Methods. We performed single SNP (single nucleotide polymorphism), linkage disequilibrium and haplotype studies on 353 alcohol-dependent patients of whom 102 individuals had a history of at least one suicide attempt and 305 healthy controls with 20 SNPs covering the entire gene region of TPH2.

Results. Neither single SNP, nor haplotype analysis could detect significant associations with alcohol dependence and/or suicidal behavior among alcohol-dependent patients. One major haplotype block of strong linkage disequilibrium between introns 5 and 8 of the TPH2 gene has been found in alcoholics and controls which is in concordance with recent reports.

Conclusions. In conclusion, our results suggest that single SNPs, respectively haplotypes of the TPH2 gene are unlikely to play a major role in the pathophysiology of alcohol dependence or the alcoholism-related phenotype suicidal behavior. Further analysis are needed to confirm these results.

PA3-3
ASSOCIATION OF HARRIS LINES AND SHORTER STATUTE WITH ETHANOL CONSUMPTION DURING GROWTH
González-Reimers E, Pérez-Ramírez A, Santolaria-Fernández F (Spain)

Aims. Ethanol consumption may impair bone growth. Transverse radiopaque lines (Harris lines) have been interpreted as manifestations of bone growth...