prefrontal cortex in alcoholics compared with healthy controls. Cue-induced activation of these brain areas was pronounced in alcoholics who subsequently relapsed during the observation period. The basolateral amygdala was found to have a significantly diminished volume in relapsed subjects relative to controls and abstinent patients. Baseline craving at the time of study was stronger for relapsed than abstinent patients and correlated inversely with amygdala volume, low presynaptic dopamine production and availability of D2 dopamine receptors. No such relationships were observed in healthy control subjects.

Conclusion: Together, these observations point to a relationship between dopaminergic dysfunction, cue-induced BOLD-response, amygdala volume reduction, alcohol craving and eventual relapse into alcohol consumption. A multimodal approach to illuminate alcohol relapse seems to be promising.

S-41-05

A comparative study of young, and elderly patients suffering from "alcoholism"

H. Shahpesandy. *Dept. of Psychiatry, Palucanska, Slovakia*

Objective: The aim was to compare manifestation, and complications of alcoholism in the elderly, and young adults.

Methods: 56 elderly (E) (mean age 70.2), and 59 young (Y) patients (mean age 43), diagnosed by ICD-10, and MALT. We focused on biological markers of alcoholism, (AST, GGT, MCV), and complications of alcoholism. Statistical analysis T-test was used.

Results: The family history (FH) is positive in 17.8 % of E and 47 % of Y. AST was elevated in 53.6 % of E, and 84.7 % ($p<0.05$) of Y, GGT 60.7 % of E, and 91.5 % of Y ($p<0.05$). MCV in 60.7 % of E, and 74.5 % Y. Somatic disease were found in 60.3 % of E, and 25.7% of Y, psychiatric disorders in 34.6% of E, and 18.26% of Y. By MALT, disease of liver was found in 66% of E, and 93.2% of Y ($p<0.05$), polyneuropathy in 48.2% of E, and 5% Y ($p<0.001$), consumption of 300 ml (240 ml for women) once or more a month in 49% of E, and 76.3% of Y ($p<0.01$). MALT supports the diagnosis of Alcohol Dependence in 98.2% of E, and 100% of Y, but ICD-10, in 92.8% of E, and in 79.7% of Y.

Conclusion: Young alcoholics compared to elderly have more often positive FH, drink significantly bigger amounts of alcohol which reflects in elevation of GGT. On the other hand, elderly subjects have more somatic, and psychiatric complications.

Tuesday, April 5, 2005

S-45. Symposium: Genetic analyses of treatment-relevant phenotypes in alcohol dependence

Chairperson(s): Gunter Schumann (Mannheim, Germany), Michael Soyka (Munich, Germany)
08.30 - 10.00, Gasteig – Lecture Hall Library

S-45-01

Candidate genes in alcohol withdrawal process: A relevant phenotype?

P. Gorwood, P. Pickering, C. Boni. *CHU Louis Mourier, Colombes, France*

Objective: Alcohol withdrawal is sometimes associated with severe, life-threatening, symptoms. This may help to pinpoint genetic studies to a more homogenous subgroup of patients that could share common mechanisms.

Methods: We recruited a new sample of 120 male patients with alcohol-dependence, focusing on any lifetime symptoms of severe withdrawal. Two candidate genes were analysed, and compared with their distribution in healthy controls. Two markers in the CB1 gene were analysed, because of the role of the CB1 in the tolerance phenomenum, and one SNPs in the DAT gene, because three studies, including ours, detected a significant role of the A9 allele.

Results: The DAT gene was once again associated with delirium tremens and withdrawal seizure, both symptoms being found in excess when the A9 is present (linear trend, $p=0.08$). When our two samples are considered, the A9 allele has a much more significant role. The CB1 gene was tested for two markers, with low linkage disequilibrium, thus increasing the chance to detect an effect of different haplotypes. Nevertheless, no effect was observed, nor for the previously involved MspI polymorphism, neither for the new XcmI polymorphism.

Conclusion: The DAT gene looks involved in very severe alcohol withdrawal symptoms, with a tendency for an excess of the A9 alle ein patients with these complications. This is now the fourth study showing that the A9 allele could be involved. This does not look the case for the CB1 gene, for both markers tested.

S-45-02

NPY gene in anxiety-related phenotypes and alcohol dependence

M. Heilig. *NIAAA, Bethesda, MD, USA*

Objective: Central expression of NPY is recruited as an adaptive, opposing-process stress response, mimicked by pharmacological actions of exogenous NPY. Stress-reactions are are at the core of negative affect and relapse in alcohol dependence. We have therefore carried out human genetic studies to examine a possible association between variation in the NPY gene and alcoholism; and experimental animal studies to evaluate the potential of this system as a treatment target.

Methods: Human studies: Haplotype based analysis of 5 polymorphic markers for association with diagnosis of alcoholism, or more narrowly defined phenotypes in appr 500 alcohol dependent Swedes and appr 200 healthy volunteers. Experimental studies: Intracranial injections of the NPY-Y2 antagonist BIIE0246 to augment central NPY transmission through blockade of presynaptic receptors, combined with operant alcohol self-administration in animals with or without a history of dependence.

Results: Human: A haplotype-based association between the diagnosis of alcoholism and several of the markers was found. Association was further strengthened when restricted to late-onset alcoholics, characterized by anxious personality traits Experimental: Dose dependent and behaviorally selective suppression of alcohol self-administration by BIIE0246; markedly increased sensitivity to this effect in animals with a history of dependence.

Conclusion: Variation in the preproNPY gene contributes to susceptibility for alcoholism, in particular the late onset type characterized by anxious personality traits. Potentiation of central NPY transmission is a promising novel principle for treatment of alcoholism.

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S-45-03

Glutamatergic signalling genes and their association with alcohol dependence and associated phenotypes

G. Schumann. *CIMH Psychiatry and Psychotherapy, Mannheim, Germany*

Objective: Alcohol dependence is a disorder with strong genetic influences and heritability estimates ranging between 40-60%. Ethanol-induced glutamatergic signal transduction has been shown to influence pathophysiological mechanisms central to the development of alcohol dependence, including tolerance, withdrawal symptoms, craving, relapse and ethanol-related neurotoxicity.

Methods: Ethanol acts specifically by inhibiting ionotropic N-methyl-D-aspartate (NMDA) receptors. Glutamatergic activation of NMDA-receptors initiates a Ca2+-mediated signal transduction cascade which involves the Ca2+-binding molecule calmodulin (Cam). Cam activates Calmodulin-dependent kinase (CamK) and the Ras pathway, leading to activation of the transcription factor CREB. Phosphorylation and expression of CREB and CamKIV in the nucleus accumbens and other brain structures relevant for ethanol dependence are influenced by ethanol consumption and withdrawal. Other proteins activated by NMDA receptors via PSD 95 include neuronal nitric oxide synthase (nNOS) and its effector GMP-kinaseII as well as Phosphatidyl Inositol Kinase 3 and the MAP kinase pathway. The goal of the present study is to systematically analyse genetic variations of NMDA-receptor subtypes and functionally related signal transduction genes which are known to be involved in glutamatergic neurotransmission in ethanol dependence in a large sample of German patients with alcohol dependence and unrelated controls. We attempted to include those NMDA-related genes where evidence for an alteration of alcohol drinking behaviour has been given in behavioural tests using knock-out mice. To this end we identified 10 genes involved in glutamatergic signal transduction and performed a SNP-discovery programme by sequencing analysis of the regulatory domains, exons and exon-intron boundaries of each gene. Next we performed haplotype analyses and genotyped those SNPs which account for the 95% most frequent haplotypes in a sample of 600 patients with alcohol dependence and 500 controls.

Results: Genotype-phenotype analysis with particular emphasis on oligogenic interactions was performed using a classical regression analysis.

Conclusion: The results of this project will be presented.

S-45-04

Genetic analysis of treatment-relevant phenotypes in alcohol dependence

M. Soyka, V. Hesselbrock, U. W. Preuss, G. Koller, P. Zill, B. Bondy. *University of Munich, Departme, Munich, Germany*

Objective: A number of different neurotransmitters are involved in mediating alcohol effects including serotonin, GABA and glutamate (Spanagel et al 2005). Recent studies have suggested that genetic variants of the GABA-A receptor alpha2 subunit gene (GABRA2) are associated with alcohol dependence.

Methods: 291 (231 male) treatment-seeking alcohol-dependent individuals and 295 (153 male) control subjects were enrolled into the study. Characteristics of alcohol dependence were obtained using the SSAGA (Semi-Structured Assessment of the Genetics of Alcoholism, German Version). Genotyping of 10 SNPs across the GABRA2 gene was performed following previous reports and using PCR.

Results: One genetic variant was detected to significantly differ between alcohol-dependent subjects and controls. Two common haplotypes and their complements were identified containing this SNP and were present in 90.5% of controls and 93.5% of the alcohol-dependent individuals. One of these haplotypes, complimentary to the one identified previously, was significantly associated with characteristics of alcohol withdrawal and severity of alcohol dependence.

Conclusion: These findings support and extend the two previous studies implicating the GABA-A receptor as contributing to the genetic risk for alcohol dependence. Possible implications of these findings are discussed. Spanagel R, Pendyala G, Abarca C, Zghoul T, Sanchis-Segura C, Magnone MC, Lascorz J, Depner M, Holzberg D, Soyka M, Schreiber S, Matsuda F, Lathrop M, Schumann G, Albrecht U (2005): The clock gene Per 2 influences the glutamatergic system and modulates alcohol consumption. Nat Med 11: 35-42

Tuesday, April 5, 2005

S-59. Symposium: Difficult to treat addicted patients

Chairperson(s): Anne-Marie Pezous (Paris, France), Christian Haasen (Hamburg, Germany)
16.15 - 17.45, Gasteig - Lecture Hall Library

S-59-01

Heroin assisted treatment of opiate dependence in five European countries

C. Haasen. *University Hospital Eppendorf, Hamburg, Germany*

Methadone has been established as the "gold standard" of maintenance treatment for opiate dependence in most European countries, with the exception of France, where buprenorphine is the main substance used in maintenance treatment. Despite its established effectivity, there is still a high rate of non-response to maintenance treatment with methadone and buprenorphine, which is characterized by additional drug use and insufficient compliance. A diversification of substances used for maintenance treatment is underway in most countries, including heroin assisted treatment, which has been initiated in five European countries: United Kingdom, Switzerland, the Netherlands, Germany and Spain. In most cases heroin assisted treatment has been initiated in the context of clinical trials, each with different goals and objectives and with different treatment designs. These differences and the potential future of heroin assisted treatment in Europe will be discussed.

S-59-02

Treatment of pregnant drug dependent patients

G. Fischer. *Univ-Klinik für Psychiatrie, Wien, Austria*

S-59-03

Comorbidity of drug dependence and ADHD syndrome

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