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

M. Casas. *Unitat de Psychiatria Hospital, Barcelona, Spain*

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S-59-04

Street work with crack addicted patients in the North of Paris

A.-M. Pezous. *ECIMUD Service de Psychiatrie, Paris, France*

S-59-05

Resistant patients are not difficult patients. The role of compliance.

A. Gual. *Hospital Clinic Institute of Nervous System, Barcelona, Spain*

Objective: In Psychiatry in general, and in the addictions field particularly, Resistance to treatment has usually been approached from a simplistic point of view. Instead, compliance is often a key issue to which psychiatrists pay scarce attention. This presentation pretends to underscore the role of compliance in resistance to treatments.

Methods: Review of literature addressing the issue of compliance with treatments in both clinical and psychosocial treatment trials.

Results: Compliance rates are low for many medical diseases, where the average non-adherence rate is 25%. In the field of Psychiatry bad compliance may be higher than 40% in the short term, and reach even higher rates (64%) in the long term management of diseases like bipolar disorders. In the Addictions field, compliance is often at the heart of early drop-outs and bad outcomes. In clinical trials compliance with pharmacological treatment is usually low. Naltrexone trials have reported compliance rates between 78-43%, while in studies with unsupervised disulfiram compliance rates may be as low as 18%.

Conclusion: There's strong evidence supporting the fact that better compliance leads to better outcomes. Hence, minimizing drop-outs should always be a priority for clinicians. Ways of improving compliance include patient factors (reactance, self-management), doctor factors (empathy, psycho education), drug factors (dosage, side effects) and family factors (supervision).

Sunday, April 3, 2005

SS-03. Section symposium: Neuroimaging in addiction research

Chairperson(s): Andreas Heinz (Berlin, Germany), Sophia Frangou (London, United Kingdom)
14.15 - 15.45, Gasteig - Philharmonie

SS-03-01

Structural neuroimaging and neuropsychological impairment in alcohol dependence

L. Reed. *Institute of Psychiatry Psychological Medicine, London, United Kingdom*

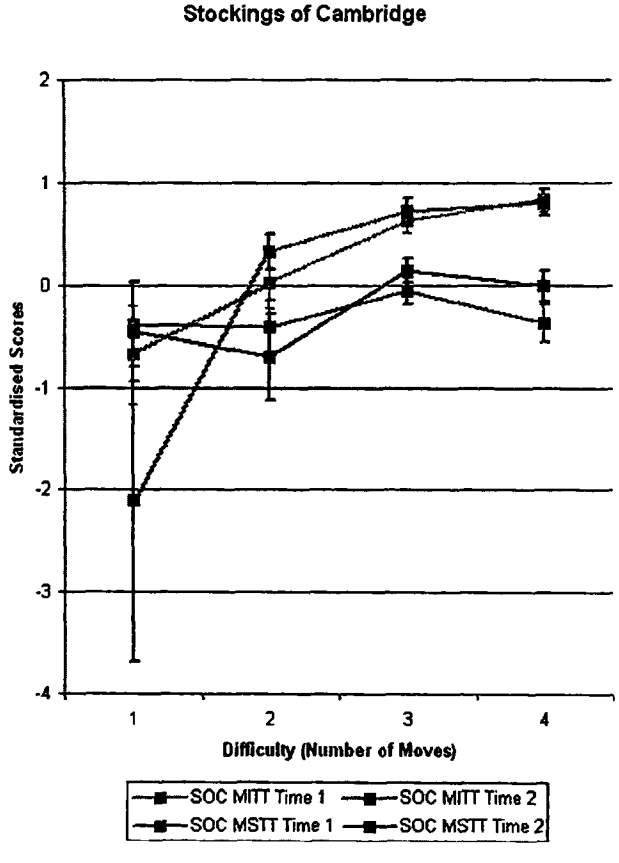
Objective: Alcohol dependence is associated with neuronal damage via direct and indirect mechanisms, detectable using magnetic resonance imaging (MRI) and associated with a range of cognitive impairments. The current pilot study examines neuropsychological functioning in a sample of alcohol dependent in-patients undergoing a medically-assisted alcohol withdrawal programme and aimed to investigate the trajectories of recovery of both memory and executive function deficits over the course of the treatment programme, and their association with MRI abnormalities.

Methods: Patients attending for inpatient medically assisted alcohol withdrawal completed neuropsychological assessment on days 1 – 5 and a second time on days 21 – 28. The neuropsychological battery comprised tests of general intellectual functioning, declarative memory function and executive function including the CANTAB Stockings of Cambridge SOC (planning ability) and Intra/Extra-dimensional Shift ID/ED - rule learning (non-verbal inhibition).

Results: The sample was predominantly male (19/30), mean age = 44.0 years, mean problem drinking history = 11.7 years. CANTAB subtests PAL (Paired Associate Learning) and PRM (Pattern Recognition Memory) at times 1 and 2 showed significant impairment and significant improvement over time, indicating partial recovery of memory function. The SOC subtest showed wide distribution of scores with some subjects markedly impaired on problems solved, there was no significant improvement over time for any measure.

Conclusion: Alcohol dependence is associated with substantial of deficits in memory and executive function which affect treatment compliance and understanding of complex treatments. While substantial improvements in memory, working memory and fluency tasks were observed by time 2, impaired planning and impulsivity measures were shown on CANTAB ED/ID and SOC tasks and showed no improvement over this time period. These latter deficits may indicate poorly reversible deficits in abstinence after alcohol withdrawal, and may predispose to relapse and may be associated with identifiable patterns of neuroimaging deficits particularly in ventrostriatal integrity.

Figure shows scaled scores (comparison with matched control data in units of standard deviation) for performance on the various levels of difficulty on the Stockings of Cambridge planning task. Mean initial thinking time (MITT), a measure of anticipatory :



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