The pleasant effects of food and alcohol intake are partially mediated by mu-opiate receptors in the ventral striatum, a central area of the brain reward system. Dopamine release, on the other hand, was associated with attribution of incentive salience to reward-predicting stimuli. Once excessive alcohol consumption is established, GABAergic and glutamatergic neuroadaptation underlie tolerance development and withdrawal symptoms. Combined functional brain imaging studies and studies wit positron emission tomography suggest that in the brain reward system, neuroadaptation in dopaminergic and opioidergic neurotransmission seems to augment neuronal responses to well-established, alcohol-associated stimuli while interfering with the acquisition of new, reward-seeking behavior patterns. In imaging studies with positron emission tomography, the availability of central mu-opiate receptors was measured with the radioligand carbon 11-labeled carfentanil in the ventral striatum of alcoholics and controls matched for mu-opiate receptor genotype. An increased availability in the ventral striatum, the core area of the brain reward system, and in the medial prefrontal cortex was found in alcoholics correlated with the severity of alcohol craving as assessed by the Obsessive Compulsive Drinking Scale (OCDS). Dysfunction of dopaminergic and opioidergic neurotransmission may contribute to alterations in positive and negative affect. In detoxified alcoholics, a high brain activity elicited by affectively positive cues was associated with a reduced relapse risk and may thus provide a protective factor that could be influenced by psychotherapy or additive medication.

CS05.02

Alcoholism, new data on gene X environment interaction

P. Gorwood [1,2], Y. LeStrat [1], M. Wohl [1,2], N. Ramoz [1]. [1] *Inserm U675, Paris, France* [2] *AP-HP (University Hospital Louis Mourier, Paris VII), Paris, France*

The presence of a Gene-Environment interaction means that when both factors are detected, the risk is increased compared to the sum (or the multiplication) of each of them.

A first way to use such interaction is to fix a known environmental factor (for example when all patients are being exposed to alcohol) and see how some genes may be involved on related- or endo-phenotypes.

The survival status of a male alcohol-dependent sample (n=126), recruited 9 years before, was for example analysed. We found that the C allele of the 5-HT1b gene, and tobacco dependence, were found in excess in the non-surviving patients, but that no endo-phenotypes are being directly involved.

With this same GxE approach, we also found that a haplotype of the DAT gene was involved in the risk of withdrawal seizures (Le Strat et al., in press) when all patients stopped, at least once in their lifetime, drinking alcohol.

A second strategy is to analyse some environmental factors potentially involved (such as early aggression) and compare these risk factors in patients with or without genetically related vulnerability (such as high initial tolerance to alcohol or familial history of dependence) to explain alcohol abuse or dependence. We will present a new study (S.A.G.E.) based on 3.000 young adults assessed for these factors.

Gene-Environment interactions approach could help to select more accurately specific candidate genes, identify more homogenous subgroups of patients, and ultimately, may lead to more focused, i.e. more efficient, prevention strategies.

CS05.03

Mouse strain related effects of cannabinoid and serotonergic ligands on alcohol appetence

L. Lanfumey [1,2], S. Kelai [1,2], M. Hamon [1,2]. [1] *INSERM u 677, Paris, France* [2] *UPMC, Paris, France*

Because cannabinoid (CB) and serotonin (5-HT) systems have been proposed to play an important role in drug craving, we investigated whether CB1 and 5-HT1A receptor ligands could affect voluntary alcohol intake in two mouse strains, C57BL/6J and DBA/2J, with marked differences in native alcohol preference. When offered progressively (3% to 10% ethanol) in drinking water, in a free-choice procedure, alcohol intake was markedly lower (~70%) in DBA/2J than in C57BL/6J mice. In DBA/2J mice, chronic treatment with the CB receptor agonist WIN 55,212-2 increased alcohol intake. This effect was prevented by both chronic CB1 receptor blockade by rimonabant or chronic 5-HT1A receptor stimulation by 8-OH-DPAT, which, on their own, did not affect alcohol intake. In C57BL/6J mice, WIN 55,212-2 had no effect but CB1 receptor blockade or 5-HT1A receptor stimulation significantly decreased alcohol intake. Parallel autoradiographic investigations showed that chronic treatment with WIN55,212-2 significantly decreased 5-HT1A-mediated [35S]GTP-γ-S binding in the hippocampus of both mouse strains. Conversely, chronic rimonabant increased this binding in C57BL/6J mice.

These results show that CB neurotransmission can exert a permissive control on alcohol intake, possibly through CB1-5-HT1A interactions. However, the differences between C57BL/6J and DBA/2J mice indicate that such modulations of alcohol intake are under genetic control.

CS05.04

Which treatment for whom? Data from project predict

K. Mann [1], F. Kiefer [1], M. Smolka [2], T. Lemenager [1]. [1] *Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany* [2] *Section of Systems Neuroscience, Dept. of Psychiatry & Psychotherapy, University of Dresden, Dresden, Germany*

A synopsis of current treatment options shows only moderate effect sizes. They could be improved considerably if individual predictors were available.

Previous attempts to identify predictors for the treatment response in alcoholism have mainly concentrated on social and personality variables. Project MATCH was such an attempt which finally failed. The same holds true for similar attempts in pharmacotherapy. Therefore, we set out for a large oligocentre trial ''Project PREDICT''. 432 patients are randomly assigned to treatment with acamprosate, naltrexone or placebo. At baseline patients are assessed with a battery of interviews, questionnaires and biological examinations (e.g. genetics). Specific emphasis is put on patients' individual pathways into relapse. It is determined whether relapse drinking respresented a positive reinforcer (''reward craving'') or a negative reinforcer (''relief craving''). This is assessed with questionnaires, the startle reflex and fMRI. We hypothesize, that patients who are a priori identified as ''positive reinforcers'' better respond to naltrexone. Negative reinforcers should benefit most from acamprosate.

All patients have been included by now. Preliminary analyses suggest that it is possible to distinguish between the two craving types. The equivalent of positive reinforcement in the startle reflex correlates with fMRI responses to cues with a positive valence of about 0.7. These methods might offer a platform for a targeted pharmacotherapy in alcoholism.

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