differences. Amisulpride is a selective antagonist at D_2/D_3 receptors with preferential activity at presynaptic autoreceptors. In marked contrast, clozapine and risperidone show higher affinity for $5HT_2$ and α than for D_2/D_3 receptors. Many traditional models used for drug screening involve the antagonism of effects induced by dopamine agonists and may be more relevant to positive symptoms (or even motor side effects) than to negative symptoms. However, a number of recent studies have attempted to develop alternative behavioural procedures modelling different psychotic symptoms. In such studies, amisulpride has been found to exert pro-hedonic activity and clozapine has been reported to reduce spontaneous or drug-induced social withdrawal. Further pharmacological analysis of these models may eventually provide more sensitive procedures and allow the discovery of more effective antipsychotic drugs.

NEURAL NETWORKS, NEUROPLASTICITY, AND NEUROMODULATION: A FRAMEWORK FOR UNDERSTANDING FORMAL THOUGHT DISORDER AND DELUSIONS

M. Spitzer. *Experimental Psychopathology Section, Department of Psychiatry, University of Heidelberg, Voss-Str. 2, D-69115 Heidelberg, Germany*

From a neurocomputational perspective, the cortex can be viewed as a computational surface that creates and maintains dynamic maps of representations of important sensorimotor and higher level aspects of the environment and the organism. Most importantly, representations of information in the cortex and in these maps have been demonstrated to dynamically change according to salience and frequency of the input. This feature is referred to as neuroplasticity. The fact that general operational characteristics of computational maps in the cortex can be fine-tuned according to specific processing needs is referred to as neuromodulation. Within this framework of cortical maps and their computational models, the following hypotheses regarding formal thought disorder as well as acute and chronic delusions are discussed:

(1) Formal thought disorder is caused by dysfunctional lexical access which can be modeled in terms of low signal-to-noise ratio within network information processing. Evidence for the crucial role of dopamine modulating signal-to-noise is presented and a model of schizophrenic thought disorder is developed, which allows a parsimonious explanation of a number of otherwise inexplicable or unrelated clinical phenomena and experimental results. (2) Acute delusions may represent a state of too high signal-to-noise, as suggested by some experimental studies and clinical features. (3) In chronic delusions, cortical representations become deformed as the result of long-term dysfunctional activation of the network.

In conclusion, the neurocomputational approach to schizophrenic symptoms provides new insights into psychopathological phenomena. The approach is detailed enough to allow empirical testing and has therapeutic implications.

S8. Craving reduction in alcoholism

Chairmen: H Sass, K Mann

ADDICTIONS AND DEPRESSIVE DISORDERS

J. Adès, M. Lejoyeux. *Service of Psychiatry, Hospital Louis Mourier, 92700 Colombes, France*

The frequent co-occurrence between addictions and depressive disorders is well established, even if many questions are unsolved concerning the nature of this interrelation. Three situations can be emphasized: Some addictive disorders, especially alcoholism, opiate and cocaine addictions are secondary to depressive disorders, and can be explained through the "self treatment" hypothesis of depression mood by psychoactive substances. The principal data are here discussed, for alcoholism and heroine addictions: the frequency of primary depressive disorders is well established in opiate addiction, better than for alcoholism.

- In most cases, depressive disorders are secondary to addictive disorders: this is especially the case for alcoholism, as well as about 80% of depressive disorders appear after the onset of alcohol abuse and wean with proctacted withdrawal. In those cases, depression could be due to the pharmacological and psychological effects of alcoholic intoxication, as many pharmacological data demonstrate the negative effects on mood of alcoholic during use.

The third hypothesis will be discussed involving an accidental co-occurrence of depressive disorders and addictions, considering the high prevalence of those troubles in the general population.

RESULTS OF A CONTROLLED MULTICENTER STUDY WITH RITANSERIN AND THE EFFECTIVENESS OF OTHER SEROTONERGIC AGENTS IN ALCOHOLISM

J. Boening, G.A. Wiesbeck. *Department of Psychiatry, University of Wuerzburg, Fuechsleinstr. 15, 97080 Wuerzburg, Germany*

There is considerable evidence from both human and animal studies that serotonergic mechanisms play an important role in the modulation of alcohol intake and dependence (LeMarquand et al 1994). Yet, only a few serotonergic substances have been tested in clinical trials with a satisfying methodological design (Boening 1996). *Fluvoxamine,* a specific serotonin reuptake inhibitor, showed no efficacy in a controlled European multicenter study with 530 alcohol dependents who were treated for six months (Chick, unpbl.). *Fluoxetine* also failed to be superior to placebo in a 12-week trial with 101 alcohol dependent patients (Kranzler et al 1995). In animal studies the $5\text{-}HT_2$ receptor antagonist *ritanserin* was able to significantly reduce both the preference for and the intake of alcohol and cocaine. In an early phase II trial positive effects of *ritanserin* were shown in humans as well (Monti and Alterwain 1991). Therefore, it was hypothesized that *ritanserin* is more effective than placebo in preventing relapse in detoxified alcohol dependents. In a controlled double-blind European multicenter study 493 chronic alcoholics were treated with three doses (2.5/5/10 mg) *ritanserin* versus placebo over a period of six months.

Ritanserin was well tolerated. The most frequent adverse experiences were headache and insomnia. A small increase in weight in the ritanserin-treated patients and a small QTc prolongation in the ritanserin 10 mg group were observed. There was no significant difference between *ritanserin* (2.5/5/10 mg daily) and placebo in the number of relapses, the time to relapse, the craving for alcohol, and the drinking habits after relapse. So far, no serotonergic substance has shown its effectiveness in relapse prevention in clinical trials with demanding methodological designs. Maybe that only subgroups of alcoholics (Cloninger Type II, high impulsivity, etc.) can be considered for the relapse prevention with serotonergic substances.

OPIATE RECEPTORS: ROLE IN ADDICTION AND RELAPSE IN ALCOHOL DEPENDENCE

J.D. Chick. *Royal Edinburgh Hospital, Edinburgh EH10 5HF, Scotland*

The endogenous opiate transmitters, endorphins, are released as one of many acute actions of ethanol on the limbic system. Research in

https://doi.org/10.1016/0924-9338(96)88426-4 Published online by Cambridge University Press

families with a high genetic loading for alcohol dependence have suggested that some may inherit an oversensitivity to this effect, and it has been suggested that this might contribute to the loss of control experienced by some drinkers [1]. Opiate antagonists such as naltrexone reduce ethanol-seeking in alcohol-dependent animals.

Two published double-blind randomised controlled studies in detoxified patients taking part in an out-patient treatment programme report that naltrexone 50 mg daily reduces the risk of self-reported relapse, at least for three months [2]. Objective markers of alcohol consumption have helped to support this result. Results of longer studies in larger samples are awaited.

Some patients who resume drinking while taking naltrexone report that they feel less of the ethanol 'high'. Perhaps they then experience less impulse to carry on drinking [2]. However, studies have found an increase in the numbers of patients who report achieving total abstinence as well as a reduction of drinking overall.

Naltrexone is not addictive in the sense that there is a withdrawal syndrome, it is well tolerated and it has a good safety record. Follow-up has not indicated rapid relapse on cessation of the drug.

More information is needed on which patients respond, which is the optimal timing and duration of use, and which psychological and social interventions are necessary compliments. As with other treatments psychological approaches enhancing compliance will be an important factor in determining the effectiveness of opiate antagonists in routine clinical practice.

[1] Gianoulakis, C. and De Waele, J-P. (1994) Genetics of alcoholism: the role of the endogenous opioid system. Metabolic Brain Disease, 9, 105–131.
[2] Volpicelli, J.R., Volpicelli, L.A. & O'Brien, C.P. (1995) Medical management of alcohol dependence: clinical use and limitations of naltrexone treatment. Alcohol and Alcoholism, 30, 789–798.

INCREASE IN NEURO-INHIBITORY AMINO-ACIDS DURING ALCOHOLIZATION AND IN NEURO-EXCITATORY AMINO-ACIDS DURING WITHDRAWAL

Ph. De Witte, A. Dahchour. *Lab. Biologie du Comportement, University of Louvain, Place Croix du Sud 1, B-1348 Louvain-la-Neuve*

During alcoholization, acute or chronic, an increase in the extracellular concentration of taurine, a major inhibitory amino-acid, was observed in the limbic system of male rats using the microdialysis technique. These studies were done on awake freely moving animals after implantation of micro probes into specific parts of the brain. The dialysates collected through these probes were then injected into HPLC coupled with electrodetection technique after derivatization with OPA. After chronic alcoholization using pulmonary alcoholization, amino-acids were also estimated during this withdrawal period. After 4 hours withdrawal a dramatic increase in glutamate, a major excitatory amino-acid, was observed and lasted for 32 hours. Both phenomena, i.e. increase in inhibitory amino acid taurine during alcoholization and increase in excitatory amino-acid glutamate during withdrawal, produce hyper-excitability in animals detected by tilting procedure.

New molecules were tested in order to decrease these combined amino-acids effects.

Sponsored by Lipha.

DIFFERENT STRATEGIES OF RELAPSE PREVENTION: A META-ANALYSIS OF DRUG EFFICIENCY

R.R. Engel, C. Schöchlin. *Psychiatric Hospital, University of Munich, Nussbaumstr. 7, D-80336 Muenchen, Germany*

Newer approaches of pharmacological treatment of alcohol dependence/abuse try to reduce the craving for alcohol by manipulation of the endogenous "reward" circuit. A meta-analysis of placebo controlled clinical trials with anti-craving substances was performed in order to establish their overall efficacy and to examine the possible influence of study characteristics.

Eleven placebo controlled, randomised studies with a minimum length of three months were included. The following substances were taken into account: acamprosate, naltrexone, nalmefene, GHB, tiapride, atenolol and bromocriptine.

There was a significant overall efficacy of $r = 0.22$, corresponding to a verum-placebo responderrate difference of 22 percentage points. Naturally, the influence of drugs was confounded with design elements of the studies. Nevertheless, two variables, namely drinking status of the patients and the choice of the response criterion seemed to influence study results: Effect sizes of studies including non-detoxified patients were higher than effect sizes of studies with detoxified patients. Three of the anti-craving substances showed higher efficacy with controlled drinking than with abstinence as response criterion.

According to these results, the published studies show that anti-craving substances are superior to placebo in the treatment of alcohol dependence, and the effect size compares favorably to other Drug treatments in psychiatric disorders. Study design variables may have a large influence on the results.

LONG-TERM FOLLOW-UP OF ACAMPROSATE TREATMENT IN ALCOHOLIC PATIENTS

Henning Sass. *Psychiatric Clinic of the Technical University Aachen, Pauwelsstr. 30, D-52057 Aachen*

In a total of 14 centres both the "old" Federal republic and the former East-Germany 272 patients took part in this II Phase study over a period of 2 years. In a randomised, double-blind design 136 patients received acamprosate treatment and 136 patients received placebo. 22.4% of the patients were female. In addition to the usual recording of patient's history and demographic details, extensive assessments of psychological status and social environment were performed.

134 (49.3%) patients completed the study after one year. The most sensitive indicator of efficacy proved to be cumulative duration of abstinence. The mean value in the acamprosate group was 178.5 days compared to 113.8 days in the placebo group. The difference between treatment groups is highly significant, with a p value of 0.0001. The differences were reflected in a similar way in the life-tables. A very marked difference between acamprosate and placebo treatment developed between 30 and 90 days after the start of therapy. The absolute value of this difference increased only slightly on further treatment. The Log Rank test, which is the usual method of statistical comparison on life-table data, yielded a similar result ($p = 0.0054$). At the end of the first year, the proportion of abstinent patients was twice as high in the acamprosate group. This is apparent from the course of the life-table curve, but can also be expressed using a direct comparison of patients at the end of the study. 42.8% of patients were abstinent in the acamprosate group and 20.7% in the placebo group.

The second year of the study was organized as a medication-free follow-up. At the end of this period 104 patients were still under observation, 66 on acamprosate and 38 on placebo. 5 to 6% of the patients in each group relapsed in the second year. At the end of the follow-up 40% of the remaining patients on acamprosate and 17% on placebo had never relapsed. This difference between the two groups was highly significant. There were no rebound phenomena at the termination of study medication.

The implications of the differences in drop-out rates and retention rates between the two groups during study medication and follow-up over 2 years are discussed.