domestic animal species. Infection may course neurobehavioral disturbances and/or fatal neurologic diseases. Since BDV antibodies were detected in humans, neuropsychiatric diseases were considered to be potentially associated with human BDV infections. Further evidence that BDV may act as an etiopathogenic co-factor in these disorders derived from findings such as the isolation of human strains of BDV from patients with recurrent mood disorders. In addition, the antiviral drug amantadine appears to have antidepressive effects partly due to its antiviral efficacy on BDV.

This report stresses the role of BDV in patients with affective and obsessive–compulsive disorders (OCD). Furthermore, the use of amantadine in the treatment of BDV infected patients with major and bipolar depression as well as OCD will be shown with a special emphasis to clinical experiences and virological data: Amantadine reduced depressive symptoms in these disorders. In addition, clinical improvement was paralleled by a reduction of BDV infection parameters in the clinically responding patients.

S21. Gene expression in addictive disorders

Chairs: Y. Hurd (S), M. Heilig (S)

S21.1

Opioid genes in the actions of drugs of abuse: perspectives from human and experimental animal models

Y. Hurd*. *Karolinska Institute, Department of Clinical Neuroscience, Section of Psychiatry, Stockholm, Sweden*

Opioid neuropeptide genes are highly expressed in limbic-related brain regions that are considered important neuroanatomical substrates for drug addiction. It has been well documented that alterations in opioid neuropeptide gene expression occur not only after administration of opiate drugs, but also following the use of different types of psychoactive substances. The use of psychostimulant drugs such as cocaine whose primary pharmacological actions are at dopamine neurons have been shown in both humans and animal models to have strong effects on the mRNA expression of the dynorphin opioid peptide and its receptor, kappa. Recent studies have also demonstrated a tight interaction between the cannabinoid and opioid neuropeptide systems. The issues to be addressed relate to whether opioid neuropeptides might serve as common targets for "all" drugs of abuse, whether there is a limbic regional specificity of the opioid neuropeptide gene alterations following drug use, and what are the specific patterns of the opioid gene expression for different types of addictive substances.

S21.2

Gene expession in addictive disorders

M.J. Kreek*. *The Rockefeller University, Laboratory of the Biology of Addictive Diseases, New York, USA*

Studies from several laboratories have shown that gene expression of many specific genes may be altered during administration of drugs of abuse. Of importance are the dramatic time-related changes which have been observed with respect to alterations in gene expression, specifically with the expression of some genes changed by acute exposure to a drug of abuse, and the expression of fewer and more selected genes altered during sub-acute and chronic exposure to a drug of abuse, and with yet a different profile possibly present in the abstinent state following withdrawal from chronic exposure. Gene expression changes may be large for some genes. However, for many genes, which may in fact be critical to the alterations observed in behaviors during and following exposure to a drug of abuse, the changes may be very small in magnitude and thus require sensitive techniques for the detection and measurement. Very different alterations have been observed following exposure to any specific drug of abuse (or potential therapeutic agent) depending not only on the duration and dose of exposure, but also on the precise mode and pattern of exposure. Thus, the development of novel animal models, which mimic either the human patterns of abuse or the exposures which pertain during pharmacotherapeutic interventions, are critical for elucidating the molecular changes and, thus, peptide, other neurochemical and behavioral effects which occur during such exposure.

S21.3

Microarray analysis of brain gene expression in human alcoholism

R.A. Harris[1]*, R.D. Mayfield[2], J. Lewohl[2], P. Dodd[2]. *University of Texas at Austin, USA*
University of Queensland, Australia

The goal of our work is to identify genes which are differentially expressed in the brains of human alcoholics as compared with non-alcoholics. We used cDNA microarrays to compare the relative levels of over 7000 gene transcripts from frontal and motor cortex. RNA samples were obtained from three independent case groups of alcoholics and compared to controls cases which were matched across a number of variables such as age, sex, and postmortem delay. We identified approximately 190 and 130 changes in gene expression in frontal and motor cortex, respectively. Of these changes, 56 were common to both frontal and motor cortex. The data were analyzed by hierarchical expression profiling of functionally related families of genes. The most striking and consistent changes in expression were in two functional clusters: genes coding for myelin-related proteins (50 named genes) and genes important for protein trafficking (45 named genes). There were also changes in mRNAs coding for proteins involved in neuroprotection and cell survival, calcium signaling, and regulators of the cell cycle. These results indicate an extensive reprogramming of gene expression in frontal and motor cortex by alcoholism.

S21.4

From phenotype to genes and back: a functional genomics approach to alcohol dependence

M. Heilig*, W. Sommer, R. Rimondini, C. Arlinde. *Karolinska Institute, Stockholm, Sweden*

Animal paradigms can model important aspects of alcoholism, and have produced clinically effective treatment of this disorder, incl. naltrexone, acamprosate and ondansetrone. These compounds have been developed based on a priori knowledge of the role of opioid, amino acid and serotonergic transmission, respectively. Recently, functional genomics strategies have provided novel tools in the search for novel treatment targets. For this purpose, we have developed a model which allows us to study gene regulations underlying the transition from a low- to high-drinking state. Following repeated cycles of EtOH vapor intoxication and mild withdrawal, a persistent and acamprosate-sensitive high voluntary EtOH consumption is induced. In rats subjected to this procedure, the Affymetrix Rat Neurobiology GeneChip reveales long term differential gene expression of limited groups of genes in cingulate cortex and

https://doi.org/10.1016/S0924-9338(02)80150-X Published online by Cambridge University Press

amygdala. Among regulated genes are both systems previously implicated in alcoholism, e.g. several glutamatergic genes and manoamine oxidase, as well as interesting novel candidates, such as the cannabinoid CB1 receptor, and several kinases in the mitogen-activated protein (MAP) kinase pathway. Our findings illustrate that this strategy has an ability to identify targets which are not only correlative but may also be causally related to the alcoholic phenotype: both acamprosate, a partial agonist at glutamatergic NMDA-receptors, and a CB1 antagonist suppress alcohol drinking in subjects with a history of dependence, but not in regular laboratory rats. The application of this strategy promises to provide attractive targets for future drug developments efforts.

S22. Nosology, epidemiology and biology of somatoform disorders – Part I

Chairs: A. Janca (AUS), M. Maes (NL)

S22.1

Measurement of somatisation: a cross-cultural perspective

A. Janca*. *University of Western Australia, Perth*

Objectives: To develop and evaluate cross-cultural applicability and reliability of instruments for the assessment of medically unexplained somatic symptoms in different cultures.

Method: A set of assessment instruments based on ICD-10 and DSM-IV criteria for somatoform disorders was developed and evaluated in the context of the WHO International Study of Somatoform Disorders, which included 11 countries and 1200 patients presenting with medically unexplained somatic symptoms in primary care and general medical settings.

Results: WHO instruments for the assessment of somatoform disorders were found to be suitable and reliable tolls for the assessment of medically unexplained somatic symptoms in different cultures. Patients with somatoform disorders were found in all cultures. However, there was a significant difference in the prevalence of specific diagnostic categories of somatoform disorders across cultures.

Conclusions: Somatisation is a universal phenomenon and the most frequent symptoms of somatisation are multiple and medically unexplained aches and pains. A number of culture-specific symptoms of somatisation have to be taken into account in order make diagnosis of somatisation in specific cultures, which may explain the difference in prevalence rates of somatoform disorders across cultures.

S22.2

The epidemiology of somatization

P. Fink*. *The Research Unit for Functional Disorders, Psychosomatics and CL Psychiatry, Aarhus University Hospital, Denmark*

The essential feature of somatization is that the patients present physical complaints suggesting a physical disease that cannot be adequately explained on the basis of any known organic pathology or pathophysiological mechanism.

Physical symptoms and sensations are extremely common in the general population and a high proportion of patients seeking health care present with medically unexplained physical symptoms. About $\frac{1}{4}$ of the patients in various medical settings including primary care fulfil the diagnostic criteria for an ICD-10 or a DSM-IV somatoform disorder. Somatization may thus be considered as a spectrum of severity ranging from a normal reaction to very severe illness.

Somatization is associated with a wide range of other mental disorders.

Medically unexplained symptoms and somatoform disorders are more prevalent in females than males. As females more often seek health care than males, the gender difference might be due to likelihood of presentation to health care rather than real prevalence differences in the general population.

Beside the suffering that somatoform disorders cause the individual patient, the patient group poses a considerable financial burden to health and social service provision due to the high prevalence figures and their high health care utilization.

A major problem in the studies on the somatoform disorders is that the area is dogged by terminological confusion and the validity of the current ICD-10 and DSM-IV classifications of somatoform disorders are dubious.

S22.3

The significance of stress in the development of fibromyalgia syndrome

U.M. Anderberg*. *Stress Related Disorders (CEOS)/Social Medicine, Department of Public Care and Sciences, Uppsala University and Hospital, Sweden*

About 7% of all women in industrial countries are struck by fibromyalgia syndrome (FMS). Ninety percent of the patients are women. Recent studies have found that long lasting stress in one form or another often precedes the onset of this disorder and that stress also may worsen and maintain the symptoms.

In our studies, we have found that 65% of the patients with FMS have had some kind of stressful life events that affected them emotionally very negatively in relation to the onset of the FMS. Also in child-hood and adolescence the patients had more stressful events compared to healthy controls. Many patients also developed the disorder close to physical stress such as long-standing infections, low back pain and accidents. Others have developed the disorder after sudden changes in the sex hormones as at postpartum and after abortion. Forty-four percent of the patients also had co-morbidity with the premenstrual dysphoric disorder (PDD), and the same proportion also had some kind of affective disorder. The influence of the sex hormones on the symptomathology was illustrated with significantly higher scores on pain, stress, physical and psychological symptoms perimenstrually compared to in the ovulatory phase of the menstrual cycle, beside perturbed neuropeptide levels. Furthermore, in a personality study, 82% of the patients scored high on the temperament variable "harm avoidance", which means that these patients get easily anxious/distressed.

The results are interpreted as a vulnerability in women in general for developing stress related disorders and that FMS may be a late phase in a continuum of a chronic stress states. Women with stressful life events, earlier depressions and an anxious personality with high ambition, loyalty and a stressful every day life, are probably more likely for developing the FMS or other stress related disorders. Highly qualified care-givers focused on psychosocial and individual interventions, stress-reducing treatments and education are needed to help high risk women from developing the FMS and to help those of them who already are struck by the disorder.

https://doi.org/10.1016/S0924-9338(02)80150-X Published online by Cambridge University Press