S15. Gene expression in schizophrenia

Chairs: H. Hall (S), A.A. Fienberg (USA)

S15.1

Genome-wide expression analysis reveals dyregulation of myelination-related genes in chronic schizophrenia

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To identify molecular substrates associated with schizophrenia, DNA microarray analysis was used to assay gene expression levels in post-mortem dorso-lateral prefrontal cortex from patients with schizophrenia and controls. Genes determined to have altered expression levels in schizophrenics relative to controls are involved in a number of biological processes, including synaptic plasticity, neuronal development, neurotransmission and signal transduction. Most notable was the differential expression of myelination-related genes suggesting a disruption in oligodendrocyte function in schizophrenia. Follow-up studies to this initial series of experiments as well as the advantages/disadvantages of various data analysis paradigms will be presented.

S15.2

The use of the microarray-technology in schizophrenia

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Changes in gene expression have been observed in schizophrenia and other neuropsychiatric disorders. In particular, alterations in gene products related to neurotransmission (e.g. Schramm et al. 1998) or second messenger systems have been observed. However, each of these studies have focused on only one or a few gene products at a time, without the ability to investigate the simultaneous expression of large number of genes. Microarray technology provides an opportunity for application of gene expression analysis to complex clinical diseases and these approaches have been successful in addressing fundamental biological questions in human cancer. However, due to the inherent complexity of nervous tissue and the need to utilize postmortem material, few microarray studies of the human central nervous system in schizophrenia have been conducted so far (e.g. Mirnics et al. 2000). Published studies and own data are presented and inherent problems are discussed. They are e.g. the moderate extent of change (often not exceeding a 2-fold change), the clinical heterogeneity in psychiatric disorders and the interpretation of the findings.

Schramm et al. (1999) J Neural Transm 106,329–35.
Mirnics et al. (2000) Neuron 28: 53–67.

S15.3

Serotonin receptor gene expression in the pathology of schizophrenia

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There is considerable evidence for the involvement of serotonin (5-HT) receptors in the pathophysiology of schizophrenia. We have investigated 5-HT1A, 5-HT2A, 5-HT2C, 5-HT6 and 5-HT7 receptor mRNA abundance, and binding site densities in various neocortical and hippocampal regions of schizophrenic and control subjects. Age, agonal state (brain pH) and post mortem interval were included where necessary as covariates in our analyses. In schizophrenics, 5-HT1A receptor binding site densities, but not mRNA, were significantly increased (+23%) in the dorsolateral prefrontal cortex. 5-HT2A receptor binding sites were decreased in the dorsolateral prefrontal cortex (-27%) and parahippocampal gyrus (-38%) in schizophrenia, whereas 5-HT2A receptor mRNA abundance was reduced in the frontal, temporal and striate cortices only. Finally, a reduction in the abundance of 5-HT2C and 5-HT6 receptor mRNAs was observed in the hippocampus in schizophrenia, but not the dorsolateral prefrontal cortex. 5-HT7 receptor mRNA abundance was decreased in the dorsolateral prefrontal cortex but not hippocampus. The molecular and regional specific alteration of 5-HT receptor genes in schizophrenia will be considered in terms of the local pathology and aberrant connectivity proposed in this disorder.

S15.4

Glutamate system gene expression in schizophrenia

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Objective: do gene expression studies suggest glutamate function is abnormal in schizophrenia? Are there differential changes in frontal vs temporal structures as we have previously suggested?

Method: review of gene expression studies in the context of earlier data and new data from our group.

Results: 1) glutamate AMPA receptor expression is not altered in prefrontal cortex and decreased in the hippocampus. 2) Glutamate uptake site binding is decreased in left polar temporal cortex and increased in the orbitofrontal region of the prefrontal cortex, however, mRNA studies report reductions in both prefrontal cortex and hippocampus. 3) We found gene expression for the obligatory NMDA receptor subunit NR1, decreased in left-sided regions of the hippocampus, but in dorsolateral prefrontal cortex single studies have reported an increase, no change and a decrease. In orbitofrontal cortex increased NMDA receptor binding and mRNA for a metabotropic glutamate receptor have been reported but we now report no change in NR1 expression in orbitofrontal cortex in the Stanley Consortium brains.

Conclusion: No generalised changes in glutamate function from gene expression studies. Losses mainly in the hippocampus & more on the left.

S15.5

Neuropeptide gene expression in psychiatric subjects

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Dysfunction of endogenous neuropeptides has been proposed in the pathophysiology of psychiatric disorders. We have been interested

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in the possible role of the opioid peptide, dynorphin (DYN), and the neuropeptide Y (NPY) neural systems in psychiatric disorders. DYN is involved in psychomimetic and dysphoric effects, whereas NPY has been mainly implicated in the neurobiology of depression and anxiety. We have used in situ hybridization histochemistry to monitor the mRNA expression pattern and levels of DYN, NPY, and their receptors in subjects diagnosed with bipolar disorder, major depression, or schizophrenia. Brain areas of interest include the cerebral cortex (anterior cingulate and prefrontal), amygdala, and striatum. The results accumulated thus far indicate a greater abnormality in subjects diagnosed with affective disorders in the expression levels of, e.g., the DYN mRNA in amygdaloid complex or of the NPY-related genes in the cerebral cortex. There are indications of striatal abnormalities in the DYN mRNA expression in schizophrenic subjects. Thus, overall, the DYN and NPY-related genes appear to be more impaired in association with affective disorder than with schizophrenia.

S15.6
Oligodendroglial reduction in the prefrontal cortex in schizophrenia

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Previously we found ultrastructural signs of apoptosis and necrosis of oligodendrogliocytes (Ol) in postmortem prefrontal area 10, layer VI and caudate nucleus in schizophrenia (SCH). We hypothesized that the numerical density (Nv) of Ol might be decreased in schizophrenic brains as compared to control brains. Nv of Ol was estimated by optical disector method in area 10, layer VI and adjacent white matter in 25 cases of SCH (ICD-10 diagnostic criteria) and 20 normal controls. Mean Nv of Ol decreased significantly in layer VI (−32%): and in adjacent white matter (−11%): Three-way ANOVA with diagnosis, age and postmortem delay as independent factors showed a significant effect of the diagnosis on Nv of Ol in both layer VI: $F(1,37)=12,55$, $p=0,001$ and adjacent white matter: $F(1,37)=6.67$, $p=0.014$. The result is consistent with our previous data of a decreased Nv of Ol in area 9, layer VI in SCH in the brain sections from the Stanley Foundation Neuropathology Consortium, and suggests a wide spread pathology of Ol in SCH brain.

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SAL04. Bipolar disorders

SAL04
The diagnosis and management of bipolar disorder: developments and controversies

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No more than twenty years ago, bipolar disorder was predominantly viewed as a relatively rare condition characterised by periods of euphoria and depression, which was easy to diagnose and to treat, whose treatment was exclusively pharmacological, and whose outcome was usually good.

This perception has changed dramatically in the last two decades. It has become clear that the label "bipolar disorder" actually encompasses a variety of conditions, whose overall lifetime prevalence in the general population may be as high as 5%. The concept of bipolar II disorder has been validated by research; mixed and psychotic forms of bipolar disorder have turned out to be much more frequent than previously believed; the concomitance of alcohol or drug abuse and of anxiety disorders has been found to be common in bipolar patients and to mask in several cases the disorder of mood. The diagnosis of bipolar disorder has been shown to be difficult in some cases, in particular the mild and the atypical ones. Moreover, the onset of the disorder in childhood or adolescence has been reported to be not rare, and to generate further diagnostic problems.

The impact of long-term lithium monotherapy on the course of bipolar disorder has been found to be often not satisfactory. Several alternative drugs have been introduced in clinical practice, and the choice of the most appropriate drug or combination of drugs in the individual patient has become much more complex. The specific problems posed by the treatment of the depressive phase of bipolar disorder have been recognised. Research has documented that some psychosocial interventions may be a useful addition to pharmacotherapy in bipolar patients. The outcome of bipolar disorder has been proved to be frequently poor, from both the psychopathological and the psychosocial viewpoint, and the social and economic burden of the disorder has been reported to be huge.

The debate about some of the above issues, however, remains open. For instance, it has been argued that the concept of bipolar spectrum lacks an organizing principle and may reduce the reliability of the diagnosis of bipolar disorder. Moreover, the definition of "mood stabiliser" remains controversial, and indeed the mood stabilising properties of the various available drugs are not consistently evaluated by researchers.

The above developments and debate have had only a limited impact on clinical practice worldwide. In fact, the concepts of bipolar spectrum and bipolar II disorder have been incorporated in clinical routine only in a few countries. Long-term treatment of bipolar patients with standard antipsychotics remains a common practice. New mood stabilisers remain underused in many countries (while they are possibly overused in some others), and the popularity of the individual compounds varies significantly from one country to the other. Psychosocial interventions for bipolar disorder are unknown to the majority of psychiatrists around the world. Bipolar patients with psychotic symptoms and a deteriorating course are still likely to receive a diagnosis of schizophrenia in several clinical contexts.

This lecture aims to review the above-mentioned developments and controversies concerning the diagnosis and management of bipolar disorder, and to provide European psychiatrists with a balanced update of currently available scientific evidence and clinical wisdom.

SAL05. Anxiety

SAL05
Anxiety

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