Monday, April 4, 2005

S-33. Symposium: Molecular foundations of schizophrenic psychoses

Chairperson(s): Johannes Thome (Swansea, United Kingdom), Gavin Reynolds (Belfast, United Kingdom)
14.15 - 15.45, Holiday Inn - Room 1

S-33-01

Genetics of electrophysiological endophenotypes in schizophrenia

G. Juckel. *Campus Charite Mitte, Berlin, Germany*

For many years, changes haven been consistently found in the electrophysiological parameters in schizophrenic patients. The event-related auditory P3000 which is considered as expression of general cognitive processes such as attentionn, and the mismatch negativity (MMN) which is associated with the working memory function, both show amplitudes lower than those found in healthy controls. The so-called loudness dependence of auditory evoked potentials (LDAEP), currently in discussion as an indicator of the central serotonergic function, is lower in schizophrenic patients, which suggests excessive serotonergic activity in these patients. These electrophysiological changes, however, are not found in all patients, a fact which might indicate the existence of biologically homogenous subgroups. In the talk, various studies will be presented which point out that genetic polymorphisms are related to the electrophysiological endophenotypes in schizophrenic patients above mentioned. A close relationship was found on the one hand between the P300 and polymorphisms of COMT and of the D3-receptor and on the other hand between loudness dependence of auditory evoked potentials and the serotonin transporter polymorphism.

S-33-02

M. Noethen. *Centre for Medical Genetics University of Antwerp, Antwerp, Belgium*

S-33-03

Neurotransmitter pathology of schizophrenia

G. Reynolds. *Queen's University Belfast Dept. of Neuroscience, Belfast, United Kingdom*

Objective: The role of neurotransmitter systems in schizophrenia is far from fully understood. One can identify three different ways in which neurotransmitters may be involved in the disease; there are those neurotransmitters associated with the neuronal deficits reflecting brain pathology, those demonstrating dysfunction secondary to that neuronal pathology, and those affected by antipsychotic drug treatment. Thus while GABA and glutamate in the first group, dopamine is in the second and third groups.

Methods: The neurotransmitters most strongly associated with the neuropathology of schizophrenia are GABA and glutamate. We have investigated these pathologies in human brain tissue collected at post mortem by identifying GABAergic neurons containing calcium binding proteins, by assessing markers for glutamatergic synapses and by determining levels of N-acetylaspartate, a marker for the integrity and viability of neurons.

Results: We have identified, in the hippocampus and frontal cortex, specific deficits of a subtype of GABAergic neurons, defined by the presence of parvalbumin, as well as dysfunction of glutamate systems as demonstrated by e.g. losses of N-acetylaspartate and glutamate uptake sites. Whether these abnormalities are present during early development, or appear later as the psychotic symptoms emerge, remains unclear. However it has been hypothesised that GABAergic deficits may occur in a vulnerable period during development and this would subsequently lead to effects on glutamate systems. Some of the findings (e.g. NAA deficits in the cortex, parvalbumin deficits in the hippocampus) can be mimicked in certain animal models of the disease.

Conclusion: The involvement of neurotransmitters in many aspects of the pathophysiology and pharmacology of schizophrenia has been a source of confusion, but understanding this involvement is the one way in which we may successfully bridge the substantial gap in understanding how drug action can influence the effects of brain pathology in schizophrenia.

S-33-04

J. Thome. *School of Medicine, Dept. of Psychiatry, University of Wales, Swansea, United Kingdom*

Objective: Traditionally, alterations in neural plasticity have been postulated as important factors involved in the etiopathogenesis of schizophrenic psychoses. Using molecular biological methodologies including genomics, epigenomics and proteomics, it is possible to test such hypotheses and to clarify the role of neural plasticity in schizophrenias. For example, neurotrophic factors and synaptic vesicle proteins represent interesting molecule families which are possibly involved in the pathogenesis of at least some forms of schizophrenia and also regulated by antipsychotic drugs. The phenomenon of neurogenesis represents a further form of neural plasticity with potential relevance for psychotic disorders and their treatment.

Monday, April 4, 2005

S-30. Symposium: New challenges to the dichotomy schizophrenia versus affective disorder - Part I

Chairperson(s): Heinz Häfner (Mannheim, Germany), Wolfgang Maier (Bonn, Germany)
14.15 - 15.45, Gasteig - Black Box

S-30-01

Depression as prodrome of schizophrenia

H. Häfner. *Central Institute of Mental Health, Mannheim, Germany*

Objective: Depression is a frequent comorbidity diagnosis and a depression factor the fourth symptom dimension of schizophrenia. Risk factors common to both are genes, pre- and perinatal complications, mild structural brain anomalies and neuroticism, all more pronounced in schizophrenia.

Methods: We studied temporal and psychopathological associations between schizophrenia and depression in a representative sample of 130 first admissions for schizophrenia, individually matched by age and sex, 130 first admissions for unipolar depression

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and 130 healthy population controls. Early illness course, mostly drug-naive, was assessed retrospectively using the IRAOS,6-month follow-up was done using the PSE and other instruments.

Results: Depressed mood was the most frequent first symptom of schizophrenia. It was followed by anxiety, negative symptoms and functional impairment. With progressing illness this core syndrome increased in number and severity until the climax of the first psychotic episode, subsequently falling to a low level with remitting positive symptoms. In 333 relapse episodes assessed at 12-year follow-up of the ABC schizophrenia sample depressed mood was the most frequent symptom.

Conclusion: Considering the common neurobiological risk factors of schizophrenia and depression, the role of the depressive syndrom as a prodromal stage of schizophrenia and numerous other brain diseases we explained the depressive symptom, the most frequent mental disorder in the general population, as a genetically performed reaction pattern of the human brain. It can be triggered by a diversity of causes involving mild brain dysfunction including schizophrenia. As the dysfunction progresses transition to psychosis, in still more severe cases to delirium/confusion and dementia may occur.

S-30-02

The epidemiology of subclinical mania and subclinical psychosis comorbidity in the general population

M. C. Marcelis, N. Kaymaz, J. van Os, R. de Graaf, W. Vollebergh, L. Krabbendam. *Dept. of Psychiatry Maastricht University, Maastricht, Netherlands*

Objective: It is increasingly recognised that in the general population, symptoms of mania and psychosis are more broadly distributed than their associated clinical syndromes. Little is known about how these subclinical population phenotypes co-vary with and impact on each other.

Methods: In a random population cohort of 7076 adults, prevalence of mania and psychosis symptoms were assessed at baseline, one and two years later. The degree of comorbidity between subclinical continuous mania and psychosis symptom scores was examined, and the impact of subclinical comorbidity on social impairment and prospective post-baseline prediction of incident DSM-III-R diagnosis.

Results: Lifetime population prevalences of at least one manic and one psychotic symptom were 4.1% and 4.2% respectively. Excluding individuals with any lifetime DSM-III-R bipolar or psychotic disorder diagnosis, these prevalences were 2.3% (subclinical mania) and 2.8% (subclinical psychosis). 17% of subclinical mania was shared with subclinical psychosis and 14% of subclinical psychosis was shared with subclinical mania (OR=8.3, 95%CI: 5.3, 12.9). For a given level of subclinical mania, comorbid subclinical psychosis produced more interference with functioning and was more predictive of future bipolar disorder. Subclinical comorbidity was predicted by social disadvantage, trait anxiety, familial loading and cannabis use.

Conclusion: In the general population, subclinical phenotypes of mania and psychosis are more prevalent than their clinical counterparts and cluster together frequently. Several risk factors for clinical bipolar and clinical psychotic illness may act in part by facilitating the formation of more "toxic" combinations of subclinical symptoms in the general population with higher probability of transition to clinical illness.

S-30-03

Prediction of psychosis by depressive symptoms among high-risk subjects

S. Lawrie, P. Miller, D. Owens, E. Johnstone. *Division of Psychiatry University of Edinburgh, Edinburgh, United Kingdom*

Objective: The prodrome to schizophrenia needs to be discovered rather than invented.

Methods: The Edinburgh High Risk Study of initially well young adults with at least two schizophrenic relatives started in 1994. 162 high risk subjects provided some clinical, neuropsychological and/or imaging data in the first five years and most were repeatedly assessed over up to 10 years. Symptoms were elicited with the Present State Examination (and latterly the PANSS too).

Results: Approximately one-half of the sample had isolated psychotic symptoms, some of which resolved, and 21 developed schizophrenia (on average after 944 days). At study entry, the mean level of depressive symptoms (as well as situational anxiety and nervous tension) was higher in high risk subjects who became ill than those who did not. Affective symptomatology remained high with illness onset.

Conclusion: In genetically predisposed individuals, affective symptoms and indeed psychotic symptoms are prominent before the behavioral and subjective changes which accompany the onset of schizophrenia per se.

S-30-04

Current status of molecular genetics of schizophrenia and bipolar disorder

N. Craddock. *Dep. of Psychological Medicine University of Wales College, Cardiff, United Kingdom*

Results: The high heritabilities of schizophrenia and bipolar disorder have stimulated much work aimed at identifying susceptibility genes using both positional and functional molecular genetic approaches. As a result, several strong and well-established linkages have emerged in schizophrenia. Three of the best-supported regions are 6p24–22, 1q21–22 and 13q32–34 where single studies have achieved genome-wide significance at $P<0.05$ and suggestive positive findings have also been reported in other samples. Other promising regions include 8p21–22, 6q21–25, 22q11–12, 5q21–q33, 10p15–p11 and 1q42. Substantially fewer families have been studied to date in bipolar disorder and the linkage findings are less consistent but several genomic regions of interest have been identified including 6q16-q21, 12q24 and regions of 9p, 10q, 14q, 13q, 22q and chromosome 18. Recently, evidence implicating specific genes or loci has been reported for both disorders – and, crucially, replicated. Currently, the weight of evidence supports NRG1 and DTNBP1 as schizophrenia susceptibility loci, though work remains before we understand precisely how genetic variation at each locus confers susceptibility and protection. The evidence for COMT, DISC1, DAOA(G72) and DAO is promising. For bipolar disorder the strongest evidence supports BDNF and DAOA(G72)/G30. While it is essential that further replications are established, the respective contributions of each gene, relationships with aspects of the phenotype and the biological mechanisms all need investigation. There is increasing evidence for an overlap in genetic susceptibility across the traditional Kraepelinian dichotomy – most notably with association findings at G72(DAOA)/ G30, DISC1 and NRG1. As functional

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psychosis susceptibility genes are identified over the next few years, this will have a major impact on our understanding of disease pathophysiology and nosology. This presentation will give an overview of the current state of knowledge and the directions in which the field is moving.

S-30-05

Anomalous asymmetry as the key to the pathophysiology of schizophrenia and bipolar disorder

T. Crow. *POWIC - Dept. of Psychiatry University of Oxford, Oxford, United Kingdom*

Monday, April 4, 2005

S-37. Symposium: Pharmacogenetics of antipsychotic treatment: Predicting clinical efficacy and side effects

Chairperson(s): Dan Rujescu (Munich, Germany), Robert Kerwin (London, United Kingdom)
16.15 - 17.45, Gasteig - Black Box

S-37-01

Effects of polymorphisms in the cytochrome p450 system on response to antipsychotics

J. Brockmöller. *Abteilung Klinische Pharmakolo, Göttingen, Germany*

S-37-02

Towards pharmacogenomics: A large scale association study on response to haloperidol

D. Rujescu, I. Giegling, M. Schafer, N. Dahmen, T. Sander, A. Szegedi, M. R. Toliat, B. Bondy, A. M. Hartmann, H. H. Stassen, H. J. Möller. *University of Munich Dept. of Psychiatry, Munich, Germany*

Haloperidol is highly efficient in the treatment of acute psychosis, especially when severe symptoms predominate. This study investigates the association of response to short-term haloperidol treatment with 120 microsatellites and 200 SNPs in various candidate genes selected based on their role in neurotransmission. One hundred patients with acute psychosis (schizophrenia, schizoaffective, brief psychotic, and substance-induced psychotic disorder) were treated with haloperidol for up to 28 days. Diagnosis was established by applying the SCID I and II interview. Patients were assessed at baseline and on days 3, 7, 14, 21and 28. Improvement and response were measured by using the Positive and Negative Syndrome Scale. Haloperidol plasma levels were also obtained. We will present, for the first time, data on this ongoing large-scale association study on response to haloperidol. Genotyping of further 400 SNPs is under way.

S-37-03

Genetic predictors of response to clozapine and other atypical antipsychotics: Current status and implications of pharmacogenomics

M. J. Arranz, R. Kerwin. *Institute of Psychiatry Clinical Neuropharmacology, London, United Kingdom*

Psychopharmacogenetic research, focusing on evidence selected candidate genes, has identified several contributors to antipsychotic variability. Metabolic enzymes participating in drug biotransformation were identified as important contributors to response variability as early as the 1950s. Polymorphisms of functional significance have been described in several cytochrome P450 enzymes (Nebert, 2000) and their contribution to antipsychotic biotransformation and treatment related side-effects has been proved (Scordo et al., 2002). Additionally, genetic variants of neurotransmitter receptors and transporters have also been associated with treatment and variability. In particular, dopaminergic, serotonergic and adrenergic gene alterations may contribute to clinical outcome. Current pharmacogenetic investigations include the combination of genetic information for the selection of the most beneficial treatment according to the individual's pharmacogenetic profile. Pharmacogenomic research, using high-throughput techniques, is aiming at better understanding the mechanism of action of psychotropic drugs. Several strategies have been developed using human or animal brains and DNA micro-array technologies for this purpose. Although still at early stages, multi-gene micro-array analyses of brains from drug-treated animals can provide information on the systems altered by antipsychotic treatment and improving our knowledge on drug mechanisms of action. By comparing results from similar studies in human brains, novel targets for antipsychotic activity can be discerned. Pharmacogenomic research will produce a wealth of information during the next decade that hopefully will serve to develop improved and safer psychotropic drugs.

S-37-04

Genetic markers and mechanisms of antipsychotic drug-induced weight gain

G. Reynolds. *Queen's University Belfast Dept. of Neuroscience, Belfast, United Kingdom*

Objective: Weight gain is increasingly recognised as a major problem in treatment with antipsychotic drugs, with effects on both treatment adherence and long-term morbidity. The substantial differences between individuals in the occurrence of this side effect suggests the importance of genetic factors.

Methods: We have undertaken association studies of common promoter region polymorphisms in two candidate genes, the 5-HT2C receptor and leptin, both of which are implicated in the control of feeding and body weight. These studies have been undertaken in first-episode drug-naive psychotic subjects from Chinese Han and Spanish Caucasian populations.

Results: We have reported that the -759C/T polymorphism of the 5-HT2C receptor gene strongly influences short-term treatment-induced weight gain in previously untreated Chinese patients receiving antipsychotic medication. This was also seen in a series of Spanish first-episode patients, in which the genetic effect was sustained over 9 months. In both series, we have found association of antipsychotic drug-induced weight gain with a functional polymorphism of the leptin gene, an effect that appears to be greater in the longer term. Along with initial BMI, these two pharmacogenetic factors account for 30% of the variance in drug-induced weight gain. Studies in the Spanish series demonstrate that leptin levels before treatment were strongly associated with 5-HT2C receptor genotype.

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