S-12-04

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S-12-05

Using cellular systems to understand glucocorticoid resistance in depression

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Objective: Depression is characterised by an over activity of the hypothalamic-pituitary-adrenal (HPA) axis and by increased concentrations of circulating cortisol. The picture is further complicated by the fact that increased cortisol levels in the bloodstream do not necessarily translate into increased effects of cortisol on the brain. In fact, brain sensitivity to cortisol is also regulated by the function of the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), the receptors that mediates the effects of the cortisol on target tissues, as well as by efflux systems for cortisol at the blood-brain barrier. Nevertheless, the "glucocorticoid resistance" model is supported by the evidence, in cellular systems, that GR function is reduced in the lymphocytes of depressed patients, and that antidepressants enhance cortisol action in the brain by increasing the expression and the function of the GR and the MR.

Methods: I will summarise our work on the effects of antidepressants on the HPA axis in "in vitro" cellular models and in healthy controls.

Results: Antidepressants enhance GR function in vitro by inhibiting the multidrug resistance p-glycoprotein, a steroid transporter that regulate the intracellular concentration of glucocorticoids. These transporters also regulate GR function in lymphocytes, and the access of glucocorticoids to the brain. Furthermore, antidepressants enhance glucocorticoid-mediated negative feedback on the HPA axis in humans after as little as 4 days of treatment.

Conclusion: Taken together, these findings further support the notion that one of the mechanisms by which antidepressants exert their therapeutic effects is by inhibiting steroid transporters localised on the blood-brain barrier, in lymphocytes and in neurones, like the multidrug resistance p-glycoprotein, and thus by increasing the access of cortisol to the brain and the glucocorticoid-mediated negative feedback on the HPA axis. These molecular mechanisms can be studied in humans using in vitro cellular systems. Acknowledgements: My research is funded by the UK Medical Research Council (MRC), the NARSAD, and the GENDEP project from the European Commission's Framework 6 Programme.

Sunday, April 3, 2005

S-15. Symposium: Progress in pharmacogenomics: Focus on treatment and adverse effects

Chairperson(s): Brigitta Bondy (Munich, Germany), Finn Bengtsson (Linköping, Sweden)
16.15 - 17.45, Gasteig - Lecture Hall Library

S-15-01

Genetic polymorphisms of psychotropic drug metabolizing enzymes: Clinical relevance

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In a very recently published consensus paper on therapeutic drug monitoring (TDM) of psychotropic drugs, some recommendations concerning its combination with pharmacogenetic tests (phenotyping, genotyping) were included (Baumann et al., 2004). As a matter of fact, both environmental and genetic factors contribute to the large interindividual variablility of plasma drug concentrations observed in patients, and the study of the clinical relevance (response, occurrence of adverse effects) of these observations is an important research field. CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 are the main isoforms of cytochrome P-450 implicated in the metabolism of psychotropic drugs, and for some of them, genetic polymorphisms have been described, while for others, the interindividual variability in activity remains unexplained. For methodological reasons, relatively few prospective studies were carried out in groups of phenotyped and/or genotyped patients on the relationship between pharmacogenetic, pharmacokinetic and clinical parameters. On the other hand, rous case reports illustrate the usefulness of pharmacogenetic tests in patients treated with antidepressants or antipsychotics, as they constitute a potent diagnostic tool with regard to the individual drug metabolising capacity. In conclusion, pharmacogenetic tests are increasingly recommended in phase II-IV studies, but also in pharmacovigilance programs, and in patients, who poorly respond or tolerate psychotropic medication. P. Baumann, C. Hiemke, S. Ulrich, I. Gaertner, M.-L. Rao, G. Eckermann, M. Gerlach, H.-J. Kuss, G. Laux, B. Müller-Oerlinghausen, P. Riederer, G. Zernig. The AGNP-TDM expert group consensus guidelines: Therapeutic Drug Monitoring in Psychiatry. Pharmacopsychiatry 37 (2004) 243 - 265

S-15-02

The pharmacogenetics of antipsychotics

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Since a considerable number of psychotic patients treated with antipsychotic medication do not or not fully respond to treatment and some, but not all, suffer from serious side effects, scientific interest has centered on genetic factors determining individual susceptibility to antipsychotic treatment. Genetic polymorphisms of metabolizing enzymes (especially cytochrome P450) have been shown to influence kinetics of antipsychotics and consequently treatment outcome and side effects. Furthermore there are a number of studies investigating the association between genetic polymorphisms of neurotransmitter receptors targeted by antipsychotics and effectivity of treatment, as well as agranulocytosis, weight gain and extrapyramidal symptoms, being the most prominent side effects. The association studies conducted so far are mainly addressing dopamine and serotonin receptor polymorphisms, yielding promising results. These results will be presented and prospects for an individualized treatment will be discussed.

S-15-03

The influence of ABCB1 transport proteins (MDR1, P-glycoprotein) on the blood-brain barrier function: Therapeutic implications

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Objective: The clinical efficacy of drugs targeting the central nervous system critically depends on the compounds' ability to pass the blood-brain barrier, which is regulated by active transporter molecules, such as ABCB1 (MDR1, P-glycoprotein (P-gp). One of the reasons for an only partial response or refractoriness is an insufficient intracerebral concentration. We hypothesized that genetic variability in ABCB1 influence the response to drugs with central nervous system (CNS) actions, including the clinical response to antidepressants. We used transgenic mice lacking the two homologues of the human ABCB1 drug transporter gene (abcb1a and abcb1b) to assess whether antidepressants were substrates of P-gp following subchronic administration. We than genotyped 56 single nucleotide polymorphisms (SNPs) in ABCB1 in 286 depressed in patients treated with antidepressants and tested for associations with treatment response. The animal experiments showed that the intracerebral concentrations of some but not all antidepressants were regulated by P-glycoprotein. In the human genetics studies, there was an association of ABCB1 SNPs with remission status after 6 weeks of antidepressant treatment. This association was present in patients treated with antidepressants that are substrates of P-gp, but not in patients treated with antidepressants that are not substrates of P-gp. Our findings indicate that polymorphisms in ABCB1 influence intracerebral concentrations of antidepressants and by that response to treatment. Genotyping ABCB1 polymorphisms may thus help to optimize antidepressant treatment. These implications are likely to extend to other classes of CNS drugs.

S-15-04

Adverse drug reactions: Role of pharmacogenomics

P. Zill. *Psychiatric CLinic, Munich, Germany*

Objective: The inter individual variability of drug response is a major problem in clinical practice and drug development, which can lead to therapeutic failure or adverse effects in patients. There is growing evidence that not only the involvement of pharmacokinetic factors (drug metabolism) might predispose to adverse effects, but also genetic variations in drug targets (pharmacodynamic factors) play an important role. Moreover the existence of comorbid disorders, as for example the metabolic syndrome, characterized by elevated abdominal obesity, triglycerides, blood pressure, fasting glucose, which has been suggested to be associated with depression and schizophrenia is supposed to have an impact on the incidence of side effects after psychopharmacological treatment. rous previous studies could demonstrate an involvement of polymorphisms in drug metabolizing enzymes (e.g. Cyp450 system), as well as in drug target genes and the incidence of adverse effects, but these results remain partially inconclusive.

Results: In own studies with 160 schizophrenic patients and 272 patients with major depression we found that a –579C/T polymorphism in the 5-HT2C gene seems to be involved in weight gain during neuroleptic and antidepressant treatment. The 5HT2C –597 C/T and a ß2-adrenergic receptor polymorphisms (Arg16Gly) might also be involved in glucose metabolism.

Conclusion: These results suggest that symptoms of the metabolic syndrome are among the common side effects, but these findings have to be replicated in further prospective studies. Knowledge from these studies will ultimately lead to the individualization of psychiatric drug treatment, as well as to future treatment strategies. This project is supported by the German Federal Research Ministry within the promotional emphasis "Competence Nets in Medicine"

Monday, April 4, 2005

S-21. Symposium: Anxiety and depression, first results of the DSM-5 steering group

Chairperson(s): David Goldberg (London, United Kingdom), Kenneth S. Kendler (Richmond, USA)
08.30 - 10.00, Gasteig - Philharmonie

Monday, April 4, 2005

S-35. Symposium: Psychosocial aspects of depressive disorders in ethnic minority groups

Chairperson(s): Francis Creed (Manchester, United Kingdom), Christian Haasen (Hamburg, Germany)
14.15 - 15.45, Holiday Inn - Room 6

S-35-01

Prevalence of depression in people of Pakistani origin in U.K.

F. Creed. *University of Manchester, Manchester, United Kingdom*

Objective: To assess whether depression is more common in people of Pakistani origin than white Europeans living in U.K. To assess also whether the prevalence is associated with life stress.

Methods: Survey of population based sample of 928 people of Pakistani family origin and 947 white Europeans. Two phase study using Self-Report Questionnaire (SRQ) and SCAN diagnostic interviews to assess depression. Life Events and Difficulties Schedule for life stress.

Results: At baseline there was a higher prevalence of depression among Pakistani women (32%) compared with European women (19%), European men (13%) and Pakistani men (9%). Depression was particularly prevalent in older Pakistani women and was closely associated with severe social stress and lack of support. There was no difference in the course of depression over 6 months between the different ethnic groups.

Conclusion: The high prevalence of depression in Pakistani women is a result of severe social stress and lack of adequate social support.

S-35-02

Depression among migrants of Turkish and Russian origin living in Germany

C. Haasen. *University Hospital Eppendorf, Hamburg, Germany*

A depressive reaction to the stress associated to migration and the acculturation thereafter has been described in the literature. Furthermore, depressive syndromes among migrants are reported by clinicians to involve somatization more frequently, despite the fact that somatization has not been found to be more frequent in different regions of the world. There is insufficient evidence on the