criteria allows qualify psychotic level of depression, which demands principally more intensive therapy than the one used everywhere under continual approach (which falsely identifies intensity and depth of depression). We face here the choice of fundamentally different ways of further development of our subject.

S-05-04

Transcultural specific features of affective disorders in the European North of Russia

A. Bogdanov. *Arkhangelsk, Russia*

There are noticeable differences in frequency of presence and registration of affective disorders in the Ninets population (the Mongoloid Race) in comparison with Russians (the European Race) living in the European North of Russia. Differences in clinical picture, first of all, of depressive syndromes and in their subjective – personal assessment by patients have also been noted. The noted special features refer not only to "pure" affective syndromes, but also to other complicated psychopathological conditions for instance in the framework of schizophrenia. Possible hypotheses and causes of differences in clinical qualifications and statistical registrations of affective disorders among the Nenets´ and the Russians have been discussed. As principal hypotheses one should consider the historic-cultural hypothesis and also adaptive-adjustive one.

S-05-05

Affective spectrum disorders: On the way to unitary concept

V. Krasnov. *Moscow Research Institute of Psychiatry, Moscow, Russia*

Objective: Purpose of this study is to assess of the prevalence of affective spectrum disorders in primary care settings.

Methods: screening questionnaire, semistructured psychiatric interview, SCL-90, Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS).

Results: 14,230 adult out-patients from 18 to 55 years in several primary care settings have been screened over six years. 51.3% of the screened out-patients showing different affective (depressive and anxious) disturbances and somatoform disorders. In the majority of cases, the anxiety symptoms overlapped with depression. During the six-year study, 30.3% of the patients were identified with depression by standardized clinical instruments; in 23.9% the HDRS score was 15 or more. At the same time, there were different combinations of depression with anxiety and somatoform disorders-with similar score levels of somatization, depression and anxiety by SCL-90, and HARS score average of about 20. In clinical course, anxiety and/or somatoform disorders usually preceded depression or combined with it at early, and further on were replaced by typical depressive syndrome. Anxiety clearly dominated in only 4.7%, but included background subsyndrome depression in the majority of cases. Separate somatoform disorders without depressive and anxiety features were identified only in rare cases. Treatment with SSRIs and others modern antidepressants has shown significant positive response for both depression and anxiety, as well as for persistent somatoform disorders.

Conclusion: The data have been obtained in favour of the unity concept of a single affective spectrum, which considers anxious-depressive affective disorder with psychovegetative components as a cohesive entity.

Sunday, April 3, 2005

S-09. Symposium: What can we learn from naturalistic observational studies and medication trials in bipolar disorder?

Chairperson(s): Heinz Grunze (Munich, Germany), Eduard Vieta (Barcelona, Spain)
14.15 - 15.45, Gasteig - Lecture Hall Library

S-09-01

E. Vieta. *University of Barcelona Hospital Clinic, Barcelona, Spain*

Objective: To address the issues related to the gap between efficacy and efectiveness in the treatment of bipolar disorder.

Methods: A systematic review of the literature, including all relevant contrlled and naturalistic trials, was conducted.

Results: The management of bipolar disorder has traditionally focused upon the treatment of acute mania and although this is a fundamental aspect of patients' care, other aspects of mood stabilisation, e.g. treatment of depression, have been overshadowed. Most of the problems come when decisions are based only on the potential efficacy of treatments, rather than effectiveness. Efficacy responds to the question: Does a treatment work under ideal conditions?, whereas effectiveness responds to the question: Does a treatment work under the conditions of routine care? The answer to the second question should be more relevant to clinicians. Indeed, the mood-stabilising agent lithium, introduced in 1949 as a treatment for mania is the mainstay of long-term treatment of bipolar disorder and is in widespread clinical use. However, lithium has a slow onset of action and is not very well tolerated, so despite its efficacy, effectiveness is quite low. Of those patients with bipolar disorder who receive treatment, noncompliance with medication is a significant problem. When associated with lithium treatment in particular, noncompliance increases the risk of relapse. The need for well-tolerated agents with efficacy in depression as well as mania, has led researchers to evaluate the potential of a variety of anticonvulsants, antidepressants and antipsychotics as primary or adjunctive, which have proved to be efficacious and generally safer than the older drugs. However, research in this area has basically been conducted for registration purposes, and little is known about the true effectiveness of novel treatments in clinical practice.

Conclusion: There is a gap between research and clinical practice. Large, unbiased open randomised and observational studies are urgently needed to learn more about the true effectiveness of novel treatments for bipolar disorder.

S-09-02

H. Grunze. *LMU Psychiatry, Munich, Germany*

S-09-03

R. Bottlender. *Psychiatrische Klinik der Ludw, München, Germany*

Sunday, April 3, 2005

S-12. Symposium: Stress, glucocorticoids and affective disorders: From bench to bedside

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Chairperson(s): Peter Gass (Mannheim, Germany), Isabella Heuser (Berlin, Germany)
14.15 - 15.45, Holiday Inn - Room 2

S-12-01

Stress system regulation, glucocorticoid receptors and traumatic early life events

M. Oitzl, E. Leo, d. K. Ron. *University Hospital Div. Med. Pharmacogy, Leiden, Netherlands*

Objective: Traumatic events in early life are considered to increase the susceptibility for psychiatric disorders. In animal models, manipulations of mother-pup interaction have been shown to produce long lasting changes in emotional, cognitive and neuroendocrine reactivity. Evidence accumulates that the mechanisms underlying these long-term effects of early adversity are to be found in the glucocorticoid-related stress system (hypothalamic-pituitary-adrenal (HPA) axis). Glucocorticoid effects in the brain are mediated by the high affinity mineralocorticoid receptor -MR, and the low affinity glucocorticoid receptor -GR. MR and GR control the basal and stress-induced secretion of the hormone, determine neuronal excitability and distinct behavioural domains.

Methods: Rat/mice pups were separated from their mother for a certain period (once or repeatedly for 8 or 24 hours) at different postnatal days. We studied both, the immediate and long-term effects of this early life trauma, measuring a series of neurochemical markers of stress-system (re)activity and behaviour.

Results: During the postnatal period, when glucocorticoid concentrations are kept actively low by maternal care, separation of mother and pup severely disrupts the developmental pattern of the stress system. Frequency and duration of deprivation differentially affect the stress sensitivity and individual response characteristics.

Conclusion: Maternal deprivation disrupts the normal development of the brain and stress system. As a consequence, the animal is exposed to oscillating high and low levels of glucocorticoids, while negative feedback regulation seems to be dysfunctional and cognitive performance impaired in later life.

S-12-02

Glucocorticoid receptor transgenic mice as models of depression

P. Gass. *Zentralinstitut Psychiatry, Mannheim, Germany*

Objective: Impaired glucocorticoid receptor (GR) signaling is a postulated mechanism for the pathogenesis of affective disorders, such as major depression and posttraumatic stress disorder. Since in vivo expression and functional studies of GR are not feasible in humans, we have generated different mouse strains that over- or underexpress GR. This presentation will summarize neuroendocrinological and behavioral findings that have been obtained in several mouse strains that turned out to be highly interesting for depression research:

Methods: Using transgenic techniques we generated i) mice that lack GR specifically in the brain; ii) mice with a 50% GR gene dose reduction (GR heterozygous mice); iii) mice with a 100% GR gene dose elevation (GR transgenic mice).

Results: i) mice that lack GR selectively in the CNS show a disinhibition of the hypothalamic-pituitary-adrenal (HPA) system similar to depressed patients, but reduced anxiety and despair behavior. Due to the lack of GR in the brain, they represent a behavioural model for a depression-resistant mouse strain. ii) heterozygous mice that underexpress GR exhibit normal baseline behaviors, but after stress exposure they demonstrate helplessness and despair. Similar to depressed patients they show a disinhibition of the HPA system and a pathological DEX/CRH test. Thus they represent a murine depression model with good face and construct validity. iii) mice that overexpress GR by a yeast artificial chromosome (YGR) are more resistant to develop helplessness and despair following stress exposure, i.e. they show the opposite phenotype as mice that underexpress GR. They same is true for their HPA system, which is more resistant to stress, and the DEX/CRH test, where they are oversuppressors. Thus they represent a model for a stress-resistant mouse strain.

Conclusion: These mouse strains can be used to study long-term plasticity changes underlying the pathogenesis of depressive episodes. Using modern genomic or proteomic techniques they may turn out to be valuable tools to detect new molecular targets for antidepressive therapy, and thus open new therapeutic avenues for faster and better treatment with less side-effects.

S-12-03

Genetic factors have an impact on cortisol and ACTH responses to psychosocial stress

S. Wüst, I. Federenko, E. F. C. Van Rossum, J. W. Koper, R. Kumsta, S. Entringer, D. H. Hellhammer. *Department of Psychobiology, U, Trier, Germany*

Objective: In the present study the impact of genetic factors on hypothalamus-pituitary-adrenal axis responses to psychosocial stress was investigated.

Methods: Three times at one week intervals 33 monozygotic (MZ) and 25 dizygotic (DZ) male twin pairs were exposed to a laboratory stressor including a free speech and mental arithmetic tasks in front of an audience ('Trier Social Stress Test, TSST'). Salivary cortisol, total plasma cortisol and ACTH responses were assessed and intrapair correlations for the areas under the curves (AUC) were computed. Furthermore, the impact of two polymorphisms of the glucocorticoid receptor gene on TSST responses was studied. The 'N363S' polymorphism is located in exon 2 and the 'BclI' polymorphism is sited 646 nucleotides downstream from the 3'-end of exon 2.

Results: AUC heritabilities increased across sessions for all measures (free cortisol: TSST1: rMZ=.38/rDZ=.34, T2: .70/.42, T3: .78/.27; total cortisol: T1: .51/.35, T2: .58/.40, T3: .66/.17; ACTH: T1: .17/.15., T2: .63/.04, T3: .66/.13). Regarding the BclI polymorphism allelic discrimination identified 48 CC subjects, 18 GG subjects, and 46 heterozygotes. Ten CC carriers were additionally either heterozygous (AG, n=8) or homozygous (GG, n=2) N363S carriers. Salivary cortisol responses to the TSST exposures differed significantly between genotypes (all $p<.05$). Compared to participants with the rather common genotype? BclI CC & N363S AA?, carriers of the N363S G allele showed an enhanced cortisol response while the response in BclI GG subjects was diminished. ACTH responses to the first TSST as well showed a trend towards higher values in N363S carriers compared to BclI GG subjects.

Conclusion: The observed rise of heritabilities across sessions suggests that situational variables are initially dominant and might mask existing genetic factors. This is the first investigation that documents an impact of GR polymorphisms on adrenocortical responses to psychosocial stress.

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S-12-04

I. Heuser. *Psychiatrische Klinik, Freie U, Berlin, Germany*

S-12-05

Using cellular systems to understand glucocorticoid resistance in depression

C. Pariante. *Institute of Psychiatry, London, United Kingdom*

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

P. Baumann, E. Jaquenoud, C. Eap. *Unite de biochimie et psychopharmacologie clinique, Prilly-Lausanne, Switzerland*

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

J. Scharfetter. *Uni-Klinik f. Psychiatrie Abt. f. Allg. Psychiatrie, Wien, Austria*

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

M. Uhr. *Max Planck Institute for Psychiatry, München, Germany*

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