S-07-04

The contribution of modern neurophysiologic methods to our understanding of cortical neuroplasticity

P. Eichhammer, B. Langguth, G. Hajak. *University of Regensburg Dep. of Psychiatry, Regensburg, Germany*

In the last decade, transcranial magnetic stimulation (TMS) has been used increasingly as a tool to explore the mechanisms and consequences of cortical plasticity in the human cortex. Depending on the stimulation frequency, TMS can induce neurobiological effects resembling those used in animal studies of neuroplasticity in which electrical stimulation was used. In rodent auditory cortex, known for learning-induced plasticity, rTMS from 1 to 10 Hz resulted in long-term potentiation (LTP)-like and more durable long-term depression (LTD)-like changes in evoked spike rate (Wang et al., 1996). In support of this study, low-frequency 1-Hz rTMS, targeting the left temporoparietal cortex, causes a remarkable and sustained reduction of auditory hallucinations in schizophrenia, which is interpreted as the result of TMS-induced lasting changes in synaptic efficacy. Based on these results, we studied whether structural neuroplasticity is involved in mediating clinical effects of low-frequency rTMS in a group of healthy volunteers by means of voxel-based morphometry, a magnetic-resonance imaging technique, which is able to detect subtle changes in cortical grey and white matter. Our results point to the fact that TMS may be able to induce regenerative neuroplastic processes in specific brain areas depending on the site of TMS stimulation. These findings are in line with current studies investigating the neurobiological effects of central acting agents like antidepressants and underscore that the induction of neuroplastic processes may be essential for a variety of different treatment strategies.

Tuesday, April 5, 2005

S-03. Symposium: New aspects in therapeutic drug monitoring

Chairperson(s): Michael Riedel (Munich, Germany), Markus J. Schwarz (Munich, Germany)
14.15 - 15.45, Holiday Inn, Gasteig - Black Box

S-03-01

Insights in stereopharmacology in modern antidepressant treatment

F. Bengtsson. *Dept Clin Pharmaco Uni Linköp Faculty of Health Sciences, Linköping, Sweden*

Our knowledge of the biochemical and pharmacological complexity in space, sometimes existing when a three-dimensional view is applied on such molecules, dates back a long time. This insight has prompted an awareness that both the metabolism of a molecule as well as the bioactivity of the molecule may be altered if the molecule possesses a so called chiral center. If a drug comprise a chiral center, this is made up of (at least one) carbon atom(s) that provides for different and in-exchangeable three-dimensional structures of the same molecule referred to as separate stereoisomers. Since it has been quite complicated to, at least in an industrial scale, separate the different setereoisomers of a so called racemic (i.e. 50/50 mixture of isomers) drug, many such racemates have been the only available compound for prescription on the market. However, the insight that such a chiral or racemic drug tentatively may bring about different both pharmacokinetic (PK) and pharmacodynamic (PD) activities for each stereoisomer has necessitated a deeper analysis of the problem. This in order to better understand drug dosing (e.g. linear or non-linear kinetics?) as well as drug actions (effects, side-effects and toxicity). Recently also the possibilities to separate stereoisomers from each other in a racemic preparation has advanced so that it can be done both in an experimental scale, for testing of the individual stereoisomers, as well as for production of larger quantities so that a stereochemically "pure" drugs can now be offered to the clinic. One of the worlds most commonly prescribed drug entities are the antidepressant, or thymoleptic, drugs. Interestingly, the vast majority of these thymoleptics are marketed as racemic drugs, i.e. comprising of at least two stereoisomers of the same compound. Since, inevitably, all such drugs undergo an extensive metabolism in the body the stereoisomeric outcome may be very different from drug to drug as well as for the same drug between different patients. Moreover, since this metabolism creates a number of catabolites, these metabolites will commonly bear the same stereopharmacological aspects as their parent compound, why the complexity increases even further regarding the "true" PK-outcome of such an antidepressant. Finally, since the PD-activities may vary between all these stereoisomers (parent compounds as well as metabolites), the ability to point out real causality of the outcome of any such drug exposure when viewed in the clinic of modern antidepressant treatment has to take this whole new pharmacological paradigm into consideration. The present lecture will provide information on the most common antidepressant drugs, old as well as new, in the view of their specific PK and PD-related stereopharmacological features. This will give an insight into the new pharmacological paradigm that has to be taken into account when evaluating antidepressant treatment in greater detail in the modern age.

S-03-02

Therapeutic drug monitoring of psychotropic durgs in the era of pharmacogenetics studies

C. Eap. *Unité de Biochimie et Psychoph, Prilly-Lausanne, Switzerland*

Like for other drugs, there is a large inter-individual variability of the plasma concentrations of psychotropic drugs for a given dose, which is the main rationale for therapeutic drug monitoring. TDM is performed to avoid toxicity (due to high and poorly tolerated plasma levels) and inefficacy (due to low and ineffective plasma levels). Within the last decade, a large amount of studies in pharmacogenetics / pharmacogenomics allows us to understand the importance of genetic and environmental factors on the disposition of drugs in the organism. Thus, high and low plasma levels might concern the so-called poor and ultrarapid metabolizers, respectively, either due to a genetic basis or an environmental factor, e.g. co-administration of inhibiting or inducing drugs. Several genotyping and phenotyping methods now allow the determination of the activity of several key enzymes involved in the pharmacokinetics of drugs, in particular those of the cytochrome P450 family. Proposals of genotype specific dosages of drugs have been made (i.e. a low dose for the poor metabolizers and a high dose for the ultrarapid metabolizers), which will lead to, admittedly, equivalent plasma concentrations in all patients. Advantages and limitations of such proposals will be discussed. Finally, arguments with practical examples, clinical cases and some cost-benefit considerations, on how

https://doi.org/10.1016/S0924-9338(05)80119-1 Published online by Cambridge University Press

a rational use of TDM with genotyping / phenotyping strategies could improve pharmacotherapy, will be presented.

S-03-03

Therapeutic drug monitoring of risperidone in relation to MDR1 genotype and hormone levels

M. Riedel. *Psychiatric Hospital, LMU Muni, Munich, Germany*

S-03-04

Therapeutic drug monitoring of quetiapine and its major metabolites quetiapine-sulfoxide and 7-hydroxy-quetiapine

M. J. Schwarz, *Psychiatric Hospital, LMU Muni, Munich, Germany*

I. Spellmann, A. Müller-Arends, S. Dehning, R. Musil, M. Opgen-Rhein, J. Zach, H.-d. Li, N. Müller, H.-J. Möller, M. Riedel.

Quetiapine is one the most frequently prescribed new atypical antipsychotic drugs. After oral administration, it is rapidly absorbed and extensively metabolised, resulting in relatively low serum concentrations of the parent drug. For years, quetiapine was believed to be mainly (if not exclusively) metabolised by the cytochrome P450 enzyme 3A4. Recent in vitro data, however, show that Cyp2D6 is also an important component of quetiapine metabolism. We were interested in the relationship between different metabolites and the parent drug in serum, the daily dose, and the clinical effect of quetiapine therapy in schizophrenic patients. Forty patients were included into a six-week monotherapy study with variable dose of quetiapine. Response to treatment was monitored by weekly assessment of the PANSS. We established a HPLC method for the simultaneous determination of quetiapine and seven of its metabolites including quetiapine-sulfoxide and 7-OH-quetiapine after solid phase extraction. Serum levels of quetiapine showed a strong correlation with quetiapine-sulfoxide, but not with the daily dose. 7-OH-quetiapine moderately correlated with the daily dose, while an unspecified metabolite, which we called 'metabolite 6', strongly correlated with the daily dose. No relationship between either quetiapine or one of its metabolites with therapy response was found. To confirm these data, we investigated 100 schizophrenic in-patients, who underwent quetiapine treatment (mostly in combination with other antipsychotics) with repeated therapeutic drug monitoring during a one-year period. Again, we found a strong correlation between metabolite 6 and daily dose, but not between quetiapine and daily dose. Moreover, there was again no relationship between quetiapine or metabolite 6 levels and therapy response as indicated by the clinical global impression scale. Since metabolite 6 appeared very early during the first week of quetiapine administration, we propose that it is a direct quetiapine metabolite. We propose that this metabolite may be produced by CYP2D6, but in vitro studies will have to confirm this hypothesis.

Tuesday, April 5, 2005

S-20. Symposium: Evolutionary psychiatry

Chairperson(s): Pierre Schulz (Chêne-Bourg, Switzerland), Thierry Steimer (Genf, Switzerland)
16.15 - 17.45, Holiday Inn - Room 8

S-20-01

What is evolutionary psychiatry?

T. Steimer. *Clinical Psychopharmacology, Genf, Switzerland*

The clinical approach to psychiatric disorders has been mainly phenomenological and empirical. Progress in the understanding of the biological substrates underlying some pathologies (e.g. the neuroendocrine stress system in depression) has led to more theoretical considerations regarding the etiology and physiopathology of mental illness. Animal models of psychiatric disorders, on the other hand, have shown a role for adaptive vs maladaptive responses to environmental and social challenges, and the importance of genetic vs environmental influences during ontogenesis. These findings have been incorporated into the current "biopsychosocial model". Recently, evolutionary psychiatry has emerged as a new theoretical framework, based on concepts derived from evolutionary theories, also including ethology and sociobiology. It is an attempt to reconsider psychopathology within the context of phylogenesis and alternative adaptative strategies: behaviours have been selected – or retained - for their adaptive value. Although this new way of considering psychiatric diseases is interesting and potentially fruitful, it has to be assessed critically. First, the "evolutionary explanation" may not apply to all kinds of psychiatric diseases, or their individual manifestations. Some of them are more likely the result of dysfunctions which, being of limited prevalence, can be tolerated as part of natural variation. Second, evolutionary theories themselves are open to criticism and, in particular, the "adaptationist" view must be considered with some caution, because adaptation may not be a driving force of evolution. In this Introduction, we will try to give a balanced account of the evolutionary approach to psychiatric syndromes and consider some of its further developments.

S-20-02

A. Langaney. *Dpt. of Anthropology and Ecolo, Geneva, Switzerland*

S-20-03

Therapeutic implications of Darwinian psychiatry

A. Troisi. *Dpt. of Neurosciences, Univers, Roma, Italy*

Darwinian psychiatry applies the concepts and methods of evolutionary biology to the study of mental disorders. As a new approach to the explanation for the origin of psychopathology, Darwinian psychiatry has attracted much interest among clinical and research psychiatrists. However, its utility in terms of treatment strategies and therapeutic interventions has been repeatedly questioned. The aim of this presentation is to demonstrate that, contrary to this common prejudice, Darwinian psychiatry has relevant therapeutic implications and can contribute to improve treatment strategies in psychotherapy and psychopharmacology. Unlike the biomedical model of mental disorders, Darwinian psychiatry distinguishes between dysfunctional and adaptive symptoms. Dysfunctional symptoms reflect neurobiological damage and their therapeutic elimination (if possible) does not entail any risk for the patient. By contrast, adaptive symptoms are evolved responses that serve the function of limiting or offsetting the adverse consequences of maladaptive circumstances. Symptoms of anxiety and depression may act as alarm signals and may favor the implementation of alternative behavior strategies. The use of drugs or psychological therapies to eliminate these

https://doi.org/10.1016/S0924-9338(05)80119-1 Published online by Cambridge University Press