Laboratory diagnoses: – basic research

ANTIBODY REACTIVITY AGAINST NERVE GROWTH FACTOR IN MENTAL DISORDERS

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The nerve growth factor (NGF) is hypothesised to be involved in the regeneration of cholinergic neurones. The influence of NGF as one contributory factor in the development of mental disorders is unknown.
Serum from patients with mental disorders (schizophrenic psychosis, N=38; major depressive disorder, N=37; schizoaffective psychosis N=20) was examined for antibodies against nerve growth factor (NGF) by DOT-ELISA. Results were compared with psychiatric controls (patients with chronic alcoholism (N=41) and Alzheimer's disease (N=20)), immunological controls (patients with chronic rheumatic diseases (N=29) and multiple sclerosis (N=20)) and a control group of healthy volunteers (N=30). Frequency of antibody positive sera was about 60% in healthy controls and alcoholics, nearly similar in patients with schizoaffective psychosis and Alzheimer's disease (about 40-45%) but significantly suppressed in sera of patients with schizophrenic psychosis, major depressive disorder and multiple sclerosis (about 5%).
These results are discussed on the basis of the possible role of NGF in regenerative processes of the brain.

USE OF RADIOLIGAND METHODS IN EARLY DIAGNOSTICS OF MENTAL DISORDERS

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Methods of direct research of neuroreceptors of a man in his lifetime are missing at present. This is why main research studies of changes in their characteristics with various psychopathologic syndromes are conducted as an experiment on animals. We have used radioligand methods to have a comparative study of serotonin, dopamine receptors and GAOA-benzodiazepine receptor complex on thrombocytes of peripheral blood with sane and insane patients. These types of receptors have been investigated by us, as well, in the "reserve" blood and in placenta. The results have been compared to peculiarities of psychic status of newly born, having in view antenatal harm.
The above research allows us the following: 1. Single our groups of indices, reflecting specific changes in the state of thrombocytes receptors at various mental disorders. 2. Conduct a correlation analysis of the state of thrombocytes receptors of the "reserve" placenta blood and placenta with the peculiarities of the newly born mental condition. 3. Use the results received to elaborate effective methods of early diagnostics of mental disorders. 4. suggest a purposeful search of specific pharmacological means for therapy of psychopathological disorders.

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AN OPTIMIZED METHOD FOR MEASURING SEROTONIN (5-HT) UPTAKE IN HUMAN BLOOD PLATELETS.

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In humans, presynaptic 5-HT reuptake is often studied indirectly by measuring 5-HT uptake in blood platelets. However, different studies carried out on patients with affective disorders tend to use different uptake assays. The purpose of this study was to determine, what are the optimal analytical conditions for measuring 5-HT uptake in human blood platelets suspended in an artificial medium. Our results indicate that *1)* the blood should be anticoagulated with a rather high final concentration of EDTA (25.2 mM), *2)* the medium, best suited for resuspension of the platelets is a Krebs-Ringer bicarbonate buffer with magnesium and calcium, *3)* the measurements of uptake should be performed immediately after preparation of the blood platelets, *4)* the incubation time has to be short (15 seconds) and *5)* uptake should be measured at 5-HT concentrations in the range 0.1875-2 μM. After optimization of the assay, its reproducibility was evaluated by measuring 5-HT uptake in two blood samples (sample 1 and 2) taken from 10 healthy subjects. In blood platelets prepared from sample 1 and 2, V_{max} (pmol/10^8 platelets/min)(mean $\pm$ SD) was 231 $\pm$ 79 and 216 $\pm$ 74 and K_m (μM) (mean $\pm$ SD) was 0.80 $\pm$ 0.51 and 0.72 $\pm$ 0.48, respectively. The analytical coefficient of variation (CV) of V_{max} and K_m measured in blood platelets prepared from the two samples was 7.4% and 14%, respectively. The interindividual biological CV was 33% and 63%. It is concluded that this optimized assay may be used for studying both trait- and state-dependent changes in human blood platelet 5-HT uptake.

Obsessive - compulsive symptoms, sleep-, and neuroendocrine investigations in Gilles de la Tourette Syndrome.

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The Gilles-de-la-Tourette Syndrome (GTS) is characterized by motor tics, vocalisations, mutilations and obsessive compulsive symptoms (OCS). The pathogenesis is unclear.
The evaluation of OCS showed marked or severe OCS in more than 60 % of the patients. A comparison of GTS patients with patients suffering from obsessive-compulsive disorder (OCD) showed significantly higher scores in both groups of patients in the Hamburg obsessive-compulsive inventory (HZI) than a control group. A discriminant analysis between the patients was able to reveale specific differences in the OCS of GTS compared to OCD. 90% of the patients could be correctly classified in respect to their diagnosis.
This result leads to the conclusion that the differential observation of the psychopathology of obsessions and compulsions can contribute to the differential diagnosis in OCD and GTS. The different psychopathology may reflect differences between a neurotic and an organic source of obsessions and compulsions.
By sleep investigations we observed periodic leg movements in sleep in two thirds of GTS-patients, pathophysiological parallels to the restless legs syndrome are discussed.
Since therapeutic efficiency of opiate-antagonists was reported before, we treated the patients with naltrexone in an open dose-response trial with benefit in only some of the patients.
Because clonidine is widely used in the therapy of GTS, an involvement of the noradrenergic system in the pathophysiology of GTS is discussed. Therefore the growth hormone (GH) response to clonidine was investigated in 9 GTS patients compared to age and sex matched controls. In most of the GTS patients, a blunted GH response was found and it was significantly reduced compared to controls.

ACUTE INTERMITTENT PORPHYRIA AND DISTURBANCES IN AMINO-ACID METABOLISM IN A PSYCHIATRIC IN-PATIENT POPULATION

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In recent years an enhanced catabolism of serine, with or without the existence of porphyria, has been demonstrated in relation to a specific subtype of psychosis, according to ICD-10 criteria, the acute polymorphic psychosis with or without symptoms of schizophrenia. Since sensory perceptual distortions play a key role in the symptomatology, patients with this disorder are referred to as Acute Polymorphic Psychosis plus Psychosensory phenomena (APP+). Theoretically, a disturbed serine metabolism can lead to the endogenous formation of compounds with hallucinogenic properties. In most patients with APP+, oral loading with serine during symptom-free intervals, induced the characteristic psychedelic and psychotic symptoms. In plasma of these patients, concentrations of serine and methionine are decreased, while the concentration of taurine is enhanced. APP+ can be suspected by an elevated TSM ratio on combination with a lowered taurine concentration. TSM ratio is defined as the ratio of 100 times the taurine concentration in plasma and the product of the plasma concentrations of serine and methionine. In a retrospective study, including a total of 140 psychiatric patients, we investigated the prevalence of Acute Intermittent Porphyria (AIP) and APP+. No subjects with AIP were found. In two patients APP+ could be demonstrated, based on both clinical characteristics an positive biochemical markers, i.e. lowered plasma serine concentration and increased TSM ratio. In three patients the psychotic disorder was suspected to be present.
It is concluded that careful psychiatric diagnosing may reveal specific psychotic disorders with a distinct biological pathogenetic factor.

INFLUENCE OF SYNAPTIC DOPAMINE CONCENTRATION ON THE IN VIVO ^{3}H MAZINDOL AND ^{3}H COCAINE BINDING TO THE MOUSE STRIATUM

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When interpreting positron emission tomography (PET) results in pathological conditions modifying the synaptic dopamine levels (schizophrenia, depression or Parkinson's disease), the effect of these dopamine levels on the binding of radioligands to the dopamine uptake sites should be considered.
For that purpose, we have studied the striatal in vivo binding of ^{3}H mazindol (1 µCi i.v., 45 min before sacrifice) or ^{3}H cocaine (2µ Ci i.v., 10 min before sacrifice) in mice. Radiactivity was mesured in the striatum (total binding) and the cerebellum (non specific binding) following i.v. injection of the ligand to control and drug pretreated mice.
We have first determined the effect of a reduction in the synaptic dopamine concentration elicited by a blockade of dopaminergic neurons impulse flow using gammabutyrolactone 750 mg/kg i.p., 45 min before sacrifice. This pretreatment did not modify the in vivo binding of ^{3}H mazindol in vivo binding.
Cocaine has a lower affinity for dopamine uptake sites than mazindol and thus ^{3}H cocaine in vivo binding could be subject to a competition with synaptic dopamine concentration. However, neither ^{3}H cocaine nor ^{3}H mazindol binding were sensitive to extraneuronal dopamine levels, suggesting that their binding sites could be mainly located extra junctionally and thus may not be directly influenced by the synaptic dopamine. Therefore, these radioligands could be useful tools for PET measurements of the density of dopamine uptake sites in neuropsychiatric diseases, reflecting the dopaminergic innervation status even in treated patiens.

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MAO-A DEFICIENCY AND PSYCHIATRIC SYMPTOMS

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A new chromosomal disorder, in which there is a total lack of MAO-A, was recently identified in a Dutch family (Brunner et al., 1993). The disorder is X-linked and expressed only in male probands. The biochemical profile of this particular disorder is compatible with a surplus of mono-amines and a very low excretion of mono-amine metabolites. In 24-h urine analysis marked elevations were noted for the MAO substrates such as normetanephrine, 3-methoxytryptamine and tryptamine. Reduced amounts of the MAO products vanilacetic acid, vanylglycolic acid, 3 methoxy-4-hydroxy-phenylglycol and 5-hydroxy-indol-3-acetic acid were found. The clinical syndrome in these patients is characterized by symptoms of behavioral disinhibition (aggressive and sometimes violent acts), cognitive disturbances (specific learning problems and frontal dysfunction with an IQ within the normal range), and emotional symptoms. Data about the clinical picture of 9 probands will be presented and the possibilities of pharmacological intervention will be discussed. It is speculated that treatment with 5-HT_{1a} agonistic compounds might induce beneficial effects on the symptoms of behavioral disinhibition. Further research into the combination of MAO-A-gene polymorphism and psychiatric disorders might be worthwhile considering.

Brunner, H.G. et al. (1993) X-linked Borderline Mental Retardation with Prominent Behavioral Disturbance: Phenotype, Genetic Localization and Evidence for Disturbed Monoamine Metabolism. Am. J. Hum,. Genet.52: 1032-1039.