FC67 *Neurosciences, psychopharmacology and biological psychiatry*

SYNAPTOGENESIS, SYNAPTIC PRUNING AND SCHIZOPHRENIAS

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An understanding of the pathogenesis of schizophrenia as described by the neurodevelopmental theory requires knowledge of the links between potential etiological factors occuring early in the developmental phase and symptom onset which occurs late in adolescence or early childhood. Synapse pruning, a phenomenon in which a large proportion of the huge quantity of synapses produced during the developmental stage disappears, occurs during the same period and might play a causal role in triggering schizophrenia. On the basis of other cerebral anomalies reported in the literature as well as clinical and epidemiological data currently available on schizophrenia, the most probable hypotheses integrate synaptic pruning as part of a wider disturbance of cerebral development in the prefrontal, temporal and limbic regions. These perturbations may occur early in the pre- or perinatal period or late during adolescence. It cannot be excluded that abnormal synapse pruning alone may be the underlying cause in a sub-group of schizophrenic patients.

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QUALITY OF LIFE OF DEPRESSIVE PATIENTS UNDER MEDICATION

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The main purpose was to evaluate the level of social functioning (SF) and quality of life (QoL) changes during the course of drug treatment of depressive patients. Ninety outpatients treated with different antidepressants (amitriptyline, fluoxetine, tianeptine) were examined. The severity of depression and its dynamics was assessed according to 17 items HAMD. SF and QoL were evaluated using the original inventory. These data were compared with simultaneous reduction of depressive symptoms. Therapeutic dynamics was the following In patients treated with amitriptyline the pronounced clinical effect has developed after 3-4 weeks of medication ($p<0.001$). The same dynamics has been shown in patients treated with fluoxetine ($p<0.001$). Tianeptine has been characterized with stage type of therapeutic effect development - quite quick but mild efficacy on the initial stage (1-2 weeks of medication) and deferred complete reduction of depression after 5-6 weeks of medication ($p<0.001$). Dynamics of SF and mental health related QoL have shown similar tendencies, while global QoL changes differed in medication groups. Anxious depressive patients treated with amitriptyline demonstrated permanent improvement of global QoL. In all other groups this dynamics was undulating which had certain impact on patients' compliance to medication. The results are important for better assessment of therapeutic efficacy.

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Involvement of vasopressin in hypothalamic-pituitary-adrenal (HPA) system alterations

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In human aging and psychiatric disorders like depression the HPA system becomes gradually disinhibited as reflected e.g. by the combined dexamethasone (DEX)/CRH test which has proved to be the most sensitive measure of subtle changes in HPA system regulation. To further explore the mechanisms underlying the neuroendocrine abnormalities in an animal model, the combined DEX/CRH test was established in young male Wistar rats (3 months) and then used in aged rats (24 months): After DEX (30 µg/kg, given at 1200h), not only ACTH levels were significantly higher in aged than in young rats, but also ACTH response to CRH (50 ng/kg, given at 2000h) was significantly increased. Thus, the HPA system is profoundly altered also in rats during aging, the elevated basal ACTH levels reflect DEX non-suppression and might indicate feedback disturbances probably at a suprapituitary level, whereas the elevated ACTH release after the CRH challenge suggests alterations of the endogenous synergisms of CRH with other factors responsible for ACTH secretion, e.g. vasopressin. To test the latter hypothesis, a second set of experiments was performed in aged animals (24 months): a vasopressin receptor antagonist was administered 8h after DEX and 15 min before CRH resulting in a significant reduction in CRH stimulated ACTH release compared to age-matched controls treated with vehicle (AUC: 577 ± 420 vs. 2811 ± 780, $p<0.01$). This is the first direct evidence for the involvement of endogenous vasopressin in the altered DEX/CRH test outcome and, thus, in alterations of the HPA system regulation in aging.

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TRACK 1: AUTORECEPTORS IN DEPRESSION (ANTIDEPRESSANT ACTION)

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The objective is to study aumentation of the antidepressant paroxetine with pindolol, a $_5HT_{1A}$ autoreceptor blocker, in a double blind, randomised, placebo-controlled trial. Eighty out-patients (mean age 36 [range 19-65], 48 female, 32 male) were recruited as described by Tomé et al. (1996), each patient receiving paroxetine (20 mg o.d.) plus, randomly, either pindolol (2.5 mg t.d.s.) or placebo for six weeks. Paroxetine (open label) was offered to all patients for a further 18 weeks. Follow-up assessments of sixty-nine patients, using the Global Impression [GI]; Montgomery-Asberg Depression Rating Scale [MADRS]; Beck Depression Inventory [BDI], took place at weeks 8, 16 and 24. Patients originally treated with pindolol (n=32) showed significantly better clinical outcome at week 24, when compared with patients originally taking paroxetine alone, whether they complied fully with follow-up treatment or not. Compliance with follow-up treatment had a significant positive effect on outcome at weeks 16 and 24 in those patients originally treated with paroxetine alone (n=37). The combination of pindolol and paroxetine is well tolerated. The reduced latency and possibly superior antidepressant efficacy of pindolol augmentation of SSRI antidepressants may have considerable implications for the future management of depression.

https://doi.org/10.1016/S0924-9338(97)80514-7 Published online by Cambridge University Press