Hippocampal Pathology in Schizophrenia: Disturbed Synaptogenesis, Neuroneogenesis or What Else?

Volume reduction of the hippocampus is quite prevalent in schizophrenia and can be found in the different stages of the illness. Metaanalyses demonstrate a bilateral 6% volume reduction in chronic schizophrenia. Although this volume decrease is accompanied by clinically relevant deficits in episodic memory, the underlying mechanism still are unclear. In a recent study examining the hippocampus volume in families uni- and multiply affected with schizophrenia a bilateral decrease was shown in family members suffering from schizophrenia and to a lesser extent in their first degree relatives. Interestingly the biggest effect was due to the at-risk-haplotype of Neuregulin-1, while obstetric complications formed an additional independent risk factor.

Using stereology we have examined which cellular compartment is involved in the volume reduction revealed in the hippocampus of schizophrenics. Preliminary results on 10 patients with schizophrenia and 10 control subjects post mortem we could see a significant decrease of the macroneurons in the subiculum and an overall reduction of the volume of the macroneurons in all subsegments of the hippocampus. Interestingly a circumscribed reduction of the number of oligodendrocytes was revealed while sparing astrocytes and interneurons. The findings could indicate a disturbance of micro- and macroconnectivity in the hippocampus of schizophrenia.

Finally I would like to mention the study where we examined the influence of exercise on psychopathology, cognition and brain structure in schizophrenia. We found a marked increase of the hippocampus bilaterally in controls as well as schizophrenia patients performing defined exercise over three months. In comparison to that, patients with schizophrenia performing a control condition over the same period of time showed a significant worsening of the psychopathology, no improvement of cognition and no increase of the hippocampal volumes.

In summary there is increasing evidence that disturbed synaptic and possibly mechanisms of neuroneogenesis underlie the pathophysiology seen in the limbic system in schizophrenia.

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Antipsychotics: Which Neurotransmitters to Tackle?

Coincidental clinical observations with drugs that could alleviate or elicit symptoms of schizophrenia, have led to hypotheses on possible involvement of defective signaling of three different neurotransmitter systems in schizophrenia: dopamine, 5-hydroxytryptamine (5HT) and glutamate.

The first generation of antipsychotic drugs was discovered and developed based on the dopamine hypothesis. Research with these drugs showed that blockade of dopamine-D2 receptors could alleviate positive symptoms of schizophrenia. However, dopamine D2 receptor blockade also underlies potential side effects such as extrapyramidal symptoms and prolactin elevation. The discovery of 5HT2 receptors, later classified as 5HT2A receptors, and the study of the pharmacological and clinical properties of drugs that blocked these receptors, led to the second generation of so-called atypical antipsychotics; a right balance in blockade of 5HT2A and D2 receptors appeared to alleviate positive and negative symptoms of schizophrenia. However, atypical antipsychotics have broad pharmaceutical profiles and interact with various different neurotransmitter receptors, which more often leads to side effects rather than contributing a therapeutic benefit.

The observation that phencyclidine (also referred to as PCP), a glutamine-N-Methyl-D-Aspartate (NMDA) receptor blocker, can elicit positive and negative symptoms of schizophrenia, underlies the glutamate hypothesis and possible defective NMDA receptor signaling in schizophrenia.

Today several receptor subtypes for each of the above neurotransmitter have been identified and ample knowledge has been acquired about the signaling and regulation of the various receptors.

Five dopamine receptors, thirteen 5HT, three major classes of ionotropic glutamate receptors and eight metabotropic glutamate receptors are known.

Several of these receptors are being investigated as possible targets for drugs that can treat symptoms of schizophrenia, including positive, negative and cognitive symptoms. Various ways of modulating receptor signaling are being studied with compounds that act as antagonist, inverse agonist, full or partial agonist, positive or negative allosteric modulator at the
receptors or with compounds that inhibit intra-cellular enzymes involved in second messenger formation or breakdown. The lecture will address nowadays research along these lines.

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**New Approaches to the Development of Antidepressants**

It is generally assumed that all effective antidepressants enhance monoaminergic function in some way. Despite this belief, the mode of action of antidepressants remains an enigma. The disparity between the acute effects of antidepressants and the delay in their therapeutic action has long been recognised. The observation that the adaptive changes in post synaptic monoaminergic receptors approximately coincides with the onset of their therapeutic action has led to a change in emphasis from the pre-synaptic to the post-synaptic intracellular changes. This has resulted in the molecular hypothesis of antidepressant action that postulates that adverse environmental conditions, acting on genetic vulnerability, cause maladaptive changes in neuronal networks. Effective antidepressant treatment normalises the functioning of these networks, possibly by increasing neurotrophic factor synthesis and enhancing neurogenesis.

This new hypothesis, linking depression to malfunctioning neural networks, has stimulated novel approaches to antidepressant development. For example, the S100 beta peptide is known to be important in neurogenesis. It is linked to the 5HT 1B receptor via the p11 peptide. The p11 peptide has been shown to be reduced in post mortem brains from depressed patients; chronic antidepressant treatments, and ECT, increase the synthesis of this peptide and reverses depressive-like behaviour in rodent models of depression. This could provide a starting point for the development of new classes of antidepressants. A disruption of the circadian rhythm is a characteristic feature of depression. This has stimulated the development of agomelatin, a melatonin-1 receptor agonist and a 5HT2C antagonist. While the effects on the circadian rhythm may be of importance, it would appear that the reduction in the 5HT2C receptor function may be the main explanation for its antidepressant action. There are several non-monoaminergic approaches that are receiving attention. Several tachykine receptor antagonists have been developed. These drugs would appear to indirectly enhance serotonergic function. A more novel approach involves antagonists of the NMDA glutamate receptors. These drugs have been shown to have antidepressant activity in experimental models of depression, possibly by blocking the neurodegenerative changes in the hippocampus caused by environmental stress. The novel sigma receptor antagonist, igmesine, that exhibits antidepressant activity, may block these neurodegenerative changes by blocking the action of glycine on the NMDA receptor complex. Other amino acid receptor targets include antagonists of the G-protein coupled GABA-B receptors.

The HPA axis has become an important target for antidepressant action due to the key role that stress plays in the pathology of depression. Some success has been obtained in the development of glucocorticoid type 2 receptor antagonists such as mifepristone. In addition, centrally acting anti-inflammatory drugs such as celecoxib have been shown to enhance antidepressant response in depressed patients who fail to show an optimal response to a conventional antidepressant. As there is now substantial evidence to show that low grade inflammatory drugs play an important role in the pathology of depression, it is postulated that centrally acting anti-inflammatory drugs may have antidepressant properties in their own right.

Other more molecular approaches that could lead to novel antidepressant targets include drugs that act on mitogen activated protein kinase (MAP-kinase). This enzyme stimulates the synthesis of brain derived neurotrophic factor, a key neurotrophic factor involved in the repair of damaged neurons.

Whether any of these approaches will result in new and more effective antidepressants only the future will tell!

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