DEVELOPMENTAL AND PHARMACOLOGICAL MODELS OF SCHIZOPHRENIA: WHAT DID THEY TEACH US ABOUT CELLULAR MECHANISMS ASSOCIATED WITH THE DISEASE?

G. Grecksch1, G. Keilhoff2, T. Roskoden3, H. Bernstein4 and A. Becker1

O.-v.-Guericke University, Medical Faculty, *Institute of Pharmacology and Toxicology, 2Institute of Biochemistry and Cellbiology, 3Institute of Anatomy, 4Department of Psychiatry, Magdeburg, Germany

Schizophrenia is a neurodevelopmental disease resulting from abnormal early brain development and/or impaired postnatal maturation of the brain. The complex and varying symptoms of the disease indicate that an interplay of multiple factors rather than one single factor triggers this illness. Both genetic and epigenetic factors have been identified and a hypothesis, the “two hit hypothesis”, has been proposed explaining the origins of the disease by at least two subsequent etiological “hits”, a genetic predisposition and an epigenetic factor.

Many studies of people with schizophrenia have found subtle abnormalities in brain structure or in the way it functions caused by disturbances in cell migration, neurite outgrowth, axon fasciculation, synapse formation, and adult neurogenesis. These disturbances are in close relations with alterations in neurotrophic factors. It was hypothesised that imbalances in the neurotrophic system might contribute to alterations in the brain which are closely connected with schizophrenia. To further characterise cellular processes involved in schizophrenia we studied neurogenesis, neurotrophic factors, and effects of neuroleptic drugs in a developmental model (Vitamin D deficiency) and a pharmacological model (subchronic treatment with the non-competitive NMDA receptor antagonist ketamine). Developmental models are basing on the assumption that damage at a very early stage of ontogenesis results in structural abnormalities1-3, whereas pharmacological models are focusing on alterations in specific neurotransmitter systems with special regard to dopaminergic and glutamatergic systems4,5.

We found that subchronic ketamine treatment as well as its withdrawal enhanced the generation and/or survival of neurons in young-adult animals. On the contrary, maternal Vitamin D depletion resulted in reduced neurogenesis. This correlates with alterations in the concentration of neurotrophic factors in different brain structures found in the Vitamin D depletion model6-8 and in the ketamine model9,10. At the first view, our results obtained in the Vitamin D depletion model appear to be contrary to results obtained in the studies of McGrath’s group6,11, demonstrating an antiproliferative potency of vitamin D. However, the experimental settings differ in a crucial for neurogenetic experiments parameter as they studied the developing brain, whereas in our study adult animals were used.

The classical neuroleptic haloperidol and the atypical neuroleptic risperidone had different effects on schizophrenia-related alterations in the rats’ behaviour12-14, alterations in hippocampal long-term potentiation15 and as well as on neurogenesis16.

References

Developmental and pharmacological models of schizophrenia:


5. KNABLE MB, WEINBERGER DR. Dopamine, the prefrontal cortex and schizophrenia. J. Psychopharmacol. 1997;11:123-131.


12. BECKER A, GRECKSCH G. Pharmacological treatment to augment hole board habituation in prenatal vitamin D-deficient rats. Behav. Brain Res. 2006;166;177-183.


15. GRECKSCH G, RÜTHRICH H, HÖLLT V, BECKER A. Transient prenatal vitamin D deficiency is associated with changes of synaptic plasticity in the dentate gyrus in adult rats. Psychoneuroendocrinology 2009;34 Suppl1;S258-S264.