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

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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 abnormalities[1-3], whereas pharmacological models are focusing on alterations in specific neurotransmitter systems with special regard to dopaminergic and glutamatergic systems[4,5].

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 neurogensis. This correlates with alterations in the concentration of neurotrophic factors in different brain structures found in the Vitamin D depletion model[6-8] and in the ketamine model[9,10]. 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 group[6,11], 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' behaviour[12-14], alterations in hippocampal long-term potentiation[15] and as well as on neurogenesis[16].

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References

1. ASHE PC, BERRY MD, BOULTON AA. Schizophrenia, a neurodegenerative disorder with neurodevelopmental antecedents. Prog. Neuropsychopharmacol. Biol. Psychiatry 2001; 25; 691-707.
2. CANNON M, MURRAY RM. Neonatal origins of schizophrenia. Arch. Disease Child. 2000;78;1-3.

3. WEINBERGER DR. From neuropathology to neurodevelopment. Lancet 1995;346;552-557.
4. CARLSSON A., HANSSON LO, WATERS N, CARLSSON ML. A glutamatergic deficiency model of schizophrenia. Br. J. Psychiatry 1999;Suppl.37;2-6.
5. KNABLE MB, WEINBERGER DR. Dopamine, the prefrontal cortex and schizophrenia. J. Psychopharmacol. 1997;11;123-131.
6. EYLES DW, FERON F, CUI X, KESBY JP, HARMS LH, KO P, MCGRATH JJ, BURNE TH. Developmental vitamin D deficiency causes abnormal brain development. Psychoneuroendocrinology 2009;34;S247-S257.
7. EYLES DW, BROWN J, MACKAY-SIM A, MCGRATH JJ, FERON F. Vitamin D3 and brain development. Neuroscience 2003;118; 641-653.
8. MCGRATH JJ. Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? Schizophr. Res. 1999; 40; 173-177.
9. BECKER A, GRECKSCH G, SCHWEGLER H, ROSKODEN T. Expression of mRNA of neurotrophic factors and their receptors are significantly altered after subchronic ketamine treatment. Med. Chem.2008;4;256-263.
10. KEILHOFF G. GRECKSCH G, BERNSTEIN HG, ROSKODEN T, BECKER A. Rispiridone and haloperidol promote survival of stem cells in the rat hippocampus. Eur. Arch. Psychiatry Clin. Neurosci. 2010;260;151–162.
11. CUI X, MCGRATH JJ, BURNE TH, MACKAY-SIM A, EYLES DW. Maternal vitamin D depletion alters neurogenesis in the developing rat brain. Int. J. Dev. Neurosci. 2007;25;227-232.
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.
13. BECKER A, GRECKSCH G. Ketamine-induced changes in rat behaviour: a possible animal model of schizophrenia. Test of predictive validit., Prog. Neuropsychopharmacol. Biol. Psychiatry 2004;28;1267-1277.
14. BECKER A, GRECKSCH G, ZERNIG G, LADSTAETTER E, HIEMKE C, SCHMITT U. Haloperidol and risperidone have specific effects on altered pain sensitivity in the ketamine model of schizophrenia. Psychopharmacology (Berl) 2009;202;579-587.
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.
16. KEILHOFF G, GRECKSCH G, BERNSTEIN HG, ROSKODEN T, BECKER A. Rispiridone and haloperidol promote survival of stem cells in the rat hippocampus. Eur. Arch. Psychiatry Clin. Neurosci. 2010:260;151–162.