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Neurodevelopment and Schizophrenia: Pharmacological and Behavioral Animal Models

Autor: Juan Manuel Valentino Lima Ojeda
Institut / Klinik: Zentralinstitut für Seelische Gesundheit in Mannheim (ZI)
Doktorvater: PD Dr. med. Dragos Inta

Schizophrenia is a severe chronic neuropsychiatric syndrome defined mainly by signs of psychosis. Recent studies have provided robust evidence that schizophrenia is a collection of neurodevelopmental disorders that affect the normal brain function, where a combination of genetic and/or environmental factors and their interaction play a key role in the onset of the disease during late adolescence or early adulthood. Since the early postnatal period represents a critical time window for brain development, an early insult may influences circuit formation and regulatory processes, resulting in alterations that become manifest in a much later development stage, when the compensatory changes are not longer enough to control this dysfunction. We remain without a curative treatment or preventive strategy for schizophrenia and the main reason for this is our poor understanding of the pathophysiology of the disorder. Animal models have demonstrated to be extremely useful tools to understand pathogenesis and treatment of human diseases. In an attempt to evaluate the role of several factors associated with the pathogenesis of schizophrenia, we analyzed experimentally—in rodents—their influence in the normal development in multiple pharmacological and behavioral paradigms with potential relevance for schizophrenia.

Considering the recently discovered association between serotonin 5-HT_3 receptors and reelin, revealed by many studies as main susceptibility factor for schizophrenia, we studied in a first experiment the possible long-term behavioral effects of early postnatal exposure to the 5-HT_3 receptor antagonist tropisetrone. We found no significant cognitive, schizophrenia-like and emotional alterations in tropisetrone-treated animals compared to controls. In another series of experiments we investigated the neurotoxic effects of antagonists of glutamate NMDA and mGlu5 receptors both at perinatal and adult stages. The psychotomimetic effect of NMDA receptor antagonists like ketamine represents the basis of the glutamate hypothesis of schizophrenia and their cortical neurotoxicity is thought to correlate with these behavioral abnormalities. We found subunit-specific determinants influencing cortical overactivation and toxicity. Moreover, subunit-specific GluN2B blockade protected against global NMDA receptor blockade. Metabotropic mGlu5 receptors show a high degree of overlap of expression pattern with NMDA receptors and interact closely both structurally and functionally with them. However, we found that unlike NMDA antagonists, the mGlu5 receptor antagonist MPEP does not activate the retrosplenial and cingulate cortex as indicated by c-Fos induction.

Finally, we examined the role of chronic postnatal hypoxia in triggering protracted abnormalities associated with schizophrenia in different experimental paradigms and found no long-term behavioral alterations. Altogether, the results of our studies have shown that NMDA receptor blockade, on early brain development, produces deleterious effects associated with schizophrenia, whereas 5-HT_3 and mGluR5 blockade, at early postnatal periods, and chronic early postnatal hypoxia seem to be not enough to produce correlated symptoms of the disease.