SHORT REVIEW

Neurodevelopmental rat models of schizophrenia

Jana Murínová, Igor Riečanský

Laboratory of Cognitive Neuroscience, Institute of Normal and Pathological Physiology, Slovak Academy of Sciences, Bratislava, Slovakia.

Correspondence to: Jana Murinova, Mgr., Institute of Normal and Pathological Physiology, Slovak Academy of Sciences, Sienkiewiczova 1, 813 71 Bratislava, Slovak Republic. E-mail: jana.murinova@savba.sk

Submitted: 2016-08-25 Accepted: 2016-09-05 Published online: 2015-09-10

Key words: **animal models; schizophrenia; neurodevelopmental rat models**

Act Nerv Super Rediviva 2016; **58**(2): 43–46 ANSR580216R01

Abstract

Animal models are very valuable for biomedical research. They enable to disclose pathological processes of the diseases and their treatment possibilities. Development of appropriate animal models of complex neuropsychiatric disorders, such as schizophrenia, is challenging since many clinical symptoms are difficult to replicate and assess in animals. There is strong evidence that disturbed brain development plays a key role in schizophrenia. Neurodevelopmental rat models thus provide an important tool for schizophrenia research. Here we shortly review the most widely used models.

Introduction

Schizophrenia a heterogeneous mental disorder. This diversity concerns etiology (with numerous genetic and environmental factors contributing to the disease), symptomatology (a number of positive, negative and cognitive symptoms), time course (recurrent episodes, variable degrees of recovery) and also treatment response (Wong & Van Tol 2003, Jones *et al* 2011). Animal models are a necessary tool in revealing pathological processes of diseases and possibilities of their treatment. The development of appropriate animal models of complex neuropsychiatric disorders, such as schizophrenia, is a particularly challenging task since many clinical symptoms are difficult to assess in animals (Powell 2010, Jones *et al* 2011). Since all the symptoms associated with schizophrenia do not occur in every patient, a good rat model does not necessarily display all types of behavioral disturbances relevant to schizophrenia. Because of the disease complexity, the development of relevant rat model is based on the presence of specific symptoms associated with schizophrenia, rather than imitating the whole syndrome (Powell 2010).

Neurodevelopmental hypothesis of schizophrenia postulates that critical pathological brain processes underlying the disease begin in the prenatal period or early childhood, several years before clinical manifestation of the disease. Among other, the brain abnormalities found in schizophrenia include extension of ventricles, volume decrease of the cerebral cortex, hippocampus and amygdala, reduction of dendritic spines of hippocampal and cortical neurons. From unknown reasons this brain abnormalities lead to characteristic symptoms in late adolescence or young adulthood when prefrontal areas of the brain fully mature (Weinberger 1987). In the recent years, considerable evidence has been accumulated in support of the neurodevelopmental hypothesis schizophrenia. This supports the importance of neurodevelopmental rat models for uncovering the pathological processes leading to schizophrenia.

Neurodevelopmental models of schizophrenia can be divided into risk factor models and lesional models. Risk factor models (also termed epidemiological models) are based on exposure to known risk factors of schizophrenia. Lesional models (also termed heuristic models) are based on developmental disturbance as a

consequence of a specific experimental lesion (Lipska & Weinberger 2000, Powell 2010).

Risk factor models

Models of maternal exposure to stress

It has long been known that maternal exposure to stressful event during pregnancy is associated with the development of several physiological and behavioral changes in the offspring, including reduced birth weight, cardiovascular and neuroendocrine abnormalities, attention dysfunction, increased anxiety, and cognitive deficits (Seckl 2004).

Prenatal exposure to maternal stress

Numerous experimental studies in rats and mice have shown that prenatal maternal exposure to psychological stressors in certain periods of pregnancy leads to long-term cognitive deficits of offspring (Yang *et al* 2006, Wu *et al* 2007). Among those commonly used stressors belong e.g. exposure to unpredictable one, food deprivation, swimming in cold water, exposure to an open well-lit places or exposure to high white noise (Mueller & Bale 2008).

Prenatal exposure to glucocorticoids

Stressful environmental stimulus are most often translated into physiological responses through activation of hypothalamus-pituitary-adrenal (HPA) axis what leads to the release of glucocorticoids into the peripheral circulation. Glucocorticoids can break through the placenta in a certain amount and after the reach of fetal brain can affect the expression of many genes, including those that regulate energy metabolism, synaptic transmission, neuronal plasticity and neurogenesis (Seckl 2004).

Models of maternal infection

A large group of epidemiologic evidences indicates maternal infection during pregnancy as an important environmental factor that increases the risk of schizophrenia and related disorders in offspring. Numerous retrospective epidemiological studies revealed an increased risk for schizophrenia in offspring born to mothers with viral or bacterial infections during the first and middle stages of pregnancy (Boksa 2008).

Maternal exposure to viral and bacterial infection

Maternal influenza infection results in various neuropathological changes in the offspring postnatal brain, some of which are critically involved in the neuropathology of schizophrenia (Fate *et al* 2004). In addition, the persistent changes in the gene expression of the offspring brain may result. Prenatal exposure to influenza virus in mice also produces a number of behavioral and biochemical changes in adults, which result in positive and negative symptoms of schizophrenia, including deficits of sensorimotor gating, social interaction and increased sensitivity to the pharmacological treatment of NMDA receptors (Shi *et al* 2003).

Maternal exposure to pro-inflammatory cytokines

These experimental models are based on the effects of specific pro-inflammatory cytokines, including interleukins IL-1b, IL-6, tumor necrosis factor (TNF)-α and interferon (IFN)-γ (Smith *et al* 2007).

Models of maternal nutritional deficiency

The strongest evidence that the prenatal nutritional deficiencies are also involved in the etiology of schizophrenia comes from epidemiological studies that yielded an increased incidence of schizophrenia – in period "Dutch Hunger Winter ", a famine during the occupation of the Netherlands in the years 1944–1945 resulting in extreme food shortages, particularly protein (Hoek *et al* 1998) and during the ''Chinese Famine" in 1950 (St Clair *et al* 2005). These periods are associated with a two-fold increased risk of schizophrenia and schizoid personality disorder (Susser *et al* 1996). Such profound nutritional deficiencies mainly include reduced maternal and/or fetal level of folate, retinol (vitamin A) and other retinoids, vitamin D and proteins (Susser *et al* 2008).

Maternal protein deprivation

Research in the last two decades has provided sufficient evidence that prenatal protein deprivation has long-term negative effects on the integrity of the structure and function of the hippocampus in rats mainly involved in the neuropathology and pathophysiology of schizophrenia (Lister *et al* 2005).

Maternal vitamin D deficiency

The lack of vitamin D in mother create a schizophrenia-like behavioral in rat offspring and pharmacological abnormalities, which include elevated novelty-induced hyperlocomotion, increased sensitivity to the NMDA receptor agonist dizocilpine (MK-801), the dopamine D2 receptor antagonist haloperidol (Kesby *et al* 2006), as well as attention deficit (Becker *et al* 2005).

Models of obstetric complications

The effects of several obstetric complications, including diabetes in pregnancy, preeclampsia, intrauterine growth restriction, emergency caesarean section and perinatal hypoxia, have been extensively studied in laboratory animals. Several experimental studies have been focused primarily on acute effects on fetus or newborns and their potential long-term effects on the schizophrenic phenotype in adulthood remain largely unknown (Boksa 2004). Similar models of obstetric complications, however, analyzed the long-term implications for schizophrenia associated with the brain and pathological behavior. These include the model of caesarean section, perinatal or postnatal hypoxia and placental insufficiency (Brown 2011).

Caesarian section

C-section has been associated with an increased risk of schizophrenia in the offspring (Cannon *et al* 2002). Adult rats born by c-section exhibit significantly longer life cycle of dopamine reactions in the nucleus accumbens, diminished prefrontal cortical dopamine reaction to stress and also exhibit increased and decreased basal levels of dopamine in striatal and prefrontal cortical structures. Interestingly, these effects appear to be greater in men than in women (Brake *et al* 2000).

Perinatal and early postnatal hypoxia

Exposure to reduced oxygen levels around the birth time leads to abnormal development of brain functions and structures relevant to schizophrenia (Boksa 2004), involving the reduction of the number of granular cells in the hippocampus, the reduction of stress-induced dopamine release in the prefrontal cortex, or increased expression of kainate receptors in the hippocampus (Brake *et al* 2000). Hypoxia also enhances stereotypical motion and impairs prepulse inhibition (PPI) but reduces motor activity (Wong & Van Tol 2003).

Placental insufficiency

Insufficient blood supply of the placenta during pregnancy also contribute to the incidence of brain abnormalities associated with schizophrenia (Naeye *et al* 1989).

Model of social isolation rearing

Rats placed in cages alone just after weaning and tested in adulthood, exhibit abnormalities in the behavior relevant to schizophrenia, similar to amphetamine-treated animals. These abnormalities comprise not only many biochemical and neuroanatomical alterations but also spontaneous locomotor hyperactivity, deficits in prepulse inhibition and reduced performance in some cognitive task, (e.g. in a novel object recognition and a T-maze) (Jones *et al* 1992, Geyer 1993, Varty & Higgins 1995, Wong & Van Tol 2003, Schubert *et al* 2009).

Lesional models

Model of neonatal ventral hippocampal lesion (NVHL)

The model of neonatal ventral hippocampal lesions (NVHL) is based on the finding of impaired hippocampus in many schizophrenics and it is the best characterized neurodevelopmental animal model of schizophrenia (Lipska & Weinberger 1995). In this model the ibotenic acid, which disrupts hippocampal circuits, is bilaterally infused in the hippocampus of 7 days old newborn rats. In prepubertal period the NVHL rats begin to show deficits in social interaction as well as impaired performance in cognitive tasks oriented on working and spatial memory (Lipska & Weinberger, 1994). Also, we can observed locomotor hyperactivity (Wong & Van Tol 2003), exaggerated behavioral response to amphetamine and NMDA antagonists, deficits in prepulse inhibition (Swerdlow *et al* 2012) and a decreased expression of mRNA GAD67 consistent with reduced GAD67 in patients with schizophrenia (Lipska & Weinberger, 2000).

Methylazoxymethanol acetate (MAM) model

Metylazoxymetanol acetate (MAM) is an anti-mitotic and proliferation toxin, which affects the development of neuroblastoma and stops the process of cell division. For example, the exposure of fetus to MAM results in the destruction of rapidly dividing neurons. In this model, the MAM is intraperitoneally administered to pregnant dam either during mid (9–12. embryonic day), or late gestation (17–18. embryonic day). Through the selective disruption of proliferation and migration of neuronal precursor cells, MAM in right time and dose induces cytoarchitektonic changes in the hippocampus, entorhinal and prefrontal cortex and other specific brain areas of offspring (Grace 2000), which are in many aspects analogous to that seen in some schizophrenics. Even during adolescence offspring exhibit some features of schizophrenia, e.g. PPI deficits, increased sensitivity to dopamine, abnormalities of glutamate transmission in the hippocampus, deficits in cognition and social interaction (Moore *et al* 2006, Lodge & Grace 2009).

Conclusion

In the last two decades several neurodevelopmental animal models of schizophrenia have been created. These models importantly contribute to our understanding of brain development and its disturbance, which plays a key role in schizophrenia. Modeling symptoms of schizophrenia in animals is difficult but necessary for achieving progress in understanding of the disease. Neurodevelopmental models provide a unique insight into the schizophrenia pathophysiology its further refinement and development is warranted.

Acknowledgement

Supported by VEGA grant no. 2/0165/15 and APVV-14-0840.

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