Animal models of schizophrenia: Developmental preparation in rats

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Schizophrenia manifests itself primarily with positive symptoms, negative symptoms and cognitive disorders. Animal models of mental diseases seem to be an important tool in understanding key theories related with pathophysiology of the disorder and are used to assess efficacy of new drugs. References describe four basic groups of animal models of schizophrenia, such as: models created by pharmacological intervention, genetic models, lesion models and models of developmental disorders of primary brain structures. Of the models referred to above, the group of developmental disorder models is particularly noteworthy, as they are primarily easy to use, and the methods are highly sensitive. High scientific value of these models is associated with the neurodevelopmental theory which stipulates that at an early stage of body development, a number of interactions between genetic and environmental factors may affect the development of neurons which may cause disorders of brain cytoarchitecture development.We review six developmental models of schizophrenia in rats (MAM – methylooxymethanol acetate, prenatal stress, maternal deprivation, isolation rearing, prenatal immune challenge and maternal malnutrition) that are all validated by disruption in PPI.

Key words: schizophrenia, animals, developmental model of animal schizophrenia

INTRODUCTION

Schizophrenia is a disease of diverse picture and varied clinical course, consisting primarily in mental disintegration, both in the intra- and interpersonal zone (Pers and Rajewski 2003). The disease manifests itself primarily with positive symptoms, negative symptoms and cognitive disorders (Nagai et al. 2010) such as impaired perception or impaired expression of reality, paracusias, paranoid or bizarre delusions, which causes a major social or professional dysfunction. Considering high incidence of this disease in global population (approx. 1%) (Nagai et al. 2010), as well as continuous development of studies aimed at explaining the background of the disease, animal models of mental diseases seem to be an important tool in understanding key theories related with pathophysiology of the disorder and are used to assess efficacy of new drugs. Nowadays, there are many animal models of schizophrenia which to a smaller or greater extent (one or several symptoms) reflect the key symptoms observed in human patients suffering from this disease. None of the models is perfect as none of them reflects the full clinical picture observed in humans. As found by some authors (Grace 2002), key factors determining pathophysiological image of schizophrenia with typical symptoms of the disease are neuronal structure disorders in such brain regions as: ventral tegmentum, prefrontal cortex, hippocampus (brain structure responsible, among others, for memory function), amygdaloid body and accumbens nucleus. Studies on schizophrenia indicate that the most frequently observed cognitive function disorders affect attention, operating and verbal memory and abstract thinking (Geyer et al. 2001), thus experimental models allowing identification of memory processes, impaired in schizophrenia, have become useful in analysis of these deficits (Dawe et al. 2009); they also allow determination of drugs which, administered in schizophrenia, modify the impaired memory functions. In the past decade, it has been increasingly appreciated that cognitive deficits are also a core feature of the disorder

present from before the onset of the first acute episode of positive symptoms (Maccabe 2008). Rodent models of schizophrenia mostly display symptoms analogous to the positive symptoms of schizophrenia, with some models also having symptoms similar to the negative symptoms (Borrell et al. 2002, Kuneninn et al. 2003, Bianchi et al. 2006, Featherstone et al. 2009, Lodge and Grace 2009). Positive symptoms (e.g. hallucinations, delusions) observed in patients diagnosed with schizophrenia are of particular importance in experimental models of animal schizophrenia; due to technological limitations, however, it is not possible to study these symptoms in animals. Neurophysiological and neurochemical changes occurring in animal models of schizophrenia are identified as changes occurring in the clinical image of the disease, primarily in terms of: hyperactivity, increased locomotor mobility and stereotypy of experiments (Dawe et al. 2009). On the other hand, social withdrawal is identified as the equivalent of negative symptoms (Dawe et al. 2009).

References describe four basic groups of animal models of schizophrenia, such as: (1) models created by pharmacological intervention [e.g. using MK-801 (Manahan-Vaughan et al. 2008), ketamine (Mansbach and Geyer 1989, Geyer et al. 2001), PCP (Kapur and Seeman 2002) or methamphetamine – neurotransmitter concept explaining the role of neurotransmitters such as DA, 5-HT, GLX and GABA in the mechanism of schizophrenia]; (2) genetic models (DISC-1, NRG1, DTNBP1) (Jones et al. 2011) mutants and the model associated with the use of reline (protein found in the brain, bone marrow and blood) (Weeber et al. 2002); (3) lesion models (NVHL – Neonatal Ventral Hippocampal Lesion) (Lipska and Weinberger 2000) associated with physical induction of neurodevelopmental defects in animals; (4) models of developmental disorders of primary brain structures, using MAM – methylooxymethanol acetate (Featherstone et al. 2009, Lodge and Grace 2009), prenatal stress (Kuneninn et al. 2003), maternal deprivation (Llorente et al. 2010), isolation rearing (Bianchi et al. 2006), prenatal immune challenge (Borrell et al. 2002), maternal malnutrition (Palmer et al. 2004) (Table I).

Of the models referred to above, the group of developmental disorder models is particularly noteworthy, as they are primarily easy to use, and the methods are highly sensitive, as is reflected in a number of research studies (Borrell et al. 2002, Kuneninn et al. 2003, Palmer et al. 2004, Bianchi et al. 2006, Featherstone et

al. 2009, Llorente et al. 2010). High scientific value of these models is associated with the neurodevelopmental theory which stipulates that at an early stage of body development, a number of interactions between genetic and environmental factors may present themselves, and consequently adversely affect the development of neurons (their stratification and spatial arrangement) which may, in turn, cause disorders of brain cytoarchitecture development (Gabryel 2008). Developmental abnormalities originating in the fetal period may become permanent in the perinatal period, and are usually fully expressed in the early adolescence (Arnold and Trojanowski 1996) which in the case of experimental animals, such as rats, occurs at 35 days after birth (Ratajczak et al. 2013) by mothers subjected to experiments (Kuneninn et al. 2003) recognized as animal models of schizophrenia. Although direct evaluation of schizophrenia symptoms in animal models is inherently difficult, such effects have been related to neuropsychiatric deficits seen in schizophrenia (Braff et al. 1992). For example, administration of MAM to female rats on day 17 of pregnancy selectively affects multiple brain regions, especially cortex, in particular the late developing paralimbic regions as well as frontal and temporal cortex (Bayer and Altman 1995, Lodge and Grace 2009). On the other hand, exposure of pregnant women to chronic stress gives rise to a probability of cognitive function impairment by exposure of the developing fetal brain to maternally derived substances, such as cytokines or stress hormones (Welberg et al. 2000, Seckl 2004) which is a typical symptom in patients suffering from schizophrenia. Unfortunately, it is difficult in human studies to define critical periods of vulnerability, or to comprehensively investigate molecular changes occurring in the relevant brain regions as a result of early-life stress (Carlyle et al. 2012).

The main tool used in this experiment to verify the changes occurring in animals was the sensorimotor gating test (PPI – Prepulse Inhibition) allowing identification of the study animal's response to repeated strong stimulating signals, e.g. acoustic signals.

We review six developmental models of schizophrenia in rats (MAM – methylooxymethanol acetate, prenatal stress, maternal deprivation, isolation rearing, prenatal immune challenge and maternal malnutrition) that are all validated mainly by disruption in PPI. Only a better understanding of the various genetic factors involved and the environmental forces that modulate

their expression over time may help us develop more sophisticated animal models.

MAM - Methylazoxymethanol Acetate Model

MAM and mitotoxin, when applied to rats, cause a number of neuropathological (reduced DNA synthesis) and behavioral changes in the clinical picture of schizophrenia (Moore et al. 2006). MAM is highly selective, and affects mainly the formative cell located in the central nervous system (CNS). Administration of MAM to female rats on day 17 of pregnancy [proliferation of brain cortex regions in the fetus is complete while development of subcortical regions and cerebellum is nearly complete or stopped (Bayer and Altman 1995)] disturbs the development of brain structures in the developing embryo (Moore et al. 2006). Enlargement of ventricles is one of the most consistently replicated pathological findings in schizophrenia (Shenton et al. 2001) and structural abnormalities in limbic and temporal lobes, including the amygdala-hippocampal complex and parahippocampal gyrus, are typically observed in schizophrenia as well (Heckers 2001). Studies by other authors have shown that MAM administered to rats on day 17 of pregnancy increases the level of proteins and their metabolites in the rats' hippocampi. By changes in the levels of glutamate receptor agonist/antagonist, glutamate-glutamine cycle proteins or synaptic vesicle controlling proteins, administration of MAM also affects changes in neurotransmitter levels (Hradetzky et al. 2012). In offspring, methylazoxymethanol acetate may cause disorders of behavioural flexibility, declarative memory (especially recognition memory) (Flagstad et al. 2005), operating memory (internal memory) (Gourevitch et al. 2004) and attentional set-shifting (Featherstone et al. 2007), and may reduce the size of the hippocampus and prefrontal cortex (PFC), reduce neuronal density, and disturb DA secretion in the PFC (Flagstad et al. 2004, Moore et al. 2006). In addition to this, MAM may be successfully used in animal models of schizophrenia with comorbid dependence on psychoactive substances (e.g. amphetamine, cocaine) both because of the changes generated in the hippocampus and PFS, and increase of dopamine activity in the mesolimbic system, in particular in nucleus accumbens (Chambers et al. 2001, Taylor et al. 2009). These changes were also observed in patients dependent on active substances (Chambers et al. 2001) as abuse of psychoactive substances is typical for patients suffering from schizophrenia (Wobrock et al. 2013). MAM results in a reduced synaptic transmission in the AMPA receptor and reduced number of synapses and interaction between glial cells in the hippocampi of study rats (Matricon et al. 2010). Apart from reducing size of the hippocampus, MAM also affects structure of pyramidal cells and reduces parvalbumin expression in the hippocampus (Zgang and Reynolds 2002). Clinical studies (Matricon et al. 2010) show that MAM reduces the number of synapses and affects formations of nerve fibers, also in patients diagnosed with schizophrenia (Garey 2010). MAM treatment may also affect neurotransmission by altering the levels of specific neurotransmitters, glutamate receptor agonists/antagonists, glutamate–glutamine cycle proteins, or synaptic vesicle controlling proteins (Hradetzky et al. 2012). Social isolation, which is a typical symptom manifesting itself in humans suffering from schizophrenia, is also observed in experimental animals. In the model using MAM, deficits of memory, recognition memory, attentional set-shifting; behavioural flexibility, internal memory (as positive symptoms) and decreased social interaction (negative symptom) are observed. The main tool used in this experiment to verify the changes occurring in animals was the PPI. It has been proven that environmental factors such as stress and rearing conditions may enhance behavioral deficits induced by MAM administration (Featherstone et al. 2009). Current research focuses on verification of the dose and day of administration of MAM in order to determine the parameters that generate brain and behavior abnormalities which bear the greatest resemblance to the clinical type of schizophrenia.

Prenatal Stress Model

Previous studies (Kuneninn et al. 2003, Koenig et al. 2005, O'Donnell et al. 2009) indicate that prenatal stress increases the risk of autism or schizophrenia in the offspring. The offspring of prenatally stressed rat mothers develop the prenatal stress syndrome characterized by behavioral and physiological disorders in response to stressful stimuli (Ward et al. 2000). Prenatally stressed rats show a number of disorders in the elevated plus-maze test (Fride and Weinstock 1988), footshock (Tkahashi et al. 1988, 1990) and in the learned helplessness test (Secoli and Teixeira 1998). According to Hayashi and coworkers (1997),

Table I
Experimental models of schizophrenia in rats

	Methods	DA-related behavior	Gating	Cognitive Behavior	Social Behavior	Molecular/Morpho-logical Signature
1	Maternal Deprivation		Disrupted PPI, Effect develops after puberty Disturped Latent Inhibition), Audiotory sensory gating (N40) and startle habituation	Increased impulsivity, depressive-like responses		altered cannabinoid receptor expression in hippocampus; increased plasma glucocorticoid levels
2	Antimitotic Agent – MAM	Enhanced response to amphetamine and MK-801 (post-puberty)	Disrupted PPI (post-puberty)	Learning deficits in Morris water maze, object recognition (recognition memory), attentional set-shifting; behavioural flexibility, internal memory no change in 5-choice serial reaction time task	Decreased social interaction (deficit present prior to puberty)	Decreased brain, hippocampus weight; increased neuron density in prefrontal cortex; enhanced NAc DA release to amphetamine; increased firing of dopaminergic neurons
3	Isolation Rearing	Enhanced amphetamine-induced locomotion and DA release (strain-dependent)	Disrupted PPI (strain-dependent)	Impaired novel object recognition and attentional set-shifting , increased locomotor activity	Increased social interaction and aggression (males)	Reduced PFC volume and GAT-1 expression; altered accumbal and hippocampus protein expression, reduced accumbal and hippocampus dendritic length and spine density in pyramidal cells, reducing the amount of newly generated hippocampus neurons, altered synaptophysin expression, decreased MAP-2 expression
4	Maternal Malnutrition	Enhanced amphetamine- but not MK-801-induced locomotion and apomorphine-induced stereotopy; (females only with post-pubertal onset)	Disrupted PPI (females only with post-pubertal onset)	Decreased learning and memory		Increases in NMDA receptor binding (sex- and region-specific); increased DA receptor binding and decreased DA transporter binding in striatum (females only), decreased LTP,
5	Prenatal Immune Challenge: LPS	Increased amphetamine-induced locomotion	Enhanced acoustic startle; disrupted PPI (worse in males)		Reduced social interaction, possibly due to increased anxiety	Reduced dendritic complexity in PFC and hippocampus; increased accumbal and stria terminalis DA; elevated serum cytokine levels;
6	Prenatal Variable Stress	Increased response to amphetamine and PCP with post-pubertal onset	Disrupted PPI and N40 AMPH-induced locomotor activity	Impaired object, social recognition and social memory	Impaired social interaction present in adolescent and adult rats;	NMDA, GABAergic and presynaptic protein dysregulation Reduced weight of hippocampus, increased levels of CORT, changes in gene expression in the frontal lobe

prenatally stressed rats have a disturbed level of neurotransmitters such as 5-HT and 5-HIAA, which consequently results in memory disorders, including spatial memory impairment. Neurotransmission disorders also occur in patients diagnosed with schizophrenia (Carlsson et al. 1999). Predisposition to schizophrenia is also promoted by a dysfunctional stress response system and hypersensitive dopaminergic system (Koenig et al. 2005). Stress induces a release of the main stress mediators – glycocorticosteroids (cortisol and corticosterone) and DA – (Koenig et al. 2005) which gives rise to intracellular adaptive changes. Excessive release of cortisol may affect neurodegenerative processes and impair neurodevelopmental processes within the hippocampus (Szubert et al. 2008). Ward (Ward et al. 2000) also suggests that, as a result of prenatal stress, the immunoreactive CRF (Corticotropin Releasing Factor) centre located in the cortical and limbic regions stimulates the HPA axis which causes adrenal gland hypertrophy resulting from their overstimulation with glicocorticoids. Prenatal stress causes a reduction of the hippocampus' diameter and spatial memory disturbances in study animals (Lamaire et al. 2000). Conclusions of the published study results indicate that stress exposure related with the increase of glycocorticosteroid levels during fetal development results in disturbed development of brain structures and thus may cause a number of behavioral changes related with reduction of social interactions, enhanced body response to psychostimulants such as amphetamine and apomorphine (Mansbach et al. 1988, Campeau and Davis 1995, Geyer et al. 2001) and may generate manifestation of depression symptoms in adult life (Seckl 2001, Weinstock 2001, Welberg and Seckl 2001). At the molecular level, changes occurring in rats prenatally exposed to stress mainly affect reorganization of the expression of genes responsible for receptor coding and neurotransmitters' transmission in the frontal lobe (Kuneninn et al. 2003). In the model using prenatal stress, impaired object, social recognition and memory are identified as positive symptoms, while impaired social interaction as a negative symptom. The main methods used to verify the changes occurring in study animals include PPI sensorimotor gating test, induced locomotor activity after amphetamine AMPH treatment and auditory sensory gating (N40) test (Koenig et al. 2005). PPI deficits are commonly seen in patients with schizophrenia and reflect fundamental changes in the brain's information processing system (Green et al. 2009). Experimental animals exposed to a variable stress paradigm during the last week of pregnancy show prominent deficits in PPI (Koenig et al. 2005) without changes in acoustic startle responses (Koenig et al. 2005). Current research of this model is focused on behavioral disorders occurring in prenatally stressed rats after e.g. using substance of abuse and enrichment environment.

Maternal Deprivation Model (MD)

It has been found that traumatic experiences in early life stages (e.g. separation from the mother) may predispose to development of mental disorders, including schizophrenia and depression, in adult life in humans (Llorente et al. 2010). Negative impact on psychopathology in later life has been associated with a number of mood and anxiety disorders (Heim et al. 1997). Maternal Deprivation (MD) method consists in separation of newborn infants from their mothers for 24 hours, on day 9 after birth (during this period they are not fed by their mothers) (Llorente et al. 2007) which largely results also in an increased concentration of corticosterone in plasma of these people and furthermore causes disturbances in development of the brain structures, in particular of the hippocampus. In particular, it was found that glucocorticoid receptor down-regulation in response to trauma was corrected by escitalopram treatment [one of the selective serotonin reuptake inhibitors (SSRIs)] (Uys et al. 2006). Early life trauma caused an elevation in basal corticosterone level, which changes may be prevented by escitalopram pretreatment, indicating interactions between the neuroendocrine and the serotonergic system (Uys et al. 2006). Escitalopram treatment also partly compensated for protein changes induced by maternal separation stress which included up-regulation of proteins involved in energy metabolism and neurotransmitter release (Marais et al. 2008). Such effect may be useful in analyzing the role of the serotonin system in human depression (Binder et al. 2011) because trauma-induced neuroreceptor and memory changes can be modified by serotonin enhancing and depleting drugs (Harvey et al. 2004) – SSRI administration has been also shown to restore HPA axis function (Cassano and D'mello 2001). Expression of cannabinoid receptors and concentration of mediators in the dopaminergic and serotoninergic systems change as well (Ellenbroek

and Cools 1995, Ellenbroek et al. 1998, Marco et al. 2009). Studies by Llorente and colleagues (2010) indicate that application of MD in rats causes a significant increase of 5-HT concentration in such brain regions as the PFC, hippocampus, striatum and mesencephalon, which consequently disturbs the functioning of the HPA axis. Moreover, MD may affect the level of DA in the striatum and PFC (Llorente et al. 2010). As a result of application of the described model, cognitive disorders, increased impulsiveness and lack of resistance to stressful situations (depressive-like responses) are observed in the offspring (Marco et al. 2009). In the model using maternal deprivation, increased impulsiveness, depressive-like responses (as positive symptoms), altered cannabinoid receptor expression in the hippocampus, and increased plasma glucocorticoid levels were observed. In this model, likewise, the main tools used to verify the symptoms are the PPI sensorimotor gating test, latent inhibition mechanism weakening, auditory sensory gating (N40), and startle habituation (Ellenbroek and Riva 2003). Current research is focused on the impact of early life stress on the subsequent behavioral changes in the offspring.

Isolation Rearing Model

Not only genetic (Karayiorgou and Gogos 1997) but also epigenetic background, such as environmental factors including life event (Birley and Brown 1970), chronic stress (Leff and Vaughn 1980), and season of birth (Mortensen et al. 1999), have been thought to be risk factors and be implicated in the pathogenic mechanism(s) of schizophrenia and other psychiatric disorders. Social isolation of animals [30 days (Bianchi et al. 2006)] may generate a number of structural disorders in the hippocampus of study animals, such as reduced length and density of dendrites in pyramidal cells (Silva-Gomez et al. 2003), reduced number of newly formed neurons (Lu et al. 2003), reduced sunaptophysin protein expression (Varty et al. 1999), and reduced size of the PFC (Taylor et al. 2009). Isolation also affects stabilization of the microtubular cycloskeleton in the hippocampus, tyrosine body concentration which is one of precursors of many biologically active substances, such as DA, and reduced expression of MAP-2 (microtubule-associated proteins-2 – which suggests irregularities in dendrite development) (Lu et al. 2003, Silva-Gomez et al. 2003, Bianchi et al. 2006).

The exact mechanism responsible for changes occurring in the hippocampus is not entirely known, although some researchers pay particular attention to the brain-derived neurotrophic factor (BDNF) as one of the elements participating in the down-regulation of signaling pathways modulating microtubular dynamics of the cytoskeleton (Bianchi et al. 2006). Cognitive deficits present in this model (one of the positive symptoms), on the other hand, are mainly associated with increased DA concentration in the mesolimbic system (increased locomotor mobility is observed) (Tonkiss and Galler 1990, Fone et al. 1996, Lapiz et al. 2000). Animals studied in this model show a reduced ability to recognize novel objects and disturbed attentional set-shifting (Bianchi et al. 2006, Taylor et al. 2009) which is also corroborated by clinical studies, as the lack of insight is a prominent and enduring core feature of schizophrenia (Bora et al. 2007a,b). Indeed, poor insight or impaired awareness of the illness are highly prevalent (50–80%) among individuals with schizophrenia (Crumlish et al. 2005). In the Isolation Rearing model, the most commonly observed symptoms include impaired novel object recognition and attentional set-shifting, as well as increased locomotor activity (positive symptoms), and increased social interaction and aggression (in males only) (negative symptoms). The main tool used to verify the changes occurring in this model in study rats is the PPI sensorimotor gating test (Taylor et al. 2009). Current research can answer the question how social isolation affects cell apoptosis and level of neurotransmitters in different brain areas in rats.

Prenatal Immune Challenge Model

There are many risk factors which may – like stress – endanger the pregnancy, thus increasing the probability of various disorders, including mental diseases, in the offspring [susceptibility to infections rises in the third trimester (Mouihate et al. 2008)] even though the pregnant mother produces proinfective cytokines affecting development of the fetus, in particular its brain structures (Abdeslam 2012). Clinical studies show that fetal development may be disturbed by a number of external factors, such as bacteria, viruses and other pathogens (Vorhees et al. 2012). Prenatal influenza infection alters the development of cerebral cortex and the hippocampus which are dysfunctional in both

schizophrenia and depression. In both these areas, prenatal exposure to influenza causes a dramatic reduction in reelin expression (Fatemi et al. 1999), similar to what is observed in postmortem tissue from schizophrenic patients (Guidotti et al. 2000). According to Adams and others (1993), infection with the influenza virus may be such a factor, as it poses a large risk for correct fetal development in particular in the second trimester of pregnancy. The Prenatal Immune Challenge method is based on the use of lipopolysaccharide (LPS) – endotoxin of Gram-negative bacteria and cyanobacteria mimicking immunological activation of the body in the context of infection with Gram-negative bacteria (Andersson et al. 1992). LPS administration disturbs body temperature and neuroendocrine functions (Pauli et al. 1998), disturbs sleep (Pollmächer et al. 1993), and causes a number of other behavioral disturbances, such as reduced social interactions (Taylor et al. 2009). Studies by Borrel and coworkers (2002) indicate that LPS may also be responsible for excessive DA secretion in the nucleus accumbens which, in turn, increases immunoreactivity of tyrosine hydroxylase (TH) both in the nucleus accumbens and in the terminal stria. Increased DA concentrations in experimental animals generate PPI deficits which are found in this model both in males and females rats (in females, the deficits manifest themselves at a later time) (Loranger 1984). LPS administration also reduces the number and density of dendrites in the rats' PFC and hippocampus (Taylor et al. 2009) as well as increases the concentration of IL-2 and IL-6 interleukins important in the system of immunological response of the study animals (Borrell et al. 2002). Prenatal Immune Challenge as one of the quoted models does not cause cognitive disorders identified as positive symptoms observed in the clinical image of schizophrenia. Of negative symptoms, in turn, the most frequently observed are reduced social interaction, and increased anxiety. In this experiment, like in the previously described methods, the PPI sensorimotor gating test is used to verify the symptoms. Current research by Deslauriers and colleagues (2013) is focused on how the combination of prenatal immune challenge and restraint stress (prenatally stressed model) affects prepulse inhibition which seems to be very interesting given the high quality of outcomes in each of the presented methods.

Maternal Malnutrition Model

As early as in 1956, it has been found that malnutrition of pregnant women is a factor predisposing to schizophrenic disorders in the offspring (Pasamanick et al. 1956). Maternal and child undernutrition and micronutrient deficiencies affect approximately half of the world's population. These conditions include intrauterine growth restriction (IUGR), low birth weight, protein-energy malnutrition, chronic energy deficit of women, and micronutrient deficiencies (Ahmed et al. 2012). In animal studies, the Prenatal Protein Deprivation (PPD) model was proposed which may generate a number of deficits in the offspring, such as reduced long-term synaptic potentiation (LTP – long term potentiation) (Austin et al. 1986), disturbed development of the hippocampus (Diaz-Cintra et al. 1991), irregularities in the neurotransmitters' functioning (DA, 5-HT, GLX) (Tonkiss et al. 1998), as well as memory deficits and reduced ability to learn (Tonkiss and Galler 1990). Of all developmental models of animal schizophrenia presented herein, this model seems to be best suited to the context of studies in which the ourcome depends on sexual dimorphism. Animals subject to PPD show a greater ability to bind DA in the striatum (females only) and NMDA in the striatum and the hippocampus (both females and males) (Kornhuber and Kornhuber 1986, Eastwood et al. 1995, Palmer et al. 2004). Moreover, adult females show an ability to increase their mobility and apomorphine-induced stereotypy (Butler et al. 1996, Taylor et al. 2009).

In the Maternal Malnutrition model, decreased learning and memory function as positive symptoms are observed, with no negative symptoms manifesting. The main tool used in this model to verify the changes occurring in rats is the PPI test. In females in the PPD model, PPI is reduced with age which is one of typical clinical symptoms of schizophrenia (Palmer et al. 2004). The authors studying this model suggest, however, that PPI deficits may be reversed with apomorphine and amphetamine (Mansbach et al. 1988, Campeau and Davis 1995, Geyer et al. 2001), MK-801 (Manahan-Vaughan et al. 2008), phencyclidine (PCP) (Kapur and Seeman 2002) and ketamine (Mansbach and Geyer 1989, Geyer et al. 2001). PPD is, therefore, an effective, non-invasive and non-pharmacological method of creating an animal model of schizophrenia which should be combined with observation of clinical

symptoms of this disease (Susser and Lin 1992, Susser et al. 1996, Hoek et al. 1998). Current research is focused on the impact of food deprivation or different types of diet on the behavioral and biochemical dysfunctions observed in the rats.

CONCLUSIONS

There are many animal models of schizophrenia used in preclinical studies, all of which are, however, imperfect to some extent. Regardless of the choice of the model and type of experimental animals (mice, rats, monkeys), no animal model of mental disorders can reflect on experiment subjects a full clinical picture of the disease which comprises – among others – cognitive, perceptive, emotional deficits, biochemical and molecular changes. Animal models of schizophrenia, in spite of their imperfection, can be used as a tool to seek new, more effective methods, better reflecting the most important positive and negative symptoms observed in patients diagnosed with schizophrenia in experimental animals. The above-described animal models of schizophrenia differ both in terms of the ability to produce either "positive" or "negative" symptoms, which in animals translates into behavioral disorders. In the presented animal models of developmental disorders, the best and most effective method of model validation is the PPI sensorimotor gating test (showing the response of the study subject's body to repeated strong stimulating signals, e.g. acoustic signals), the result of which in schizophrenic humans and experimental animals is clearly poorer than in healthy subjects. Prepulse Inhibition (PPI) is a neurological phenomenon in which a weaker prestimulus (prepulse) inhibits the reaction of an organism to a subsequent strong startling stimulus (pulse). The stimuli are usually acoustic, but tactile stimuli and light stimuli are also used (Braf et al. 1992). PPI is an index frequently used in clinical treatment of schizophrenia also in animal models, as pointed out by many authors (Swerdlow and Geyer 1998, Moser et al. 2000), where PPI in animals is used as the key factor determining the correctness of model production. On the other hand, as indicated in the references, antipsychotic drugs may reduce PPI deficits in some models, such as isolation rearing (Bakshi et al. 1998), maternal deprivation (Ellenbroek et al. 1998), prenatal immune challenge, and prenatal

stress (Taylor et al. 2009). Geyer and coauthors (2001) also indicate that in the behavioral assessment of animals, a number of other validation methods, other than PPI, can be used: locomotor activity and stereotypy, habituation, gating measures, P50 gating, latent inhibition and social behavior. Both in humans and animals with observed schizophrenia symptoms, the lack of selection of information reaching the body from the surroundings (primarily the CNS responsible for receiving and interpreting them) may occur and cause a sensory overload and cognitive fragmentation (Taiminen et al. 2000). To analyze these disorders, PPI and P50 gating are used most frequently. In animal studies, also habituation is used as the simplest way of showing the reception of a specific stimulus or behavior of the study animals (Geyer and Braff 1987). Considering the reduced sensory gating in patients diagnosed with schizophrenia, experimental studies use the P50 method (similar to the PPI method) using acoustic stimulation (Freedman et al. 1994). According to the dopamine hypothesis of schizophrenia, motor hyperactivity is a common symptom in the patients (Segal et al. 1981, Creese 1983, Segal and Geyer 1985). This is related to the correlation of schizophrenia symptoms with the effect of stimulants such as amphetamine (Snyder 1973) which is also analyzed in experimental models. Impaired cognitive functions occurring in schizophrenia are usually identified using tests related to object recognition memory (Novel Object Recognition Memory), spatial memory (Morris water maze), fear conditioning (Fear conditioning, Cued and Contextual Fear Memory Testing), and discrimination memory (Can test, Spatial and Visual discrimination test).

All methods presented herein have a defined characteristics finally determining the possibility of obtaining a specific result, both in the behavioral and neurodevelopmental area. Contemporary technology and continuous scientific progress should, therefore, lead to a creation of a universal animal model of schizophrenia which would reflect actual symptoms accompanying the clinical form of this disorder much better than the present ones.

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