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Understanding schizophrenia through animal models: the role of environmental stressors

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Abstract

Schizophrenia and other related disorders represent a major clinical challenge, with environmental and genetic factors contributing to their occurrence. Animal models are indispensable tools for understanding the complex neurobiological mechanisms underlying psychosis and for developing new therapeutic approaches. This review focuses on the animal models commonly used in schizophrenia research, especially those based on prenatal and postnatal environmental risk factors. Prenatal exposure to infections, such as bacterial lipopolysaccharides (LPS) and viral components such as poly I:C, activates immune responses that lead to long-lasting structural and functional changes in the brain, including hippocampal atrophy and cortical thinning. Postnatal factors such as early life stress, social isolation and drug abuse, particularly cannabis, are also being modelled to investigate their effects on brain development and the onset of psychosis. These models allow controlled manipulation of environmental challenges and provide insights into the aetiology and pathophysiology of the disease. However, the variability of experimental protocols and lack of female representation in many studies underscore the need for more robust and inclusive animal models. Ultimately, these models are crucial for a better understanding of schizophrenia and for testing potential therapeutic interventions.

Key words: psychosis, prenatal infections, early life stress, social aversion, substance abuse

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Introduction

With around half of the population meeting the diagnostic criteria for a psychiatric disorder at least once in their lifetime, improving mental health is of great importance (1). Psychiatric disorders place a significant burden on society, and due to increased average daily stress levels in modern society, anxiety and depressive disorders are particularly common (2). Although anxiety and depression are the most common and widely discussed, psychosis remains the greatest challenge to clinical practice. According to the Global Burden of Disease Study, schizophrenia alone accounts for 1.5% of the total morbidity caused by all diseases, measured in disability-adjusted life years (DALYs) worldwide in the 24-49 age group (3).

It is well known that both genetic predisposition and environmental risk factors contribute to the onset of schizophrenia and affect individuals from conception to late adulthood. Twin studies have been instrumental in understanding the heritability of schizophrenia, a disorder that is shown to have a significant genetic component. Heritability refers to the proportion of variance in a population that can be attributed to genetic differences (4). According to a published meta-analysis of twin studies, the estimated heritability for schizophrenia is around 81% (5). This suggests that the risk of developing schizophrenia is mainly genetic and that the remaining proportion is influenced by environmental factors. Despite the strong genetic contribution, identical twins usually also share the environment in the womb and during early childhood, and the fact that identical twins do not have a 100% concordance rate emphasizes the important role of environmental influences in the development of the disorder. The most common environmental risk factors for the onset of schizophrenia are: (1) in early life: prenatal and postnatal infections, malnutrition and maternal stress, birth complications and age of birth; (2) in childhood: unfavorable upbringing, child abuse, experience of violence, growing up in poverty and head injuries; (3) in adolescence and adulthood: drug use, social influences and the stress of modern life (6).

Psychosis occurs in various psychiatric disorders, such as schizophrenia, bipolar disorder and major depression with psychotic features. It is interpreted as inadequate information processing in the brain, making it difficult to distinguish between real and imagined stimuli and between relevant and neutral contexts. The structural and molecular basis of psychosis is still not well understood, largely due to the complexity of higher brain functions and the practical and ethical limitations of studying the living human brain. Although it is not possible to mimic all of the human symptoms in animals, it is possible to study the behavioral, pathophysiological and neuroanatomical changes relevant to these complex disorders under controlled conditions (7). Since the current treatment of psychotic disorders has limited success, developing new therapeutic options would be highly relevant for the patients suffering from psychosis. Animal models can be useful tools for the preclinical investigation of the pathogenesis of mental disorders and the efficacy of their treatment. Although traditional animal models based on the “black box” approach and interpretation of behavioral tests have proven useful in the preclinical investigation of antipsychotic drug candidates, more

comprehensively validated and robust models are needed to better understand the mechanism of antipsychotic action in the development of new antipsychotics. There are numerous approaches to developing animal models of schizophrenia, both genetic and environmental. Numerous candidate genes, including DISC1, NRG1, and ErbB4, have been associated with increased risk of schizophrenia and used to create animal models to better understand the disorder (8). However, in this review article, we focus on the simulated environmental models that are most commonly used in animal research.

Prenatal risk factors

Maternal infection during pregnancy, especially in the early perinatal period, is a significant risk factor for the development of schizophrenia in the child. Epidemiological studies show that infection of the mother with the influenza virus during pregnancy increases the risk of schizophrenia in the child by a factor of 3-7 (9). As the placenta is the connection between the mother and foetus, the foetus can come into contact with mediators of the maternal immune response. Under physiological conditions, this process is strictly controlled, but in the event of a severe disruption of the mother's immune system, the mother's cytokines can be transferred to the foetus to a significant degree. The developing brain is very sensitive to a large amount of pro-inflammatory mediators, so maladaptive changes in development and molecular, structural and functional changes in the brain can occur and later in life develop into neuropsychiatric disorders (10). Numerous studies have investigated the link between activation of the maternal immune response and neurodevelopmental disorders in the offspring. Although there is a large body of research addressing this question in animal models, the results often vary depending on the dose of the immune response activator, animal strains and prenatal timing of administration.

The two animal models most frequently used to study prenatal infections are based on the exposure of the mother animal to lipopolysaccharide (LPS) and the substance poly I:C (polyinosinic:polycytidylic acid). LPS is a component of the cell wall of gram-negative bacteria such as Escherichia coli and Salmonella species, it binds to TLR4 receptors (Toll like receptor 4) and is used to simulate a bacterial infection. Poly I:C is a synthetic analogue of double-stranded RNA and is used to simulate a viral infection. Poly I:C interacts with the TLR3 receptor, which is expressed on the endosomal membrane of B cells, macrophages and dendritic cells (9). LPS and poly I:C lead to the activation of microglia and the subsequent release of other pro-inflammatory cytokines such as IL-6, IL-1β and tumour necrosis factor-alpha (TNF-alpha). After exposure of pregnant female rats to LPS and poly I:C, there is an increase in these cytokines in the foetal brain, and the elevated cytokine levels can be maintained in adulthood. High cytokine levels in young animals lead to structural and functional changes in the brain. Structural changes include a reduction in the volume of the hippocampus, an enlargement of the cerebral ventricles, or a reduction in the thickness of the cerebral cortex (11). The development of structural changes in the brain during the progression of the disease supports the neurodevelopmental theory of schizophrenia, and in addition to the changes in the brain

there are also changes in behaviour, such as anxiety-like behaviour, hypolocomotion and prepulse inhibition deficit that resemble schizophrenia-like behaviour (12, 13). In the article written by Bao et al., results from various studies utilizing different doses of LPS and poly I:C and rodent species are compiled, revealing the diverse outcomes associated with these experiments (14) (Table I, Table II).

Table I Outcomes of offspring after inducing MIA by LPS with different doses and rodent species (15-38)

Tabela I Ishodi MIA modela kod mladunaca koristeći različite doze LPS i vrste glodara (15-38)

Paper	Animals	Dose and Injection Day	Outcomes
Domínguez Rubio et al., 2017	BALB/c mice	0.26 mg/kg GD15	– Fetal brain damage – Microglial/macrophage activation – ↑ *Il1b*, *iNos*, *nNos* gene expression
Arsenault et al., 2014	C57BL6/J mice	120 μg/kg GD15–17	– Fetal brain: ↓ Astrocytic marker: glial fibrillary acidic protein (GFAP) ↓ Neuronal marker: NeuN
Qin et al., 2017	C57 mice	75 μg/ kg GD11	– Abnormal levels fat development, blood lipids, and glucose metabolism – ↑ Adipocyte differentiation markers: CEBPA, CEBPB, PPARG, and activator protein 2 (AP2)
Hsueh et al., 2017	C57BL6/J mice	100 μg/kg (total) GD15–17	– Anxiety-like behaviors – ↓ Cerebral serotonin (5-HT) – ↓ *Tph2* and *Slc6a4* gene expression
Hsueh et al., 2018	C57BL6/J mice	100 μg/kg (total) GD15–17	– Social deficits – Cerebral expression changes immune, developmental- and neuronal structural-related genes
Labrousse et al., 2018	C57BL6/J mice	0.12 μg/g GD17	– Memory deficits – Alteration fatty acid composition – ↑ IL-6 cytokine fetal brain
Fricke et al., 2018	C57BL6/J mice	100 μg/kg GD15.5	Intestinal injury
Wang et al., 2019	C57BL/6J mice	20 μL GD0–16	♂ Offspring: – Anxiety-related behaviors – ↑ Corticotropin-releasing hormone (CRH)

			protein expression – ↑ c-Fos-positive cells
Elgin et al., 2019	C57BL6/J mice	100 µg/kg GD15.5	– Intestinal injury – ↓ Goblet and Paneth cells – ↑ Serum levels of IL-6, TNF, KC/GRO, IL-10, and IL-1β
Chin et al., 2019	C57BL6/J mice	20 mg/kg GD16	♂ Offspring: – ↑ Adipose tissue – ↓ Muscle mass – ↑ Plasma leptin
Brown et al., 2017	CD-1 mice	50 µg/dam GD15	Alterations fetal brain: – ↑ Lipid metabolism – ↑ Amino acid metabolism – ↑ Purine metabolism
Li et al., 2018	D-1 mice	20 µg/kg GD7.5–17.5	– ↓ Body weight – ↑ *Cox2* expression and related inflammatory factors
Eloundou et al., 2019	CD-1 mice	25 µg in 100 µL PBS GD17	– Fetal vessel resistance – Fetal brain: ↑ *Iba1*
Lee et al., 2019	ICR mice	2 mg/kg GD16.5	Morphological changes fetal brain
Liu et al., 2017	Sprague-Dawley rats	1 mg/kg GD14	– ↑ Fetal resorption rates – ↓ Fetal weight
Wang et al., 2017	Sprague-Dawley rats	0.79 mg/kg GD8, 10, 12	– Hypertension – Renal: ↑ *Il6*, *Fli1*, *Tnfa*, *Dnmt1* and *Dnmt3b* gene expression ↑ DNA methylation
Yu et al., 2018	Sprague-Dawley rats	0.79 mg/kg GD8, 10, 12	– ↓ Body weight – Dyslipidemia – Serum and hepatic levels: ↑ Total cholesterol, triglycerides, low-density lipoprotein cholesterol ↑ Aspartate amino transferase and alanine aminotransferase – Gene expression hepatic lipid metabolism ↑ *Vldlr* ↓ *Tm7sf2*
Mouihate et al., 2019	Sprague-Dawley rats	100 µg/kg GD15, 17, 19	– ↓ Motor activity – ↑ Hippocampal expression of SERT protein

Talukdar et al., 2020	Sprague-Dawley rats	1.5 mg/kg GD12	– ↑ Anxiety-like behaviors – ↓ Social behaviors – Brain: ↑ Lipid peroxidation ↓ Total antioxidant content ↑ Inflammatory genes: *Tnfa, Il6, Il1b* ↑ Apoptotic genes: *Bax, Cas3, Cas9* ↓ Neuroprotective genes: *Bdnf, Bcl2*
Simões et al., 2018	Wistar rats	0.25 mg/kg GD15	– Behavioral impairment – Fetal brain: ↑ Cytokine levels ↑ Oxidative stress parameters ↑ Matrix metalloproteinase (MMP)-2 and MMP-9
Vieira et al., 2018	Wistar rats	0.5 mg/kg GD13, 15, 17, 19	– Endothelial dysfunction – Renal hemodynamic changes
Izvolskaia et al., 2019	Wistar rats	50 mg/kg GD12	– ↓ Body weight – ↓ Testis weight – ↓ Testosterone level – ↓ Seminiferous tubule diameter – ↓ Number Sertoli and spermatid cells – ♂ Offspring: Development of sexual disorders
Ignatiuk et al., 2019	Wistar rats	50 μg/kg GD12	– Delayed reproductive maturity – ↓ Body weight – ↓ Sex steroids ♀ offspring
Lee et al., 2021	Wistar rats	500 μg/kg GD9.5	– Microbiome abundance: ↑ *Alistipes, Fusobacterium,* and *Ruminococcus* ↓ *Coprococcus, Erysipelotrichaies,* and *Actinobacteria* – ♂ Offspring: ↓ Social behaviors ↑ Anxiety-like and repetitive behavior ↓ Hypomyelination in the prefrontal cortex and thalamic nucleus

GD, gestational days; LPS, lipopolysaccharide; MIA, maternal immune activation; ↑, increase; ↓, decrease; ♂, male; ♀, female.
GD, dan gestacije; LPS, lipopolisaharid; MIA, maternalna imunska aktivacija; ↑, povećanje; ↓, smanjenje; ♂, mužjak; ♀, ženka.

Table II Outcomes of offspring after inducing MIA by poly I:C with different doses and rodent species (39-59)

Table II Ishodi MIA modela kod mladunaca koristeći različite doze poly I:C i vrste glodara (39-59)

Paper	Animals	Dose and Injection Day	Outcomes
Juckel et al., 2021	BALB/c mice	20 mg/kg GD9	– Differences in species richness microbiome – ♂ Offspring: ↑ Abundance of four families of Firmicutes phylum – ♀ Offspring: ↑ Abundance of *Lactobacillaeles* ↓ Abundance of *Prevotellaceae* and *Porpyromonadaceae*
Mandal et al., 2011	C57BL/6 mice	20 mg/kg GD12	Preferential to Th17 cell differentiation of lymphocytes
Giulivi et al., 2013	C57BL/6J mice	20 mg/kg GD12.5	– Behavioral impairments – Adult splenocytes: ↓ Mitochondrial ATP production
Arsenault et al., 2014	C57BL/6J mice	5 mg/kg GD15–17	– ↓ Growth and sensorimotor development – Fetal brain: ↑ IL-2, IL-5, and IL-6 cytokines ↑ Metabotropic receptor 5: mGluR5
Tang et al., 2013	C57BL6/J mice	5 mg/kg GD9	– Juvenile cortex: Hypoacetylation of histone H3 and H4 ↓ Promotor-specific histone acetylation (*Gria1, Slc17a7*) – Juvenile hippocampus: ↑ *Disc1* and *Ntrk3* genes – Adult offspring: Behavioral abnormalities No changes in histone acetylation ↓ Promotor-specific histone acetylation (*Gria1, Slc17a7*)
MacDowell et al., 2016	C57BL/6J mice	5 mg/kg GD9.5	Adult frontal cortex: – Activated innate immune receptor TLR3 signaling pathway – Oxidative/nitrosative stress

			– Accumulation of proinflammatory mediators (Nfkb and iNOS)
da Silveira et al., 2017	C57BL/6J mice	5 mg/kg GD9 or GD17	– Neuroanatomical alterations – Behavioral alterations – ↓ Brain volume – ↓ Glucose preferences
Basil et al., 2018	C57BL/6N mice	5 mg/kg GD9	Hypomethylation of adult brain
Li et al., 2018	C57BL/6J mice	20 mg/kg GD12.5	– Activation of local circuit interneurons adult brain – ↑ Synaptic strength adult brain
Garcia-Valtanen et al., 2020	C57BL/6J mice	20 mg/kg GD12	– Neonate immune organs and brain: – ↑ Cytokine levels of TNFα and IL-18 – Adult: Alteration in behavioral responses
Carlezon et al., 2019	C57BL/6J mice	20 mg/kg GD12.5	– ♂ Offspring: ↓ mRNA and protein levels of TNFα/iNOS, IL-6/IL-1B, anti-inflammatory factors – ♀ Offspring: ↑ mRNA and protein levels of TNFα/iNOS, IL-6/IL-1β, anti-inflammatory factors
Barke et al., 2019	C57BL/6J mice	20 mg/kg GD12.5	Fetal and placental sex influenced: – Responses of immune genes to metabolic and inflammatory stress.
Openshaw et al., 2019	C57BL/6 mice	20 mg/kg GD12.5	– ↑ CCL5 and CXCL10 fetal brain – ↑ Cytokines/chemokines in Map2k7 Hz mice
Garcia-Valtanen et al., 2020	C57BL/6J mice	20 mg/kg GD12	– Neonate immune organs and brain: ↑ Cytokine levels of TNFα and IL-18 – Adult: Alteration in behavioral responses
Tsivion-Visbord et al., 2020	C57BL/6J mice	5 mg/kg/mL GD9	Fetal brains: – Dysregulation in brain development-related gene pathways – ↑ RNA-editing
Dabbah-Assadi et al., 2019	CD-1 mice	5 mg/kg GD12.5, 17.5	– ♂ Offspring: Alteration in social interaction ↑ *Nrg1* and *Erbb4* gene expression – Adult: Behavioral changes

Ding et al., 2019	Sprague-Dawley rats	10 mg/kg GD9	– Age-related behavioral and neuro-inflammatory changes – Activation of microglia Astrocytes activated at PND60
McColl et al., 2019	Sprague-Dawley rats	10 mg/kg GD14	Fetal brains: – ↑ Amino acid transporters – ↓ Snat*5*, *Eaat1*, and *Glyt* gene expression
Hu et al., 2019	Sprague-Dawley rats	10 mg/kg GD17	– Depressive-like behavior – Dendrite development obstruction – ↑ *Isg15* expression brain
Talukdar et al., 2020	Sprague-Dawley rats	20 mg/kg GD12	– ↑ Anxiety-like behaviors – ↓ Social behaviors – Brain: ↑ Lipid peroxidation ↓ Total antioxidant content ↑ Inflammatory genes: *Tnfa, Il6, Il1b* ↑ Apoptotic genes: *Bax, Cas3, Cas9* ↓ Neuroprotective genes: *Bdnf, Bcl2*
Meehan et al., 2017	Wistar rats	4 mg/kg Early = GD10 Late = GD19	♂ Offspring: – Sensorimotor gating deficits – ↑ *D1r* gene expression in nucleus accumbens
Hollins et al., 2018	Wistar rats	5 mg/kg GD10 and GD9	Fetal brains: – Dysregulation in brain development-related gene pathways – ↑ RNA editing Neonates: – ↑ lymphoid aggregates – Altered intestinal inflammatory profile – Disruption in GI barrier tight junction protein Adults: – ↑ Anxiety-like behavior
Kowash et al., 2019	Wistar rats	10 mg/kg GD15	– ↓ Litter size depending on Poly I:C supplier – ↓ Placenta weight ♂ Offspring: – ↓ Fetal brain weight

GD, gestational days; MIA, maternal immune activation; Poly I:C, polyinosinic:polycytidylic acid; TLR3, Toll-like receptor 3; GI, Gastrointestinal; PND, postnatal day; CCL5, chemokine (C-C motif) ligand 5; CXCL10, C-X-C motif chemokine ligand 10; ↑, increase; ↓, decrease; ♂, male; ♀, female.

GD, dan gestacije; MIA, maternalna imunska aktivacija; Poly I:C, poliinozinska:policitidilna kiselina; TLR3, receptori slični Tolu 3; GI, gastrointestinalni; PND, postnatalni dan; CCL5, hemokinski (C-C motiv) ligand 5; CXCL10, C-X-C motiv hemokinski ligand 10; ↑, povećanje; ↓, smanjenje; ♂, mužjak; ♀, ženka.

Postnatal risk factors

Early life stress

Epidemiological data suggest that unfavorable early life experiences, especially chronic stress, can have a significant impact on cognitive and emotional performance. Adverse conditions in early childhood, including poverty, parental loss, maternal substance abuse, or maternal depression, are associated with an increased likelihood of developing psychopathology later in life (60). Given all the challenges of studying children and the many uncontrollable factors, such as genetic predisposition, it is necessary to develop animal models for these studies. Animal models allow the investigation of direct cause-effect relationships, as well as complete control of the genetic background and prenatal environment. In addition, the parameters of interest can be manipulated, and subsequent interventions can be controlled throughout the study period (61). One of the models used to induce stress at a young age is to impoverish the environment by removing the sawdust from the cage and placing a plastic wire mesh raised from the floor of the cage on which the young are reared. These animals show cognitive and emotional consequences later in life, such as disturbance in learning and memory, impaired social behaviour, anxiety-like behaviour, depressive-like behaviour, dendritic atrophy, etc. This method is widely used and has been described in detail by Tallie Baram's research group (62).

Social aversion in adolescence

Although stress can cause undesirable phenotypes in all circumstances, adolescence is a particularly sensitive time for social stress (63). Adolescence is associated with increased neuronal plasticity at all levels (64, 65), and this window of plasticity closes in early adulthood as the brain reaches maturity and neuronal networks become much more rigid. Therefore, early adulthood is the period when most psychiatric phenotypes manifest (66). Despite considerable efforts, the behavioral, structural, functional and molecular changes triggered by social stress in adolescence are still not sufficiently well characterized.

As sociability is an evolutionarily conserved trait in mammals (67), the stress of social isolation and social defeat during adolescence in rodents is often used as a model to understand the relationship between social stress in adolescence and risk of psychiatric phenotypes (68). However, despite intensive research, studies conducted to date are not consistent in terms of behavioral outcomes following social isolation, as results often differ depending on the experimental protocol, rodent species, behavioral tests, and sex of the animals, as shown in a meta-analysis performed by Manojlović et al. (69). The details of the studies used in this meta-analysis can be found in Table III. In addition, most studies on social isolation in adolescence focus exclusively on male animals, although females are almost twice as likely to be affected by these disorders (70).

Table III Different rodent species, isolation time and behavioral parameters used in social isolation in adolescence paradigm (71-100)

Table III Različite vrste glodara, vreme izolacije i parametri ponašanja koji se koriste u paradigmi socijalne izolacije tokom adolescencije (71-100)

Paper	Animals	Isolation duration	Behavioural parameter
Jeon et al., 2023	C57BL/6J mice, males	PND 21-80	Social sniffing index
	C57BL/6J mice, females		Social sniffing index
Wang et al., 2022	C57BL/6 mice, males	PNW 4-12	Time in the centre of open field (%)
Zhao et al., 2022	Sprague–Dawley rats, females	PND 21-35	Time in the centre of open field (s) Social interaction (%)
Potrebić et al., 2022	Wistar Han rats, males	PND 29-43	Time spent in interaction (s)
Usui et al., 2021	C57BL/6N mice, males	PND 21-50	Time in the centre of open field (s) Social interaction (s)
Sakurai et al., 2021	C57BL/6JJcl mice, males	PNW 5-8	Time in the centre of open field (s)
Acero-Castillo et al., 2021	Wistar rats, males	For 21 days during adolescence	Open arms exploration (%)
Tan et al., 2021	C57BL/6J mice, females	PNW 3-8	Social interaction (s)
Deal et al., 2021	HS rats, male	PNW 4-9	Time in the centre of open field (s)
Amancio-Belmont et al., 2020	Wistar rats, males	PND 24-64	Time in the open arms (s)
Park et al., 2020	Wistar rats, males	PND 21-63	Time in the open arms (s)
Chen et al., 2020	C57BL/6J mice, males and females combined	PND 21-56	Time in the centre of open field (s) Total contact time (s)
Pais et al., 2019	C57BL/6J mice, males	PNW 4-8	Time in light in LDB (%) Interaction zone time (s)
	C57BL/6J mice, females		Time in light in LDB (%) Interaction zone time (s)
Mavrikaki et al., 2019	Spraque-Dawley rats, males	PND 21-63	Time spent in open arms (%)

	Spraque-Dawley rats, females		Time spent in open arms (%)
Lynch et al., 2019	Long-Evans rats, males	PND 27-69	Open arms time (s)
Lin et al., 2018	C57BL/6J mice, sex not specified	PND 21-35	Time in the centre of open field (s)
Cao et al., 2017	CD1 mice, males	PND 30-86	Open arms time (%) Time spent in interaction (s)
Zhang et al., 2016	C57BL/6J mice, males	PND 38-80	Social interaction ratio
Amiri et al., 2016	NMRI mice, males	PND 21-49	Open arms time (%)
Skelly et al., 2015	Long-Evans rats, males	PND 28-70	Open arms time (s)
Liu et al., 2015	C57BL/6 mice, males	PND 21-49	Time in the interaction zone (s)
Amiri et al., 2015	Swiss albino mice, males	PND 21-67	Time in the centre of open field (s)
Haj-Mirzaian et al., 2015	NMRI mice, males	PND 21-49	Time in the centre of open field (s)
Lopez et al., 2015	C57BL/6J mice, males	PND 21-60	Time in the dark side (s)
	C57BL/6J mice, females		Time in the dark side (s)
Karkhanis et al., 2014	Long–Evans rats, males	PND 28-74	Open arms time (min)
Butler et al., 2014	Long Evans rats, females	PND 31-73	Open arms time (s)
Butler et al., 2014	Long Evans rats, males	PND 28-70	Open arms time (s)
Wall et al., 2012	Sprague–Dawley rats, males	PND 21-49	Social interaction time (s)
	Sprague–Dawley rats, females		Social interaction time (s)
Chappell et al., 2013	Long Evans rats, males	PND 28-72	Open arms time (s)
Ros-Simó et al., 2012	CD1 mice, males	PND 21-70	Open arms time (%)

PND, postnatal day; PNW, postnatal week
PND, postnatalni dan; PNW, postnatalna nedelja

Use of cannabis in adolescence

Cannabis is the most commonly used drug, and its use often begins in adolescence. Research suggests that regular cannabis use in adolescence may increase the likelihood of developing schizophrenia by two to three times compared to people who do not use

cannabis, and this effect is likely to be dose-dependent (101). In animal models, chronic treatment with the synthetic cannabinoid receptor agonist WIN 55,212-2 in adolescence has been shown to lead to long-lasting behavioral deficits in adulthood. The results show that the behavioral deficits were more pronounced after treatment with WIN 55,212-2 in adolescence than after chronic treatment in adulthood (102). WIN 55,212-2 is a full agonist of CB1 cannabinoid receptors and it has a much higher affinity for these receptors than tetrahydrocannabinol (THC) (103). WIN 55,212-2 is also an agonist of CB2 cannabinoid receptors (104), as well as PPARα and PPARγ nuclear receptors (105).

Conclusion

Animal models are crucial for studying schizophrenia, helping to uncover neurobiological mechanisms and aiding in the development of new treatments. However, they face limitations due to interspecies differences and the complexity of the human brain. Schizophrenia models must meet three key criteria to be translatable: (1) symptom homology, reflecting core schizophrenia symptoms (positive, negative, and cognitive); (2) construct validity, replicating neurochemical and structural changes (e.g., dopamine and glutamate dysregulation); and (3) predictive validity, demonstrating the effectiveness of antipsychotics (106). However, no model fully meets all these criteria, particularly when it comes to replicating the schizophrenic mind, as animals cannot self-report symptoms like hallucinations or alogia. While animal models can replicate certain schizophrenia features, they cannot fully capture the complexity of the disorder (107).

The development of schizophrenia is influenced by a complex interaction of genetic and environmental factors, with prenatal and postnatal experiences playing a significant role in shaping risk. Animal models simulating these risk factors provide valuable insights, but must include both male and female subjects, as psychotic disorders affect these genders differently. Despite the advances, replicating the full scope of schizophrenia remains difficult, and more research is needed to understand its pathophysiology and develop effective treatments. Improved models, integrating environmental influences and more comprehensive research practices, hold the potential to advance preventive measures and treatment options for individuals at risk of psychosis.

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Declaration of Competing Interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Writing – review and editing, M.M.

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Razumevanje šizofrenije kroz životinjske modele: uloga stresora životne sredine

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Kratak sadržaj

Šizofrenija i drugi psihotični poremećaji predstavljaju značajan klinički izazov, pri čemu i genetski faktori i faktori sredine doprinose njihovom nastanku. Životinjski modeli su ključni alati za razumevanje kompleksnih neurobioloških mehanizama koji leže u osnovi psihoza, kao i za razvoj novih terapeutskih pristupa. Ovaj revijalni rad se fokusira na najčešće korišćene životinjske modele u istraživanjima šizofrenije, naročito one zasnovane na prenatalnim i postnatalnim faktorima rizika. Prenatalna izloženost infekcijama, kao što su bakterijski lipopolisaharidi (LPS) i virusna komponenta poly I:C, aktivira imuni odgovor koji dovodi do dugotrajnih strukturnih i funkcionalnih promena u mozgu, uključujući atrofiju hipokampusa i stanjivanje korteksa. Postnatalni faktori, uključujući stres u ranom dobu, socijalnu izolaciju i upotrebu droga, naročito kanabisa, takođe se modeliraju kako bi se proučavao njihov uticaj na razvoj mozga i nastanak psihoza. Ovi modeli omogućavaju kontrolisanu manipulaciju varijablama, pružajući uvide u patofiziologiju bolesti. Međutim, varijabilnost u eksperimentalnim protokolima i nedostatak učešća ženskog pola u mnogim studijama ukazuju na potrebu za robusnijim i inkluzivnijim životinjskim modelima. Na kraju, ovi modeli su ključni za unapređenje našeg razumevanja šizofrenije i testiranje potencijalnih terapeutskih intervencija.

Ključne reči: psihoza, prenatalne infekcije, stres u ranom dobu, socijalna averzija, zloupotreba droga