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Experimental Animal Models in Neurological Diseases

Nörolojik Hastalıklarda Deneysel Hayvan Modelleri

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ABSTRACT

The human brain is a structure that controls billions of neurons and trillions of connections. Having a unique anatomy with countless neurons and connections makes its understanding even more complex. The brain, divided into different regions for specialized functions such as memory, movement, sensation, and emotions, holds great significance in human cognition and behavior. Centuries of research, coupled with advancements in technology, have propelled neuroscience forward, facilitating the understanding of the neurological, behavioral, and structural characteristics of the brain. Developing treatments for neurological disorders such as Alzheimer's, Parkinson's, multiple sclerosis, amyotrophic lateral sclerosis, migraine, epilepsy, and schizophrenia as well as understanding the complex mechanisms of these diseases, require the exploration of new treatment methods, drugs, and products through direct experimentation on humans, which raises ethical concerns. Therefore, experimental animal models are needed in the treatment of neurodegenerative diseases. There are currently many experimental animal models developed to elucidate the pathophysiological characteristics of neurological disorders. The aim of this review was to summarize the experimental models of neurodegenerative diseases developed today in sections. While recognizing that an experimental animal model may not fully replicate the disease process in humans, it can at least provide guidance in understanding the disease.
Keywords: Neurological diseases; experimental animal models.

ÖZ

İnsan beyni, milyarlarca nöronu ve trilyonlarca bağlantıyı kontrol eden bir yapıdır. Eşsiz bir anatomiye sahip olan bu yapının sayısız nöron ve bağlantıya sahip olması, onun anlaşılmasını daha da karmaşık hale getirmektedir. Hafıza, hareket, duyu ve duygular gibi özelleşmiş fonksiyonlar için farklı bölgelere ayrılmış olan beyin, insanın biliş ve davranışında büyük öneme sahiptir. Yüzyıllardır süren araştırmalar, teknolojinin de gelişmesiyle sinirbilimini ileriye taşımış, beynin nörolojik, davranışsal ve yapısal özelliklerinin anlaşılmasını sağlamıştır. Alzheimer, Parkinson, multiple skleroz, amyotrofik lateral skleroz, migren, epilepsi ve şizofreni gibi nörolojik bozukluklara yönelik tedavilerin geliştirilebilmesi ve hastalıkların karmaşık mekanizmalarının anlaşılması için yeni tedavi yöntemlerinin, ilaç ve ürünlerinin doğrudan insanlarla çalışılması etik sorunlar doğuracağından nörodejeneratif hastalıkların tedavisinde, deneysel hayvan modellerine ihtiyaç duyulmaktadır. Nörolojik bozuklukların fizyopatolojik özelliklerini aydınlatmak için hali hazırda geliştirilmiş birçok deneysel hayvan modeli mevcuttur. Bu derlemenin amacı, günümüzde geliştirilen nörodejeneratif hastalıklara yönelik deneysel modellerin bölümler halinde özetlenmesidir. Bir deneysel hayvan modeli insandaki hastalık sürecini tamamen karşılayamasa bile en azından hastalığın anlaşılmasında yol gösterici olabilir.
Anahtar kelimeler: Nörolojik hastalıklar; deneysel hayvan modelleri.

INTRODUCTION

Neurological diseases encompass a wide range of disorders characterized by various abnormalities in the nervous system. These diseases affect the functions of the brain, brainstem, spinal cord, and other nerves, deeply impacting individuals' quality of life (1). Experimental animal models are frequently utilized to understand the complex mechanisms of neurological diseases and to develop treatment methods (2). In this review, basic information and disease pathophysiology of Alzheimer's, Parkinson's, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), migraine, epilepsy, and schizophrenia were mentioned under the main heading, with experimental animal models developed in recent times summarized under a subheading.

ALZHEIMER'S DISEASES AND MODELS

Alzheimer's disease (AD) is a prevalent neurodegenerative disease worldwide that leads to progressive dementia. In the clinical presentation of AD, a decrease in memory, language, judgment, and behavior is observed, while in its pathophysiology, mitochondrial dysfunction, hormonal imbalance, calcium dysregulation, increased oxidative stress, and neuroinflammation are seen (3). The disease exhibits variability in its onset, progression, and pathology, and it is classified as early-onset and late-onset (4). The specific markers of AD are neurofibrillary tangles composed of amyloid-beta (Aβ) plaques and hyperphosphorylated tau proteins. Aβ triggers mitochondrial oxidative stress, leading to disruptions in the electron transport chain and abnormalities in calcium regulation, resulting in increased harmful radicals and decreased ATP production. The decreases observed in the levels of enzymes related to energy metabolism in the brain cells of AD patients have been reported to lead to protein/DNA alterations and neuronal death (5,6). The most commonly used animal species in modeling AD are mice, however, the use of rats is also mentioned (7). In modeling, both transgenic and non-transgenic species are used. Transgenic models include those featuring amyloid precursor protein (APP), tau protein, and transgenic models capable of expressing both. Among non-transgenic models, there are induced models using substances such as streptozotocin, amyloid, colchicine, aluminum, zinc, and lipopolysaccharide (LPS) (6,7).

Transgenic AD Models

To model certain features of AD, transgenic animal models have been generated by incorporating mutant genes into the existing genetic structure or by modifying genes. Mice are the most commonly used species for transgenic modeling due to their ease of manipulation and accessibility.

APP transgenic AD model

The overexpression of APP leads to the release of harmful Aβ peptides, causing damage to neurons. Although dense plaques, gliosis, and early spatial memory impairment are exhibited in the cortex and hippocampus regions of this model, it does not sufficiently mimic the symptoms of AD (7,8).

Tau protein transgenic AD model

In this model, which can mimic some aspects of early-onset AD, excessive phosphorylation of the tau protein is induced. Excessive phosphorylated tau inhibits axonal transport, leading to the formation of tangled structures in the soma and dendrites of neurons. These alterations in AD significantly impair cognitive functions by affecting vital brain regions for learning and memory (7).

APP and Tau double transgenic AD model

This model involves genetically modifying animals to express both mutant forms of the APP and tau protein, thus enabling to explore the interactions between APP and tau and their roles in the development and progression of AD. However, while this model replicates some aspects of the disease, it may not fully capture the entire spectrum of AD pathology seen in humans (9).

Non-transgenic AD Models

Streptozotocin-induced AD model

Intracerebroventricular (ICV) injection of streptozotocin triggers free radical formation and significantly affects rat cognitive function. Developing Aβ and tau neuropathology with the ICV infusion model takes time (10).

Aβ-induced AD model

Aβ oligomers are derived from the breakdown of APP and are associated with neuronal damage, cognitive impairment, and memory loss. Aβ administered via the ICV route triggers inflammatory processes, disrupts calcium balance, increases the release of reactive oxygen species (ROS), triggers DNA/protein alterations, mitochondrial dysfunction, and various neurotoxic mechanisms such as apoptosis (11). The model not only exhibits AD-like behavioral abnormalities but also displays the Aβ pathology shared by both familial and sporadic AD, which is a common feature (12).

Colchicine-induced AD model

When colchicine derived from certain lily plants is applied to the brain, it triggers excessive free radical production and causes DNA damage, particularly affecting hippocampal cells and pathways severely. This condition leads to cholinergic neuron loss, decreased learning ability, and memory loss. However, the neurotoxic mechanism of colchicine is not fully understood (13,14).

Aluminum-induced AD model

When aluminum salts are administered intracerebrally or peripherally, they trigger the formation of neurofibrillary tangles. The neurodegenerative effect of aluminum varies depending on the route of administration, type of salt, animal species, dosage, and duration of exposure, but aluminum levels in the brain increase with age. Accumulated aluminum in neurons interacts with tau proteins, contributing to the neurofibrillary pathology of AD (15,16).

Zinc-induced AD model

Zinc, which is important for growth, cognitive functions, and neurotransmission regulation, is abundantly present in the hippocampus and cortex brain regions. Positioned in synaptic vesicles, zinc is released excessively into the synaptic cleft when cellular function is disrupted, leading to the generation of ROS and affecting enzymes and cellular respiration. This ultimately leads to the activation of apoptosis and consequently neuronal loss. Zinc has a role in Aβ accumulation, hence its effect in AD (17).

Lipopolysaccharide-induced AD model

The LPS present in the structure of gram-negative bacteria strongly stimulates microglia and astrocytes, triggering the production of endogenous IL-1 and beta-APP. This inflammation, responsible for neuronal degeneration in brain regions and affecting spatial memory, is used in AD research (18).

PARKINSON'S DISEASES AND MODELS

Parkinson's disease (PD) is a late-onset, progressive neurodegenerative disorder characterized by four primary motor symptoms (resting tremor, rigidity, bradykinesia, and postural instability). The disease is associated with degeneration of nigrostriatal dopaminergic neurons and the presence of Lewy bodies (containing alpha-synuclein and ubiquitin) (19). In PD, treatment aims to manage symptoms, and for a long time, levodopa, a precursor to dopamine, has been used. In animal modeling using rodents to test new treatment strategies for PD, neurotoxic models stand out more prominently compared to genetic models. Neurotoxic agents such as 6-OHDA (6-hydroxydopamine), MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), rotenone, paraquat, and LPS are frequently used in a disease that typically manifests with late-onset symptoms in about 90% of cases (20). Additionally, models induced by medications such as haloperidol, fluphenazine, reserpine, and methamphetamine are observed (21).

Toxin-induced PD Models

6-OHDA-induced PD model

6-OHDA is similar to endogenous catecholamines and accumulates pathologically in catecholaminergic neurons when exposed. Neurotoxic effects emerge due to oxidative damage. Damage to the dopaminergic pathway induces asymmetric rotation in subjects, allowing the study of PD (22).

MPTP-induced PD model

The lipophilic MPTP is converted into the toxic metabolite MPP (1-methyl-4-phenylpyridinium) in the body. It enters the mitochondria of dopaminergic neurons and interferes with complex I of the electron transport chain, inhibiting the oxidation reaction. Irreversible damage leads to dopamine deficiency. The MPTP model exhibits many characteristics of PD, including dopaminergic neurodegeneration, motor deficits, the formation of alpha-synuclein aggregates, and neuroinflammation (23,24).

Rotenone-induced PD model

Rotenone, both an insecticide and herbicide, is a lipophilic neurotoxin. In models predominantly using rodents, the toxin inhibits mitochondrial complex 1, increases ROS, reduces dopamine-glutathione levels, induces oxidative damage, and blocks mitosis, thereby preventing cell proliferation. Lewy bodies resulting from damage to the nigrostriatal dopaminergic pathway can be examined (25,26).

Paraquat-induced PD model

Paraquat, a herbicide with neurotoxic properties that cannot cross the blood-brain barrier, causes degeneration in dopaminergic neurons by generating ROS when applied systemically (27).

Lipopolysaccharide-induced PD model

LPS, which triggers microglial activation and sets the stage for the degeneration of dopaminergic neurons, can be administered stereotactically, systemically, and intranasally (28).

Drug-induced PD model

Haloperidol and fluphenazine cause functional dopamine deficiency in postsynaptic receptor regions, while reserpine and methamphetamine affect vesicles. These drugs represent the reduced dopamine levels in PD (21).

Genetic-induced PD Models

Six genes; alpha-synuclein, LRRK2, VPS35, Parkin, PINK1, and DJ-1, are associated with PD. However, genetic PD models created in animals do not completely align with the behaviors observed in humans (29).

MULTIPLE SCLEROSIS AND MODELS

MS is a chronic autoimmune disorder where the immune system attacks the myelin sheath of the central nervous system, mistaking it as foreign. In the unit of oligodendrocyte-myelin-axon, myelin protects and nourishes the axon while increasing its cross-sectional diameter. This structure becomes disrupted due to MS, leading to lesion formations in the white matter of the brain. In MS, decreased axonal density and volume in affected areas and seemingly normal central nervous system tissue contribute to brain and spinal cord atrophy, resulting in permanent disability (30). Among the MS animal models; experimental autoimmune encephalomyelitis (EAE), a viral-induced chronic demyelinating disease known as Theiler's murine encephalomyelitis virus (TMEV) infection, and toxin-induced demyelination are included (31).

EAE MS Model

Initially, monkeys and guinea pigs were used to establish the model, but nowadays, mice and rats are predominantly used. Here, autoimmunity against components of the central nervous system is induced through immunization with antigens derived from the basic myelin protein in susceptible mice. Paralysis starting in the tail after induction is followed by manifestations in the hind and forelimbs. Among the shortcomings of the most commonly studied EAE model are limited information about the progression of MS, challenges in studying remyelination, and inadequate treatment procedures targeting neuronal growth (31).

Virus-induced MS Model

Epidemiological studies have suggested that a viral infection early in life, in the presence of a specific genetic background, may lead to an immune-mediated attack against the central nervous system, but so far, no specific virus has been identified as a potential cause or contributor to MS. The most commonly studied viral animal model of MS is the TMEV model. In this method, which can be applied in susceptible mice, the chronic demyelination phase of MS can be examined. However, a disadvantage of the model is that demyelination and remyelination occur simultaneously (31).

Toxin-induced MS Model

Among the toxins used to model MS by inducing demyelination, ethidium bromide, and cuprizone are prominent. An important aspect of these toxins is their assistance in studying the process of remyelination. However, toxins that induce demyelination due to myelin loss and oligodendrocyte death in white matter areas are insufficient in representing all aspects of MS expression. They focus only on myelin loss and cannot simulate all inflammatory processes and immune system dysfunction (32).

AMYOTROPHIC LATERAL SCLEROSIS AND MODELS

ALS is a late-onset, progressive, etiology completely unknown neurodegenerative disease that affects cortical and spinal motor neurons. The onset of ALS symptoms in patients is actually indicative of the loss of approximately 50-70% of motor neurons. While the majority of cases arise sporadically, about 5-10% are familial. Prominent symptoms include weakness in the extremities and difficulty swallowing. As the disease progresses, daily activities decrease, and cognitive losses increase (33).

According to current data, the incidence of ALS is between 6 and 38 cases per million, and an effective treatment for the disease has not yet been discovered (34). Although ALS is generally known as a motor neuron disorder, nowadays, there is a significant amount of evidence suggesting that ALS is a non-cell autonomous disease involving astrocytes, oligodendrocytes, microglia, and immune cells. For the onset and progression of the disease, various factors have been proposed, such as excessive calcium and glutamate excitotoxicity, oxidative stress, axonal dysfunction, neuroinflammation, errors in proteins and RNA, mitochondrial stress, and damage. Animal models, often using rodents, are commonly employed to investigate early symptoms, motor neuron loss, muscle weakness, and other ALS symptoms. However, limitations exist as these models may not fully reflect ALS, and there are constraints on how applicable therapeutic approaches tested on these models will be in humans. Thus, human clinical studies still hold a crucial position (33).

Genetic ALS Models

Many of the animal models used to investigate the pathogenesis and biochemical mechanisms of ALS are studies involving genetic interventions. So far, close to 50 genes associated with ALS have been discovered. A mutation in the human superoxide dismutase 1 (SOD1) gene is reported to be a significant factor in ALS. Among other important mutated genes are TARDBP (TAR DNA binding protein), C9orf72 (chromosome 9 open reading frame 72), and FUS (Fused in Sarcoma). Transgenic animals carrying mutated genes such as VABP (VAMP-associated protein B), OPTN (Optineurin), VCP (Valosin Containing Protein), UBQLN2 (Ubiquilin-2), MATR3 (Matrin 3), TBK1 (TANK-Binding Kinase-1) have been used as models to understand the pathogenesis of ALS and test new therapies by reflecting similar symptoms observed in ALS patients (motor neuron loss, muscle denervation, tremors, paralysis, death) (35).

Environmentally-induced ALS Models

Dietary model of ascorbic acid deficiency (36), rodent model infected with motor neuron antigens from different species (37,38), L-BMAA (beta-N-methylamino-L-alanine) induced model (39,40), neurotoxin-induced model (41-43) have been created to mimic environmentally induced ALS. Since these exposures can lead to negative changes and mutations in genes, categorizing environmentally induced models separately from genetic models may not be an entirely accurate classification.

MIGRAINE AND MODELS

Migraine is a neurovascular disorder characterized by a one-sided, throbbing headache, the intensity of which can increase in response to factors such as movement, sound, and light. Migraine attacks can often be accompanied by symptoms like nausea, vomiting, and sensitivity to light. Migraine, affecting 18% of women and 6% of men, arises through the separate or combined effects of environmental and genetic factors. Although all mechanisms in migraines have not yet been fully elucidated, evidence suggests that the triggering of sensitization in the trigeminovascular system, which activates inflammatory and vasodilatory processes, is the cause of the headache (44). When sensory nerve fibers in the trigeminovascular system are activated, the release of vasoactive agents is induced, leading to vasodilation and dural plasma extravasation, resulting in neurogenic inflammation, and ultimately, an increase in the severity of pain is observed (45). Migraine is classified as with aura and without aura. In migraines with aura, visual, sensory, or motor symptoms are observed before or at the onset of the headache, and these symptoms are referred to as "aura." For example, flickering lights, dots or lines, needles, or numbness are signs of an aura. Migraine without aura starts suddenly, there are no aura symptoms, and it is generally severe (46,47). The majority of information regarding the pathophysiology of migraine has been obtained from animal models developed to investigate the nociceptive pathways of the trigeminovascular system and their transmissions reaching the brainstem and diencephalic nuclei (45). Among the experimental animal models currently used to understand the underlying mechanisms of migraine, evaluate treatment options, and develop new therapeutic strategies, there are models such as the cortical spreading depression model (48), electrical stimulation model (49), inflammatory mediator-induced migraine model (50), chemical-induced migraine model (51), and genetic migraine model (52).

Cortical Spreading Depression Model

Cortical spreading depression is induced by microinjection of potassium chloride into the brain through craniotomy, and test data is observed through an electrical activity recorder (53). Cortical spreading depression stimulates ipsilateral trigeminal axons surrounding cortical blood vessels, leading to extravasation of plasma proteins in the dura mater, activating mechanisms that induce c-Fos expression in the caudal trigeminal nucleus, causing disruption of the blood-brain barrier, enabling the activation of the trigeminovascular system, and resulting in the release of chemicals such as H+, K+, nitric oxide, and neurotransmitters into the extracellular space (48). These observed effects contribute to the understanding of migraine pathophysiology.

Electrical Stimulation Migraine Model

The model is designed to achieve trigeminovascular activation by placing a bipolar stimulating electrode near the meningeal arteries and superior sagittal sinus dural vessels. Upon activation of trigeminovascular regions stimulable by nociceptive stimulation with this electrical stimulus, Fos immunoreactivity is triggered, and efforts are made to examine neuronal populations in the trigeminovascular system (49).

Inflammatory Mediator-Induced Migraine Model

A model is created by intracranial injection of an inflammatory mixture containing prostaglandin, histamine, serotonin, and bradykinin in rodents. By interpreting the data through myographic and histological analyses, various aspects of migraine pain can be evaluated, and pain mechanisms can be scrutinized (50). The disadvantage of the model is that it alters blood-brain barrier activities and directly activates central brain regions (49).

Chemically Induced Migraine Model

The nitroglycerin model, a frequently employed method for peripheral application among chemical-induced migraine models, is conducted by administering a single dose of intraperitoneal nitroglycerin injection to rodents to trigger hyperalgesia. In the model where trigeminal and cortical structures associated with migraine pain are

sensitized, phenotypically, attacks similar to spontaneous migraine attacks are observed (51). In a recent study, repeated nitroglycerin injections are reported to hold promise for investigating the chronic course of migraine (54).

Genetic Migraine Model

Transgenic mouse models are being created to gain insights into the phenotypic consequences of mutations playing a role in migraine pathophysiology. These models primarily mimic familial hemiplegic migraine, a rare subtype of migraine with aura. So far, genes associated with migraine, namely FHM1 CACNA1A, FHM2 ATP1A2, and FHM3 SCN1A, have been identified. Mutations in these genes lead to disruptions in neuronal voltage-gated calcium channels, voltage-gated sodium channels, and Na+/K+ ATPase activities, resulting in migraine attacks. Detailed research on transgenic models enables the identification of genes associated with migraine (52).

EPILEPSY AND MODELS

Epilepsy is a neurological disorder characterized by abnormal electrical activities of brain cells. Sudden and uncontrolled increases in brain electrical activity can lead to recurrent seizures (55). Among the conditions that disrupt normal functioning and cause epilepsy seizures are genetic factors (56), brain injury (57), hormonal changes (58), infections (59), neurological disorders (60), etc. In individuals with epilepsy, irregularities in the regulation of the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the central nervous system have been reported. This irregularity can lead to increased sensitivity to seizure activity and a decrease in the ability to regulate and terminate seizures (61). Since not all epileptic seizures have the same pathophysiology due to the large number of them, it is not possible to make definitive statements about all components of the disease (62). The classification of epilepsy models is primarily based on focal onset, generalized onset, and unknown onset seizures. Subcategories can be grouped as motor and non-motor onset seizures (63). In epilepsy research, animal experiments are widely used to examine specific pathophysiology, develop new treatments, and produce therapeutic drugs. Studies often utilizing rodent species aim to investigate focal and generalized epileptic seizure models. Additionally, rats and mice are also utilized in genetic studies. These models can be created through induction with chemical agents, electrical stimulation, or genetic interventions (64).

Focal Epileptic Seizures

Focal seizures occur due to disruptions in the stability of neuron membranes leading to hyperexcitability. Seizures are characterized by motor, sensory, or autonomic symptoms that remain confined to a specific region. These symptoms may involve sensory perceptions such as vision, hearing, taste, smell, and touch, or be associated with motor manifestations such as muscle spasms, tremors, and shaking (65). In focal seizures, if information about awareness can be obtained, grouping can also be done as 'aware or impaired awareness' (63).

Chemically-Induced Focal Epileptic Seizure Models

Among the most commonly used agents for creating focal epilepsy models by chemical induction are penicillin (66), pilocarpine (67), and kainic acid (68). These agents are typically administered intracerebrally. Penicillin acts on GABA receptors (69), pilocarpine on muscarinic receptors involved in the onset of seizures (70), and kainic acid on glutamate receptors (70) to induce epileptic seizures.

Electrically Induced Focal Epileptic Seizure Models

Electrical stimulation is applied to brain regions containing limbic structures such as the amygdala, hippocampus, perirhinal cortex, and piriform cortex. The kindling model is a process where low-intensity electrical stimulation is repeatedly delivered to a brain region until it triggers an epileptic seizure (This model can also be created with a chemical agent). Electrodes are implanted into the limbic region via stereotaxy for electrical stimulation, typically using 60 Hz sinusoidal or biphasic square wave pulses lasting for 1 second. Stimulation is continued until a 5-stage seizure progression (mouth and facial clonus, head nodding, forelimb clonus, rearing, and rearing and falling) is observed (70).

Generalized Epileptic Seizures

Seizures in which epileptic activity starts simultaneously in both hemispheres of the brain are called generalized seizures. These seizures typically originate from deep regions of the brain and are characterized by prominent motor or behavioral symptoms often accompanied by loss of consciousness. There are many different subtypes of these seizures, which often begin at a young age, including tonic-clonic seizures, clonic seizures, myoclonic seizures, and atonic seizures (63).

Chemically-Induced Generalized Epileptic Seizure Models

Pentylenetetrazol is a GABA receptor antagonist convulsant commonly used in experimental models to induce tonic-clonic seizures. Behavioral changes (leg dystonia, generalized clonic, and clonic-tonic convulsions) in seizures initiated by intraperitoneal administration can be observed to examine various parameters such as onset time, duration, intensity, and frequency of seizures. In addition, the effectiveness of antiepileptic drugs in preventing or reducing seizure activity can also be evaluated (71,72). Furthermore, pentylenetetrazol, used in the kindling model as a chemical inducer, not only clarifies the convulsive effect but also allows the examination of behavioral and cognitive changes, thanks to long-term injections (73).

Flurothyl is a volatile liquid with convulsant vapor. Flurothyl, an antagonist of GABA receptors, is commonly used to induce neonatal generalized tonic-clonic seizures. During the experimental phase, animals are exposed to flurothyl in an airtight environment until tonic extension develops in their front and hind limbs, thus inducing seizures. When exposure to the agent is halted, the seizures also cease. This model provides information about epilepsy in the neonatal period (70,74).

Electrically-Induced Generalized Epileptic Seizure Models

The maximal electroshock seizures serve as a model where generalized tonic-clonic seizures are induced by delivering electroshocks through electrodes. Stimulation triggers seizures characterized by tonic extension of the forelimbs and hind limbs. The efficacy of drugs is often evaluated by measuring the duration of tonic maximum extension of the hind limb. Due to its ease of use, it is frequently employed in antiepileptic drug research, and phenytoin, discovered through this model, is used as an anticonvulsant medication (70).

SCHIZOPHRENIA AND MODELS

Schizophrenia is a complex psychiatric disorder characterized by symptoms such as detachment from reality, cognitive distortions, emotional abnormalities, and perceptual disturbances. These symptoms can significantly impair an individual's functionality and lead to difficulties in daily life. Although the pathophysiology of schizophrenia is not fully understood, abnormalities in brain regions like the frontal lobe, temporal lobe, and limbic system have been detected in brain imaging studies, and these have been associated with imbalances in neurotransmitters such as dopamine, glutamate, and serotonin systems (75,76). Schizophrenia symptoms are categorized as positive, negative, and cognitive symptoms. Positive symptoms include hallucinations and delusions, as well as poor insight, while negative symptoms consist of anergia, apathy, and social withdrawal, and cognitive symptoms include a decrease in working memory and executive function ability (76,77). The lack of specific biomarkers for schizophrenia hinders successful diagnosis and treatment. Despite the incomplete parallelism between animal models of schizophrenia and the human condition, attention is directed toward animal studies aimed at unraveling the pathophysiology of schizophrenia and devising treatment modalities. Within the spectrum of schizophrenia models lie neurodevelopmental models, pharmacological/physiological models, and genetic models (76).

Neurodevelopmental Schizophrenia Models

During the perinatal and neonatal processes, factors kind of stress (78) and viral infections (79), which affect brain development, increase the risk of schizophrenia, thus enabling neurodevelopmental investigations. Animal models are used to induce viral infections such as influenza virus (80), herpes simplex virus (81), and cytomegalovirus (82) during the embryonic period, thereby activating neuroinflammatory processes. Thus, schizophrenia symptoms and developmental processes are investigated. The stress induced by social isolation after weaning in animals leads to hyperlocomotor activity associated with schizophrenia and a decrease in cognitive functions in the adult stages. It is used in the research of new antipsychotics (83).

Pharmacological / Physiological Schizophrenia Models

The association of schizophrenia with the dopamine, glutamate, and serotonin systems has led to in-depth research on these pathways. In pharmacological/physiological models, substances that are generally effective on psychotropic drugs or neurotransmitters are often used. The dopaminergic hyperfunction model, dopaminergic hypofunction model, serotonergic model, and glutamatergic hypofunction model are examined in this category (84).

Dopaminergic Hyperfunction Model

The amphetamine used in the dopaminergic hyperfunction model reflects conditions associated with the positive symptoms of schizophrenia when administered intermittently at increasing doses (85).

Dopaminergic Hypofunction Model

The agent used in the rarely used dopaminergic hypofunction model is 6-OHDA. It is reported to be useful for modeling specific aspects of the negative symptoms of schizophrenia (86).

Serotonergic Model

The serotonergic model is a sustained substitute model following amphetamine administration, and it utilizes 2,5-dimethoxy-4-iodoamphetamine, an agonist of serotonergic receptors. Its use is not as prominent as other models due to the potential limitation of the therapeutic properties of neuropsychiatric drugs (87).

Glutamatergic Hypofunction Model

The agents used in the glutamatergic hypofunction model are phencyclidine, ketamine, and MK-801 (dizocilpine). Phencyclidine has a simple, non-time-consuming, and inexpensive administration process, and after administration, psychomotor hyperactivity and psychosis-like behaviors are immediately observed (88). Intraperitoneal administration of ketamine, an NMDA receptor antagonist, allows observation of negative and cognitive schizophrenia symptoms (89). Dizocilpine, representing hyperlocomotion and behavioral symptoms well, is mentioned in the literature as a suitable agent for mimicking acute psychotic symptoms of schizophrenia (90).

Genetic Schizophrenia Models

Genetic manipulations are used in animals to study the effects of specific genes associated with schizophrenia in humans. To understand the underlying biological mechanisms of schizophrenia and develop new treatment methods, genetic models such as DISC1 (disrupted in schizophrenia 1) models (91,92), NRG1 (neuregulin 1) models (93,94), COMT (catechol-o-methyltransferase) models (95,96), and 22q11.2 deletion syndrome models (97-99) are utilized. These genes are linked to an increased risk of schizophrenia and are utilized to model behaviors and neurodevelopmental disorders associated with the condition.

CONCLUSION

In conclusion, experimental animal models play a crucial role in elucidating the mechanisms underlying neurological diseases such as Alzheimer's, Parkinson's, MS, ALS, migraine, epilepsy, and schizophrenia. These models, mimicking important aspects of neurodegenerative diseases, hold a significant place in investigating disease mechanisms and developing potential treatment methods. Through collaboration among scientists, clinicians, and animal welfare advocates, we hope to harness the power of experimental models in the treatment of neurological diseases that affect a large portion of individuals and society.

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REFERENCES

1. Gowers WR. A manual of diseases of the nervous system. Philadelphia: P. Blakiston's Son & Co.; 1899.
2. Bansal PK, Deshmukh R. Animal models of neurological disorders: principle and working procedure for animal models of neurological disorders. Singapore: Springer; 2018.
3. Mucke L. Neuroscience: Alzheimer's disease. Nature. 2009;461(7266):895-7.
4. Piaceri I, Nacmias B, Sorbi S. Genetics of familial and sporadic Alzheimer's disease. Front Bosci (Elite Ed). 2013;5(1):167-77.
5. Rajmohan R, Reddy PH. Amyloid-Beta and phosphorylated tau accumulations cause abnormalities at synapses of Alzheimer's disease neurons. J Alzheimers Dis. 2017;57(4):975-99.
6. Shree S, Bhardwaj R, Kashish, Deshmukh R. Non-transgenic animal models of Alzheimer's disease. In: Bansal PK, Deshmukh R, editors. Animal models of neurological disorders: principle and working procedure for animal models of neurological disorders. Singapore: Springer Singapore; 2017. p.3-22.
7. Li X, Bao X, Wang R. Experimental models of Alzheimer's disease for deciphering the pathogenesis and therapeutic screening (Review). Int J Mol Med. 2016;37(2):271-83.
8. Sasaguri H, Nilsson P, Hashimoto S, Nagata K, Saito T, De Strooper B, et al. APP mouse models for Alzheimer's disease preclinical studies. EMBO J. 2017;36(17):2473-87.
9. Sahara N, Lewis J. Amyloid precursor protein and tau transgenic models of Alzheimer's disease: insights from the past and directions for the future. Future Neurol. 2010;5(3):411-20.
10. Kamat PK. Streptozotocin induced Alzheimer's disease like changes and the underlying neural degeneration and regeneration mechanism. Neural Regen Res. 2015;10(7):1050-2.
11. Pal A, Rani I, Pawar A, Picozza M, Rongioletti M, Squitti R. Microglia and astrocytes in Alzheimer's disease in the context of the aberrant copper homeostasis hypothesis. Biomolecules. 2021;11(11):1598.
12. Kim HY, Lee DK, Chung BR, Kim HV, Kim Y. Intracerebroventricular injection of amyloid-β peptides in normal mice to acutely induce Alzheimer-like cognitive deficits. J Vis Exp. 2016;(109):53308.
13. Kumar A, Dogra S, Prakash A. Neuroprotective effects of Centella asiatica against intracerebroventricular colchicine-induced cognitive impairment and oxidative stress. Int J Alzheimers Dis. 2009;2009:972178.
14. Kumar A, Seghal N, Naidu PS, Padi SS, Goyal R. Colchicines-induced neurotoxicity as an animal model of sporadic dementia of Alzheimer's type. Pharmacol Rep. 2007;59(3):274-83.
15. Savory J, Herman MM, Ghribi O. Mechanisms of aluminum-induced neurodegeneration in animals: Implications for Alzheimer's disease. J Alzheimers Dis. 2006;10(2-3):135-44.
16. Walton JR. An aluminum-based rat model for Alzheimer's disease exhibits oxidative damage, inhibition of PP2A activity, hyperphosphorylated tau, and granulovacuolar degeneration. J Inorg Biochem. 2007;101(9):1275-84.
17. Watt NT, Whitehouse IJ, Hooper NM. The role of zinc in Alzheimer's disease. Int J Alzheimers Dis. 2011;2011:971021.
18. Zhan X, Stamova B, Sharp FR. Lipopolysaccharide associates with amyloid plaques, neurons and oligodendrocytes in Alzheimer's disease brain: a review. Front Aging Neurosci. 2018;10:42.
19. Dickson DW. Neuropathology of Parkinson disease. Parkinsonism Relat Disord. 2018;46(Suppl 1):S30-S3.
20. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron. 2003;39(6):889-909.
21. Sharma N, Jamwal S, Singh S, Gill HK, Bansal PK. Animal models of Parkinson's disease. In: Bansal PK, Deshmukh R, editors. Animal models of neurological disorders: principle and working procedure for animal models of neurological disorders. Singapore: Springer Singapore; 2017. p.23-42.
22. Blandini F, Armentero MT, Martignoni E. The 6-hydroxydopamine model: News from the past. Parkinsonism Relat Disord. 2008;14(Suppl 2):S124-9.
23. Masilamoni GJ, Smith Y. Chronic MPTP administration regimen in monkeys: a model of dopaminergic and non-dopaminergic cell loss in Parkinson's disease. J Neural Transm (Vienna). 2018;125(3):337-63.
24. Smeyne RJ, Jackson-Lewis V. The MPTP model of Parkinson's disease. Brain Res Mol Brain Res. 2005;134(1):57-66.
25. Jagmag SA, Tripathi N, Shukla SD, Maiti S, Khurana S. Evaluation of models of Parkinson's disease. Front Neurosci. 2016;9:503.
26. Perier C, Bové J, Vila M, Przedborski S. The rotenone model of Parkinson's disease. Trends Neurosci. 2003;26(7):345-6.
27. Berry C, La Vecchia C, Nicotera P. Paraquat and Parkinson's disease. Cell Death Differ. 2010;17(7):1115-25.
28. Deng I, Corrigan F, Zhai G, Zhou XF, Bobrovskaya L. Lipopolysaccharide animal models of Parkinson's disease: Recent progress and relevance to clinical disease. Brain Behav Immun Health. 2020;4:100060.
29. Kalinderi K, Bostantjopoulou S, Fidani L. The genetic background of Parkinson's disease: current progress and future prospects. Acta Neurol Scand. 2016;134(5):314-26.
30. Gupta S, Kour S, Deshmukh R. Animal models of multiple sclerosis (MS). In: Bansal PK, Deshmukh R, editors. Animal models of neurological disorders: principle and working procedure for animal models of neurological disorders. Singapore: Springer Singapore; 2017. p.263-76.
31. Procaccini C, De Rosa V, Pucino V, Formisano L, Matarese G. Animal models of Multiple sclerosis. Eur J Pharmacol. 2015;759:182-91.
32. Bjelobaba I, Begovic-Kupresanin V, Pekovic S, Lavrnja I. Animal models of multiple sclerosis: Focus on experimental autoimmune encephalomyelitis. J Neurosci Res. 2018;96(6):1021-42.
33. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano PF, et al. A comprehensive review of amyotrophic lateral sclerosis. Surg Neurol Int. 2015;6:171.

34. Aktekin MR, Uysal H. Epidemiology of amyotrophic lateral sclerosis. Turk J Neurol. 2020;26(3):187-96.
35. Bonifacino T, Zerbo RA, Balbi M, Torazza C, Frumento G, Fedele E, et al. Nearly 30 years of animal models to study amyotrophic lateral sclerosis: a historical overview and future perspectives. Int J Mol Sci. 2021;22(22):12236.
36. den Hartog Jager WA. Experimental amyotrophic lateral sclerosis in the guinea-pig. J Neurol Sci. 1985;67(2):133-42.
37. Engelhardt JI, Appel SH, Killian JM. Motor neuron destruction in guinea pigs immunized with bovine spinal cord ventral horn homogenate: experimental autoimmune gray matter disease. J Neuroimmunol. 1990;27(1):21-31.
38. Engelhardt JI, Appel SH, Killian JM. Experimental autoimmune motoneuron disease. Ann Neurol. 1989;26(3):368-76.
39. de Munck E, Muñoz-Sáez E, Miguel BG, Solas MT, Ojeda I, Martínez A, et al. β-N-methylamino-l-alanine causes neurological and pathological phenotypes mimicking amyotrophic lateral sclerosis (ALS): The first step towards an experimental model for sporadic ALS. Environ Toxicol Pharmacol. 2013;36(2):243-55.
40. de Munck E, Muñoz-Sáez E, Miguel BG, Solas MT, Martínez A, Arahuetes RM. Morphometric and neurochemical alterations found in l-BMAA treated rats. Environ Toxicol Pharmacol. 2015;39(3):1232-45.
41. Wilson JM, Petrik MS, Moghadasian MH, Shaw CA. Examining the interaction of apo E and neurotoxicity on a murine model of ALS-PDC. Can J Physiol Pharmacol. 2005;83(2):131-41.
42. Tabata RC, Wilson JM, Ly P, Zwiegers P, Kwok D, Van Kampen JM, et al. Chronic exposure to dietary sterol glucosides is neurotoxic to motor neurons and induces an ALS-PDC phenotype. Neuromolecular Med. 2008;10(1):24-39.
43. Smitt PAES, de Jong JM. Animal models of amyotrophic lateral sclerosis and the spinal muscular atrophies. J Neurol Sci. 1989;91(3):231-58.
44. Harriott AM, Strother LC, Vila-Pueyo M, Holland PR. Animal models of migraine and experimental techniques used to examine trigeminal sensory processing. J Headache Pain. 2019;20(1):91.
45. Noseda R, Burstein R. Migraine pathophysiology: Anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. Pain. 2013;154(Supll 1):S44-53.
46. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annu Rev Physiol. 2013;75:365-91.
47. Lipton RB, Bigal ME, Steiner TJ, Silberstein SD, Olesen J. Classification of primary headaches. Neurology. 2004;63(3):427-35.
48. Eikermann-Haerter K, Moskowitz MA. Animal models of migraine headache and aura. Curr Opin Neurol. 2008;21(3):294-300.
49. Andreou AP, Summ O, Charbit AR, Romero-Reyes M, Goadsby PJ. Animal models of headache: from bedside to bench and back to bedside. Expert Rev Neurother. 2010;10(3):389-411.
50. Lukács M, Haanes KA, Majláth Z, Tajti J, Vécsei L, Warfvinge K, et al. Dural administration of inflammatory soup or Complete Freund's Adjuvant induces activation and inflammatory response in the rat trigeminal ganglion. J Headache Pain. 2015;16:564.
51. Sufka KJ, Staszko SM, Johnson AP, Davis ME, Davis RE, Smitherman TA. Clinically relevant behavioral endpoints in a recurrent nitroglycerin migraine model in rats. J Headache Pain. 2016;17:40.
52. Barrett CF, van den Maagdenberg AMJM, Frants RR, Ferrari MD. Familial hemiplegic migraine. Adv Genet. 2008;63:57-83.
53. Moskowitz MA, Nozaki K, Kraig RP. Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms. J Neurosci. 1993;13(3):1167-77.
54. Pradhan AA, Smith ML, McGuire B, Tarash I, Evans CJ, Charles A. Characterization of a novel model of chronic migraine. Pain. 2014;155(2):269-74.
55. Cano A, Fonseca E, Ettcheto M, Sánchez-López E, de Rojas I, Alonso-Lana S, et al. Epilepsy in neurodegenerative diseases: related drugs and molecular pathways. Pharmaceuticals (Basel). 2021;14(10):1057.
56. Poduri A, Lowenstein D. Epilepsy genetics--past, present, and future. Curr Opin Genet Dev. 2011;21(3):325-32.
57. Olney JW. Excitatory transmitters and epilepsy-related brain damage. Int Rev Neurobiol. 1985:27:337-62.
58. Taubøll E, Sveberg L, Svalheim S. Interactions between hormones and epilepsy. Seizure. 2015;28:3-11.
59. Vezzani A, Fujinami RS, White HS, Preux PM, Blümcke I, Sander JW, et al. Infections, inflammation and epilepsy. Acta Neuropathol. 2016;131(2):211-34.
60. Meisler MH, Kearney JA. Sodium channel mutations in epilepsy and other neurological disorders. J Clin Invest. 2005;115(8):2010-7.
61. Sarlo GL, Holton KF. Brain concentrations of glutamate and GABA in human epilepsy: A review. Seizure. 2021;91:213-27.
62. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51(4):676-85.
63. Fisher RS. The New Classification of Seizures by the International League Against Epilepsy 2017. Curr Neurol Neurosci Rep. 2017;17(6):48.
64. Löscher W. Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs. Seizure. 2011;20(5):359-68.
65. Ighodaro ET, Maini K, Arya K, Sharma S. Focal Onset Seizure. [Updated 2023 Sep 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
66. Prabhu S, Chabardès S, Sherdil A, Devergnas A, Michallat S, Bhattacharjee M, et al. Effect of subthalamic nucleus stimulation on penicillin induced focal motor seizures in primate. Brain Stimul. 2015;8(2):177-84.
67. Curia G, Longo D, Biagini G, Jones RSG, Avoli M. The pilocarpine model of temporal lobe epilepsy. J Neurosci Methods. 2008;172(2):143-57.

68. Lévesque M, Avoli M. The kainic acid model of temporal lobe epilepsy. Neurosci Biobehav Rev. 2013;37(10 Pt 2):2887-99.
69. Sutter R, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic drugs. Neurology. 2015;85(15):1332-41.
70. Raol YH, Brooks-Kayal AR. Experimental models of seizures and epilepsies. Prog Mol Biol Transl Sci. 2012;105:57-82.
71. Gholami M, Saboory E, Zare S, Roshan-Milani S, Hajizadeh-Moghaddam A. The effect of dorsal hippocampal administration of nicotinic and muscarinic cholinergic ligands on pentylenetetrazol-induced generalized seizures in rats. Epilepsy Behav. 2012;25(2):244-9.
72. JelenkoviĆ A, JovanoviĆ M, NinkoviĆ M, MaksimoviĆ M, BokonjiĆ D, BoŠKoviĆ B. Nitric oxide (NO) and convulsions induced by pentylenetetrazol. Ann N Y Acad Sci. 2002;962:296-305.
73. Becker A, Grecksch G, Thiemann W, Höllt V. Pentylenetetrazol-kindling modulates stimulated dopamine release in the nucleus accumbens of rats. Pharmacol Biochem Behav. 2000;66(2):425-8.
74. Isaeva E, Isaev D, Khazipov R, Holmes GL. Selective impairment of GABAergic synaptic transmission in the flurothyl model of neonatal seizures. Eur J Neurosci. 2006;23(6):1559-66.
75. Hany M, Rehman B, Azhar Y, Chapman J. Schizophrenia. [Updated 2023 Mar 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
76. Winship IR, Dursun SM, Baker GB, Balista PA, Kandratavicius L, Maia-de-Oliveira JP, et al. An overview of animal models related to schizophrenia. Can J Psychiatry. 2019;64(1):5-17.
77. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-An Overview. JAMA Psychiatry. 2020;77(2):201-10.
78. Ratajczak P, Kus K, Murawiecka P, Słodzińska I, Giermaziak W, Nowakowska E. Biochemical and cognitive impairments observed in animal models of schizophrenia induced by prenatal stress paradigm or methylazoxymethanol acetate administration. Acta Neurobiol Exp (Wars). 2015;75(3):314-25.
79. Carter CJ. Schizophrenia susceptibility genes directly implicated in the life cycles of pathogens: cytomegalovirus, influenza, herpes simplex, rubella, and Toxoplasma gondii. Schizophr Bull. 2008;35(6):1163-82.
80. Meyer U, Nyffeler M, Yee BK, Knuesel I, Feldon J. Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice. Brain Behav Immun. 2008;22(4):469-86.
81. Engel JA, Zhang J, Bergström T, Conradi N, Forkstam C, Liljeroth A, et al. Neonatal herpes simplex virus type 1 brain infection affects the development of sensorimotor gating in rats. Brain Res. 2000;863(1):233-40.
82. Rothschild DM, O'Grady M, Wecker L. Neonatal cytomegalovirus exposure decreases prepulse inhibition in adult rats: Implications for schizophrenia. J Neurosci Res. 1999;57(4):429-34.
83. Gaskin PL, Alexander SP, Fone KC. Neonatal phencyclidine administration and post-weaning social isolation as a dual-hit model of 'schizophrenia-like' behaviour in the rat. Psychopharmacology (Berl). 2014;231(12):2533-45.
84. Białoń M, Wąsik A. Advantages and limitations of animal schizophrenia models. Int J Mol Sci. 2022;23(11):5968.
85. Featherstone RE, Rizos Z, Kapur S, Fletcher PJ. A sensitizing regimen of amphetamine that disrupts attentional set-shifting does not disrupt working or long-term memory. Behav Brain Res. 2008;189(1):170-9.
86. Rezvani AH, Eddins D, Slade S, Hampton DS, Christopher NC, Petro A, et al. Neonatal 6-hydroxydopamine lesions of the frontal cortex in rats: Persisting effects on locomotor activity, learning and nicotine self-administration. Neuroscience. 2008;154(3):885-97.
87. Canal CE, Morgan D. Head-twitch response in rodents induced by the hallucinogen 2,5-dimethoxy-4-iodoamphetamine: a comprehensive history, a re-evaluation of mechanisms, and its utility as a model. Drug Test Anal. 2012;4(7-8):556-76.
88. Kalinichev M, Robbins MJ, Hartfield EM, Maycox PR, Moore SH, Savage KM, et al. Comparison between intraperitoneal and subcutaneous phencyclidine administration in Sprague-Dawley rats: a locomotor activity and gene induction study. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(2):414-22.
89. Jeevakumar V, Driskill C, Paine A, Sobhanian M, Vakil H, Morris B, et al. Ketamine administration during the second postnatal week induces enduring schizophrenia-like behavioral symptoms and reduces parvalbumin expression in the medial prefrontal cortex of adult mice. Behav Brain Res. 2015;282:165-75.
90. Shahzad S, Ahmad S, Madiha S, Khaliq S, Liaquat L, Sadir S, et al. Dizocilpine induced psychosis-like behavior in rats: A possible animal model with full spectrum of schizophrenia. Pak J Pharm Sci. 2017;30(Suppl 6):2423-7.
91. Pletnikov MV, Ayhan Y, Xu Y, Nikolskaia O, Ovanesov M, Huang H, et al. Enlargement of the lateral ventricles in mutant DISC1 transgenic mice. Mol Psychiatry. 2008;13(2):115.
92. Shen S, Lang B, Nakamoto C, Zhang F, Pu J, Kuan SL, et al. Schizophrenia-related neural and behavioral phenotypes in transgenic mice expressing truncated Disc1. J Neurosci. 2008;28(43):10893-904.
93. Karl T, Duffy L, Scimone A, Harvey RP, Schofield PR. Altered motor activity, exploration and anxiety in heterozygous neuregulin 1 mutant mice: implications for understanding schizophrenia. Genes Brain Behav. 2007;6(7):677-87.
94. Chesworth R, Downey L, Logge W, Killcross S, Karl T. Cognition in female transmembrane domain neuregulin 1 mutant mice. Behav Brain Res. 2012;226(1):218-23.
95. Janetsian-Fritz SS, Timme NM, Timm MM, McCane AM, Baucum Ii AJ, O'Donnell BF, et al. Maternal deprivation induces alterations in cognitive and cortical function in adulthood. Transl Psychiatry. 2018;8(1):71.

96. Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, et al. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proc Natl Acad Sci U S A. 1998;95(17):9991-6.
97. Bassett AS, Chow EW. Schizophrenia and 22q11.2 deletion syndrome. Curr Psychiatry Rep. 2008;10(2):148-57.
98. Saito R, Koebis M, Nagai T, Shimizu K, Liao J, Wulaer B, et al. Comprehensive analysis of a novel mouse model of the 22q11.2 deletion syndrome. Transl Psychiatry. 2020;10(1):35.
99. Sun Z, Williams DJ, Xu B, Gogos JA. Altered function and maturation of primary cortical neurons from a 22q11.2 deletion mouse model of schizophrenia. Transl Psychiatry. 2018;8(1):85.