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Experimental Models of Cognitive Impairments in Schizophrenia

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Cognitive impairments in schizophrenia are currently regarded as the third key group of symptoms, along with negative and productive psychopathological symptomatology. They are encountered in a majority of patients and determine the functional outcome of illness. This article presents a review of the literature on modeling of cognitive impairments in schizophrenia in animals. Pharmacological, ontogenetic, and genetic models are discussed, along with their mechanisms and characteristic manifestations, and methods of evaluating cognitive functions in rodents. There is now a multitude of methods for modeling individual cognitive impairments typical of schizophrenia patients in animals. These models are required for further development of psychopharmacology and studies of pathophysiological mechanisms, though none as yet allows the whole set and heterogenous structure of cognitive deficit seen in patients to be reproduced. Particular attention is paid to ontogenetic models which can be used to study risk factors for the development of schizophrenia and early interventions in states posing high risks of developing psychosis.

Keywords: experimental modeling, schizophrenia, cognitive functioning, cognitive deficit, preclinical investigations.

Cognitive impairments are currently regarded as the third key group of symptoms in schizophrenia, along with negative and productive psychopathological symptomatology. They are encountered in most patients. Clinically significant impairments in at least one cognitive function are seen in 90% of cases and in two or more functions in 75% of cases. Overall, cognitive deficit in schizophrenia is generalized in nature, though its structure can be discriminated in different patients [1]. Cognitive impairments interact closely with the functional outcomes of this disorder, though the search for substances correcting them has not yet met significant success [2]. While neuroimaging using functional MRI in patients identifies the activation features of brain areas typical of schizophrenia patients, it does not yield data on their cellular mechanisms. Cognitive impairments in people arise as a result of the actions of genetic factors, developmental anomalies, and external influences, and the search for cause-effect relationships is difficult, so modeling in animals allows these relationships to be studied and targets for potential therapeutic interventions to be sought [3].

Among the cognitive functions typically impaired in schizophrenia patients are attention, working memory, problem-solving behavior (executive functions), information processing speed, visual and verbal learning and memory, and social cognitive functions. While tests have been developed for evaluation of these cognitive functions in human clinical trials (MATRICS Consensus Cognitive Battery), analogous test batteries have also been proposed for preclinical studies of potential agents for improving cognitive functions in schizophrenia, for example, the CINTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) initiative [4–6].

Approaches to modeling of schizophrenia can be divided into 1) pharmacological, 2) development-associated, 3) mediated by structural brain damage, and 4) genetic [7]. According to Lazar et al. [9], Lipska and Weinberger [8] discriminate:

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– pharmacological models based on altered dopamine transmission;

– models of impaired nervous system depression:

models testing etiological theories (prenatal protein deprivation, pre- and perinatal infections, etc.),

models of impaired neurogenesis,

models of perinatal stress,

models of neonatal injury;

– models of glutamatergic hypofunction;

– genetic models.

The challenge of translational research and the correspondence of models to human disorders requires consideration of the concept of validity. Types of validity include: 1) construct validity, reflecting the correspondence of etiology; 2) face (a variant of content) validity, indicating the extent to which the model reflects symptomatology and the external manifestations of the disorder in animals; 3) predictive validity, determining the applicability of the model to predicting the efficacy of therapeutic substances in clinical conditions. Achievement of these criteria is a difficult task because of various factors including insufficient study of the etiology of many mental disorders and the inability to reproduce the whole range of symptomatology in distant phylogenetic relatives. To overcome these barriers at this stage, some authors have proposed the parallel use of two main groups of models: those with high predictive and face validity and those directed mainly to investigating the pathogenesis of disorders (with high construct validity) [10].

Wong and Josselyn [11] take the view that the causes of the limited effectiveness of models of schizophrenia overall and cognitive impairments in schizophrenia in particular may be: 1) that signs of mental illness may not be the simple sum of individual symptoms; 2) the inability to achieve equivalence between behavior in animals and psychopathological symptoms in humans; 3) that model animals may not suffer from the same diseases as humans. It should be added that in the epoch in which the development of these models started, cognitive impairments had not yet been identified as a separate and significant domain of schizophrenia, but at best were regarded as part of the negative symptomatology [2].

The aims of the present study were to describe and analyze selected pharmacological, development-associated, and genetic models of schizophrenia in rodents, with the accent on their applicability to studies of cognitive deficit in schizophrenia.

Methods of Assessing Cognitive Functions and Their Impairments in Different Models of Schizophrenia. *1. Attention.* The most widely used method of assessing attention in rodents is a test in which the animals must respond to the appearance of a light signal in one of five openings and respond to it by inserting the snout into this opening to receive a food reward (five-choice serial reaction-time task, 5-CSRTT, a test for the time taken to respond while tracking five stimuli). Apart from attention, this test evaluates the extent of impulsivity in terms of the number of responses before appearance of a signal and compulsive behavior in terms of the number of repeat responses. Modifications of this task include the test of maintaining constant productivity while tracking five stimuli (five-choice continuous performance test, 5C-CPT), which additionally includes trials without any light signal during which the animals must not react [12–14]. The effects of NMDA antagonists in relation to attention have been well studied: acute single doses decrease accuracy in the 5-CSRTT, while repeated dosage degrades results in the 5C-CPT test but not the 5-CSRTT test [15]. Damage to the ventral part of the hippocampus also leads to degradation of attention, which can be additionally impaired using phencyclidine. Early social isolation (after maternal feeding) and prenatal administration of methylazoxymethanol acetate (MAM) have no effects on performance of the 5-CSRTT. Mice overexpressing catechol-*O*-methyltransferase (COMT) take longer to perform this test, though after stabilization of the results their scores are no different from those of normal animals. Attention is not impaired on deletion of the NR1 subunit of the NMDA receptor in the prefrontal cortex (PFC) or hippocampus [16].

2. Working memory. The simplest methods of assessing working memory in rodents are the T and Y mazes, which are based on the tendency to alternate the choice of different sectors, though it should be noted that apart from memory, interest in novelty also contributes to the results of these tests. More complex tests, recommended by CINTRICS, are the operant delayed non-match-to-position (DNMTP) and the delayed match-to-position (DMTP) tests, in which the animal has to choose between two levers (left and right), whereby pressing the levers in the correct sequence yields a food reward (alternating pressing on different levers or consistent pressing of just one lever, depending on the test, is required). This test can also be run in an eight-arm maze in which the food reward is located in the previously (at the preliminary stage) unvisited sectors. Thus, the task for assessment of working memory is usually to remember information on the space in which the reward was obtained. The odor span task was developed to assess the volume of working memory – a new container tagged with a new odor is presented in each trial and the rat has to find the hidden reward by detecting the novel containers [17].

Impairments to working memory induced by single doses of NMDA antagonists are detected in the DNMTP task; those produced by repeated injection of phencyclidine are detected in the test with consistent alternation; those produced by prenatal administration of MAM and damage to the ventral part of the hippocampus are detected in the test with the eight-arm maze and the spontaneous alternation task. Activation of the mother's immune system affects performance of the DNMTP in adult rats. Impairments to working memory also occur in transgenic mice with the COMT-Val polymorphism, mutations in the dysbindin gene, and overexpression of D_2 receptors in the striatum.

Decreases in the volume of working memory are seen in rodents after administration of NMDA antagonists and in immunological models [16].

3. Problem-solving behavior. Problem-solving behavior reflects the executive functions required for control of behavior and its coordination; cognitive flexibility is among the executive functions and provides correction of behavior according to changing external conditions, thus supporting adaptation. Schizophrenia patients are characterized by lack of cognitive flexibility, which is apparent, for example, as perseveration in card sorting tasks in the Wisconsin test. Cognitive flexibility of rodents is assessed using the attention set-shifting test (ASST), in which the animal has to switch between two properties (for example, the odor and structure of a material covering a food-containing feeder) to make a correct choice of the location of the reward and receive food reinforcement. Cognitive flexibility in both humans and rodents is mediated by the PFC and its assessment yields valuable and clear information from the point of view of translational research. Apart from this test, another method for assessment of executive functions in rodents consists of a reversal learning task, which exists in a multitude of modifications, including tests for selection a maze sector or automated operant chambers [18–20].

Impairments to cognitive flexibility have been demonstrated in many models of schizophrenia, including acute, repeated, and postnatal doses of ketamine or phencyclidine in mice and rats, and in models linked with development, including the early social isolation method and genetic models (mice with the COMT-Val polymorphism or deletion of the NR2A NMDA receptor subunit) [16].

4. Information processing speed. Information processing speed is one of the basic characteristics of cognitive functioning and is often impaired in schizophrenia. This function can be evaluated in rodents using reaction time tasks requiring an operant response – pressing a pedal or placing the snout in an opening (more often in rats and mice, respectively). For example, the 5-CSRTT provides for assessment of the rapidity of correct responses, which decreases after single or repeated doses of NMDA antagonists or injury to the ventral part of the hippocampus, but not in models of isolation or use of MAM [16].

5. Visual learning and memory. While assessment of visual memory in humans uses a variety of tasks involving reproduction of complex geometrical figures or sets of separate figures, the rodent analog is the novel object recognition test, which is based on the innate interest of these animals in novelty. In this test, at the first, preparatory, stage, the animal is presented with the opportunity to explore two objects, and at the second stage one of these objects is replaced with an alternative, novel, object, which in normal conditions attracts more attention. The advantages of this method include the absence of any need for prolonged training and stress, while the drawbacks include the fact that many potential drugs demonstrate efficacy in rodents in this test but not in human clinical trials [21]. A modification was suggested to ensure a high level of similarity of the task with assessments of short-term memory in humans, using spatial cues and substitution not of the object but its location, demonstration of objects, both of which had previously been demonstrated but at different times (the object studied longer ago must be the more actively explored), etc. [22]. The CINTRICS initiative identified a task using associative memorization of pairs of objects and locations (touchscreen object-location paired-associate learning, PAL) as the most valid method of assessing long-term visual memory.

One of the most widely used methods for screening for the efficacy of compounds in relation to cognitive deficit in schizophrenia consists of using the compounds in impaired recognition of novel objects resulting from administration of NMDA antagonists. Recognition is also degraded after neonatal lesioning of the ventral part of the hippocampus, activation of the immune response in mothers, and early social isolation, as well as in genetic models [16].

6. Social cognitive functions. Impairments to cognitive functions significantly determine the functional outcome of schizophrenia and reflect the extent of daily functioning. Processing of emotional information in humans is assessed using the emotional recognition test, in which the subject is shown images with different facial expressions [23]. Social interaction tests are used in rats, for example measuring the duration of repeated communication or comparing its duration with two other rats – a previously familiar animal and one encountered for the first time. Social activity can also be evaluated by giving the rat a choice between being in sectors with and without access to another animal (the three-chamber test) [24]. Rats' sound signals depend on the social situation and can be divided into those with negative coloration (22 kHz, lower-frequency sounds which can be emitted when encountering a predator or in aggressive intermale interactions) and positively colored high-frequency signals (50 kHz) [25].

Impairments to social functioning have been demonstrated in models of acute and repeated administration of NMDA antagonists and exposure to phencyclidine in the neonatal period. Insufficiency of social interactions is also typical of other dysontogenetic models [26] and a number of transgenic mice, including those with impairments to the functioning of the *DISC1* gene [16]. For example, exposure to phencyclidine during development leads to stable impairments to social interactions, decreased motivation for the corresponding behvior in the place preference test; results obtained using antipsychotics in relation to social cognitive functions in these animals differ, while long-term effects were not obtained at all [16]. Models of intrauterine immune reactions led to impairments to social interactions, empathy, and vocalizations; the associated mechanisms remain to be studied [27].

Pharmacological Models. Among the pharmacological models the most important role is played by methods

based on blockade of glutamatergic NMDA receptors; the development of these methods started at the end of the 1980s. Acute, repeated, or early postnatal administration of NMDA antagonists (phencyclidine, ketamine, dizocilpine) led to the development of schizophrenic symptomatology in rodents, including cognitive impairments. Repeated administration of phencyclidine has been shown to lead to significant neurochemical and behavioral impairments, even long after administration ends [28]. One of the first pharmacological models of schizophrenia remains relevant – the amphetamine model, based on treating animals with the dopamine subtype 2 receptor agonist amphetamine (phenamine).

The amphetamine model of schizophrenia. Chronic administration of amphetamine to rodents leads to sensitization to its activatory effect and impairment of cognitive functions associated with the PFC (cognitive flexibility, attention), though it does not decrease interest in social interactions or impairment to spatial visual memory, i.e., hippocampal functioning [29–32].

We proposed an alternative dopaminergic model of schizophrenia using the antiparkinsonism drug Levodopa + Carbidopa (Nakom®). Administration of Levodopa + Carbidopa to rats has been shown to induce hypersensitivity to sound stimuli and stereotypical behavior and also to reduce social interactions and exploratory and movement activity in rats [33, 34].

Overall, models associated with activation mainly of the dopaminergic system are good in terms of reproducing positive symptomatology but no cognitive impairments, i.e., their face validity in relation to cognitive functioning is inadequate.

A functional model of schizophrenia. Administration of phencyclidine, an NMDA receptor antagonist, to healthy volunteers induces reversible psychotic symptoms, which are also accompanied by cognitive impairments, which is evidence that glutamate has a role in the pathogenesis of cognitive deficit in schizophrenia [35]. Acute, repeated, or perinatal administration of phencyclidine leads to impairments to memory, attention, and learning [36].

In rodents, acute administration of phencyclidine induces motor arousal, social detachment, and impaired cognitive functions, though subchronic or repeated administration (for example, twice daily for seven days) followed by seven days without use of phencyclidine) has greater translational value as it leads to recovery of motor function and motivation and reproduces effects in monkeys. These protocols induce impairments to working memory, attention, and information processing speed (in the 5-CSRTT task), visual memory (in the object recognition task), and problem-solving behavior (in mazes and cognitive flexibility tasks), i.e., deficit of at least five of seven of the major domains of cognitive functioning [37, 38]. However, it should be noted that impairments to prepulse inhibition settle quickly after termination of phencyclidine administration, which may be linked with its varying effects in different experimental conditions (administration of phencyclidine five days in a row with assessment of cognitive functions at three rather than seven days after the last dose in subchronic administration is required for detection of cognitive deficit [7, 39].

The mechanisms of induced cognitive impairments involve regulation of genes responsible for apoptosis – expression of the neurotoxic action of NMDA antagonists mainly in the frontal cortex, as well as decreases in the volume of the hippocampus and synaptic dysfunction [40]. Studies in a model using neonatal administration of the NMDA antagonist dizocilpine (MK-801) showed that cognitive impairments were linked with impairments to synaptic plasticity in the hippocampus, particularly field CA1 [41, 42], and that these could be prevented by environmental enrichment, which restores the brain-derived neurotrophic factor level in the hippocampus [43]. These are not unimportant data as they evidence the applicability of this model to studies of risk factors for the development of schizophrenia, i.e., its construct validity. In 2020, Kozela et al. showed that memory impairments in rats after repeated administration of ketamine are linked with changes in the transcription of a number of genes in astro- and microglial cells associated with synaptic plasticity and can be reversed with single doses of cannabidiol [44]. Unfortunately, the predictive validity of this model in relation to the treatment of cognitive impairments leaves much to be desired: in animals they can be reversed by second-generation antipsychotics, contradicting results from clinical trials [7]. Modifications were proposed to increase the validity of the model, with repeat administration of phencyclidine during the postnatal period instead of using adult animals [36]. Data on long-term cognitive impairments arising as a result of these manipulations, including social recognition, were variable.

The methionine model of schizophrenia was proposed by Wang et al. [45] on the basis of previously obtained data showing that prolonged administration of methionine induces behavioral reactions imitating certain of the symptoms of schizophrenia, such as social deficit and prepulse inhibition [46]. Modeling was by administration of the amino acid L-methionine (750 mg/kg) to male Swiss Webster mice aged 8–11 weeks, as two doses with a seven-day interval. The authors showed that administration of methionine induces behavioral reactions reflecting all three domains of schizophrenia symptoms, which can be reversed using the antipsychotics haloperidol and clozapine. Cognitive impairments in animals are seen in tests for social interactions, prepulse inhibition, novel object recognition, and learning ability. It should be noted that cognitive impairments in schizophrenia patients which can be assessed at the remission stage cannot be cured using antipsychotics, i.e., the predictive validity of the model in relation to cognitive disorders is inadequate.

Models of Developmental Impairments. Models of development-associated schizophrenia are produced by administration of mitotoxin (MAM) during pregnancy, mater-

nal immune activation, or lesioning of the ventral part of the hippocampus in the neonatal period. Epidemiological studies point to a link between infections during pregnancy and schizophrenia, so rodent models use maternal infections such as administration of lipopolysaccharide to induce immune responses of the type seen in responses to bacterial infections and administration of synthetic double-stranded RNA to simulate viral infections. Among development-associated models, there are also models including stress at early age, for example, maternal separation or social isolation after the maternal feeding period.

Administration of MAM on day 17 of pregnancy. MAM selectively degrades proliferation of neuroblasts in the central nervous system without influencing other organs, the number of pups in litters, or their body weight [47]. In rats, peak neurogenesis occurs on day 15 of pregnancy, so administration of MAM at this time leads to particularly severe changes in the brain (microcephaly, decreases in cortical volume to 70%). Milder pathology, reflecting the pathology of schizophrenia, can be modeled by administration of MAM on day 17 of pregnancy, when cortical neuron proliferation decreases. This yields more limited and selective reductions in the volumes of the neocortex and parts of the limbic system, including the PFC, entorhinal, and occipital cortex, and the hippocampus (the number of neurons in field CA2 decreases and cell morphology is altered in its other zones), though the ventricular dilatation characteristic of schizophrenia patients is absent [48].

Impairments to behavior change in accordance with the duration of MAM administration: its use on day 14 of gestation produces increased exploratory behavior in offspring, while use on day 15 produces nocturnal hyperactivity and administration on days 16–17 decreases activity (degradation of cholinergic neurons in the corpus striatum is replaced by death of dopaminergic neurons). Dopaminergic neurons in the ventral tegmental area in rats given MAM on day 17 of intrauterine development show increased spontaneous electrical activity, accompanied by increased movement activity in response to administration of amphetamine; these changes can be reversed by inactivation of the ventral part of the hippocampus. Increased activity in the latter area may be linked with the fact that administration of MAM leads to loss of GABAergic parvalbumin-containing interneurons, which is typical of schizophrenia patients, and this is evidence that the model has construct validity [49].

The face validity of this model in relation to cognitive symptoms is also good. The cognitive impairments in rats given MAM on day 17 of intrauterine development include impairments to cognitive flexibility (retraining in a Y-maze task, test for spatial memory) [49], direct spatial memory in adulthood [50], as well as novel object recognition and social cognitive functions, which is linked, inter alia, with decreased contents of oxytocin and its receptor in the PFC and oxytocin, vasopressin, and their receptors in the hypothalamus [51]. It is surprising that no pharmacological drugs have been tested in this model, i.e., its predictive validity remains unknown.

The maternal immune activation (MIA) model. The second model is produced by prenatal immune activation by systemic administration of the side product of viral replication polyriboinosine-polyribocytidylic acid (poly I:C, 4 mg/kg GD15) to pregnant females, inducing acute increases in cytokines, with investigation of the consequences of this immunization for the offspring [28]. This result of this action was that the offspring developed cognitive impairments: increases in the time taken to reach the platform in a retraining test in a T-maze and in a water maze [52]. Quite large amounts of evidence indicate that rodent and primate offspring exposed to MIA during pregnancy show the anatomical, neurochemical, electrophysiological, and behavioral changes seen in schizophrenia [54–57] and other developmental abnormalities, including autism [58]. Recent studies using this model have indicated changes in parvalbumin interneurons the perineuronal networks connected with them (structures of the extracellular matrix involved in structural and synaptic plasticity) in the prefrontal cortex and hippocampus, which are associated with cognitive impairments [59–61]. In addition, Yim et al., [62] demonstrated in mice that behavioral changes in offspring after MIA are based on impairments in the primary somatosensory cortex.

Social isolation after maternal feeding. Social deprivation in rat pups at young age leads to impaired brain development and behavioral changes at adult age, including impairments to the filtration of sensory information and cognitive impairments [63, 64]. Among the neurobiological changes in these animals linked with cognitive functioning and analogous to those seen in schizophrenia are reductions in the volume of the PFC [65], decreases in dendritic spine density [66], impairments to cytoskeletal morphology, decreases in the numbers of GABAergic interneurons (candelabra cells) in the hippocampus and PFC [67], and decreases in the density of subtype 1 dopamine receptors [68]. Among the cognitive impairments typical of this model are decreases in memory in the novel object recognition test [64] and cognitive flexibility, which are linked with impairments to connections between the PFC and the corpus striatum, but not visuospatial memory [69]. While this model is undoubtedly simple and accessible, its main drawback is the probability that behavioral effects are reversible as a result of repeated tactile contact with people and an excess of tests at the developmental stage [70], as well as dubious predictive validity in relation to correction of cognitive functions: for example, studies have shown that clozapine improves measures of cognitive flexibility in rats, which does not occur in humans [71]. Studies in recent years using this model have tested, for example, the effects of agonists of the glycine site of NMDA receptors, some of which can improve memory in rats without influencing hyperactivity [72].

Lesioning of the ventral part of the hippocampus in the neonatal period. Lesioning of the ventral part of the hip-

pocampus in rats, which corresponds to the anterior part of the hippocampus in humans, on day 7 of life by bilateral injection of ibotenic acid into this area leads to behavioral impairments in the postpubertal period, associated with impairments to the development of the medial PFC and nucleus accumbens, which in health receive marked innervation from the ventral part of the hippocampus [73]. Impairments to spatial and working memory arise on about day 25 of life, with decreased social activity and increased aggression on day 35; the whole spectrum of symptomatology, including elevated locomotor activity in response to stress, increased sensitivity of the reinforcement system (which does not correspond to the manifestations of schizophrenia), and increased sensitivity to dopamine and NMDA receptor agonists, etc., appears on about day 56 [74]. Deficit of spatial memory in these rats was shown to be linked with impaired functional connections between the hippocampus and the PFC, but not between the hippocampus and nucleus accumbens [75]. Decreases in cognitive flexibility, attention, and visual information processing are also linked with dysfunction the PFC, which reflects clinical reality [76]. The drawbacks of this method are its lethality, which reaches 15%, and the production of only unilateral lesioning of the hippocampus, which is seen in 30–33% of cases [7].

Overall, models using impaired development of the nervous system allow processes leading to the development of cognitive impairments in schizophrenia to be studied in the prodromal phase of illness and aid the potential development of prophylactic treatment to prevent cognitive impairments and progression of psychosis. An important aspect is the face validity of these models in relation to the time of development of pathology: long-term impairments arise in the postpubertal period, just as in schizophrenia patients.

Genetic Models. The contribution of the genetic factor to the pathogenesis of schizophrenia has long been studied and has become the basis for a number of animal models. Numerous candidate genes are associated with increased risk of developing schizophrenia, and most of these genes are linked with proteins related to neuronal plasticity, glutamatergic and dopaminergic transmission, and synaptogenesis [77, 78]. To date, the largest study of associations of the whole genome, including data from 37,000 patients and 113,000 controls, was published in 2014 [79]. A total of 108 schizophrenia-associated loci were extracted from this dataset. Many of these genes have been used to create animal models of schizophrenia, and new loci will allow ever more models to be created, primarily in mice [28].

Considering the value of genetic factors in the development of schizophrenia, corresponding models based on impairments to dopaminergic and glutamatergic transmission are also used. For example, COMT is an enzyme responsible for breaking down dopamine and polymorphisms in its gene (the variant with valine in place of methionine at codon 158) lead to increased activity and decreased dopamine levels in the PFC, apparent as cognitive impairments in mice bearing the corresponding mutation. Apart from this model, mouse strains overexpressing D_2 receptors in the striatum and deficiency of particular NMDA receptor subunits (NR1, NR2A, or NR2B) have been created [16].

The DISC1 gene (disrupted-in-schizophrenia 1). The *DISC1* gene, which encodes a synaptic protein required for successful formation of neurons in the pre- and postnatal period and takes part in producing synapses, neuron migration, and synaptic plasticity, was one of the first genes regarded as a cause of the development of schizophrenia. Seven transgenic mouse strains were created with impairments to *DISC1* gene functioning [80], and were characterized by dilated lateral ventricles, decreased cortical thickness and volume, and some by impairments to dendrite structure in the hippocampus. Data on behavioral deviations in these mice differed, though there is evidence for impairments to spatial working memory, social, cognitive, and executive functions with retention of spatial memory and successful recognition of novel objects [27].

The gene encoding dysbindin protein. Dysbindin is a synaptic protein regulating exocytosis, including the release of excitatory neurotransmitters. The gene is regarded as a candidate gene associated with the development of schizophrenia, and decreases in its expression are seen in both the dorsolateral PFC and hippocampus in patients. Mice homo- and heterozygous for the gene encoding dysbindin have a number of features reminiscent of the symptomatology of schizophrenia. Among the cognitive symptomatology are impairments to the filtration of sensory information and working and spatial memory, along with loss of interest in social interactions [7]. Assessment of the predictive validity of these models in relation to correction of cognitive impairments has yet to be carried out.

The gene encoding the protein reelin. Reelin is involved in forming synapses and CNS plasticity and its expression is decreased in the cerebellum, hippocampus, and frontal cortex of schizophrenia patients. While knockouts display significant functional impairments, spontaneous heterozygotic mutants have signs allowing them to be regarded as a model of schizophrenia, including, for example, decreases in dendritic spine density in the cortex of the frontal lobes and hippocampus; it was unexpected that these animals would be found not to have impaired cognitive functions associated with the PFC (cognitive flexibility, spatial and working memory, attention) [81].

Mouse with knockout of the cyclin D2 gene. This model was proposed for studies of an endophenotype typical of schizophrenia, i.e., hyperactivity of the anterior part of the hippocampus (elevated metabolism in field CA1), which predicts conversion from the prodromal phase to manifest psychosis in humans. This is also seen in animals after prenatal exposure to MAM. Considering the pathophysiological bases of cognitive impairments, animals with knockout of the cyclin D2 gene show decreased contents of parvalbumin-containing neurons in the hippocampus, especially field CA1, and part of the neocortex, but not the medial PFC. The

cognitive impairments include impaired cognitive flexibility and working memory, but not impaired attention; comparison of these facts widens the concept of the pathophysiological interactions from genetic factors through neurobiological characteristics to cognitive manifestations [82].

LgDel+/– mice. Deletion of part of chromosome 16 in mice produces an analog of 22q11.2 deletion syndrome in humans. These mice show reductions in the content and plasticity of parvalbumin-containing interneurons and their associated cognitive impairments, including deficit of executive functions and impairments to social behavior, which may be reversible using chemogenetic activation of parvalbumin-containing neurons or administration of subtype 2 dopamine receptor antagonists into the ventral part of the hippocampus or medial PFC during late adolescent age – a critical period of development. Thus, this model provides for testing methods of early interventions in states of high risk for the development of schizophrenia, which highlights it among other methods [83].

Conclusions. Thus, there are many methods of modeling the individual cognitive impairments typical of schizophrenia patients in animals, which are needed for the further development of psychopharmacology and studies of pathophysiological mechanisms, though none of these methods as yet allows reproduction of al the complex and inhomogeneous structure of cognitive deficit in patients. Particular attention is paid to ontogenetic models, for example, models with prenatal administration of NMDA antagonists and the LgDel+/– and cyclin D2 gene knockout genetic models, which can be used for investigating risk factors for the development of cognitive impairments in schizophrenia and early interventions in states of high risk for the development of psychosis, among which methods of cognitive remediation, among others, are currently used [84].

Analysis of the data presented here leads to the conclusion that the construct validity of most of the models considered is far from ideal, as they only provide fragmentary reflection of the pathogenesis of cognitive disorders and schizophrenia overall. Face validity is better satisfied: all models show individual cognitive impairments, though one of the problems may be a lack of attention to cognitive functioning and use of a limited set of tests for validation of models and in preclinical pharmacological studies.

Overall, despite the complex heterogeneous etiology of schizophrenia an the cognitive impairments seen in this condition, including the effects of environmental factors and genetic factors, animal models widen our knowledge of brain pathology in schizophrenia. Further improvements in models and in our understanding of the pathophysiology of cognitive impairments typical of schizophrenia will allow further identification of pathways for pharmacotherapy, improved testing of potential new pharmacological agents, and the development of more effective treatment methods.

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