Review Article
Experimental Models of Schizophrenia: A Review

ABSTRACT

Schizophrenia is a severe psychiatric disease that has a lifetime prevalence of 1% in most of the populations studied. The neuropathology and psychopathology of schizophrenia are still poorly understood. This is attributed to the paucity of adequate animal models. Schizophrenia is a disorder of the human brain. Consequently, the potency of animal models in schizophrenia research is limited to certain aspects of the disease. One of the most difficult aspects of modelling schizophrenia in animals has been the lack of a clear and explicit conceptual framework for this disorder. This review discussed drug-induced animal models of schizophrenia such as Ketamine (NMDA receptor antagonist), Phencyclidine (NMDA receptor antagonist) etc. It also discussed genetic animal models of schizophrenia which include but not limited to Schizophrenia susceptibility Genes, Neuregulin-1(NRG1), DAT gene, Zinc finger DHH-type3 containing 8 (ZDHHC8) and Dysbindin. It went further to discuss fetal models schizophrenia, postweaning social isolation and ended with In-Vitro animal models. The use of animal models to improve understanding of the neurochemical and structural CNS changes that precipitate development of schizophrenia, rather than a focus on treating the symptoms, is a prerequisite to enable new more effective therapeutic strategies to be developed. The complex and unclear nature of gene–gene and gene–environment interactions in the aetiology of schizophrenia means that the challenge to develop more reliable predictive animal models of this disorder, probably through using multiple early-life intervention, is still ongoing.

Keywords: Schizophrenia, Psychopathology, In-Vitro animal models, Gene-environment interactions, Postweaning social isolation, Dysbindin.

1. INTRODUCTION

Schizophrenia is a severe psychiatric disease that has a lifetime prevalence of 1% in most of the populations studied. Schizophrenia represents a highly complex psychiatric disorder characterised by three main categories of symptoms: positive symptoms (e.g., hallucinations, delusions and thought disorder), negative symptoms (e.g., deficits in social interaction, emotional expression and motivation) and disorganized/cognitive dysfunction (e.g., impairments of attention and working memory). The neuropathology and psychopathology of schizophrenia are still poorly understood. This is attributed to the paucity of adequate animal models. Schizophrenia is a disorder of the human brain. Consequently, the potency of animal models in schizophrenia research is limited to certain aspects of the disease [1,2] . Several studies postulate that the development of schizophrenia results from abnormalities in multiple neurotransmitters, such as dopaminergic, serotonergic, and alpha-adrenergic hyperactivity or glutaminergic and GABA hypoactivity. Genetics also plays a fundamental role - there is a 46% concordance rate in monozygotic twins and a 40% risk of developing schizophrenia if both parents are affected. The gene neuregulin (NGR1), which is involved in glutamate signalling and brain development, has been implicated, alongside dysbindin (DTNBP1), which helps glutamate release, and

catecholamine O-methyl transferase (COMT) polymorphism, which regulates dopamine function [6]. The dopamine (DA) hypothesis is the oldest neurochemical hypothesis of schizophrenia. In 1974 it originated from the pharmacological observations that certain neuroleptic drugs selectively inhibit the dopamine receptor 2 (DR2) whereas dopamine agonists, such as amphetamine mimicked schizophrenic symptoms in healthy individuals. Several years later, evidence was accumulating that the dopamine excess hypothesis only holds true for positive schizophrenic symptoms and could not explain the negative and cognitive symptoms. This led to a reformulation of the classical hypothesis. Today, the predominant view for dopaminergic involvement in schizophrenia suggests an imbalance between subcortical and cortical DA systems. Whereas subcortical systems could be hyperactive (due to hyperstimulation of DR2) and result into positive symptoms, negative symptoms and cognitive impairment might be due to cortical projection which are hypoactive (hypostimulation of DR1). Specific neurons in the prefrontal cortex that use the inhibitory neurotransmitter γ-aminobutyric acid (GABA) seem to be very important in the synchronization of neuronal activity which underlies working memory. Impaired working memory function is an important cognitive symptom in schizophrenia. Indeed, several post mortem studies revealed some indirect evidence by finding reduced expression of two isoforms of the enzyme glutamic acid decarboxylase (GAD). GAD 67 and GAD 65 convert Glutamate into GABA. GAD 67 was consistently found to be reduced, primarily in the prefrontal cortex and the temporal lobes, cingulate cortex and cerebellum. GAD 65 might be reduced in some of these areas and in others not. GABAergic interneurons play an important role in regulating glutamatergic, excitatory activity. Missing inhibitory regulation on glutamatergic pyramidal cells by GABA interneurons could perturb the neuronal activity in the prefrontal cortex, leading to a desynchronization of neuronal signalling which causes disrupted working memory functioning. Additionally, patients with schizophrenia show a 30 % to 50 % reduction in Reelin levels. This protein is expressed by GABA interneurons and regulates the migration of neurons. This indirectly indicates the reduction of GABAergic interneurons and the regulation of glutamatergic activity in schizophrenia [5]. Antipsychotic drugs have become the cornerstone of treatment for schizophrenia. The first-generation “conventional” antipsychotic drugs are high-affinity antagonists of dopamine D2 receptors that are most effective against psychotic symptoms but have high rates of neurologic side effects, such as extrapyramidal signs and tardive dyskinesia. The introduction of second-generation, or “atypical,” antipsychotic drugs promised enhanced efficacy and safety.2 The atypical agents differ pharmacologically from previous antipsychotic agents in their lower affinity for dopamine D2 receptors and greater affinities for other neuroreceptors, including those for serotonin (5-hydroxytryptamine1A, 2A, 2C, 3, 6, and 7) and norepinephrine (α1 and α2) [3]. Although numerous antipsychotic drugs are available to mitigate the symptoms of schizophrenia, the response rate to these drugs is lower than desired, they are slow-acting, and they often produce serious adverse side effects. While the etiology of schizophrenia is still poorly understood and the biochemical focus has been on dopamine and glutamate, multiple neurotransmitters and neuromodulators, including 5-hydroxytryptamine (5-HT), gamma-aminobutyric acid (GABA), glycine, D-serine, and neuroactive steroids, have been implicated in its pathophysiology. Based on the limited understanding of the biological origins of schizophrenia, there is a continued need for improved animal models of the disorder to better identify the origins of the varied symptoms and to develop and validate novel therapies. This article provides a brief overview of the models currently available and the complexities involved in attempting to develop and use such models [4]. Abnormalities in neurotransmission have provided the basis for theories on the pathophysiology of schizophrenia. Most of these theories center on either an excess or a deficiency of neurotransmitters, including dopamine, serotonin, and glutamate. Other theories implicate aspartate, glycine, and gamma-aminobutyric acid (GABA) as part of the neurochemical imbalance of schizophrenia. Abnormal activity at dopamine receptor sites (specifically D_2) is thought to be associated with many of the symptoms of schizophrenia. Four dopaminergic pathways have been implicated (Figure 1). The nigrostriatal pathway originates in the substantia nigra and ends in the caudate nucleus. Low dopamine levels within this pathway are thought to affect the extrapyramidal system, leading to motor symptoms. The mesolimbic pathway, extending from the ventral tegmental area (VTA) to limbic areas, may play a role in the positive symptoms of schizophrenia in the presence of excess dopamine. The mesocortical pathway extends from the VTA to the cortex. Negative symptoms and cognitive deficits in schizophrenia are thought to be caused by low

mesocortical dopamine levels. The tuberoinfundibular pathway projects from the hypothalamus to the pituitary gland. A decrease or blockade of tuberoinfundibular dopamine results in elevated prolactin levels and, as a result, galactorrhea, ammenorrhea, and reduced libido [7].

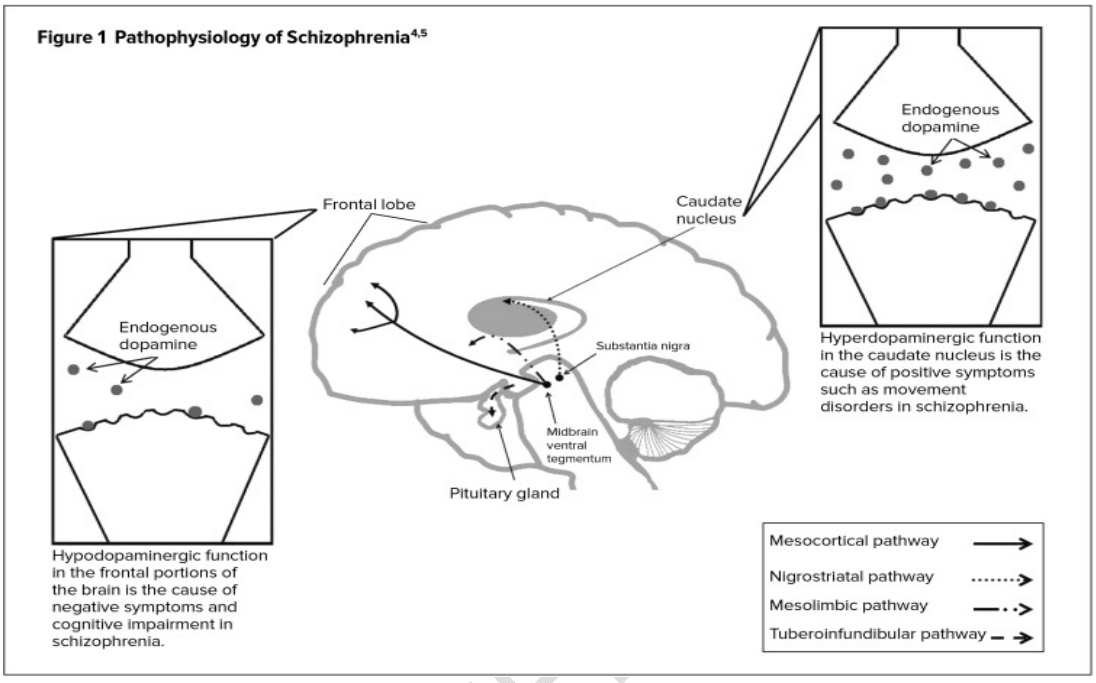

Figure 1 Pathophysiology of Schizophrenia

2. ANIMAL MODELS OF SCHIZOPHRENIA

Drug induced animal models of schizophrenia include:

- Ketamine (NMDA receptor antagonist)
- Phencyclidine (NMDA receptor antagonist)
- Amphetamine (dopamine D1/D2 receptor agonist)
- Apomorphine (dopamine D1/D2 receptor agonist)
- Capsaicin (vanilloid 1 (TRPV1) receptors agonist)
- Scopolamine (muscarinic receptor antagonist)
- MK-801(NMDA receptor antagonist)
- Methylazoxymethanol acetate (MAM)
- Neonatal ventral hippocampal ibotinic acid lesions
- Murine model of juvenile cortical lesions

2.1 Ketamine induced schizophrenia

In the early development of the central nervous system, changes in function of glutamatergic N-Methyl-D-aspartate (NMDA) receptors can possibly result in the development of psychosis, cognitive impairment and emotional dysfunction in adulthood [8.] Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that has been found to induce schizophrenia-type symptoms and is a potent and fast-acting anti-depressant [9.] **Acute** blockade of glutamate N-methyl-D-aspartate receptors (NMDAR) by ketamine induces negative and positive symptoms similar to those found in schizophrenia [10] along

with induction of biochemical and electrophysiological alterations [11.] Various findings suggest that chronic ketamine use may be associated with widespread disruption of white matter integrity, and white matter pathways between subcortical and prefrontal cortical areas may in part predict individual differences in dissociative experiences due to ketamine use [9] It has been observed that ketamine administration causes hyperlocomotion [8.] Previous research suggests that N-methyl-D-aspartate glutamate receptors (NMDA-Rs) have a crucial role in working memory (WM). Ketamine administration has been observed to reduce the spatial WM and brain activation [12]. It has been also suggested that ketamine leads to an abnormal distribution of PV-positive cells, which may be indicative of aberrant migratory activity and possibly related to cognitive deficits [13.]

2.2 Phencyclidine induced schizophrenia

Glutamate NMDA receptor antagonists, phencyclidine can induce a phenotype similar to that seen in schizophrenia [14.] In recent years revealed that the NMDA receptor antagonist phencyclidine (PCP) produces psychotomimetic effects in prefrontal cortex (PFC) along with hypoglutamatergic state [15.] Phencyclidine (PCP) may represent a valid model of the negative [16,] psychotic and cognitive symptoms [17] of schizophrenia. PCP administration has been observed to cause a long lasting reduction of total bone mass. PCP also causes behavioral abnormalities like hyperlocomotion and prepulse inhibition (PPI) deficits [18.]

2.3 Amphetamine induced schizophrenia

Amphetamine, a dopamine D1/D2 receptor agonist and dopamine releaser has been observed to induce hyperlocomotion [19.] AMP acts via presynaptic mechanisms to increase the release of a number of neurotransmitters, including noradrenaline and serotonin, as well as DA [20] AMP produces a wide variety of behavioral effects, including psychosis, locomotor hyperactivity, stereotypy, self-administration, and disruption of sensori motor gating in a variety of species [21] Previous studies have demonstrated that amphetamine (AMP) induces dopamine (DA) release in the prefrontal cortex [22] which further induces positive symptoms of schizophrenia like hyperlocomotionand hyperactivity. AMP disrupts latent inhibition and may be specific to processes involved in learning to ignore irrelevant stimuli, as locomotor hyperactivity [20.]

2.4 Apomorphine induced schizophrenia

Apomorphine, a dopamine D1/D2 receptor agonist has been observed to mimic schizophrenia-like behaviors that is stereotyped behavior, climbing behavior and increase in locomotor activity [23] along with disruption of prepulse inhibition (PPI) of the acoustic startle reflex [24] ·The PPI is used as a measure of sensorimotor gating, and significant deficits in PPI are observed in patients with schizophrenia and some other neurological disorders, which may contribute to sensory overload and related symptoms [25.] Apomorphine dose-dependently impaires recognition memory and causes cognitive deficit by producing DA dysfunction in brain [26.]

2.5 Capsaicin induced schizophrenia

Capsaicin acts on transient receptor potential vanilloid 1 (TRPV1) receptors, which are calcium-permeable ion channels gated by reduced pH and high temperature [27]. These receptors are located on a population of neuropeptide-containing unmyelinated primary afferent neurons which mediate nociception, axon reflex flare and neurogenic inflammation [28]. It has been observed that deficits in pain sensation are present in subjects with schizophrenia and their relatives [29], and vascular responsiveness is altered, as shown by a reduced niacin skin flare in many subjects with the disorder [30]. These observations suggested that capsaicin-sensitive primary afferent neurons might be abnormal in schizophrenia [31]. Subcutaneous administration of capsaicin induced hyperactivity, coronal brain sections had smaller cross-sectional areas, reduced cortical thickness, larger ventricles and aqueduct, smaller hippocampal area and reduced corpus callosum thickness. Neuronal density was increased in several cortical areas and the caudate

putamen, but not in the visual cortex. It is already reported neonatal capsaicin treatment of rats produces brain changes that are similar to those found in brains of subjects with schizophrenia [31].

2.6 Scopolamine induced schizophrenia

Scopolamine, a muscarinic receptor antagonist induces cholinergic impairments in auditory processing which further induces memory impairment by causing cognitive dysfunction, sensorimotor gating deficits and retention deficits which are seen in schizophrenia patients [32]. It evokes a range of cognitive and psychotic symptoms in healthy subjects that are commonly referred to as the "anti-muscarinic syndrome" resembling some clinical features of schizophrenia [33]. Scopolamine also induces PPI disruption has therefore been proposed as an antimuscarinic model of schizophrenia [34]. Previous studies have suggested that scopolamine induces PPI disruption stems mainly from a blockade of inhibitory muscarinic autoreceptors in the midbrain leading to an increase in cholinergic activity in dopaminergic cells of the ventral tegmental area (VTA) and substantia nigra (SN) [35].

2.7 MK-801 induced schizophrenia

Blockade of the NMDA receptor by the use of MK-801, a non-competitive NMDA receptor antagonist, during the early postnatal period has been proposed to be an experimental model which induces behavioural changes that mimic several aspects of schizophrenia [36]. MK-801 stimulates locomotor activity (LA), and to impair novel object recognition (NOR) also including signal detection behaviour [37].Various studies has reported that MK-801 induces increase of 5-HT and glutamate in the medial Prefrontal Cortex in brain which further causes learning and memory impairment [38].

2.8 Methylazoxymethanol acetate (MAM) induced schizophrenia

Methylazoxymethanol acetate (MAM) is a rodent model of schizophrenia. MAM rats are observed to exhibit reductions in specific components of auditory evoked potentials in the orbitofrontal cortex and an abolition of the graded response to stimuli of differing intensities indicating deficient intensity processing in the orbitofrontal cortex. Therefore, the ability for sensory input to modulate the ongoing background activity may be severely disrupted in schizophrenia yielding an internal state which is insufficiently responsive to external input [39]. Prenatal administration of methylazoxymethanol (MAM) impairs the sensorimotor gating process in adult but not adolescent animals and evokes changes in the methylation patterns of histone H3 during postnatal life [40].

2.9 Neonatal ventral hippocampal ibotinic acid (NVHLs) lesions induced schizophrenia

Neonatal ventral hippocampal lesions (NVHLs) in rats lead to reduced prepulse inhibition (PPI) of startle and other behavioral deficits in adulthood like neural processing deficits including reduced prepulse inhibition (PPI) of acoustic startle and impaired sensory processing that model abnormalities in schizophrenia patients. Lesions are produced by the administration of ibotenic acid into the ventral hippocampus. This model of VH-mPFC-NAC network dysfunction after NVHLs may have implications for understanding the neural basis for PPI- and related sensory processing deficits in schizophrenia patients [41]. NVHLs reproduce both sensory (N40) and sensorimotor (PPI) gating deficits exhibited in schizophrenia (Swerdlow et al., 2012). NVHLs display dopaminergic activity like increased dopamine prefrontal outflow and behavioral alterations consistent with a dysfunctional prefrontal cortex after puberty in schizophrenia [42].

2.10 Murine model of juvenile cortical lesions induced schizophrenia

A small experimental cryolesion to the right parietal cortex of juvenile mice causes late-onset global brain atrophy with memory impairments, reminiscent of cognitive decline, and progressive brain matter loss in schizophrenia. It has been shown that based on

comprehensive stereological analysis, that early unilateral lesion causes immediate and lasting bilateral increase in the number of microglia in cingulate cortex and hippocampus, consistent with a chronic low-grade inflammatory process [43]. Whereas the total number of neurons and astrocytes in these brain regions remain unaltered, pointing to a non- gliotic neurodegeneration (as seen in schizophrenia), the subgroup of parvalbumin-positive inhibitory GABAergic interneurons is increased bilaterally in the hippocampus, as is the expression of the GABA-synthesizing enzyme GAD67. Also the lesion causes a decrease in the expression of synapsin1, suggesting impairment of presynaptic functions/neuroplasticity [43].

3. GENETIC ANIMAL MODELS OF SCHIZOPHRENIA

There are several genetic animal models related to the neurodevelopmental hypothesis of schizophrenia. It has been reported that taken together, these animal models suggest that mutations in these genes may confer greater risk for the development of schizophrenia. They are:

3.1 Schizophrenia susceptibility Genes

Studies show the importance of genetic factors affecting susceptibility genes suggesting substantial genetic and phenotypic complexity. A notable finding is the overlap of susceptibility in schizophrenia for several individual risk alleles and for the polygenic risk. By contrast, genomic structural variation seems to play a large part in schizophrenia [44].

3.2 Neuregulin-1(NRG1)

NRG1 regulates various neurodevelopmental processes, including neuronal migration, myelination, synaptic plasticity, and neurotransmitter function [45]. NRG1 knockout mice exhibited hyperactivity in the novel open field test, enhanced aggressive behaviors in the social interaction test, and sensorimotor gating deficits in the PPI test [46]. The experience of psychosocial stress during adolescence may trigger further pathobiological features that contribute to the development of schizophrenia, particularly in those with underlying NRG1 gene abnormalities [47].

3.3 Dysbindin

Dysbindin (also known as dysbindin-1 or dystrobrevin-binding protein 1) was identified 10 years ago as a ubiquitously expressed protein of unknown function. In the brain, however, dysbindin has been proposed to associate into multiple complexes with alternative binding partners, and to play a surprisingly wide variety of functions including transcriptional regulation, neurite and dendritic spine formation, synaptic vesicle biogenesis and exocytosis, and trafficking of glutamate and dopamine receptors [48]. More recently, the role of Akt signaling in the functions of schizophrenia genes such as, dysbindin-1 has been reported. Thus, Akt deficiency may create a context permissive for the expression of risk-gene effects in neuronal morphology and function [49].

3.4 Neurotrophins such as brain-derived neurotropic factor (BDNF)

Neurotrophins such as brain-derived neurotropic factor (BDNF), play critical role in neuronal survival, synaptic plasticity and cognitive functions. BDNF is known to mediate its action through various intracellular signaling pathways triggered by activation of tyrosine kinase receptor B (TrkB) [50]. Higher BDNF levels were observed in subjects with the paranoid subtype of schizophrenia. Low serum BDNF levels were associated with reduction in hippocampal volume (HV) at the onset of schizophrenia [51].

3.5 Reelin

Reelin is a neuroprotein with crucial role during neurodevelopment and also in postnatal period. It regulates neuronal migration and positioning in developing neocortex and cerebellar cortex. Postnatally it participates in regulation of dendritic and axonal growth, synaptogenesis, neurotransmission and it contribute to synaptic plasticity necessary for

learning and memory functions. Role of Reelin seems to be rather complex, profound research gradually uncovers its further functions. Deficits of Reelin were detected in neuropsychiatric disorders such as schizophrenia [52].

3.6 NMDA receptor subunit 1 (NR1)

Based on functional hypotheses, gene modifications within five model systems are described which included glutamate (NMDA receptor subunit 1 (NR1)). N-methyl d-aspartate (NMDA) receptor subunit NR1 knockdown (NR1-KD) animals have a global reduction of NMDA receptors, enabling their use as a genetic model to study the role of NMDA receptors in the pathophysiology of schizophrenia. This targeted mutation results in a spectrum of altered behaviors that are similar to those induced by NMDA receptor antagonists, which have long been used to model schizophrenia in animals [53].

3.7 Proline dehydrogenase

The human PRODH gene has been shown to have unique roles in regulating cell survival and apoptotic pathway and there are multiple genetic links between schizophrenia and a deficit of proline dehydrogenase (PRODH) enzyme activity [54]. PRODH, encoding proline oxidase (POX), has been associated with schizophrenia through linkage, association, and the 22q11 deletion syndrome (Velo-Cardio-Facial syndrome).It has been shown in a family-based sample that functional polymorphisms in PRODH are associated with schizophrenia, with protective and risk alleles having opposite effects on POX activity [55].

3.8 Catechol-O-methyltransferase (COMT)

Catechol-O-methyltransferase (COMT), a key dopamine regulator in the brain, contains a co-dominant allele in which a valine-to-methionine substitution causes variations in enzymatic activity leading to reduced synaptic dopamine levels. Previous findings reaffirm the importance of baseline-dependency and suggest a subtle relationship between COMT genotype and baseline-stratified levels of sensory gating, which may help to explain the variability of cognitive abilities in schizophrenia populations [56].

3.9 D-amino acid oxidase activator (DAOA)

DAOA is a NMDA receptor mediated signalling gene which have the ability to modulate synaptic plasticity and glutamatergic transmission trough N-methyl-D-aspartate receptors (NMDARs). It might be differentially involved in schizophrenia susceptibility according to gender and gene interaction mechanisms [57]. DAOA has also been associated with schizophrenia-related characteristics such as frontal lobe volume change susceptibility to methamphetamine psychosis, response to antipsychotic treatment and progression of prodromal syndromes to first episode psychosis [58].

3.10 Dystrobrevin binding protein I (DTNBP)

It has been shown to affect personality traits intelligence, attention capacity, verbal fluency and several memory domains in both healthy subjects and patients with schizophrenia. In particular, negative symptoms in schizophrenia have been shown to be associated with several SNP of the DTNBP1 gene [59]. The effect of DTNBP1 on cognitive functions has been supposed to be mediated by the glutamate neurotransmitter system, acting via the prefrontal cortex [60]. Previous reports showed that DTNBP1 is involved in the pre-synaptic protein expression and release of glutamate and that schizophrenia patients have reduced DTNBP1 mRNA levels especially in the prefrontal cortex . It has been supposed that particular DTNBP1 alleles increase the risk for schizophrenia and affect cognitive functions mediated by the glutamate neurotransmitter system directly affecting the development, maturation, and adult function of the prefrontal cortex [60].

3.11 Reticulon-4 receptor

The reticulon-4 receptor is encoded by RTN4R, limits axonal sprouting and neural plasticity by inhibiting the outgrowth of neurites. Previous studies have implicated mutations in RTN4R in the development of schizophrenia, including the identification of several rare nonconservative missense mutations of RTN4R in schizophrenia subjects [61]. The gene maps to the 22q11.2 schizophrenia susceptibility locus and is thus a strong functional and positional candidate gene. A recent meta-analysis of several expression profiling studies revealed a ~10% decrease of *RTN4R* transcript levels in brains of individuals with schizophrenia [62].

3.12 Zinc finger DHH-type3 containing 8 (ZDHHC8)

ZDHHC8 is a putative palmitoyl-transferase (PAT), which belongs to a 23-member family of enzymes that share a conserved cysteine-rich signature catalytic domain (DHHC domain)[63]. The zinc finger DHHC domain-containing protein 8 (ZDHHC8) is located in the 22q11 microdeletion region and may contribute to the behavioral deficit and polymorphisms of ZDHHC8 have been reported to be associated with the risk of schizophrenia [64]. Individuals with 22q11.2 microdeletions have cognitive deficits and a high risk of developing schizophrenia.

3.13 Snap-25

Synaptosomal-associated protein of 25 kDa (SNAP-25) regulates exocytosis of neurotransmitters and is thought to be involved in the neuropsychiatric disorders such as schizophrenia. SNAP-25 knock-in (KI) mice behaviorally show severe deficits in working memory. Translational convergent functional genomic study demonstrates that SNAP-25 is one of the top 42 candidate genes for schizophrenia. Therefore, SNAP-25 KI mice also have strong construct validity for schizophrenia [65].

3.14 Complexin

Complexins play a critical role in the control of fast synchronous neurotransmitter release. Complexins is thought to stabilize and clamp the SNARE complex in a highly fusogenic state, thereby providing a pool of readily releasable synaptic vesicles that can be released quickly and synchronously in response to an action potential and the concomitant increase in intra-synaptic Ca^{2+} levels [66]. Abnormal expression of complexin 1 (Cplx1) is seen in several neurodegenerative and psychiatric disorders in which disturbed social behaviour is commonplace like schizophrenia. Decreases in expression of both complexin isoforms at the mRNA and protein level have been described in schizophrenia along with social deficits are seen in the disease where complexin expression is altered [67].

3.14 Netrin-1

The most characterized member of the netrin family of guidance cues, netrin-1, is an approximately 65-kDa secreted protein evolutionarily related to the extracellular matrix protein laminin. Netrin-1 is made up of 3 domains (VI, V and C) and an amino terminal signal peptide. It participates in the developmental organization of neural networks as a bifunctional cue, either attracting or repelling extending axons and dendrites [68]. Netrins are developmental cues that organize brain wiring, including the mesocorticolimbic DA circuitry. It has been observed that changes in netrin-1 receptor function could be one of the mechanisms producing enduring changes in DA function in nVH-lesioned animals in schizophrenia [69].

3.15 Slitrks

The Slitrk gene family is composed of six members (Slitrk1 - Slitrk6), which are highly expressed in the central nervous system (CNS). A recent series of human and mouse genetic studies have identified Slitrks as candidate genes involved in the development of neuropsychiatric conditions. Slitrk2 is another member of the Slitrk family that has recently been associated with a neuropsychiatic disorder, namely schizophrenia [70].

3.16 Glyoxalase 1

Glyoxalase 1 (GLO1) is an enzyme in the glyoxalase system, a metabolic pathway that detoxifies oxoaldehydes, particularly methylglyoxal (MG), a cytotoxic byproduct of glycolysis that induces protein modification (advanced glycation end-products, AGEs), oxidative stress, and apoptosis. Recently, findings have linked GLO1 to numerous behavioral phenotypes, including psychiatric diseases like schizophrenia [71]. Recently, two studies have suggested a role for GLO1 in schizophrenia. In a single schizophrenic patient, a frameshift mutation in GLO1 was correlated with reduced GLO1 enzymatic activity. In a separate study, schizophrenic patients were found to have increased AGE accumulation compared to control subjects [72], suggesting reduced GLO1 function.

3.17 DAT gene

The strength and duration of extracellular dopamine concentrations are regulated by the presynaptic dopamine transporter (DAT). Activation of D2autoRs increases DAT trafficking to the surface whereas disruption of this interaction compromises activities of both proteins and alters dopaminergic transmission 73. Candidate genes, relevance to dopaminergic neurotransmission with risk-alleles that are also considered in the etiopathogenesis of schizophrenia that have also been associated with schizotypy are the SLC6A3-gene (encodes for the dopamine active transporter, DAT) [74].

3.18 PTEN (Phosphatase and Tensin homolog on chromosome ten)

PTEN negatively regulates the activity of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, which in the central nervous system modulates synaptic plasticity, a mechanism underlying learning and memory processes. PI3K/AKT signaling contributes to both metabolic and cognitive activities [75]. Psychiatric problems like schizophrenia have been reported in patients and their motor-asymptomatic relatives with mutations in the recently detected PTEN [76].

3.19 Neuroligin

Neuroligins and neurexins function as synapse-organizing proteins, mediating cell adhesion and recruiting components to developing synapses [77]. Mice lacking neuroligin-1 exhibit selective deficits in NMDA receptor-mediated glutamatergic transmission, and additional knockdown of neuroligin-3 suggests that neuroligin-1 cooperatively contributes to AMPA receptor-mediated transmission [78]. Recent genetic studies implicated a number of synaptic cell adhesion molecules and their intracellular partners in both autism spectrum disorders (ASDs) and schizophrenia [79].

3.20 Major Histocompatibility Complex (MHC)

Various findings implicate the MHC region in hippocampal structure and functioning, consistent with the role of MHC proteins in synaptic development and function and showed independent, replicated evidence of association with delayed episodic memory. MHC region has the potential to provide insights into the pathophysiology of schizophrenia and cognition [80]. Chromosome 6p21-p22.1, spanning the extended major histocompatibility complex (MHC) region, is a highly polymorphic, gene-dense region. It has been identified as a susceptibility locus of schizophrenia. Many previous genetic studies reported an association between schizophrenia and locus 6p22-24, which includes the human major histocompatibility complex (MHC) region. Although some studies have found negative results, this locus, especially the MHC region, is still a high susceptibility factor in schizophrenia [81].

3.21 CACNA1C

The gene coding for the calcium channel, voltage-dependent, L type, alpha 1C subunit (CACNA1C) has been reported to be associated with schizophrenia [82]. It has been suggested that the CACNA1C genotype may account for some heterogeneity in the effects of hemisphere and diagnosis on amygdala volume when comparing patients with SZ and controls and point to disturbed Ca^{2+}-signaling as a plausible mechanism contributing to the pathology in patients with SZ [83]. It is involved in learning, memory and brain plasticity. Genetic studies reported evidence of association with the CACNA1C single nucleotide polymorphism rs1006737 with functional correlates of episodic memory encoding and retrieval, especially activations in the hippocampus [84].

3.22 KCNN3

KCNN3, encoding the small conductance calcium-activated potassium channel SK3, harbours a polymorphic CAG repeat in the amino-terminal coding region modify cognitive performance, in a large sample of schizophrenic patients. KCNN3 overexpression/channel hyperfunction, leads to selective deficits in higher brain functions [85]. In contrast, family-based studies claimed a connection between shorter CAG repeats and schizophrenia [86]. A meta-analysis concluded that overall, the CAG repeat length of KCNN3 does not augment the risk of schizophrenia, although a small but significant risk appeared associated with CAG repeats longer than the modal value [87].

3.23 HERG1

HERG1 (also referred as KCNH2 or Kv11.1) belongs to a particular subtype known as H or Kv11 subfamily of the voltage-gated potassium channels, along with HERG2 (KCNH6, Kv11.2) and HERG3 (KCNH7, Kv11.3) [88]. Cardiac HERG1 channels (human ether-a-go-go-related gene potassium channels 1) are blocked by antipsychotic agents. The HERG1 channel is encoded by HERG1 (KCNH2, Kv11.1) gene and is most highly expressed in heart and brain. The blockade of HERG1 channels by antipsychotics might also be significant for their therapeutic mode of action, indicating a novel mechanism in the pathogenesis of schizophrenia [89]).

4. FETAL MODELS OF SCHIZOPHRENIA

Maternal infection is a risk factor for schizophrenia and autism. In the case of schizophrenia, a wide variety of infections during pregnancy (viral, bacterial, and parasitic) are associated with increased risk for this disorder in the offspring. Summing these risks, Brown and Derkits1 estimate that 30% of schizophrenia cases would be prevented if infection could be averted in pregnant women [90]. The fact that such a diverse set of pathogens is associated with risk suggests that it is the mother's response to the infection that is critical for altering fetal brain development [91]. The proposal that maternal vitamin D deficiency could be a risk-modifying agent for schizophrenia was made 11 years ago [92]. This model describes structural brain changes such as ventriculomegaly baseline cognitive abnormalities in domains of attention and behavioural sensitivity to both N-methyl-D-aspartate antagonists and amphetamine meaning this model possesses strong face and construct validity [93]. Abnormal development of the fetal brain in utero is now thought to contribute to the etiology of many functional and behavioral disorders that manifest throughout life. While differences in genetic makeup contribute to this, an 'adverse' intrauterine environment is a strong modulator of abnormal development. It appears that prenatal inflammation is the greatest determinant of subsequent adverse outcomes for the offspring. A fetus is exposed to intrauterine inflammation in a woman with preterm labor and/or preterm birth or at any point in gestation when there evidence of chorioamnionitis (infection/inflammation of the fetal membranes). Inflammation is believed to be a leading cause of preterm birth which is defined as delivery at less than 37 weeks of gestation [94]. Intrauterine inflammation, documented by histological examination of the placenta, occurs in approximately 20% of all pregnancies. However, the prevalence of histological chorioamnionitis is dramatically increased in preterm births with approximately 85% of very preterm births demonstrating this finding [95]. It has been demonstrated that local intrauterine inflammation, sufficient to induce preterm birth, also causes significant fetal brain injury including loss of proligodendrocytes, a reactive astrogliosis and a significant disruption in

neuronal development [96]. It has been also further demonstrated that neurons injured in utero by inflammation can continue to induce injury in other neurons in a cytokine-independent fashion [96]. Placental insufficiency is another prenatal risk factor for schizophrenia which involves loss of blood flow to the developing fetus. Placental insufficiency is achieved experimentally in guinea pigs by ligation of the uterine artery and results in decreased PPI, enlargement of the lateral ventricles, reduced volume of the basal ganglia and septum, and reduced hippocampal BDNF [97]. Another set of prenatal and perinatal risk factors that have been well documented are obstetric complications. Obstetric complications have been well documented and linked to schizophrenia in several independent studies. Specifically, birth complications such as preeclampsia, cesarean section, and perinatal hypoxia are associated with an increased risk of schizophrenia [98].

5. ANIMAL MODEL OF VIRAL EXPOSURE

Epidemiological studies have linked prenatal exposure to viral and bacterial infections during early to mid-gestation with an increased risk for schizophrenia. Early studies focused on the link between influenza and schizophrenia, but other infectious agents such as toxoplasmosis and bacterial infections [99] have also been associated with the disease. To examine and identify the causal relationship between the neural and behavioral consequences of prenatal exposure and immune challenges, the effects of maternal challenges with influenza virus, as well as other viruses (e.g., borna disease virus, lymphocytic choriomeningitis, cytomegalovirus), and immune activating agents have been investigated in animal models [100]. These animal models involve exposure of pregnant rats or mice to an immune challenge with either influenza, the bacterial endotoxin lipopolysaccharide (LPS), or the viral mimic polyriboinosinic–polyribo-cytidilic acid (PolyI: C) during gestation and corresponding assessment of brain and behavioral effects in the offspring. Exposure of mice to influenza virus on gestation day 9 results in behavioral and brain abnormalities reminiscent of schizophrenia. Specifically, influenza-exposed mice showed deficits in PPI, decreased exploratory behavior, and decreased social interaction [101]. PolyI: C has been extensively studied in both rats and mice with varying outcomes based on the timing of exposure. Additional behavioral, neuropathological, and neurochemical studies further supported the prenatal Poly I: C model as a valid model of schizophrenia. Specifically, behavioral impairments in PPI, LI, reversal learning, novel object recognition, and working memory in addition to an increased sensitivity to dopamine agonists and glutamate antagonists are all observed in the offspring of mice and rats exposed to gestational PolyI: C [102]. Administration of the bacterial endotoxin LPS to mammalian species mimics the innate immune response that is typically seen after infection with gram-negative bacteria. Hence, neurodevelopmental animal models of schizophrenia have also utilized LPS as an infectious agent during gestation. Initial studies with prenatal LPS conducted by Borrell and Romero and colleagues administered LPS every other day throughout pregnancy [103].

6. POSTWEANING SOCIAL ISOLATION

Social withdrawal and isolation are common features of schizophrenia that have received recent attention because of the role social factors play in the risk for schizophrenia and conversion to psychosis in prodromal patients. Indeed, social functioning, among other factors, predicts conversion to psychosis in patients at a high risk of developing psychosis [104]. Because of this observation, coupled with social factors contributing to the etiology of schizophrenia, it was categorized as social isolation rearing, an epidemiological model in this review. Postweaning social isolation can be considered a model of a more proximal risk factor – social isolation. Social isolation rearing of rodents is a developmental model relevant to schizophrenia that involves more subtle environmental manipulations leading to profound effects on behavior and brain development. Social isolation rearing of young rodents provides a nonpharmacologic method of inducing long-term alterations reminiscent of several symptoms seen in schizophrenia patients [105]. Rearing animals in social isolation is particularly consequential for species that rely on social contact after being weaned from the mother. Specifically, isolation rearing deprives rodents of social interactions during a developmental period in which play behavior emerges. Thus, as a consequence of social isolation, animals are deprived of stimuli critical to behavioral and neurobiological development [106]. The lack of early social contact provides a model of the social isolation and social withdrawal which occurs early in the course of schizophrenia and predicts

conversion to psychosis in patients at a high risk of developing psychosis [104]. Behavioral and neurochemical changes after isolation rearing in rats provide a nonlesion and non-pharmacological model to enhance our understanding of the developmentally linked emergence of neural and behavioral abnormalities in schizophrenia patients [105].

7. IN-VITRO ANIMAL MODELS

Recent genetic evidence has implicated the bromodomain containing 1 gene (BRD1) with brain development and susceptibility to Schizophrenia. The BRD1 protein, which is essential for acetylation of histone H3K14, is a putative regulator of transcription during brain development and in the mature CNS and which is expressed in neurons may occur in a short and a long variant. However, several issues remain to be clarified for example regarding the regulation of the BRD1 gene upon environmental interventions [107]. Polyclonal rabbit antibodies were raised against three different BRD1 epitopes [108]. A recent study published by our group implicated the bromodomain containing protein 1 (BRD1) gene located at chromosome 22q13.33 with schizophrenia (SZ) that provided evidence suggesting a possible role for BRD1 in neurodevelopment. It has been shown that common SNPs in the BRD1 gene account for a substantial proportion of the genetic risk for schizophrenia in the population [109].

By modifying the genetic sequence packaged in these particles, one can deliver genetic instructions that modify expression of specific genes in neurons or glial cells without expressing other viral genes that harm these cells. In animals, this method provides a powerful tool to determine how changes in gene expression, within a particular brain region, modify brain function and behavior. Development of synthetic viruses can be used to manipulate gene expression within a specific brain region or a cell type [110].These in vitro models are use to induce schizophrenia in animal.

8. CONCLUSION

One of the most difficult aspects of modelling schizophrenia in animals has been the lack of a clear and explicit conceptual framework for this disorder. Despite the prevalence of the neurodevelopmental theory, it has remained difficult to develop specific hypotheses that can be tested experimentally. Implicit in this task is the importance of developing models that allow for both the confirmation and the falsification of specific hypotheses, a cardinal feature of scientific investigation that is sometimes lacking in modelling exercises. Accordingly, the most appropriate use of many of the current models is in the testing of narrowly focused hypotheses regarding specific aspects of the disorder. The neonatal VH lesion model holds promise in helping to elucidate the underlying molecular circuitry involved in the pathophysiology of schizophrenia. Clearly, the direct relevance of severe damage models to the subtle and widespread changes observed in the schizophrenic brain is questionable. But models of this sort may help to illuminate what has historically been one of the major difficulties with the neurodevelopmental hypothesis of schizophrenia, namely, explaining how brain abnormalities that occur in early life could result in the delayed manifestation of symptoms in adulthood. Moreover, these models allow for identification of pathways for pharmacotherapy and improved screening and validation of potential novel antipsychotics. With continued refinement of the models and our understanding of the pathophysiology of schizophrenia, the development of more rapidly acting therapies with reduced side effect profiles compared to the agents currently available is possible.

The use of animal models to improve understanding of the neurochemical and structural CNS changes that precipitate development of schizophrenia, rather than a focus on treating the symptoms, is a prerequisite to enable new more effective therapeutic strategies to be developed. The complex and unclear nature of gene–gene and gene–environment interactions in the aetiology of schizophrenia means that the challenge to develop more reliable predictive animal models of this disorder, probably through using multiple early-life intervention, is still ongoing.

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