Review Article

Pathophysiology and Animal Models of Schizophrenia

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Abstract

Animal models of schizophrenia are important for research aimed at developing improved pharmacotherapies. In particular, the cognitive deficits of schizophrenia remain largely refractory to current medications and there is a need for improved medications. We discuss the pathophysiology of schizophrenia and in particular the possible mechanisms underlying the cognitive deficits. We review the current animal models of schizophrenia and discuss the extent to which they meet the need for models reflecting the various domains of the symptomatology of schizophrenia, including positive symptoms, negative symptoms and cognitive symptoms.

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The Pathophysiology of Schizophrenia

Schizophrenia is a debilitating condition with a mean lifetime morbidity risk of approximately 1:100.[1] The current diagnosis of schizophrenia is based primarily on DSM IV. Symptoms of schizophrenia have classically been divided into 2 groups: the positive and negative symptoms. The positive symptoms are symptoms added on to normal behaviour or function. For example, psychotic symptoms such as hallucinations, delusions and other thought disorders. The negative symptoms are symptoms subtracted from normal behaviour or function. For example, social withdrawal, blunted affect and lack of motivation. In addition, those suffering from schizophrenia often exhibit other symptoms including aggression and varying degrees of cognitive dysfunction. In the past decade, it has been increasingly appreciated that cognitive deficits are also a core feature of the disorder present from before the onset of the first acute episode of positive symptoms.[2] As the cognitive deficits are strongly associated with functional disability and are largely refractory to current medications, the amelioration of cognitive dysfunction has become an important target for psychopharmacological research into improved pharmacotherapies for schizophrenia.[3]

The aetiology of schizophrenia and its pathophysiology are poorly understood. A meta-analysis of twin studies has estimated the heritability as high as 73% to 90%.[4] Family studies show that even the kin of patients who are unaffected by schizophrenia show some form of cognitive deficits.[5] It has been suggested that the inheritance is polygenic.[6,7] More than 30 genes have been reported to be linked with risk of developing schizophrenia.[8-10] However, abnormalities in these genes are not diagnostically specific for schizophrenia as many are also associated with other psychiatric disorders, especially bipolar disorder.[10] It has also recently become apparent that genomic structural rearrangements, including deletions and duplications, may be associated with schizophrenia.[11-15] In most cases it is unclear how the pathways in which these genes are expressed are interrelated, however a common feature among several of the implicated genes is a role in neurodevelopment, including axonal guidance and synaptogenesis. Genes receiving particular attention in recent years that have effects on neurite outgrowth include disrupted in schizophrenia (DISC) and Neuregulin-1 (NRG-1).[16]

That there is an environmental component to the aetiology of schizophrenia is also without doubt as identical twins show only 50% concordance.[17] Many hypotheses regarding environmental factors contributing to schizophrenia have been proposed. Many of these hypotheses rely heavily on epidemiological correlations, which has lead to some seemingly improbable associations that are hard to empirically test in animal models, an extreme example being the apparent historical association between the advent of high-heeled foot wear and increasing incidences of schizophrenia.[18] Among the more established environmental factor hypotheses is the idea that obstetric complications,

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including maternal infection during pregnancy.[19] Environmental influences may also lead to epigenetic modulation.[20]

The exact pathophysiology of schizophrenia is as yet unknown. The initial observation that the D2 receptor antagonism of typical antipsychotic drugs, such as haloperidol (Table 1), correlated with the doses required for clinical efficacy led to speculation that a hyperdopaminergic state existed in schizophrenia.[21] D2 receptor antagonism remains a key feature of more recent antipsychotics (e.g. clozapine, olanzapine and risperidone), although affinity for other receptors including 5-HT_{2A} and/or 5-HT_{2C} receptor antagonism is also a feature of many of these drugs (Table 1). Also amphetamine, a drug that causes increased dopamine release in the brain, was able to reproduce many of the psychotic symptoms associated with schizophrenia. Imaging studies also revealed that D2 receptor hyper-stimulation caused positive symptoms and D1 receptor hypo function led to negative symptoms further supporting the role of dopamine in the pathophysiology of schizophrenia.[22] Measures of the levels of dopamine also showed that, in patients with predominantly psychotic symptoms, dopamine levels were increased while in patients with mainly social withdrawal dopamine levels were decreased.[23] Thus rather than a straight forward hyperdopaminergic state, it seemed that an imbalance of either too little or too much dopamine cause the various symptoms. An excess of dopamine could also lead to increased risk of oxidative damage, which would be compounded by the lack of glutathione that has been found in the brains of schizophrenic patients.[24]

However, the symptoms that were relieved by typical antipsychotics were mainly the positive symptoms of hallucinations, delusion and disinhibition. These D2 antagonists had no effect on negative symptoms such as flattened affect and social withdrawal, or cognitive deficits that were also associated with schizophrenia. Administration of ketamine and phencyclidine, drugs that act as N-methyl-D-aspartate (NMDA) receptor antagonists in the human brain, leads to increase of positive and negative symptoms associated with schizophrenia.[25] This led to a hypoglutamatergic hypothesis of schizophrenia. Novel antipsychotic strategies in clinical development include activation of mGlu2/3 receptors,[26] which are known to form complexes with 5-HT_{2A} receptors.[27] More recently, it has been shown that ketamine can also induce cognitive deficits mirroring those seen in schizophrenia.[28-30] It was also observed that in patients with schizophrenia, there were decreased levels of glutamate, and increased levels of N-acetylaspartylglutamate (NAAG) and kynurenate, which in vivo reduce or antagonize NMDA receptor function.[25] In addition, it was observed that treatment with D-serine and glycine, both positive regulators of the NMDA receptor, augmented the efficacy of various neuroleptics in the treatment of positive, negative as well as cognitive symptoms of schizophrenia.[29,31]

Interestingly, the administration of ketamine to prepubescent children did not reproduce any of the symptoms of schizophrenia indicating that there could be a time course to the development of schizophrenia.[31,32] This perhaps also indicated the increased plasticity of the growing brain as compared to that of a mature adult brain. Studies also showed that there were morphological changes in the brains of the schizophrenic patients, mainly in the prefrontal cortex where there was a reduced volume as well as a decreased metabolic rate. There were also decreased dendritic spines, disarray of neuronal orientation and reduced synaptic proteins and these changes also appear to interfere with cortical networks.[23,25,33,34] Thus some form of neuronal damage was implicated in the pathogenesis of schizophrenia. A decrease in the levels of GABA and a compensatory increase in the expression of GABA receptors were also observed leading to speculation of the possibility of disinhibition of various neurotransmission systems by a decrease in the stimulation of GABA release leading to neurotoxicity.[25,34]

Thus the current theory of the pathogenesis of schizophrenia is that of a mixed origin with genes dictating

Table 1. Relative Affinities of Some Widely Used Antipsychotics for Selected Receptors

	D1	D2	D3	D4	5-HT_{2A}	5-HT_{2C}	α_1	H_1	mACh
Haloperidol	++	++++	++++	++++	+++	-	++++	+	-
Clozapine	+++	++	++	+++	+++	+++	++++	++++	++++
Olanzapine	+++	+++	+++	+++	++++	+++	+++	++++	++++
Quetiapine	++	+	+	-	++	-	++++	+++	-
Risperidone	++	++++	+++	+++	++++	+++	++++	+++	-
Ziprasidone	+	++++	++++	+++	++++	++++	+++	+++	-
Aripriprazole	++	++++	++++	++	+++	+++	+++	+++	-

Receptor affinities according to Rosenbaum et al[60]

dysfunction of various proteins that make up the NMDA receptor complex leading to NMDA receptor hypofunction. This NMDA receptor hypofunction leads to a disinhibition of the mesolimbic dopaminergic systems leading to the development of positive symptoms of schizophrenia, as well as neurotoxicity leading to morphological changes, and a decrease in mesocortical dopamine leading to negative symptoms as well as cognitive deficits[22,29,31] (Fig. 1).

The Mechanism of Cognitive Deficits in Schizophrenia

The mechanisms underlying the cognitive deficits in schizophrenia are currently the subject of much research. Given that administration of the NMDA receptor antagonists, phencyclidine (PCP) and ketamine, produces increases in positive and negative symptoms of schizophrenia as well as deficits in semantic memory, procedural learning, psychomotor speed/executive functioning, perceptual priming and free recall, working memory and source memory/episodic memory, it seems likely that NMDA receptor defects are responsible for the cognitive deficits observed in schizophrenia.

NMDA receptors are known to be necessary for long term potentiation (LTP) which is a critical step in learning and memory.[7,29,30,32] Defects in NMDA receptor systems would thus be expected to produce cognitive deficits. The fact that partial NMDA agonists, such glycine and D-serine, are able to augment neuroleptic efficacy in improving cognition in schizophrenic patients lends weight to the theory that NMDA receptor dysfunction leads to cognitive deficits.[25,31]

Dopamine has also been implicated in cognitive dysfunction in schizophrenia. Firstly it has been observed that schizophrenics have reduced prepulse inhibition (PPI) and latent inhibition (LI). Dopamine is postulated to be involved in gating of sensory input. With the imbalance in the levels of dopamine in the brain, the ability to filter out irrelevant stimuli leads to impaired PPI and LI as well as to cause deficits in learning, thus leading to cognitive fragmentation.[35] Dopamine is also involved in the control of motor activity as evidence by the motor impairments seen in Parkinson's disease, which could affect patient performance in motor task testing cognitive functions. Also given that many addictive drugs regulate dopamine release, it is postulated that dopamine is involved in a reward function. Thus without a proper gating function to sieve out irrelevant stimulus and the lack of a reward system when a task is completed, dopamine could well be involved in the cognitive deficits in schizophrenia.[36]

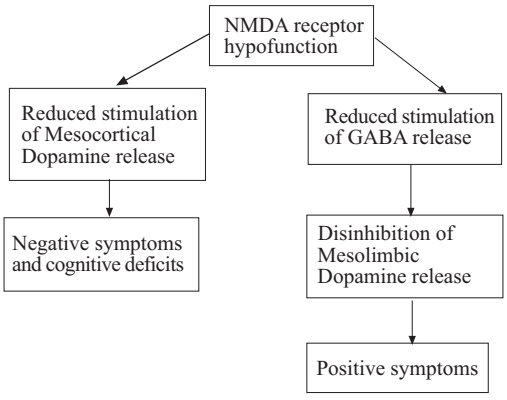

Fig. 1. A schematic representation of the association between NMDA receptor hypofunction and the positive and negative symptoms of schizophrenia.

In addition, the various structural deficits in the brain including decreased dendritic spines, disarray of neuronal orientation and reduced synaptic proteins, which were postulated to be due to neurotoxicity induced by NMDA receptor dysfunction, could lead to cognitive deficits. The disinhibition of neurotransmission is also likely to distort aspects of pyramidal neuron function, which is important for working memory.[34]

Animal Models of Schizophrenia

There are various animal models of schizophrenia, which seek to replicate the symptoms that are observed in human schizophrenics (Table 2). However, it has been difficult to find a particular model that is able to completely replicate all the symptoms observed in humans. In animal models, hyperactivity, hyper-locomotion and stereotypic behaviour is considered as representative of positive symptoms in humans. Social withdrawal is considered to be the animal version of negative symptoms. Deficits in sensorimotor gating and processing of salience are tested by measuring PPI and LI. Cognitive deficits are often tested by various maze tasks.

Amphetamine elevates dopamine release in rats and mice and manages to reproduce the positive symptoms of schizophrenia such as hyperactivity and behavioural disinhibition, also PPI and LI are reduced in animals treated with amphetamine.[37] This models the PPI and LI deficits in humans with schizophrenia.[38-40] However amphetamine treated models are not able to induce social withdrawal which corresponds to lack of negative symptoms. Thus amphetamine models while adequate in replicating positive symptoms of schizophrenia is not suitable as a complete model of schizophrenia. Dopamine transporter knockout mice (DAT-KO) displayed hyperactive behaviour, stereotypic behaviour, and cognitive impairments in spatial cognitive tests. They also show significant deficits in sensorimotor gating. The DAT-KO mice do not show any social withdrawal symptoms, and they are thus unable to replicate the negative symptoms of schizophrenia.[41]

Table 2. Summary of Commonly Used Animal Models

Model	Positive symptoms	Negative symptoms	Cognitive deficits	Limitations
Amphetamine models	+	-	+	Do not reproduce negative symptoms
DAT-KO	+	-	+	Do not reproduce negative symptoms
NVH lesion models	+	+	+	Brains of human schizophrenics do not show significant lesions
NR1 deficient models	+	+	+	Humans with schizophrenia do not show significant decrease of NMDA receptor expression
Adult ketamine/PCP models	+	+	+	Does not address the hypothesis that schizophrenia may have a developmental basis

Neonatal Brain Lesion models of schizophrenia have been postulated and tested. Neonatal ventral hippocampal (NVH) lesions in rats have led to abnormalities in early adulthood that could mimic those found in schizophrenia. At postnatal day 35, NVH rats exhibited reduced social behaviour compared to controls, also at postnatal day 56; they showed motor hyper responsiveness to stressful stimuli as well as increased stereotype behaviour. They also showed increased sensitivity to NMDA antagonist PCP and dizocilpine, deficits in PPI and latent inhibition, impaired social behaviour and deficits in working memory. These deficits are normalised by many of the antipsychotic drugs. Also the fact that the symptoms only appear at early adulthood coincides with observations in humans that ketamine induces no deficits in children but causes schizophrenic symptoms in adults. However, the human brain does not show any signs of a comparable lesion and thus while these NVH models or rats may be used to test the efficacy of antipsychotic drugs, it is not a really accurate model of schizophrenia.[41-43] For this reason, the maternal infection model, which can also produce working memory deficits, may be preferable.[44]

NMDA receptor antagonist models of schizophrenia often utilise ketamine, dizocilpine or PCP.[45] In laboratory animals, PCP and ketamine as well as other NMDA antagonists produce impaired cognitive function such as deficits in performance in spatial alternation tasks as compared to controls. Administration of NMDA antagonist also had a greater impact on further impairment of spatial impairment in rats treated perinatally with PCP compared to control rats treated with saline, as well as altered social behaviour, hyperactivity and sensory gating deficits.[46,47] Mutant mice which express 8% of the normal NMDA receptor levels exhibited hyper locomotion, stereotypic behaviours as well as social withdrawal, these observations correlated with the human versions of positive symptoms and negative symptoms. The hyperlocomotion and stereotypic behaviours were attenuated with haloperidol as well as clozapine, while the social withdrawal could be treated with clozapine.[48]

Other genetic mouse models for schizophrenia have been developed but as yet have been less widely adopted for the screen of novel therapeutic candidates. A number of mice with expressing mutant DISC1 or with disrupted expression of DISC1 have been developed and show considerable promise, especially in the modelling of cognitive dysfunctions.[49-52] The heterozygous reeler mouse, which shows reduced reelin expression and GABAergic neurotransmission in the prefrontal cortex, has been proposed as a model for schizophrenia and shows deficits in reversal learning that appear to be related to dysfunction in visual attention.[53] Trace Amine 1 receptor knockout mice show impaired PPI and increased sensitivity to amphetamine.[54] Stable tubule-only polypeptide (STOP) null mice show deficits in memory tasks.[40] One of the most interesting models from the perspective of facilitating screening for the efficacy of novel pharmacological agents is the *chakragati* (*ckr*) mouse insertional mutant.[55] This mouse show a spontaneous circling response that can be reduced by antipsychotic drug treatment[56] and so provides an easily measured readout of antipsychotic drug actions. The mouse also shows hyperactivity modeling positive symptoms[57] social withdrawal modeling negative symptoms[58] and deficits PPI and LI modeling abnormal sensorimotor gating and processing of salience.[59] However, it has not yet been determined whether this model exhibits cognitive deficits in working memory and executive function.

Conclusion

With many animal models of schizophrenia suggested and tested, the question remains which animal model would be the most appropriate as a model of the human disease. Amphetamine models as well as DAT-KO animal are not capable of reproducing the negative symptoms of schizophrenia thus it is not suitable as a model of the human

disease. NVH models do reproduce the majority of the symptoms that humans exhibit, however the drawback of the NVH lesion model is that there is obvious damage to the brain of the animals. This damage is not observed in humans with schizophrenia. Thus, maternal infection models may be preferable.

While mice with decreased expression of the NMDA receptor are capable of reproducing both positive and negative symptoms, test on cognition using this model has not been done. Theoretically, with a decreased expression of NMDA receptors, there should be cognitive deficits; however, humans with schizophrenia do not exhibit decreased NMDA receptor expression. Thus while promising; this model is not entirely suitable as a representation of the human disease.

Currently, the most representative animal model of schizophrenic dysfunction seems to be those involving the administration of NMDA antagonist. These animals exhibit the classic triad of schizophrenic symptoms, positive symptoms, negative symptoms as well as cognitive deficits. These symptoms parallel those observed in healthy humans infused with ketamine. Thus animals which were treated with NMDA antagonists could be used as a model of several aspects of schizophrenic dysfunction in humans. Alternatively, the model may be selected that best represent the particular aspects of the disease required for a specific experiment. The genetic mouse models show particular promise and are likely to be increasing adopted for screening new drug candidates. For higher-throughput drug screening, models such as the circling *ckr* mouse model that allow for robust behavioural readout may be advantageous.

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