Review Paper
Examen critique

Animal models of schizophrenia: a critical review

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Current research into schizophrenia has remained highly fragmented, much like the clinical presentation of the disease itself. Differing theories as to the cause and progression of schizophrenia, as well as the heterogeneity of clinical symptoms, have made it difficult to develop a coherent framework suitable for animal modelling. However, a number of limited animal models have been developed to explore various causative theories and to test specific mechanistic hypotheses. Historically, these models have been based on the manipulation of neurotransmitter systems believed to be involved in schizophrenia. In recent years, the emphasis has shifted to targeting relevant brain regions in an attempt to explore potential etiologic hypotheses. The specific animal models developed within these frameworks are described in this review. Emphasis is placed on the critical evaluation of currently available models because these models help to shape the direction of future research.

La recherche en cours sur la schizophrénie demeure très fragmentée, tout comme la manifestation clinique de la maladie même. Comme les théories sur la cause et l'évolution de la schizophrénie diffèrent et compte tenu de l'hétérogénéité des symptômes cliniques, il est difficile d'établir un cadre cohérent qui convient à une modélisation animale. On a toutefois mis au point des modèles animaux limités pour explorer diverses théories relatives aux causes et vérifier des hypothèses mécanistes précises. Sur le plan historique, ces modèles reposent sur la manipulation des systèmes neurotransmetteurs que l'on croit impliqués dans la schizophrénie. Depuis quelques années, on cherche plutôt à cibler des régions pertinentes du cerveau afin d'explorer des hypothèses étiologiques possibles. On décrit dans cette critique les modèles animaux précis mis au point dans le contexte de ces cadres. On met l'accent sur l'évaluation critique des modèles actuellement disponibles parce qu'ils aident à orienter la recherche future.

Introduction

Differing theories as to the origin and course of schizophrenia are as old as the clinical identification of the disorder itself. Indeed, Kraeplin's original description more than a century ago of "precocious dementia," closely followed by Clouston's concept of "developmental insanity," form the basis of the current neuro-

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degenerative and neurodevelopmental theories of schizophrenia, respectively. Although extensively redefined, these fundamentally contrasting principles remain as hotly debated today as ever. The past several decades have also brought tremendous advances in neuropharmacology that have extended our understanding of schizophrenia at both a neurochemical and neuroanatomical level. However, despite the advent of sophisticated analysis and imaging tools, or perhaps even because of them, our ability to synthesize a coherent model of schizophrenia remains as elusive as ever. Although there have been several attempts in recent years to unite these divergent frameworks into a unified theory,[1–6] much of the current research on schizophrenia remains highly fragmented.

The purpose of this article is to critically review many of the animal models of schizophrenia presently under investigation, as a prelude to further research. The scientific exploration of human disorders has necessitated the development of suitable, if limited, animal models. Psychiatric conditions are no different in this regard and remain perhaps the most heavily modelled of all human conditions.[7] This may at first seem surprising, given the lack of convincing evidence that any animal, with the probable exception of nonhuman primates, suffers from an identifiable mental illness. However, the prevailing modern view of neuroscience,[8] for which there is extensive experimental evidence, is that clinically relevant psychiatric conditions have at their source a primary dysfunction of neuronal systems. Given that disruptions in neuronal activity can affect both human and animal behaviour, animal models can be developed to test various predictive and causative theories that cannot be addressed in human studies. Particular emphasis has been placed on pharmacological models in this review because they have played a dominant role in focusing experimental research efforts in this field.

There are several potential difficulties associated with modelling schizophrenia in animals, including the standard caveat of faithfully reproducing what is generally perceived to be a cognitive disorder in less cognitively developed animals. More specifically, heterogeneity in clinical symptoms, course of the disorder and potential causative factors represent significant obstacles to model building. Patients typically experience a combination of symptoms, often divided into positive (e.g., hallucinations, delusions, thought disorganizations), negative (e.g., loss of motivation, affective blunting, alogia, social withdrawal) and cognitive (e.g., deficits in attention, memory and executive functions).[9–11] Many patients with schizophrenia also experience a wide range of catatonic phenomena such as catalepsy, stereotypies, echopraxia and unusual posturing and mannerisms.[11,12] Similarly, the course and outcome of schizophrenia are remarkably variable, with only a minority of patients following a chronic, deteriorating course,[13–16] despite enduring symptoms or functional deficits in most patients.[13,14] Finally, a variety of environmental and genetic susceptibility factors[17–19] have been proposed as potential causative agents.

Accordingly, current animal models of schizophrenia are not intended to serve as the complete animal equivalent of the human disorder. Rather, they are often designed to test specific causative or mechanistic hypotheses regarding schizophrenia. The models can be validated on the basis of how well their performance in a given test predicts the performance of humans with schizophrenia and on whether the model provides a sound theoretical rationale. These characteristics are referred to as predictive and construct validity, respectively, and are quite variable in models of psychiatric disorders. How accurately an animal model reproduces the symptoms of a human condition, known as face validity, is clearly the most difficult to establish for schizophrenia. However, as will be discussed later, a variety of behavioural correlates in animals may serve as approximate markers for psychiatric disturbances in humans.

For the purposes of this review, we define "animal model" as an experimental manipulation that elicits behavioural or neurochemical changes that can be related to schizophrenia using the criteria for predictive, construct and face validity. Measures that are reliable indicators of schizophrenia in humans, such as altered prepulse inhibition of startle (PPI) and latent inhibition (LI), are therefore not considered animal models in their own right, although they have sometimes been referred to as such.[20,21] Rather, we consider these to be important features in establishing the validity of animal models. For those seeking a more detailed discussion of the implications of recent models and the appropriateness of modelling schizophrenia in general, the reader is referred to the recent review by Lipska and Weinberger.[6]

Pharmacologic models

Pharmacologic animal models of schizophrenia are based on our current understanding of the alterations

in various neurotransmitter systems. As such, these models generally have some degree of construct validity, although it is extremely limited given our poor understanding of the fundamental basis of thought and cognition. Also, as expected, these models suffer from limited face validity. In contrast, predictive validity, although somewhat variable, is often fairly good because most pharmacologic models involve the administration of drugs that induce or exacerbate schizophrenic symptoms in humans.[22] Perhaps the best known pharmacologic model, which is based on the dopamine hypothesis of schizophrenia, involves amphetamine administration.[23,24]

Dopamine

The dopamine (DA) hypothesis of schizophrenia proposes that dysfunction in DA neurotransmission is the underlying cause of the symptoms of the disorder. Specifically, hyperactivity of mesolimbic dopaminergic neurons is suggested to produce the positive symptoms of schizophrenia such as psychosis.[25,26] A hypodopaminergic state in the frontal-cortical terminal fields of mesocortical DA neurons has also been proposed to be the basis of negative symptoms.[27]

Mesolimbic dopaminergic hyperactivity in schizophrenia may be maintained by pre- or postsynaptic mechanisms. Evidence for presynaptic hyperactivity includes excess DA release in response to amphetamine[28–30] and increased L-DOPA decarboxylase levels in schizophrenia.[30] Further, amphetamine and related substances such as 3,4-methylenedioxymethamphetamine (MDMA) have been shown to produce psychotic symptoms in healthy subjects.[31,32] In addition, many patients with schizophrenia experience an exacerbation of psychotic symptoms in response to psychostimulants such as amphetamine and methylphenidate at doses that are not psychotogenic to normal controls.[33–35]

Postsynaptically, an increased number of DA receptors or associated signal transduction elements could also result in heightened sensitivity to DA. Although initially classified into D_1 and D_2 receptors based on differing biochemical and pharmacological profiles,[36] these DA receptors are now recognized as 2 distinct receptor families.[37–39] All typical antipsychotics are D_2 receptor antagonists, and there is a strong correlation between clinical efficacy (i.e., antipsychotic effect) and the degree of D_2 receptor antagonism.[40–42] Similarly, D_2 receptor density, as measured in post-mortem tissue and more recently in in vivo brain imaging studies, has been reported to be increased in schizophrenia.[30,43–45] However, the effects of long-term antipsychotic treatment on D_2 receptors is a common confound in many of the earlier studies.[42] Changes in other DA receptors have also been reported in schizophrenia,[46–48] but many of these studies suffer from similar limitations.[49,50]

In animal studies, the administration of amphetamine and related psychostimulants reliably stimulates behavioural alterations such as hyperlocomotion and stereotypy.[23,51] Although the relevance of these motor disturbances to those shown by patients with schizophrenia is debatable, their reliable expression allows for a comparison among animal models. Moreover, amphetamine-induced stereotypic behaviour can be attenuated by treatment with antipsychotics,[52] further supporting the validity of this model.

The face validity of dopaminergic animal models is also supported by the disruptive effects of DA receptor agonists on PPI.[20,53] PPI is a test of preattentional sensorimotor gating, which is impaired in schizophrenia.[54–56] Stimulus-evoked changes in PPI are similar in humans and rats, and the DA agonist apomorphine can disrupt PPI in both species, mimicking the PPI deficits observed in patients with schizophrenia.[53] The administration of antipsychotic drugs can restore PPI function in rats treated with apomorphine, and this response has been correlated with both clinical antipsychotic potency and D_2 receptor affinity. Interestingly, the atypical antipsychotic clozapine can also restore PPI in apomorphine-treated rats.[53] Although the mechanism of action of clozapine in this regard is unclear, it does not appear to support a direct D_2-receptor-mediated effect as with apomorphine on PPI. Finally, PPI can be disrupted in rats by the direct infusion of DA into the nucleus accumbens (NAC), an effect which can be also blocked by antipsychotics,[53] thus supporting some degree of both predictive and construct validity for this model.

Despite the longevity of the DA hypothesis and its general usefulness in framing research on schizophrenia, the underlying mechanism by which DA activity is believed to be altered remains unknown. Indeed, there is relatively little direct evidence that DA plays a primary causal role in the development of the disorder.[6,57–59] Also, some patients with schizophrenia, particularly those with predominantly negative symptoms, respond poorly or not at all to treatment with DA antagonists.[60] Accordingly, despite the emphasis placed

on this model in the literature, the construct validity of DA animal models of schizophrenia remains limited.

Glutamate

Nonparanoid schizophrenia, especially when it includes negative symptoms, can perhaps be mimicked more faithfully by the administration of phencyclidine (PCP),[61,62] which appears to act predominantly on glutamatergic *N*-methyl-D-aspartate (NMDA) receptors.[63] PCP and other NMDA receptor antagonists induce schizophrenic-like symptoms in healthy subjects and precipitate psychoses in patients with schizophrenia who have stabilized.[64–70] This has led to the suggestion that schizophrenia may involve hypofunction of NMDA receptors.[64,71–73]

Long-term potentiation is disrupted by NMDA antagonists,[74,75] and Kornhuber and colleagues[76] reported increased binding to NMDA receptors in post-mortem frontal cortex of patients with schizophrenia.[76] Similarly, a decreased release of glutamate has been reported in the frontal and temporal cortices of patients with schizophrenia,[77] as have higher blood concentrations of glycine, glutamate and serine.[78] Reduced expression of non-NMDA glutamate receptor subtypes in the medial temporal lobe of patients has also been reported.[79–81]

Glutamate may also be involved in schizophrenia through its interactions with DA,[82] subtle forms of excitotoxicity[73] or the developmental abnormality of corticocortical connections.[83] Repeated exposure to PCP has been reported to reduce both basal and evoked DA utilization in the monkey prefrontal cortex (PFC), an effect which persisted even after PCP treatment was stopped.[84] Taken together, these findings implicate altered glutamate neurotransmission and NMDA receptor function, in particular, in the negative and cognitive deficits observed in schizophrenia.

As in the case of DA receptor agonists, PCP administration can disrupt PPI and startle habituation in rats.[20,85,86] Further, PCP and PCP-like drugs have also been shown to disrupt rat performance in the Morris water maze, 2-level alternation task and Y-maze brightness discrimination task.[87] Altered social interactions have also been reported after treatments with PCP.[88,89] Moreover, PCP produces amphetamine-like effects in rodents, including increased locomotor activity, stereotyped movements, circling and ataxia,[64,87] and these effects are attenuated by antipsychotics and 6-hydroxydopamine lesions of the mesolimbic DA system.[90,91] Repeated administration of PCP in monkeys also causes deficits in PFC-dependent tasks that can be ameliorated by the atypical antipsychotic clozapine.[84] Taken together, these findings clearly support claims of face and predictive validity for this model, although construct validity remains difficult to ascertain, as with many current models of schizophrenia. Nevertheless, the glutamatergic basis of schizophrenia features prominently in many theories on the pathogenesis of this disorder, and the psychotropic effects of many neuroactive agents are believed to involve direct effects on this system.

An important aspect of NMDA antagonist animal models is that many of the studies to date have involved single injections. The relevance of this mode of administration to the hypothesized persistent disruptions of glutamatergic systems in schizophrenia remains unclear.

In contrast, long-term PCP administration has been reported to produce differential electrophysiological and neurochemical effects compared with single injections.[84,92,93] Behaviourally, in monkeys, subchronic PCP treatment (i.e., twice a day for 14 days) produces performance deficits on a task involving PFC function,[84] and continuous treatment has also been associated with a decrease in stereotyped locomotion and an increase in scanning behaviours.[94] Behavioural tolerance to long-term PCP administration has also been reported for a trained response task in monkeys,[95] and in rats, repeated PCP injections increase immobility time in the forced swim test, a feature associated with depressive symptoms.[93,96] Differential effects of short- and long-term administration of PCP have also been shown on behavioural measures in the neonatal ventral hippocampus lesioned rat model of schizophrenia.[93] For a more detailed overview of NMDA receptor models of schizophrenia, see Jentsch and Roth.[97]

Serotonin

The serotoninergic (5-HT) system has also been frequently implicated in schizophrenia.[22] The 2 major classes of psychedelic hallucinogenic drugs, the indoleamines (e.g., lysergic acid diethylamide [LSD]) and phenethylamines (e.g., mescaline),[98–100] are believed to mediate their effects through 5-HT_{2A} receptors.[101] Polymorphisms of the 5-HT_{2A} receptor gene are reported to be a minor risk factor for schizophrenia.[102] A

loss of PFC 5-HT_{2A} receptors along with an accompanying increase in 5-HT_{1A} receptors[103,104] and a blunted neuroendocrine response to 5-HT_{2A} agonists[105] have been reported in schizophrenia. However, recent positron emission tomography studies have been somewhat equivocal in regard to 5-HT_{2A} receptor changes in schizophrenia (for example, see Trichard et al[106]). Nevertheless, the relatively high affinity of atypical antipsychotics such as clozapine for the 5-HT_{2A} receptor supports a role of 5-HT systems in schizophrenia.[107,108]

As in the case with dopaminergic and glutamatergic animal models, LSD has been shown to disrupt startle habituation and PPI in humans and rats.[109] Further, this effect is believed to be mediated through direct stimulation of 5-HT_{2A} receptors.[110] Indeed, the disruptive effects of PCP on PPI have also been proposed to be mediated through indirect activation of 5-HT_{2A} receptors.[86] Interestingly, both LSD and mescaline have been shown to enhance glutamatergic transmission in rats.[86] 5-HT_3 receptor antagonists have also been shown to attenuate the behavioural hyperactivity caused by PCP,[111] as well as amphetamine administration,[112] but 5-HT_3 receptor binding sites are not altered in schizophrenia,[113] and the efficacy of 5-HT_3 antagonists in clinical trials of schizophrenia has been variable.[114–116]

Despite evidence for altered serotonergic markers in schizophrenia, there is comparatively little evidence of a primary dysfunction of serotonergic systems in this disorder. Moreover, the relevance of LSD administration in animal models is unclear; repeated administration of LSD in humans or animals leads to behavioural tolerance, unlike the situation in schizophrenia.[117] Thus, despite some support for face and predictive validity in this model, construct validity remains as difficult to establish as in the DA and glutamate animal models.

GABA

Alterations in γ-aminobutyric acid (GABA) neurotransmission in the PFC of patients have also been proposed, on the basis of both theory and experimental evidence.[118–121] An interaction between dopaminergic and GABAergic systems in schizophrenia is supported by the fact that GABA neurons in the middle layers of PFC receive direct synaptic input from DA terminals, exert inhibitory control over excitatory output of layer III pyramidal neurons and undergo substantial developmental changes in late adolescence, the typical age of onset for schizophrenia.[119,120,122] Evidence for reduced GABA uptake sites in the temporal lobe,[123] increased $GABA_A$ receptor binding in superficial layers of cingulate cortex[124] and reduced gene expression for glutamic acid decarboxylase in the prefrontal cortex[125,126] provides direct support for GABAergic involvement in this disorder.

In animal studies, the $GABA_A$ receptor antagonist picrotoxin has been shown to reduce PPI in rats when injected into the medial PFC.[118] Further, pretreatment with the DA antagonist haloperidol antagonized this effect, suggesting that blockade of GABA receptors in PFC impairs sensorimotor gating in a DA-dependent manner. However, the lack of any other reported GABA-induced behavioural deficits related to schizophrenic symptoms makes the face and predictive validity of this model difficult to establish. Further studies are required to establish the relevance of GABA-based pharmacological models of schizophrenia.

Lesion models

There has been considerable debate over the years about whether schizophrenia could be considered a neurodegenerative or neurodevelopmental disorder.[127–130] The clinical deterioration that occurs in some cases suggests that neurodegenerative processes may be involved.[71,130–136] Similarly, enlarged ventricles and decreased cortical volume may reflect an ongoing neurodegenerative process, but ventricular size does not seem to correlate with the duration of illness[137] and appears to be present at the onset of symptoms, if not earlier. Moreover, this hypothesis suffers from both a lack of data supporting adult onset of pathologic cerebral changes and a lack of evidence of gliosis.[50] Proliferation of glial cells is seen in most neurodegenerative conditions, and the absence of gliosis suggests that neuropathologic events occurred before the responsivity of glial cells to injury (i.e., before the third trimester of gestation).[138] However, caution should be exercised in overinterpreting the lack of data supporting gliosis because the link between this injury marker and neurodegeneration remains unclear.

The neurodevelopmental theory of schizophrenia[122,139,140] postulates that the pathogenic conditions leading to schizophrenia occur in the middle stage of intrauterine life, long before the formal onset of symptoms.[140–146] Damage before this time would affect neurogenesis and thus lead to severe structural and cellular cortical abnormalities, which are not observed in schiz-

ophrenia.[138] Further support for the theory is provided by reports of minor physical anomalies, based on the assumption that pre- or perinatal pathologic events may also lead to more visible physical abnormalities. Abnormal limb length and angle, fingerprint patterns and ridge counts and webbed digits have been reported in schizophrenia.[147] Some studies also suggest the existence of premorbid neurologic abnormalities such as motor function and attention.[148,149]

Some animal models of schizophrenia, based on the concept of pre- or perinatal insults, suggest that various obstetric complications[150–155] (e.g., genetic, ischemic, hemorrhagic, infectious agents) could result in abnormalities in pruning, cell death and developmental connectivity.[139,156] However, such injuries are typically characterized by gliosis[141] and are difficult to reconcile with the cytoarchitectural changes seen in schizophrenia. The nature of delivery complications also varies considerably between studies, making comparisons difficult.[157] Nevertheless, studies of cesarean delivery and perinatal hypoxia or anoxia in rats have shown increased dopaminergic hyper-responsivity to psychostimulants[154,158–160] and stress.[161,162] Further, the effect has been shown to depend on the genetic background of the animal.[163] Although these models provide some degree of validity, further research is required to determine the potential mechanism(s) of action of obstetric complications in schizophrenia.

To address some of the issues surrounding progressive neurodevelopmental or neurodegenerative changes in schizophrenia, a number of targeted lesion animal models have been developed. Although these can take the form of electrolytic or aspiration lesions, they more typically involve excitotoxic agents, which destroy neuronal tissue through stimulation of excitatory glutamate release or by acting as direct glutamate receptor agonists.

Given the evidence for the involvement of the PFC in schizophrenia, it is not surprising that this region has drawn a lot of interest in lesion studies. The PFC is involved in higher cognitive functions such as attention, working memory, emotional expression and social interaction.[164,165] Hypofunction of dopaminergic projections at the level of the dorsolateral PFC, in particular, has been implicated in the metabolic hypofrontality seen in patients with schizophrenia.[166,167] Moreover, the role of this region in regulating subcortical DA activity[168,169] makes PFC lesions particularly amenable to study in the current behavioural testing paradigms validated in pharmacological models of schizophrenia. Lesions of the adult rat PFC result in an enduring hyper-responsiveness to stress,[170,171] as well as transient increases in locomotor exploration and amphetamine-induced stereotypy.[172–175] As well, adult rats with PFC lesions show reduced PPI after apomorphine injections[176] and reduced cataleptic response to haloperidol,[174] suggesting that postsynaptic striatal DA neurotransmission is increased.

The hippocampal formation has also received a great deal of experimental attention because this region modulates PFC activity, especially at the level of its projections to the NAC.[59] Thus, it exerts direct control over the mesolimbic dopaminergic system, believed to be affected in schizophrenia.[177] Aspiration lesions of the hippocampus in adult rats have been reported to selectively increase locomotor behaviour after amphetamine or DA receptor agonist administration.[178] Interestingly, excitotoxic lesions of the dorsal hippocampus (DH) and ventral hippocampus (VH) produce different behavioural profiles, with DH lesions having no effect on amphetamine-induced locomotion[179] and VH lesions resulting in increased spontaneous and DA-agonist-induced locomotor activity.[180–182] The behavioural changes induced by VH lesions have been detected approximately 2 weeks postoperatively.[174,176,181] However, these rats do not show PPI deficits in the absence of apomorphine[176] or exaggerated locomotion in response to stress. As well, they exhibit a decrease in stereotypic behaviours.[183]

A similar model involves the intracerebroventricular (ICV) administration of kainic acid,[184,185] which results in immediate as well as delayed neuronal loss in the DH and has been proposed as an animal model of neurodegeneration that may be comparable to schizophrenia.[184] Unlike the DH lesion model, however, ICV administration of kainic acid has been reported to enhance locomotor response to novelty and saline injection, as well as to amphetamine and MK-801 administration.[186] Increased DA receptor binding in the NAC has also been reported in this model,[185] similar to that reported after adult hippocampal lesions.[178]

The thalamus is another potential target for lesion studies because this region is generally believed to act as a "relay station," filtering or gating sensory information.[187] Abnormalities in limbic corticothalamic circuitry that correspond with deficiencies in sensorimotor gating (i.e., PPI) have been observed in schizophrenia.[188] Some, but not all, post-mortem studies have revealed

reductions in thalamic volume,[189,190] and similar reductions have also been found in nonpsychotic siblings of schizophrenic patients.[191] Reduced PPI has been found in rats with thalamic lesions, but this reduction was only apparent after an infusion of muscimol, a $GABA_A$ agonist.[192]

Despite reasonable claims for predictive and face validity for many of these adult lesion models, the size and "adult nature" of the lesions limits their construct validity as animal models of schizophrenia.

Neonatal lesion models

A number of neonatal lesion models have also been developed to test neurodevelopmental theories of schizophrenia.[6] One of the principal advantages of these models is the ability to demonstrate a delayed onset of symptoms that corresponds to the clinical presentation of schizophrenia in humans. For example, Goldman[193] first showed that perinatal ablations of the PFC did not impair performance on a delayed response task until after adolescence. One possible explanation for this postpubertal emergence is that other brain regions compensate for damage before puberty, but by adolescence the brain becomes developmentally committed to use the cortex for this activity. This interpretation is consistent with data suggesting that limbic abnormalities evident in schizophrenia are associated with an early developmental injury that does not manifest until adulthood.[149,166,194] Previously, in rats that received PFC lesions as neonates, we reported a postpubertal increase in locomotor activity in response to amphetamine and stress, with concomitant changes in DA receptors and DA release in the NAC.[195,196] Although discrepant data have been reported,[197] the behavioural and biochemical profile of these animals remains to be fully characterized.

In contrast, most of the research on neonatal lesion models of schizophrenia have focused on the VH. This is not surprising given the major role of this region in regulating subcortical DA.[59] Rats with neonatal excitotoxic lesions of the VH demonstrate delayed onset of hyperdopaminergic behaviours. Although these animals are behaviourally similar to controls at postnatal day 35 (PD35), postpubertally at PD56 they display increased locomotion in response to novelty, forced swim stress and after saline or amphetamine injection.[183,198] Interestingly, these behavioural effects are not observed after neonatal DH lesions. The postpubertal changes induced by neonatal VH lesions are believed to be the result of increased mesolimbic DA function but reduced DA release.[199,200] The PD56 rats also exhibit reduced haloperidol-induced catalepsy and enhanced apomorphine-induced stereotypies.[201] As in the case of dopaminergic pharmacological models, rats with VH neonatal lesions also show impaired PPI.[202–204] Further, the behavioural deficits exhibited by these animals are ameliorated after antipsychotic administration.[174] Neonatal VH lesions also cause disturbed latent inhibition comparable to that seen in patients with schizophrenia.[205]

In terms of negative symptoms of schizophrenia, alterations in social interaction and increased aggressive behaviour have also been reported in rats with neonatal VH lesions.[206,207] However, deficits in social interaction are present both pre- and postpubertally.[206] Further, the atypical antipsychotic clozapine had no effect on social interaction deficits despite ameliorating hyperlocomotion in this model. The source of these social interaction deficits is unclear but does not appear to involve anxiety; there were no differences observed between rats with lesions and control rats in the elevated plus maze.[207] Interestingly, lesions of the VH in adult rats have no effect on social behaviour, suggesting that lesion-induced impairments are of a neurodevelopmental nature. These findings are not limited to rodent studies; similar results have also been obtained in primates with perinatal lesions of the medial temporal lobe, where greater deficits in locomotor activity and social interaction were observed with perinatal than with adult lesions.[208,209]

Interestingly, ICV kainic acid administration in preweanling rats has also been reported to produce a predominantly delayed neuronal loss in the hippocampus, unlike the immediate effects observed with adult lesions.[210]

One possibility for the postpubertal emergence of symptoms in the VH model may be a delayed effect on the dopaminergic system that occurs later in life. Both hippocampal physiology and the dopaminergic system are influenced by sexual maturation and related hormonal changes.[211] It is also possible that the VH lesion affects the development of other neural systems, such as the PFC, which regulates mesolimbic DA activity during stress.[170,212,213] Interestingly, PFC physiology is immature prepubertally and continues to develop into adulthood.[214] In support of the theory of hypoactive glutamatergic function in the PFC in schizophrenia, increased specific glutamate binding and decreased

[^{3}H]aspartate release in the frontal cortex of adult rats after neonatal VH lesions has been reported.[215] As well, Bernstein et al[116] found reduced numbers of neurons and increased immunostaining for ornithine decarboxylase and nitric oxide synthase in the PFC.

Neonatal lesions of the VH have also been shown to alter levels of DA and its metabolites in the NAC.[181,182,200] However, despite the enhanced locomotor response to amphetamine in these rats, DA release is attenuated in both the PFC and NAC in response to amphetamine or stress in these animals.[199,200,217,218] In a similar model involving neonatal temporal lobe lesions in primates, PFC regulation of DA release in the NAC is disrupted.[219] Neonatal VH lesions have also been reported to be associated with increased sensitivity to D_2 receptor agonists such as quinpirole,[220] and altered levels of DA receptors have been reported in various brain regions in this model.[198,215,221]

One caveat with all experimentally induced lesion models is that they reflect far greater damage than what is seen in the brains of those who had schizophrenia. However, the postpubertal emergence of several DA-related behaviours (e.g., increased locomotor activity, reduced PPI) and their amelioration in response to antipsychotics demonstrate the comparatively good face, predictive and construct validity of these models. Although the relevance of hyperlocomotion to schizophrenic symptoms may be contentious, this behaviour can be reliably induced in animals in response to psychostimulants and may thus serve as a useful behavioural correlate of altered dopaminergic function.

Conclusions

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.

As was first demonstrated by Kennard,[222] the degree of functional sparing after brain damage increases as the postinjury interval increases. Based on this principle, it would be expected that any damage occurring in early life would be undetectable by adulthood. Moreover, it is now well established that the immature brain is capable of a high degree of plasticity or sparing of behavioural function after injury.[223,224] However, it must be emphasized that this high degree of plasticity occurs during narrow "windows of opportunity" in development.[225] For example, rats lesioned on postnatal day 1 (PD1) show much less dendritic branching and more severe water task deficits when tested as adults, whereas those lesioned on PD10 show considerable dendritic sprouting and sparing of function relative to those lesioned as adults.[224] These results suggest that neurodevelopmental windows exist when brain damage can or cannot be successfully compensated for, depending on the brain region involved. An even narrower window of opportunity was demonstrated recently by Ikonomidou et al,[226] where blockade of NMDA receptors for even a few hours during late fetal development or early neonatal life triggered apoptotic neurodegeneration in the developing rat brain.

What about the development of new models of schizophrenia? Historically, modelling exercises have focused on alterations in specific neurotransmitter systems, but the current pharmacological models appear to have reached the limit of their predictive or explanatory capabilities. One possible further avenue, building on the pharmacological approach, is the examination of synaptic terminal proteins in general. Increasing attention is being focused on the role of these proteins in a variety of processes involving plasticity, particularly in learning and memory.[227–229] Changes in synaptic proteins such synapsin, synaptophysin and SNAP-25 have been reported in schizophrenia.[230–235] More recently, the newly identified synapsin III has been associated with a susceptibility locus for schizophrenia.[236–238] These find-

ings point toward a role for altered synaptic neurotransmission in this disorder. However, it is important to recognize that the current models serve solely as an intermediate step in our development of more sophisticated frameworks for characterizing neurodevelopmental deficits.

The past decade has also brought tremendous advances in our understanding of molecules that guide the development of the nervous system. Cell adhesion molecules (CAMs) such as NCAM and L1 have already received extensive study, and their role in regulating neurite outgrowth and axon fasciculation are well known.[239–243] Previously, we demonstrated reduced levels of embryonic polysialylated isoform (PSA-NCAM) residues in the hippocampus of the schizophrenic brain.[244] Further, NCAM-180 knockout mice reveal deficits in neuronal migration,[245] increased ventricle size and PPI deficits[246] reminiscent of schizophrenia.

Several gene families that regulate the development of the cerebral cortex have been discovered that may be relevant in modelling schizophrenia. For example, reelin, an extracellular matrix glycoprotein secreted by Cajal-Retzius cells in the marginal zone during development, is crucial for the radial organization of the cortical plate and eventual cortical lamination.[247,248] The reeler mouse, a natural mutant with disrupted reelin, displays aberrant migration of cortical neurons and motor ataxia,[249] and decreased levels of reelin have been reported in several brain regions of patients with schizophrenia.[250] Reelin has thus been suggested to be a putative vulnerability factor in schizophrenia. Moreover, defective corticogenesis and reduction in reelin expression in cortex and hippocampus have recently been reported in prenatally infected neonatal mice.[251]

Other neurodevelopmental molecules of interest include the netrin family of axon guidance molecules known to act as chemoattractants during development.[252–256] More recently, the Eph family of receptor tyrosine kinases and their transmembrane and GPI-anchored ligands known as ephrins have been implicated in the regulation of axon guidance in various CNS regions.[257–260] In particular, members of this family of molecules seem to inhibit axon outgrowth[261–265] and may prove of great interest in the study of schizophrenia. Similarly, the semaphorin family of axon guidance molecules represent a second major inhibitory system for axonal pathfinding,[266,267] although they may also have some attractive roles as well.[268–271] This family consists of a large number of transmembrane and soluble semaphorins that bind to complexes of transmembrane receptors known as neuropilins and plexins.[272,273]

These families of axon guidance molecules work together in an intricate fashion to regulate axon development. However, they form the barest beginning of our understanding of developmental processes at a molecular level. New molecules are constantly being discovered, and as the interplay between these factors becomes better understood, it is possible that more sophisticated animal models of schizophrenia based on perturbations of these molecules may be developed.

Much of the current research into the development of animal models has benefited from tremendous advances in our understanding of the role of genetic factors in human development and disease. In particular, targeted gene deletion and overexpression techniques in animals have helped to elucidate the biochemical pathways underlying many human conditions. Although schizophrenia is a highly heritable disorder, it is generally believed to involve the interaction of a large number of genes,[236,274,275] and it is thus unlikely to be faithfully modelled in its entirety by this approach. However, even limited models can have profound implications for our understanding of human disorders. There are already a large number of promising candidate genes available for study in schizophrenia, including many of the neurodevelopmental markers listed above as well as classical neurotransmitter signalling components (for a recent review, see Lipska and Weinberger[6]).

It is in this manner than the various neurodegenerative–neurodevelopmental and genetic–environmental aspects of the disorder may ultimately be united. Multiple factors at work over time may contribute to abnormal brain maturation up to puberty, with the ensuing emergence of symptoms and their progression over time. A greater understanding of the various genetic factors involved and the environmental forces that modulate their expression over time may help us to develop more sophisticated animal models. Ultimately, these future models may help to expand our knowledge of this poorly understood disorder, which strikes at the very core of what it means to be human.

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