Current Topics

Translational Research in Neurodevelopmental Disorders: Development of Etiology-Based Animal Models

Animal Model for Schizophrenia That Reflects Gene-Environment Interactions

Taku NAGAI, Daisuke IBI, and Kiyofumi YAMADA*

Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine; 65 Tsuruma-cho, Showa-ku, Nagoya 466-8560, Japan.

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Schizophrenia is a devastating psychiatric disorder that impairs mental and social functioning and affects approximately 1% of the population worldwide. Genetic susceptibility factors for schizophrenia have recently been reported, some of which are known to play a role in neurodevelopment; these include *neuregulin-1*, *dysbindin*, and *disrupted-in-schizophrenia 1 (DISC1)*. Moreover, epidemiologic studies suggest that environmental insults, such as prenatal infection and perinatal complication, are involved in the development of schizophrenia. The possible interaction between environment and genetic susceptibility factors, especially during neurodevelopment, is proposed as a promising disease etiology of schizophrenia. Polyriboinosinic–polyribocytidilic acid (polyI:C) is a synthetic analogue of double-stranded RNA that leads to the pronounced but time-limited production of pro-inflammatory cytokines. Maternal immune activation by polyI:C exposure in rodents is known to precipitate a wide spectrum of behavioral, cognitive, and pharmacological abnormalities in adult offspring. Recently, we have reported that neonatal injection of polyI:C in mice results in schizophrenia-like behavioral alterations in adulthood. In this review, we show how gene-environment interactions during neurodevelopment result in phenotypic changes in adulthood by injecting polyI:C into transgenic mice that express a dominant-negative form of human DISC1 (DN-DISC1). Our findings suggest that polyI:C-treated DN-DISC1 mice are a well-validated animal model for schizophrenia that reflects gene-environment interactions.

Key words schizophrenia; animal model; gene-environment interaction; polyriboinosinic–polyribocytidilic acid; disrupted-in-schizophrenia 1

1. INTRODUCTION

Schizophrenia is a devastating psychiatric disorder that impairs mental and social functioning and affects approximately 1% of the population worldwide.¹⁾ Typical symptoms can be separated into positive symptoms (e.g., hallucinations, delusions, and thought disorder), negative symptoms (e.g., deficits in social interaction, emotional expression, and motivation), and cognitive dysfunction (e.g., impaired attention/information processing, problem-solving, processing speed, verbal and visual learning, and memory and working memory).^{2,3)}

Schizophrenia is considered a complex disease with multiple factors contributing to its pathogenesis. The basic risk profile mainly depends on susceptibility genes, which is highlighted by the heritability of schizophrenia being up to 80% in monozygotic twins.⁴⁾ Genetic studies have been used to identify proteins of candidate genetic risk factors for schizophrenia, including *MHC class I* genes,^{5–7)} *dysbindin*,⁸⁾ *neuregulin 1*,⁹⁾ *catechol-O-methyltransferase*,¹⁰⁾ and *disrupted-in-schizophrenia 1 (DISC1)*.¹¹⁾ Other hypothetical risk factors include season and location of birth, socioeconomic status, and maternal infections.^{12,13)}

Although the disease etiology remains poorly understood, various hypotheses, including dopamine hyperfunction, glutamatergic hypofunction, GABAergic deficits, stress vulnerability, and impaired neurodevelopment have been proposed as the etiology/pathophysiology of schizophrenia.^{14,15)} Among them, the neurodevelopmental hypothesis of schizo-

phrenia, supported by clinical, neuroimaging, neuropathologic, and genetic studies, is a more fundamental theory that does not conflict with other hypotheses.^{16,17)}

Development of animal models is a crucial issue in biological psychiatry for the search for novel drug targets and for the screening of candidate compounds. Many lines of genetic mouse models based on susceptibility genes for schizophrenia have become available and characterized mainly by behavioral alterations.^{18–22)} Nonetheless, only a few studies have addressed possible gene-environment interactions in the context of schizophrenia.²³⁾ On the basis of the epidemiologic findings in schizophrenia, we propose the following factors in this review: 1) impact of perinatal immune activation as an environmental factor; 2) a possible interaction of genetic and environmental factors by injecting polyriboinosinic–polyribocytidilic acid (polyI:C) into transgenic mice that express a dominant-negative form of DISC1 (DN-DISC1).

2. PERINATAL IMMUNE ACTIVATION AS AN ENVIRONMENTAL FACTOR

PolyI:C is a synthetic analogue of double-stranded RNA that leads to the pronounced but time-limited production of pro-inflammatory cytokines after administration to mammalian organisms through the activation of toll-like receptor 3.²⁴⁾ Maternal immune activation by polyI:C exposure in rodents is known to precipitate a wide spectrum of behavioral, cognitive, and pharmacological abnormalities in adult off-

* To whom correspondence should be addressed. e-mail: kyamada@med.nagoya-u.ac.jp

spring.^{25–29}) There are some concerns about the prenatal polyI:C treatment model of schizophrenia. First, prenatal treatment with polyI:C in pregnant dams is reported to increase the rate of abortion. More than half of the dams administered polyI:C could not bear live pups owing to abortion.³⁰ Second, it is controversial to match pregnancy stages between rodents and humans. Regarding brain development at the cellular level, neonatal rodents have very immature brain structures compared with human neonates. Glial proliferation and migration, as well as the establishment of the blood-brain barrier (BBB), peak during the early postnatal period in rodents.^{14,31,32} In humans, such a critical developmental stage occurs *in utero*, more specifically in the late period of the second trimester of pregnancy, which is the period with the highest risk for schizophrenia.^{14,33}

To develop a novel mouse model of viral infection during the perinatal stage, neonatal ICR mice were daily injected intraperitoneally (i.p.) with polyI:C (5 mg/kg) for 5 d from postnatal day 2 to day 6, and their cognitive and emotional behaviors as well as glutamatergic neurotransmission in the hippocampus were analyzed in adolescence. Neonatal polyI:C-treated mice display anxiety-like behavior, impaired recognition memory and social behavior, and sensorimotor gating deficits.³⁴ In parallel, high potassium-induced glutamate release in the hippocampus is diminished in polyI:C-treated mice compared with that of vehicle-treated control mice.³⁴ These findings suggest that polyI:C treatment during the perinatal stage leads to the development of emotional and cognitive deficits in adolescence, which are accompanied by the dysfunction of glutamatergic neurotransmission in the hippocampus. In fact, abnormal behaviors in polyI:C-treated mice are ameliorated by treatment with haloperidol, clozapine, and the *N*-methyl-D-aspartate (NMDA) receptor co-agonist D-serine (unpublished data).

Aberrant locomotor activity and the potentiation of methamphetamine-induced hyperlocomotion, which are exhibited by other pharmacologic or genetic animal models of schizophrenia,³⁵ are not evident in the neonatal polyI:C treatment model. Because schizophrenia is considered to develop as a result of the interactions of several genetic and environmental factors,^{36,37} partial and subtle manifestation of schizophrenia-related behavioral changes in mice caused by a single environmental factor (e.g., viral infection during neurodevelopment) supports this hypothesis. Additional genetic factors and/or other environmental insults to perinatal viral infection are required for full manifestation of the clinical symptoms and pathophysiology of schizophrenia in rodent models. Thus, the present model of perinatal viral infection may have advantages for testing gene-environment interactions for schizophrenia (see next section). There may be considerable difference in the new behavioral consequences of neonatal polyI:C treatment among the mouse strains. For instance, behavioral deficits induced by neonatal polyI:C treatment at the dose of 5 mg/kg in C57BL/6 mice are minimal compared with those in ICR mice. PolyI:C-treated C57BL/6 mice exhibit the impairment of object recognition memory in a novel object recognition test, but their performance in other behavioral tests, including prepulse inhibition test, open-field test, and social interaction test, was comparable with the performance of vehicle-treated control mice (data not shown). However, prepulse inhibition deficit and

impaired social interaction are observed when C57BL/6 mice are injected with polyI:C at a dose of 10 mg/kg (data not shown).

We have also found that neonatal polyI:C treatment in ICR and C57BL/6 mice significantly increases *tumor necrosis factor (TNF)- α* mRNA levels in the hippocampus 2 h after final polyI:C treatment compared with those of vehicle-treated controls.³⁸ Furthermore, *interferon-induced transmembrane protein 3 (IFITM3)* mRNA levels induced by type I interferon³⁴ are significantly increased, at least up to 24 h after polyI:C treatment.³⁴ These findings suggest that repeated polyI:C treatment in neonatal mice causes an immune inflammatory response in the hippocampus. Interestingly, it has been reported that mRNA levels of IFITM3 are markedly increased in the brains of patients with schizophrenia,³⁹ bipolar disorder,⁴⁰ and autism.⁴¹ We believe that understanding of the molecular function of IFITM3 in brain development may provide a new insight into neurodevelopmental disorders.

3. POSSIBLE INTERACTION OF GENETIC AND ENVIRONMENTAL FACTORS

By using the method of neonatal polyI:C treatment, we sought to develop a more realistic animal model for schizophrenia that reflects gene-environment interactions. We chose DISC1 as a genetic factor on which to focus because its role during neurodevelopment is well characterized.^{19,42} DISC1 was originally found through breakpoint mapping in an extended family in which a balanced chromosomal translocation on chromosome 1q42 co-segregated with psychiatric disorders including schizophrenia, bipolar disorder, and recurrent major depression.⁴³ DISC1 is involved in neurite outgrowth and neuronal migration^{44–46} and is expressed in brain regions that are known to be involved in schizophrenia, including human cerebral cortex and hippocampus.^{47–49} Transgenic mice that express DN-DISC1 under the α CaMKII promoter show some behavioral (sensorimotor gating deficits, depression-like behavior, and hyperactivity) and histological endophenotypes relevant to schizophrenia.¹⁸

To study how gene-environment interaction during neurodevelopment results in phenotypic changes in adulthood, DN-DISC1 mice and C57BL/6 wild-type littermates were injected with polyI:C during the neonatal stage, and their behavioral and histological phenotypes were examined in adulthood. Neonatal polyI:C treatment in DN-DISC1 mice results in synergistic effects in the deficits of short-term memory in Y-maze test and short-term object recognition memory in novel object test after puberty, although polyI:C treatment or DN-DISC1 expression by itself has little influence on wild-type mice.⁵⁰ Furthermore, polyI:C-treated DN-DISC1 mice exhibit signs of impairment of social recognition and interaction, hippocampus-dependent fear memory, and augmented susceptibility to MK801-induced hyperactivity compared with vehicle-treated wild-type mice.⁵⁰ These results suggest that neonatal polyI:C treatment in DN-DISC1 transgenic mice results in synergistic and additive effects on some behavioral phenotypes in adulthood.

The effects of antipsychotics on the behavioral deficits in polyI:C-treated DN-DISC1 mice in adulthood were investigated. Cognitive impairment in the polyI:C-treated DN-

Table 1. Comparison of Behavioral Changes between Prenatal and Postnatal PolyI:C Injection Models

	Ibi <i>et al.</i> ³⁴⁾	Ozawa <i>et al.</i> ³⁰⁾	Meyer <i>et al.</i> ²⁶⁾	Smith <i>et al.</i> ⁵⁸⁾	Zuckerman <i>et al.</i> ^{59,60)}
Animal	ICR mouse	BALB/c mouse	C57BL/6J mouse	C57BL/6J mouse	Wistar rat
PolyI:C injection period	PD2-6	GD12-GD17	GD9	GD12.5	GD15
Dose of polyI:C (mg/kg)	5	5	5 or 10	20	4
Cognition/learning and memory					
Novel object recognition	Impairment	Impairment	—	—	—
Prepulse inhibition	Impairment	Impairment	Impairment	Impairment	—
Latent inhibition test	No change	—	Impairment	Impairment	Impairment
Emotional behavior					
Social interaction	Impairment	—	—	Impairment	—
Anxiety-like behavior in open-field	Increase	Decrease	Increase	Increase	—
Psychomotor excitation					
Locomotor activity	No change	No change	No change	Decrease	No change
Methamphetamine-induced hyperactivity	No change	Increase	Increase	—	Increase
MK801-induced hyperactivity	No change	—	—	—	Increase

—, Not determined; PD, postnatal day; GD, gestation day.

Table 2. Validity of Animal Models with Regard to Mental Disorders^{35,61)}

Face validity	The phenomenological similarity between the behaviors exhibited by the animal model and the specific symptoms of the human condition
Construct validity	Shared etiology involving similarity of underlying neurobiological mechanisms
Predictive validity	The model's ability to correctly identify drugs with potential therapeutic value in humans
Neuropathological validity	Translatable anatomical and neuropathological characteristics between humans and rodents

DISC1 mice is ameliorated by repeated administration of the atypical antipsychotic clozapine, but not the typical antipsychotic haloperidol.⁵¹⁾ Both antipsychotics suppress the enhancement of MK801-induced hyperactivity.⁵¹⁾ These findings are consistent with the clinical evidence that clozapine is superior to typical antipsychotics in improving cognitive deficits, and both antipsychotics are effective in treating positive symptoms in schizophrenia.⁵²⁾

Anatomical and neuropathological changes are currently regarded as a pathological hallmark of schizophrenia, which is likely to underlie the cognitive dysfunction in patients with schizophrenia.^{53,54)} Enlarged ventricles at the gross anatomic level have been reported in brain imaging studies.⁵⁵⁾ Dendritic changes in the pyramidal neurons⁵⁶⁾ and alteration of specific subtypes of interneurons⁵⁷⁾ are known to be important in the pathology of schizophrenia. Hikida *et al.*¹⁸⁾ have demonstrated a significant impact of DN-DISC1 expression on the number of parvalbumin-positive interneurons in the medial prefrontal cortex (mPFC). Importantly, the additive effect of neonatal immune activation induced by polyI:C treatment and the genetic impact of DN-DISC1 were evident as a marked decrease in parvalbumin-positive interneurons in the mPFC of polyI:C-treated DN-DISC1 mice in adulthood.⁵⁰⁾

Because polyI:C-treated DN-DISC1 mice display a disturbance of hippocampus-dependent fear memory, we have examined whether there were histological alterations in the hippocampus of polyI:C-treated DN-DISC1 mice. Although there are no changes in Nissl staining and immunostaining of Ki67 (a marker of cell proliferation), a significant increase in the number of BrdU-positive cells in the granule cell layer of the hippocampus is observed 4 weeks after the labeling.⁵⁰⁾

4. CONCLUSION

We provided an overview of the novel mouse models for schizophrenia, which were based on epidemiologic findings in patients with schizophrenia. Table 1 summarizes the differences of behavioral phenotypes between prenatal and postnatal polyI:C injection models. Impairments of social interaction, memory, and prepulse inhibition are evident in both prenatal and postnatal polyI:C injection models. PolyI:C treatment in pregnant dams increases the sensitivity to methamphetamine and disrupts latent inhibition in offspring, while neonatal treatment of polyI:C has no effect on these behaviors. The results suggest that there may be some commonality but also difference between the effects of neonatal and prenatal polyI:C treatments on phenotypic changes in adulthood.^{26,30,58–61)}

Some criteria have been proposed to assess the validity of animal models for mental disorders^{35,62)} (Table 2). Face validity refers to the phenomenological similarity between the behavior exhibited by the animal model and the specific symptoms of the human condition. Construct validity is a shared etiology involving similarity of underlying neurobiological mechanisms. Predictive validity is the model's ability to correctly identify drugs with potential therapeutic value in humans. Neuropathological validity is translatable characteristics between humans and rodents. It is important to evaluate the animal models for mental disorders from these points of view.

Table 3 summarizes adult endophenotypes in DN-DISC1 mice with neonatal polyI:C treatment. Neonatal polyI:C treatment in DN-DISC1 mice results in the exhibition of deficits of short-term, object recognition, and hippocampus-dependent fear memories in adulthood, and signs of impairment of social recognition and interaction with augmented sensitivity to MK801-induced hyperactivity (face validity).

Table 3. Adult Endophenotype in DN-DISC1 Mice with Neonatal PolyI:C Treatment

Behavioral analyses	PolyI:C+DN-DISC1	+Haloperidol	+Clozapine
Cognition/learning and memory			
Short-term memory (Y-maze test)	Impairment	No effect	No effect
Recognitive memory (Novel object recognition test)	Impairment	No effect	Improvement
Contextual fear memory (Fear conditioning test)	Impairment	No effect	No effect
Sensorimotor gating function (Prepulse inhibition test)	No change	—	—
Emotional behavior			
Social interaction (Social interaction test)	Impairment	No effect	No effect
Aggressive behaviors (Social interaction test)	Increase	No effect	No effect
Psychomotor excitation			
MK801-induced hyperactivity	Increase	Improvement	Improvement
METH-induced hyperactivity	No change	—	—
Anatomical analyses			
Parvalbumin-positive cells in the mPFC	Decrease	—	—
Ki67 (cell proliferation marker)-positive cells in the DG	No change	—	—
BrdU-positive cells in the DG	Increase	—	—
Nissl staining in the PFC and hippocampus	No change	—	—

DN-DISC1, dominant-negative form of disrupted-in-schizophrenia 1; DG, dentate gyrus; METH, methamphetamine; mPFC, medial prefrontal cortex; polyI:C, polyribonucleic acid; —, not determined.

The model mice reflect gene (DISC1)-environment (perinatal immune activation) interactions (constructive validity). Administration of antipsychotics, such as clozapine and haloperidol, ameliorate some, but not all, behavioral abnormalities in the polyI:C-treated DN-DISC1 mice (predictive validity). Importantly, they reveal a marked decrease in parvalbumin-positive interneurons in the mPFC (neuropathological validity). Taken together, we believe that neonatal polyI:C treatment in DN-DISC1 mice is a well-validated animal model for schizophrenia that reflects gene-environment interactions. To identify a novel drug target, we are currently investigating the molecular mechanism by which polyI:C treatment during neurodevelopment impairs the brain function after puberty.

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