Review Articles

Can The Rat Get Mad?: The Relevance of Schizophrenic Animal Models to the Patients

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Abstract

Schizophrenia is a severe mental disorder in which there is impaired judgement and loss of contact with reality. The lifetime prevalence of schizophrenia is approximately 1% worldwide. To understand the mechanisms and investigate the treatments of schizophrenia, the studies in animal are necessary. Several schizophrenic animal models have been produced. Some animal models have been reported irrelevant to the disorder and no longer used. To date, there are three valuable animal models, which show the most similarity to clinical aspects of schizophrenia: 1) Sub-chronic phencyclidine (PCP) administration, 2) Amphetamine administration, and 3) Isolation rearing model. "Can these animals truly express the symptoms relevant to schizophrenic patients?" is always the question. Locomotor hyperactivity, decreased capability of memory in novel object recognition (NOR) test and prepulse inhibition (PPI) deficit have been reported in these animal models. These behavioral tests showed similarity to clinical aspects of schizophrenia, so sub-chronic PCP administration, amphetamine administration and isolation rearing could be valuable animal models for studying the neurobiological basis, pathological mechanism and, to some extent, treatment of schizophrenia.

Key words: Schizophrenia, Schizophrenic animal models

Can The Rat Get Mad?: The relevance of schizophrenic animal models to the patients

Animals, particularly rats, have been using in several medical research fields including mental health research as models of psychiatric disorders such as schizophrenia, depression, anxiety, etc. The animal models are useful for studying the basis of disorders such as mechanisms of pathogenesis and pharmacological effects of the drug treatments. However, the pathogenesis and physiological mechanisms of psychiatric disorders are extremely complicated. Some psychiatric symptoms such as alogia, anhedonia, flat affect, avolition, social withdrawal, etc. are exclusively 'human' characteristics therefore the development of animal models for these symptoms have proven difficult. The 'human' characteristic symptoms (alogia, anhedonia, flat affect, avolition, social withdrawal, etc.) are present in schizophrenia. These symptoms are known as negative symptoms in the disorder. It seems impossible to produce the animal models of negative symptoms and these symptoms might be unsuited to be modeled in animals, in that there have been doubts whether schizophrenic animal models are truly relevant to the disease. In which researches that use rat models of schizophrenia, 'can the rats get mad?' is still the question.

Apparently, it is impossible to produce the perfect animal models for any diseases. All the animal models could not perfectly relevant to the diseases. The researchers could not insist that their animals sick with exactly the same disease as diagnosed in human. However, what the researchers could do is to induce the abnormalities in the animals by the same pathophysiologic mechanisms as they found in the patients. Before the animals are

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used in the experiment, the tests to show the relevance of these animal models to the patients are necessary.

Although negative symptoms of schizophrenia are difficult to produce in animals, positive symptoms (hallucinations, delusions, thought disorder, perceptual disturbances, incongruous mood, increased motor function) could be more possible to create. The behavioral changes, mostly positive symptoms, found in schizophrenic patients are associated with brain neurochemical changes and could be modeled. There have been many evidences that showed the relevance of the behavioral changes in animal models to schizophrenic symptoms. Therefore, these animal models could be valuable models for studying the neurobiological basis of schizophrenia.

This article reviews the animal models of schizophrenia and their behavioral tests showing the relevance to the disease.

1. What is schizophrenia?

Schizophrenia is the most common functional psychosis which is defined as a severe mental disorder, with or without organic damage, characterized by derangement of personality and loss of contact with reality and causing deterioration of normal social functioning. It affects approximately 1% of populations around the world. The age at onset is usually between 15 and 30 years.

Schizophrenia was called premature dementia ("dementia praecox") in 1893 by psychiatrist Emil Kraepelin[1] after that it was changed to schizophrenia in 1908 by psychiatrist Eugen Bleuler.[2-3] The symptoms of schizophrenia are variable; however, they can be classified into two types of symptoms which are positive (e.g. hallucinations (often auditory or visual hallucinations), delusions, thought disorder) and negative (e.g. decreased initiative, blunted affect, poverty of speech and social withdrawal) symptoms. Cognitive impairment is a major problem which contributes to functional disability in schizophrenia. This impairment persists even when patients are in remission of psychotic symptoms and have, to date, eluded treatment.

The diagnostic criteria used for schizophrenia by the American Association of Psychiatry (DSM-IV, 1994)[4] and by the World Health Organization International Classification of Diseases (ICD-10, 1992)[5] are quite similar. To be diagnosed as having schizophrenia, a person must display signs and symptoms, following the diagnosis criteria of either DSM-IV or ICD-10.

There are three major causes of schizophrenia which are genetic, neurodevelopmental disorder[6-9], and changes of neurotransmitter systems.[10-39] The changes of neurotransmitters are the most popular hypothesis, which have been using in the research. There have been reported that alterations of several neurotransmitters are involved in pathogenesis of schizophrenia. Followings are summary of neurotransmitter alterations involved in schizophrenia;

1.1 Increase of dopamine and its receptors, especially subtype 2 receptor (D2)[10-19]

1.2 Decrease of GABAergic neurotransmission (GABAergic hypofunction)[20-29]

1.3 Decrease of glutamatergic neurotransmission (Glutamatergic hypofunction)[30-34]

1.4 Decrease of serotonergic neurotransmission[35-39]

Base on these neurotransmitter alterations, animal models have been produced to mimic pathogenesis of schizophrenia. Several studies showed that the behaviors and symptoms of these animal models were relevant to what have been found in schizophrenic patients such as hyperlocomotion, enhanced stereotypic behaviors, cognitive and sensorimotor gating deficits, and impaired social interactions.[40-41] The relevant behaviors of animal models to the patients are mentioned in section 3.

According to the knowledge that neurotransmitter alterations result in schizophrenia, schizophrenic animal models have been developed such as the model produced by sub-chronic PCP (phencyclidine) administration, amphetamine administration and so on. The details are mentioned in section 2.

๒. How to produce schizophrenic rat models?

There have been a few tasks of relevance to schizophrenia which have been using in laboratory experiments. This article emphasizes the three most sensible models which have been using in the schizophrenic research since 1980 and lately. These models are followings;

2.1 Sub-chronic PCP administration[42]

2.2 Amphetamine administration[43]

2.3 Isolation rearing model[44]

2.1 Sub-chronic PCP administration

PCP is a non-competitive N-methyl-d-aspartate (NMDA) receptor antagonist. As mentioned earlier that decreased glutamatergic neurotransmission is one possible cause of schizophrenia,[29-34] PCP blocks NMDA receptor then results in decreased glutamatergic neurotransmission. Therefore, PCP is likely to produce schizophrenic-like psychosis.

It has been suggested that one process in the development of schizophrenia is a disinhibition, modeled by NMDA receptor antagonism, due to GABAergic hypofunction (mentioned in 1.2, section 1). This may result in glutamatergic excitatory activity at a level which induces a neurodegeneration underlying the progressive cognitive dysfunction in schizophrenia[45-46] (Figure 1).

In order to prepare this animal model, Phencyclidine HCl (Sigma, USA) was dissolved in 0.9% saline and administered bi-daily (09.00hr and 16.30hr) for 7days at a dose of 2mg/kg i.p. (sub-chronic). Control animals received vehicle solution (0.9% saline) with the same dosage regime.[42]

2.2 Amphetamine administration

The most widely studied neurotransmitter with regard to amphetamine action in the central nervous system is dopamine. All of the addictive drugs appear to enhance dopamine neurotransmission, including amphetamine and its derivatives, methamphetamine.[43]
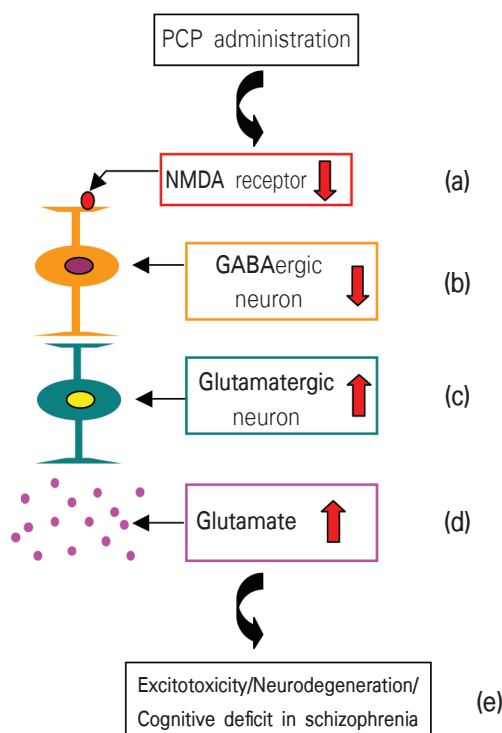

Figure 1 Schematic illustration of GABAergic disinhibition occurred by PCP administration. PCP, NMDA receptor antagonist (a) decreases inhibitory neurotransmission from GABAergic neuron (b). Excitatory glutamatergic neurotransmission is increased due to loss of GABAergic inhibition (c). Increased excitatory glutamatergic neurotransmission (d) results in excitotoxicity which can produce neurodegeneration leading to cognitive deficit in schizophrenia (e). (PCP = phencyclidine)

The hypothesis that dopamine hyperactivity is involved in schizophrenia emerged in 1963 when Carlsson and Lindqvist found that drugs effectively reducing psychotic symptoms were dopamine receptor antagonists[11] and their clinical potency was strongly correlated with their ability to block dopamine D2-like receptors.[12] Moreover, several studies reported that dopamine agonists, such as amphetamine, could induce psychotic symptoms in individuals who did not have schizophrenia[13] and exacerbated psychotic symptoms in some schizophrenic patients at doses that did not produce psychosis in controls.[14]

Amphetamine and methamphetamine administrated animals have been used as schizophrenic animal models since 1963. Lately, pseudoephedrine administrated animals have also been used as the model of schizophrenia. Pseudoephedrine, commonly found in decongestants, is a diastereoisomer of ephedrine. Both are classified as sympathomimetic drugs[47] which can produce psychoactive effects such as pleasant perceptual changes, euphoria and mental stimulation as same as amphetamine. There have been reports on the effect of pseudoephedrine in the nervous system that mediated via dopaminergic mechanism.[48] The study of drug discrimination showed that pseudoephedrine could be both partial substitution (20 mg/kg) and full substitution (40 mg/kg) for amphetamine (1 mg/kg).[49]

2.3 Isolation rearing model

This schizophrenic rat model could be produced by isolating the rat at the time of weaning, normally on postnatal day 23. The weaning rat needed to be separated from the other rats including its mother and kept in isolation housing. Isolation housing consisted of one rat per standard polycarbonate cage (25 x 48 x 20 cm).[44]

Apart from sub-chronic PCP administration, amphetamine administration and isolation rearing model, there were actually a lot of schizophrenic animal models. However, most of them had been used before some studies reported irrelevance to the patients. The example of irrelevant model is heterozygous Neuregulin1 (NRG1) mutant mice or NRG1-knockout mice model.[50] The detail of this model is not explained in this article because it is irrelevant to schizophrenia and no longer used.

Schizophrenic animal models induced by sub-chronic PCP administration, amphetamine administration and isolation rearing have been using in schizophrenic research around the world due to their relevance to the patients. There have been several publications showing the behavioral tests of these animals, which are relevant to the patients. The details of these behavioral tests are explained in section 3.

3. The relevance of schizophrenic animal models to the patients

Several behavioral tests showed that behaviors of sub-chronic PCP administration, amphetamine administration and isolation rearing models were similar to psychotic symptoms and behaviors in schizophrenic patients. The behaviors of animal models which were relevant to those of the patients were locomotor hyperactivity, novel object recognition (NOR) and prepulse inhibition (PPI) deficits.[40-41, 51]

The increase of locomotion is due to hyper-dopaminergic neurotransmission. Decrease in NOR, the test for learning and memory, is also found in these animal models. Decreased NOR represents the cognitive dysfunction, which is one of the most important problems in schizophrenic patients. NOR is the test of capability of recognizing the novel object and memory the familiar object. The procedure of NOR is mentioned in section 3.1.

3.1 Novel object recognition

NOR procedure which the author currently uses was adapted from Ennaceur and Delacour.[52] Testing took place in the same room as the social interaction task. The arena was a black plastic cube (63 x 63 x 45 cm) which was cleaned between trials with 70% alcohol. The objects to be discriminated were available in three copies and made of inert material such as glass, plastic and ceramic. All rats were initially habituated to the empty box for three sessions of 3 minutes duration over the previous two days. For the object recognition paradigm, each rat was first placed in the box and exposed for 3 minutes to two identical objects placed approximately 10 cm apart in the centre of the box (trial). The rat was then returned to its homecage for a period of 1 hour. Rats

were then returned to the arena which now contained a familiar object and a novel object (test). Rats were again exposed to the objects for 3 minutes. Both trial and test were videoed and scored for time attending to each object.[53] Test data was expressed as the d2 index ((time exploring novel object – time exploring familiar object) / total exploration time). Decreased d2 index represents decreased NOR which means cognitive impairment. Decrease in NOR has been investigated in sub-chronic PCP administration, amphetamine administration and isolation rearing models. This is relevant to a decrease of NOR found in the patients with schizophrenia.

3.2 Prepulse inhibition

PPI of the startle reflex is an operational measure of sensorimotor gating[54] which refers to the reduction in the startle response produced by a low-intensity nonstartling stimulus (the prepulse) presented shortly before the startle stimulus (Figure 2).
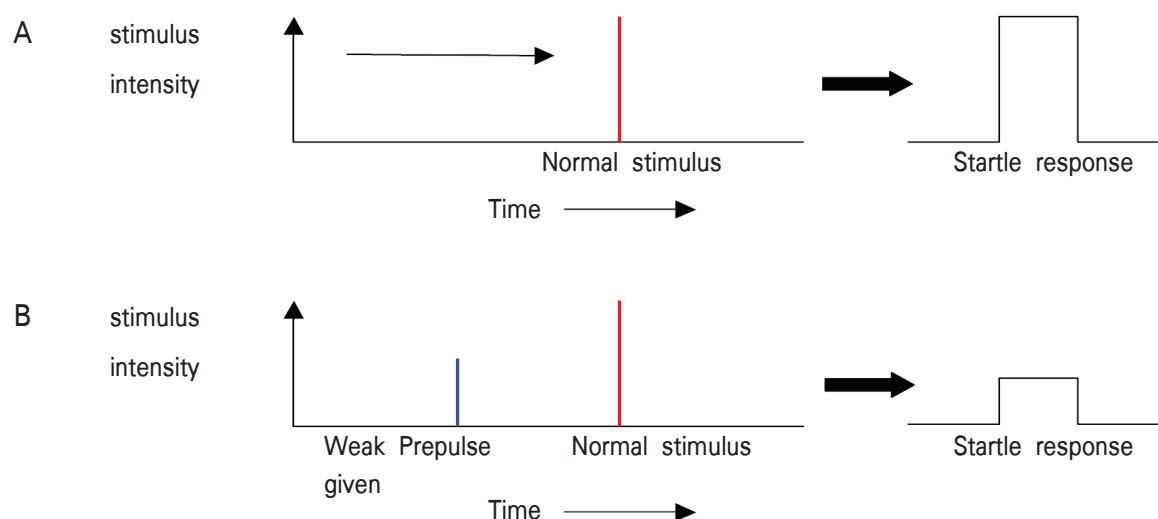

Figure 2 **(A) Startle response by normal stimulus.** Startle response occurred due to normal stimulus. Normal stimulus (red color) could be any frighten stimulus such as very loud noise and startle response would be jumping. **(B) Prepulse inhibition (PPI) in normal rats and non-schizophrenia.** Startle response in (B) is decreased compared with that in (A) when weak stimulus (weak prepulse in blue color) is given before the normal stimulus. The decrease of startle response in (B) is called prepulse inhibition or PPI. For example, people would be frightened and jump after the loud noise; however, they would be less frightened if there is some noise happening before the loud one. PPI is found in normal human and rat. Deficit in PPI is found in schizophrenia therefore the startle response of schizophrenia is always the same intensity although there is the weak prepulse stimulus.

(Modified from http://en.wikipedia.org)

In addition to hyperdopaminergic neurotransmission and decreased NOR, deficits of PPI have been reported in several neuropsychiatric conditions including schizophrenia.[51] As mentioned earlier in section 3, PPI deficits have been reported in sub-chronic PCP administration, amphetamine administration and isolation rearing models. Therefore, PPI deficits found in the animal models show the relevance of these models to the disease.

It has been demonstrated that rat pups reared in isolation from weaning exhibit deficits in sensorimotor gating as determined by reductions in PPI.[54] This effect is developmentally specific in that similar isolation of adult rats has no influence on PPI.[55] PPI deficits in rats reared in isolation arise only at or after puberty, as commonly seen in schizophrenic patients.[56] Thus the isolation-rearing paradigm provides a non-pharmacological method of inducing a schizophrenia-like behavioral deficit. The disruption of PPI seen in these isolates can be reversed by both typical[54] and atypical antipsychotics,[57] suggests that this model might also be useful for identifying novel therapeutic agents for the treatment of schizophrenia.

4. Conclusions

Schizophrenic animal models produced by sub-chronic PCP administration, amphetamine administration and isolation rearing showed the behavioral changes in several tasks such as locomotor hyperactivity, decreased capability of learning and memory in NOR task. Deficit in prepulse inhibition was also reported in these animal models. These behavioral tests in sub-chronic PCP administrated rat, amphetamine administrated rat and rat reared in isolation showed similarity to clinical aspects of schizophrenia, so sub-chronic PCP administration, amphetamine administration and isolation rearing could be valuable animal models for studying the neurobiological basis, pathological mechanism and, to some extent, treatment of schizophrenia.

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บทคัดย่อ

หนูเป็นโรคจิตได้หรือไม่: ความเหมือนของหนูที่ถูกเหนี่ยวนำให้เป็นโรคจิตเภทกับผู้ป่วยจริง

ปริศนา ปิยะพันธุ์

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　　โรคจิตเภทเป็นโรคทางจิตเวชที่มีความรุนแรงโดยมีความบกพร่องของกระบวนการคิดตัดสินใจและไม่อยู่ในโลกของความเป็นจริง อัตราการเกิดโรคนี้ประมาณร้อยละ ๑ ของประชากรทั่วโลก เพื่อที่จะเข้าใจกลไกการเกิดโรคและการรักษาจึงจำเป็นต้องศึกษาในหนูทดลอง ดังนั้นหนูทดลองที่ถูกเหนี่ยวนำให้มีอาการของโรคจิตเภทจึงได้ถูกคิดค้นขึ้นมา วิธีการเหนี่ยวนำให้เกิดอาการของโรคจิตเภทมีหลายวิธี บางวิธีมีรายงานว่าไม่สามารถทำให้หนูมีอาการของโรคจิตเภทได้จริง จึงไม่สามารถนำมาใช้ในงานวิจัยได้ จนถึงปัจจุบันมีสามวิธีที่สามารถเหนี่ยวนำให้หนูทดลองมีอาการของโรคจิตเภทได้ใกล้เคียงกับอาการผู้ป่วยจริงมากที่สุด คือ ๑) การได้รับ Phencyclidine (PCP) ๒) การได้รับ Amphetamine และ ๓) การแยกหนูให้อยู่ลำพังตั้งแต่หย่านม (Isolation rearing model) คำถามที่มักพบเสมอ คือ หนูทดลองเหล่านี้มีอาการเหมือนผู้ป่วยจริงหรือไม่ จากงานวิจัยที่ได้ทดสอบพฤติกรรมของหนูทดลองเหล่านี้ พบว่ามีการเคลื่อนไหวมากกว่าปรกติ (locomotion hyperactivity) ประสิทธิภาพด้านความจำลดลงจากการทดสอบความจำด้วยวิธีแยกแยะวัตถุใหม่ (novel object recognition; NOR) และการยับยั้งการตอบสนองของร่างกายต่อตัวกระตุ้นเมื่อมีการกระตุ้นน้อยๆ เกิดขึ้นก่อนตัวกระตุ้นที่แรงกว่า (prepulse inhibition; PPI) ลดลง การทดสอบพฤติกรรมเหล่านี้แสดงอาการของโรคจิตเภทเหมือนที่พบในผู้ป่วยจริง ดังนั้นสรุปว่าหนูทดลองที่ถูกเหนี่ยวนำด้วยวิธีการได้รับ PCP การได้รับ amphetamine และการแยกหนูให้อยู่ลำพังตั้งแต่หย่านม สามารถนำมาใช้ศึกษาพื้นฐานประสาทชีววิทยากลไกการเกิดโรค และวิธีการรักษาผู้ป่วยโรคจิตเภทได้

คำสำคัญ: โรคจิตเภท, หนูที่ถูกเหนี่ยวนำให้เป็นโรคจิตเภท