Medical Hypotheses 81 (2013) 1120–1126

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Reconsideration of animal models of schizophrenia and other psychiatric disorders with evolutionary perspective

Young-A Lee, Yukiori Goto *

Kyoto University, Primate Research Institute, Aichi, Japan

ARTICLE INFO

Article history:
Received 27 August 2013
Accepted 11 October 2013

ABSTRACT

Studies utilizing animal models for understanding biological mechanisms of such psychiatric disorders as schizophrenia have been now flourishing. Animal models are a essential part of translational research, and without them, it is not possible to develop therapeutic strategies to treat psychiatric disorders. Accordingly, importance of animal models has been increasingly emphasized. However, on the other side, limitations of such an animal model approach have been growingly deceptive. The aim of this review article is to discuss limitations of translational research utilizing animal models, and propose a new direction of research with evolutionary perspective to understand psychiatric disorders.

Introduction

Schizophrenia is a psychiatric disorder that has been under extensive investigation for long time. Schizophrenia had been once said "the graveyard of neuropathologists" [1] because of unclear pathological changes in the brains of schizophrenia patients. However, tremendous efforts, especially with recent progresses of live human imaging techniques as well as genetic understanding and engineering technologies have made significant advancement for unveiling the mystery of schizophrenia. Consequently, an optimistic belief has emerged that biological understanding of this psychiatric disorder is now within the hand, and we will eventually be able to cure the disorder. Nevertheless, the fact is that, for treatments of schizophrenia and most of other psychiatric disorders, we still do not have therapeutic methods based on the fruits of recent research, and have to rely on drugs that are based on the old serendipitous findings with considerable devastating side effects and that works in some, but not all patients.

Translational research, which is the process that develops new and better therapeutic drugs and strategies for human psychiatric disorders by applying findings in basic scientific research utilizing animals, has been currently a main research strategy (Fig. 1) [2,3]. Animal models consist of an essential part of the translational research. Accordingly, importance of animal models have been increasingly emphasized. In contrast, limitations of utilizing animal models to understand the biological mechanisms of psychiatric disorders have tended to be disregarded. This review article discusses limitations of translational research utilizing animal models for understanding such psychiatric disorders as schizophrenia, and provides a novel, alternative approach to understand psychiatric disorders with evolutionary perspective.

Animal models of schizophrenia

Following three criteria have been proposed that animal models of psychiatric disorders have to fulfill; [i] construct validity, which is whether manipulations given in animals to create models have relations to the suggested causes of the disorders; [ii] face validity, which is whether alterations observed in animal models resemble to the symptoms of the disorders; and [4] [iii] predictive (pharmacological) validity, which is whether alterations in animal models are ameliorated by currently used pharmacotherapeutic drugs or other treatment methods in human patients [5].

Animal models of schizophrenia particularly require the following additional criteria [6]; augmented responses to such psychostimulants as amphetamine and phencyclidine (PCP) and stress, which have been shown to precipitate or exacerbate symptoms in schizophrenia patients; decreased social interaction with mates, which resembles to the negative symptoms of schizophrenia; deficits in such sensory gating mechanisms as prepulse inhibition; and cognitive dysfunction, especially those relating to prefrontal cortical (PFC) function such as working memory, attention and behavioral flexibility. However, the criterion that appears to be most critical and relevant to schizophrenia is delayed onset of abnormalities. Thus, models involve manipulations given in early development (i.e., prenatal and neonatal periods), but abnormalities are quiescent in childhood, but become apparent when animals reach young adulthood. This development-dependent emergence of abnormalities resembles the typical onset age of the schizophrenia symptoms in late adolescence to young

* Corresponding author. Address: Kyoto University, Primate Research Institute, 41-2 Kanrin, Inuyama, Aichi 484-8506, Japan. Tel.: +81 (568) 63 0551; fax: +81 (598) 63 0551.
E-mail address: goto.yukiori.5c@kyoto-u.ac.jp (Y. Goto).

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http://dx.doi.org/10.1016/j.mehy.2013.10.017

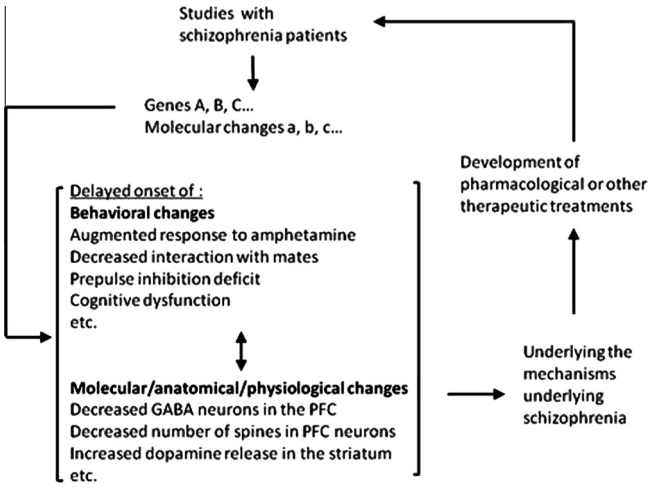

Fig. 1. A schematic diagram illustrating the process of translational research. Studies with schizophrenia patients identify potential genetic and molecular changes associated with the disorder. Based on these findings, manipulations are given in animals to examine how alterations cause alterations in animals to further understand underlying biological mechanisms. A new pharmacological or other therapeutic method is then developed.

adulthood, especially in male patients (female patients also have the peak of onset age in early adulthood, but they have another second peak on later ages around 40–70 years old [7]. Such male–female difference of the onset age of the symptoms have been barely considered in animal model studies).

To date, many animal models of schizophrenia have been proposed, which can be roughly divided into (1) lesion models; (2) pharmacological models; and (3) genetic manipulation models. Lesion models include neonatal hippocampus [8] and PFC lesion [9] in rodents as well as neonatal temporal lobe lesion in non-human primates [10]. These lesion models emphasize the face validity, which exhibit an assortment of behavioral alterations that are similar to the symptoms and abnormalities observed in schizophrenia patients. However, these models are clearly short of the construct validity, as no clear brain damage has been confirmed in schizophrenic brains. Pharmacological models include prenatal exposure to methylazoxymethanol acetate [11], prenatal immune activation [12] and exposure to such psychostimulants as amphetamine [13] and PCP [14]. In pharmacological models, both construct and face validities are balanced. Currently the main stream of animal model research is utilization of genetic models. As more schizophrenia candidate genes are recently identified, an expanding number of genetic manipulation models have been now proposed [15,16]. Genetic models emphasize the construct validity, but the models do not necessarily have to have a good face validity, as the aim of these genetic models is on endophenotype analyses, correlating dysfunction of a specific gene and a specific aspect of an abnormality observed in the disorder.

Limitations of animal model approach

Translational research bases on the idea that fundamental molecular, biochemical, anatomical and physiological architectures of animals (including rodents and non-human primates) and human brains are similar, such that findings in animals can be readily applicable to humans. This may be partly true, but it is more likely a naive presumption. However, limitations of translational research with utilization of animal models have been barely discussed to date.

One example that coins limitations of translational research with animal model approach is the case of the metabotropic glutamate receptor (mGluR) II/III agonist developed by the pharmaceutical company Eli Lilly. The study by Moghaddam and Adams published in Science in 1998 [17] is the first that suggests potential therapeutic effects of an mGluRII/III agonist on schizophrenia symptoms. They reported that the mGluRII/III agonist could reverse PCP-induced alterations in rodents. In synergy with the glutamatergic hypothesis of schizophrenia [18] and subsequent many animal model studies supporting this first finding [19,20], it appeared that the mGluRII/III agonist was the most promising novel therapeutic drug against schizophrenia. Eli Lilly then developed the mGluRII/III agonist LY2140023, and conducted clinical trials. The first phase II trial revealed significant therapeutic effects [21], but twice of subsequent phase II trials resulted in observation of no therapeutic effects of this drug. The reason why the drug had therapeutic effects in the first phase II trial, but not in subsequent trials, is unknown. However, the most important point is that in animal model studies, almost all cases have clearly demonstrated significant therapeutic potential of the mGluRII/III agonist.

Although this failure may be associated with difference of drug metabolisms that determine pharmacological responses between humans and animals, it is possible that it may also reflect limitations of animal model approach.

First, the limitation is associated with a question whether human brain is a scaled-up version of that in such animals as non-human primates and rodents. For instance, Elston and colleagues have shown that dendritic spine density of cortical neurons in humans are about twice of that in rhesus macaques and triple of that in marmosets [22]. This finding can be interpreted in two ways. One is that human brain is scaled-up version of monkey brain. The current translational research is based on this interpretation. Indeed, brains of humans and animals including non-human primates undoubtedly share some common mechanisms. The other is that this difference of the spine density is a crucial factor that distinguishes humans and non-human primates and something that we should not ignore. If emergence of such psychiatric disorders as schizophrenia originates in the common mechanisms between humans and animals, the current translational research will eventually come up into understanding of the disorders and development of new therapeutic strategies. On the other hand, if emergence of the disorders may nest in such difference between humans and animals, the current approach of translational research may not be able to reach the answer.

The second limitation is that the criteria for animal models are mostly based on indecisive evidence of human cases. In schizophrenia, a number of promising molecular, anatomical and physiological changes have been reported [23]. However, most of them have not been well replicated. Nevertheless, these alterations, although supported by only weak evidence, have been accepted as the criteria in animal models. For instance, cognitive dysfunction has been suggested as the "core" deficit underlying schizophrenia [24]. Cognitive dysfunction can be also assessed in animals, such that cognitive dysfunction has been utilized as an important criterion in animal models of schizophrenia. Nonetheless, it is particularly important to note that not all schizophrenia patients exhibit cognitive deficits. In fact, it has been estimated that up to 75% of schizophrenia patients exhibit clear cognitive dysfunction, suggesting that cognitive function in at least one fourth of schizophrenia patients are still within a normal level [25]. One explanation for this observation is that some schizophrenic patients have even higher cognitive function than normal subjects before symptom onset, and cognitive decline results in normal range of function in these patients. However, this argument does not explain why such schizophrenic patients with normal level of cognitive function still have to suffer from the symptoms and social malfunctioning. A feasibility for the argument of cognitive dysfunction as the core deficit of schizophrenia is further weakened by the fact that cognitive dysfunction can be observed in