Review

Biological Psychiatry

Caution When Diagnosing Your Mouse With Schizophrenia: The Use and Misuse of Model Animals for Understanding Psychiatric Disorders

Albert H.C. Wong and Sheena A. Josselyn

ABSTRACT

Animal models are widely used in biomedical research, but their applicability to psychiatric disorders is less clear. There are several reasons for this, including 1) emergent features of psychiatric illness that are not captured by the sum of individual symptoms, 2) a lack of equivalency between model animal behavior and human psychiatric symptoms, and 3) the possibility that model organisms do not have (and may not be capable of having) the same illnesses as humans. Here, we discuss the effective use, and inherent limitations, of model animals for psychiatric research. As disrupted-in-schizophrenia 1 (*DISC1*) is a genetic risk factor across a spectrum of psychiatric disorders, we focus on the results of studies using mice with various mutations of *DISC1*. The data from a broad range of studies show remarkable consistency with the effects of *DISC1* mutation on developmental/anatomical endophenotypes. However, when one expands the phenotype to include behavioral correlates of human psychiatric diseases, much of this consistency ends. Despite these challenges, model animals remain valuable for understanding the basic brain processes that underlie psychiatric diseases. We argue that model animals have great potential to help us understand the core neurobiological dysfunction underlying psychiatric disorders and that marrying genetics and brain circuits with behavior is a good way forward.

Keywords: Animal model, Anxiety, Behavior, Depression, Mouse, Psychiatric disorder, Rat, Schizophrenia

http://dx.doi.org/10.1016/j.biopsych.2015.04.023

Animal models have been vital for advancing knowledge in biology and developing life-saving medical treatments. Notable examples include the discovery of insulin by Banting *et al.* (1) and the work of Chain *et al.* (2) on penicillin. In 1921, Banting *et al.* (1) experimentally induced diabetes in dogs through removal of the pancreas. This allowed them to test the effects of different pancreatic extracts on metabolism, eventually leading to the identification of insulin as a treatment for type 1 diabetes. Around the same time, Chain *et al.* (2) infected mice with bacteria to test the therapeutic potential of the penicillin broth developed by Alexander Fleming (3), and these studies culminated in the development of the first antibiotic medicine. These early experiments were vital in combating previously fatal infectious diseases. More recently, mouse and rhesus macaque models were instrumental in identifying human immunodeficiency virus as the cause of acquired immunodeficiency syndrome, developing the highly effective antiretroviral drugs that have greatly reduced mortality of the disease (4–6).

In psychiatry, a major obstacle to understanding disease and developing treatments is the difficulty of generating suitable animal models. Contributing to this challenge are 1) the lack of objective clinical biomarkers for mental disorders; 2) the nonspecific nature of psychiatric symptoms such as social withdrawal, psychomotor abnormalities, or disorganized behavior; and 3) the dependence of clinical diagnosis on the interview process, language, and reporting of subjective experience. Given the challenges in diagnosing psychiatric disorders with certainty in humans, it may be prudent to avoid attempting to diagnose a mouse with a psychiatric disorder.

It is unrealistic to expect a single model to capture all the features of syndromes such as schizophrenia, autism, or depression, each of which is likely to be a heterogeneous collection of diseases that may have different causes, signs, and symptoms [for excellent discussions of this topic, see (7–10)]. However, some psychiatric illnesses may be more amenable to animal research than others. For instance, it has been argued that the essential features of drug abuse/addiction in humans can be effectively examined in rodents (11,12).

Rather than defining disorders based on a collection of signs and symptoms, the National Institutes of Health Research Domain Criteria stresses the importance of underlying biology. This initiative explicitly recognizes the need for establishing biomarkers to understand psychiatric disorders (13). A biomarker may be defined as a biological feature that can be used to assess and measure the effect of a treatment on the presence, absence, or progression of a disease (14).

 ISSN: 0006-3223

The use of biomarkers in animal research provides the opportunity for study of neurobiological and genetic features underlying psychiatric disorders, as well as the rapid screening of potential therapeutics. For example, the study of the mechanisms underlying the formation and use of fear memory in mice may give critical insight into the etiology of post-traumatic stress disorder in people, which is characterized by enduring and disruptive memories of traumatic experience. Of course, it can be tempting to anthropomorphize resulting data. Training a mouse in the typical Pavlovian fear conditioning task (in which an initially neutral cue is paired with an aversive shock) does not result in a rodent with an anxiety disorder, illustrating the perils of anthropomorphizing the results of model animals. That having been said, we believe that valuable information can derive from tapping into the brain circuits of model animals that overlap with those affected by psychiatric disease and examining behavior in the context of brain circuitry. That is, behavioral phenotypes may differ across different mutants but circuit dysfunction could be quite similar. We therefore argue that model animals have great potential to help us understand the core neurobiological dysfunction underlying psychiatric disorders and that marrying genetics and brain circuits with behavior is a good way forward.

This article is not meant to be a comprehensive survey of the literature on animal models of psychiatric disorders [for excellent recent reviews, the reader is directed to (15,16)]. Rather, we will discuss several recent examples of how animal research has contributed to understanding the basic biology underlying several psychiatric diseases. We focus on a candidate psychiatric disease risk gene, disrupted-in-schizophrenia 1 (*DISC1*), a genetic risk factor across a spectrum of psychiatric disorders and discuss the different behavioral results obtained when examining various lines of mice in which this gene was manipulated. We believe that behavioral read-outs are important and necessary in psychiatric research but that they should be interpreted in light of brain biology. That is, the best way to use model animals and gain insights into psychiatric illness will be to fully appreciate the roles and interactions of environment, genetics, brain circuits, and behavior.

DISC1: A PSYCHIATRIC SUSCEPTIBILITY GENE

Lab animals may be particularly useful for understanding pathophysiological mechanisms by which candidate susceptibility genes identified in human populations cause disease. Such studies do not necessitate a unitary model of specific psychiatric diagnoses such as schizophrenia or depression. As an example of this, we turn to the *DISC1* gene. This gene was originally discovered in a large Scottish family that had a high incidence of psychiatric illness. Family members that carried a specific mutation of the *DISC1* gene were diagnosed with some form of mental illness, including depression (10 cases), schizophrenia (7 cases), and bipolar disorder. In contrast, family members that did not carry the mutation were not diagnosed with a psychiatric condition. That a range of psychiatric conditions relate to *DISC1* dysfunction has given rise to the notion that mutations in *DISC1* can create a range of DISCopathies (17). It was later shown that the *DISC1* gene in this Scottish family was severed almost exactly in half by a balanced translocation (1q42.1:11q14.3). This mutation resulted in a relatively high logarithm of the odds score of 7.1 showing linkage between the translocation and mental illness (18–22). This makes *DISC1* a useful entry point into the biology of mental illness, as there are few instances in psychiatry where the etiology of symptoms is known (23).

DISC1 MUTATIONS SEGREGATE WITH PSYCHIATRIC DISORDERS IN HUMAN POPULATIONS

Genetic linkage of the *DISC1* locus, or association of *DISC1* variants with psychiatric illness, has been reported in many populations (24–27), including our (A.H.C.W.) own Toronto sample (28,29). Two *DISC1* missense single nucleotide polymorphisms, exon 9:Leu607Phe and exon 11:Ser704Cys, are associated with schizophrenia phenotypes (28,30). However, these mutations are distinct from that of the original Scottish family, which involves a translocation, the rarest type of genetic variant. The fact that disruptions to the same gene results in a multitude of different psychiatric disorders is a testament to the inherent limitations that may be encountered when translating pleiotropic psychiatric diseases in humans to rodents. However, the finding that translocation causes some form of psychiatric disorder in most carriers advances our understanding of how *DISC1* influences the brain. DISC1 protein acts as an intracellular scaffold, binding several other proteins for which genetic variants have been shown to independently affect risk for psychiatric illness (22). Thus, there is strong biological basis for considering DISC1 to be an important locus for psychiatric pathology.

Despite the large number of studies on *DISC1*, this body of work has been criticized because of the failure of the gene to appear in genome-wide association studies of schizophrenia or other mental disorders (31). We and others argue that, despite the lack of a link between the gene and disease in the general population, investigating the neurobiology of *DISC1* has allowed us to understand more about neurodevelopmental processes that are relevant to mental illness (32). A similar situation exists for the presenilin genes, which have been shown to be mutated in early-onset familial Alzheimer's disease but which do not account for a substantial portion of the risk of developing the disease in the general population (33). The study of presenilin genes greatly advanced our understanding of the cleavage of amyloid precursor protein, which is now known to be an important component of Alzheimer's disease pathophysiology (34).

DISC1

The DISC1 protein globular N-terminus contains nuclear localization signals, while the coiled-coil C-terminus has multiple protein binding domains (35). The Scottish family chromosomal translocation truncates the C-terminal end of the DISC1 protein, disrupting interactions with other proteins and downstream functions. This translocation mutation has been proposed to cause haploinsufficiency through reduced expression of DISC1 (36) or dimerization with the wild-type protein (37,38). However, no such reduction in DISC1 expression has been reported in human tissue from schizophrenia