Schizophrenia Bulletin vol. 36 no. 6 pp. 1066–1072, 2010
doi:10.1093/schbul/sbq106
Advance Access publication on September 24, 2010

The Role of Rodent Models in The Discovery of New Treatments for Schizophrenia: Updating Our Strategy

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The strategies used in preclinical research in schizophrenia have evolved from experiments focused on the pharmacology of existing antipsychotic or psychotomimetic drugs to the broader study of pharmacological modulation of the neurobehavioral systems affected in schizophrenia. As an additional approach, neurodevelopmental, including genetic, manipulations have become increasingly used to model disease risk factors or to induce schizophrenia-relevant neuropathology. In the vast majority of these models, behavioral testing paradigms are used to test the effects of the drugs or developmental manipulations on psychomotor, cognitive and affective processes hypothesized to be affected in schizophrenia. The term "animal model of schizophrenia" is now applied to any combination of these strategies. The expansion in animal modeling strategies has led to significant innovation in identifying novel neural mechanisms that may contribute not only to psychosis but also to the cognitive and negative symptoms of schizophrenia. Yet one cost of innovation in the discovery of truly novel treatment targets is a higher risk for false positives—drugs that have shown promise in animal models but not in clinical trials. The goals of this commentary are to first provide a brief history and conceptualization of rodent models in preclinical research and then examine the issues to be addressed in order to increase the predictive power of animal models in the identification of new treatment targets and, ultimately, new effective treatments for schizophrenia.

Key words: animal models/translational research/drug development/risk factor/neurodevelopment/ antipsychotic/psychotomimetic

The strategies employed in the design of animal experiments in schizophrenia research began with attempts to determine the pharmacology of serendipitously discovered antipsychotic drugs and have since evolved in several directions. The initial back-translational pharmacological strategy evolved into a hybrid approach informed by the pharmacology of psychotropic drugs, clinical neuroscience research in psychiatric disorders, and basic behavioral neuroscience studies of the neural systems (and related behaviors) affected in schizophrenia. In parallel, the use of neurodevelopmental and genetic manipulations to model disease risk factors or induce schizophrenia-relevant neuropathology has become increasingly important. In addition to disease models (ie, models that aim to recapitulate one or more aspects of the etiology or pathology of schizophrenia), preclinical researchers make extensive use of behavioral testing paradigms. These paradigms range from characterization of the effects of antipsychotic or psychotomimetic drugs to theoretically based paradigms that measure psychomotor, cognitive, or affective processes hypothesized to be affected in schizophrenia. Today, the term "animal model of schizophrenia" is used to refer to any combination of these strategies. Moreover, an animal model of schizophrenia can be used with the goal of simply understanding an aspect of the disease, testing the plausibility of a risk factor, identifying a drug target, or predicting the effect of a drug on the disease. These goals are distinct but interdependent. This article will focus on the strategies used for discovery of new treatments for schizophrenia.

Notably, the evolution of animal modeling strategies has not yet yielded a revolution in the treatment of schizophrenia. In this commentary, I review the major animal modeling strategies and conceptualize them in terms of the aspects of schizophrenia (or its treatment) they are thought to model. The article then examines issues to be addressed as we develop the next generation of disease models and neurobehavioral testing paradigms to identify new treatment targets and predict efficacy of novel drug treatments in schizophrenia. With these aims, this article is meant to complement the many excellent review articles available on the individual animal

modeling strategies used in schizophrenia research. Many of these articles are cited herein and in the tabular summary of animal models available at the Schizophrenia Research Forum website.[1]

An Overview of Animal Modeling Strategies in Schizophrenia Therapeutics Research

The first antipsychotic drugs were not prospectively designed but rather discovered serendipitously.[2] Phenothiazines had been employed as antiseptics, antihelminthics, antimalarials, and antihistamines during and after World War II. One of the drugs in this class, chlorpromazine, was found in the early 1950s to markedly reduce agitation and hallucinations. By 1960, the term ''neuroleptic'' had been applied to chlorpromazine and similar drugs, and their use had revolutionized the treatment of psychotic disorders. This psychopharmacological revolution initiated ''back-translational psychopharmacology'' research: research aimed at elucidating the mechanisms of action of known therapeutic drugs. Examples of this strategy include the early studies characterizing the motor effects of reserpine and chlorpromazine,[3–6] as well as the pharmacological dissection of drugs such as haloperidol and clozapine from the behavioral to the molecular level.[7–10] The overarching goal of this strategy has been to understand molecular mechanisms (usually receptors) underlying the effects of antipsychotic or psychotomimetic drugs. This long line of inquiry has led to subsequent generations of antipsychotics that are widely used today primarily due to their decreased liability for the motor and some cognitive side effects associated with neuroleptics.[11,12] More importantly, it also spurred research that has greatly increased our understanding of major mechanisms of psychosis, particularly with regard to the dopamine (DA) system.[5,6,13,14] Moreover, characterization of the pharmacology of clozapine and psychotomimetics, including amphetamine, phencyclidine (PCP), and lysergic acid diethylamide, has revealed serotonergic, glutamatergic, and other non-dopaminergic mechanisms that may contribute significantly to psychopathology in schizophrenia.[6,12,15,16] However, the drugs discovered with this approach are necessarily constrained by the pharmacology of preexisting drugs. As a result, the second-generation drugs have shown no greater efficacy than first-generation antipsychotics and, like first-generation antipsychotics, do not adequately treat negative or cognitive symptoms. Moreover, these drugs have serious metabolic and other side effects that limit the therapeutic window they were designed to expand.[17,18]

The next significant advance in animal models of schizophrenia resulted from the integration of information from the multiple types of research: (1) characterization (with brain imaging or cranial electrophysiology) of neural correlates of the symptoms of schizophrenia,[19–21] (2) neuropsychological and neuroscience-informed operationalization of these symptoms,[17,22] (3) systems and behavioral neuroscience research in animals,[23] and (4) the psychopharmacology of other brain disorders (not just psychosis). This broader, more clinical and basic neuroscience-informed approach is exemplified in the investigations of glutamatergic mechanisms in schizophrenia. The designs of the relevant animal models have drawn from the following lines of evidence: N-methyl-d-aspartate (NMDA) antagonists can (1) cause psychosis in humans, (2) impair sensorimotor gating, an early cognitive process impaired in psychosis and disrupted by other psychotomimetic drugs in experimental animals, and (3) impair aspects of cognition that have been shown in humans and animal models to recruit/require the prefrontal cortex and are impaired in schizophrenia patients.[24–26] The convergence of these findings spurred investigations of glutamate markers in the brains of schizophrenia patients[27–29] and, in parallel, animal studies on the effects of NMDA antagonists on mesostriatal DA systems and neurotransmission within the prefrontal cortex.[24,25,30] One of the unexpected findings from the animal experiments was that NMDA receptor blockade causes an increase in glutamate efflux, and overstimulation of non-NMDA glutamate receptors, in prefrontal and other cortical regions. Moreover, reducing glutamate efflux with metabotropic glutamate receptor (mGluR) 2/3 receptor agonists was shown to mitigate some of the cognitive and behavioral abnormalities caused by NMDA receptor blockade in rodents.[30] An mGluR 2/3 agonist has since been shown to have some efficacy in the treatment of schizophrenia.[31] Thus, while the straightforward back-translational psychopharmacology approach focused on drugs that augment NMDA receptor function (an approach that was also productive), the ''neuroscience-informed psychopharmacology'' approach identified intervening mechanisms, including excess glutamate and decreased DA transmission in the prefrontal cortex, that also led to additional novel therapeutic targets.[25,32]

A comparison of drugs in phase 2 or 3 trials in 2007[12] vs 2010[33] reveals the expanding influence of neuroscience-informed psychopharmacology strategies. Whereas in 2007, phase 2/3 trials consisted almost entirely of DA D2/serotonin 5HT2A receptor ligands discovered through back-translational psychopharmacology; phase 2/3 drugs today are much more diverse in their mechanisms of action and with respect to the symptom domains they target.[32–35] On the other hand, this more expansive strategy has shown the potential to lead to false positives—drugs identified as ''hits'' by rodent experiments that showed little or no efficacy in clinical trials. This is evidenced in the literature by the dozens of drugs that have been shown to block or reverse specific behavioral, neurochemical, or neurophysiological effects of PCP or other psychotomimetics, only a few of which are likely to be related to viable treatment targets in schizophrenia. The causes of the decrease in the predictive power of these newer strategies are complex and involve every

stage of drug development. As discussed below, our newly expanded ability to identify potential treatment targets must be counterbalanced by experimental design principles that enhance predictive validity.

In addition to the pharmacological strategies described above, major animal modeling strategies in schizophrenia include (1) developmental manipulations that lead to schizophrenia-relevant neuropathology or pathophysiology and (2) genetic and other developmental models of risk factors. The neonatal ventral hippocampal lesion (NVHL), the MAM E17, and maternal immune activation (MIA) models are examples of "developmental neuropathology" models, with MIA also modeling a well-established risk factor (see below).[36–39] In the case of the NVHL, an excitotoxin is infused into the ventral hippocampus at postnatal day 7. In the MAM E17 and MIA models, a DNA alkylating agent (methylazoxymethanol acetate) or immune-activating agent (Poly I:C) is administered to pregnant rat dams at gestation day 17 or 15, respectively. There is considerable similarity across these models in the neuropathological, neurochemical, and cognitive and behavioral phenotypes that emerge across development. The effects of MAM E17 and MIA are consistent with epidemiological evidence for prenatal "stressors" disrupting the development of the hippocampus. The NVHL, MAM E17, and MIA models support the hypothesis that neurotoxic events within the hippocampus during embryonic development can lead to abnormal limbic (hippocampal and/or medial prefrontal) cortical regulation of subcortical DA systems, as well as neurobehavioral abnormalities relevant to psychosis. This is evidenced in these models, in part, by abnormally high responsiveness to amphetamine, related abnormal increase in striatal DA transmission, and impairment of sensorimotor gating.[23,36,37,40] The "isolation rearing" model, in which rats are socially isolated after weaning, can be also considered a developmental neuropathology model targeting adolescent neurobehavioral development. This manipulation may model the effects of social isolation during a potentially sensitive period for limbic circuit development and a period during which many individuals who eventually develop schizophrenia begin to experience a marked social withdrawal.[41–44] This manipulation also disrupts the function of the striatal DA system and sensorimotor gating in adulthood.[26,45] Unlike most back-translated models, the above developmental neuropathology models exhibit neurobehavioral and cognitive phenotypes relevant to the motivational, social behavioral, and cognitive impairments in schizophrenia patients. Thus, these models might be useful in predicting the efficacy of candidate therapies in treating negative symptoms or cognitive impairments. However, more information is needed on neurodevelopmental mechanisms disrupted in these models and the neuropharmacological mechanisms underlying their neuropathology and psychopathology. Uncovering these mechanisms is necessary for these models to significantly advance discovery of new prevention or therapeutic strategies for schizophrenia.

The most rapidly growing domain of animal models of schizophrenia is "risk factor models." There are now at least 952 proposed susceptibility genes for schizophrenia[46,47] and multiple well-established early environmental risk factors including paternal age, prenatal maternal stress or immune activation, birth complications (hypoxia), and winter or urban births.[48,49] The increasing genetic and genomic data in schizophrenia populations and the availability of genetic mouse models have generated great optimism for identifying new treatment targets, as evidenced by hundreds of reviews and commentaries[50,51] and a recent volume of *Progress in Brain Research* dedicated to this topic.[52] At this point, however, the commentaries on genetic mouse models outnumber the neurobehavioral data articles; thus, there is much work to be done before this modeling strategy will help advance target discovery. Critical issues here include (1) the robustness of the association between the gene and the risk for schizophrenia and (2) our ability to accurately model the disease-related genetic structural variant in mice. For rare gene copy number variations, chromosomal deletions (eg, 22q11 deletions), or translocation of a segment of the gene (eg, *DISC 1*), the gene mutation carries a very high-risk load and may be able to be modeled in the mouse genome. Studying the shared effects of these mutations in mice is likely to reveal major molecular and neural mechanisms involved in the pathogenesis of schizophrenia.[53] However, for the vast majority of susceptibility genes, there are one or more polymorphisms weakly associated with schizophrenia risk. Most of these polymorphisms cannot be recapitulated in the mouse because they occur in noncoding regions that are not homologous between humans and mice. Moreover, biological effects of the polymorphisms cannot be modeled because they are unknown for the most part. For such genes, the approach has been to study the effects of overexpression or underexpression of the gene on schizophrenia-relevant neurobiological processes or behaviors. This approach has the potential to reveal many candidate susceptibility molecular pathways, most of which will have little relevance to schizophrenia. The design and interpretation of the behavioral assays used with the model thus becomes crucial to discerning the relevance of the gene manipulation to schizophrenia.[50,51,53,54]

Increasing the Validity and Predictive Power of Animal Modeling Strategies

Overall, the neuroscience- and genetics-informed animal modeling strategies have increased our ability to identify novel neural mechanisms that may underlie the psychopathology or pathogenesis of schizophrenia and/or

underlie the therapeutic effect of a drug. However, the power of these strategies to ''predict'' an effective treatment for schizophrenia is still not clear.[55] Moreover, we do not know what level of predictive power to expect when embarking on these strategies in which the targets to be discovered are not predicted by known targets. The predictive power (and efficiency) of traditional back-translational pharmacology derived in large part from our a priori knowledge that DA D2 receptor blockade and the pharmacology of clozapine reduce psychotic symptoms. Perhaps one of the most important steps in developing new strategies for treatment discovery in schizophrenia is to accept the amount of time and effort such strategies require. As part of this process we might ask, ''What rate of false positives should we tolerate in order to find a truly new and important treatment mechanism, and how can we limit the false positive rate?'' Generally, the rate of false positives can be reduced by requiring convergent evidence (from clinical, preclinical, and basic studies) that the neuro[cell]biological pathways regulated by the candidate drug target can, in turn, regulate neurobehavioral processes affected in schizophrenia. Along this line of thinking, the predictive power of animal models can be increased by improving our ability to (1) systematically and selectively measure schizophrenia-relevant cognitive and affective processes in rodent models, (2) identify neural mechanisms underlying these processes, and (3) model putative etiologic or pathogenic mechanisms that lead to these abnormalities.

The concepts of validity and reliability of a model (or measurement) have long been central to the field of experimental psychology and, many argue, must now be used to ground the process of rational treatment discovery in psychiatry. A model (in this case, an animal model) can possess multiple forms or levels of validity that interact to determine the model's ability to predict the actual behavior of the target population (in this case, schizophrenia patients). The reader is referred to the influential work of Willner[56,57] on this topic. For animal models of schizophrenia, predictive power can be gained by maximizing 2 forms of validity known as ''content'' or ''etiologic'' validity and ''construct'' validity.[23] For example, in the case of mouse genetic models, this means prioritizing the study of models that faithfully recapitulate the genetic mutations with the most robust associations with schizophrenia (etiologic validity) using neurobehavioral paradigms that faithfully measure cognitive and affective processes disrupted in schizophrenia (construct validity).[23,53] The outcomes of behavioral pharmacological experiments in rodents cannot accurately predict a drug's therapeutic efficacy unless it is first determined whether the rodent's behavior within the paradigm represents the cognitive, motivational, or affective process that we want to normalize in schizophrenia. This first requires a critical mass of clinical neuroscience studies that isolate the neurocognitive or neuroaffective processes (constructs) that mediate the major behavioral symptoms of schizophrenia.[22] It further requires the establishment of construct validity in paradigms used to measure those processes in humans and rodents. The criteria for construct validity in preclinical schizophrenia research can be summarized as follows: First, the behavioral index of the cognitive, motivational, or affective process must show the same environmental or psychological determinants across species. For example, operating a joystick, pressing a button or bar, or running down the arm of a maze can all be used to quantify ''volition'' if the behavior is dependent on the value of the reinforcer (eg, food, water, sex, or money), relative to the deprivation state of the animal with regard to the reinforcer. The second criterion for neurocognitive or neurobehavioral construct validity is that the process must be mediated by homologous neural circuits. With the above example, behavioral indices of volition that depend on (or correlate with activity of) the mesolimbic DA system in both rodents and human would be considered homologous, and the task used to assay the behavior would be considered to have ''neurobehavioral construct validity''. (The reader is referred to reviews by Salamone et al[58,59] for further discussion of motivation or volition as a neurobehavioral construct.) Thus, a behavioral paradigm in rodents has neurobehavioral construct validity if it isolates and measures a behavioral process with similar environmental regulators and neural mediators as the process of interest humans. Unfortunately, the behavioral assays most commonly used in rodents have very low construct validity; instead, interpretation of these paradigms relies heavily on ''face validity'' (essentially the real or imagined similarity between the rodent's behavior and a symptom). For example, depending on the disorder of interest to the investigator, an increase in locomotor activity might have face validity as a model of ''hyperactivity,'' ''agitation,'' or ''increased motivation.'' Face validity rarely translates to predictive power. On the other hand, the use of paradigms with high construct validity allows for more precise predictions of the human neurobehavioral systems modulated by the drug. The most predictive power is achieved by assessing schizophrenia-relevant behaviors across multiple cognitive and affective domains with a set of standardized tasks with sufficient construct validity.[51,53,60]

One approach by which neurobehavioral construct validity can be established in cognitive tasks is to start with the operational definition of a cognitive process (i.e. the construct) such as working memory, as established in human cognitive studies. Information on the cognitive constructs affected in schizophrenia can be found in a number of review articles.[23,53,60–62] Criteria derived from the operational definition are then used to design a task that manipulates and measures the construct in nonhuman primates and/or rodents. The animal experiments are conducted to determine the neural

mechanisms underlying the construct, and the definition of the construct is updated to include its neural substrates. The tasks developed with this process thus measure the neurocognitive construct and can be back-translated for use in human studies where they are often revalidated by studies in lesion patients. An example of a test battery produced through the above-described process is the Cambridge Neuropsychological Test Automated Battery (CANTAB) that has been used in now over 50 clinical studies to assess frontal and temporal cortical circuit function in schizophrenia and other psychiatric and neurologic patient populations.[61] A related and complementary approach to establishing neurocognitive construct validity in psychological tests in humans is to use brain imaging as a tool in developing the tasks. The psychological definition of the construct is used to design the task; as brain imaging reveals the neural circuits recruited by the task, task demands can be refined to selectively recruit (thus assay the function of) neural circuits centrally involved in a cognitive construct. An example of an ongoing initiative that uses a combination of the above approaches to increase construct validity in the neuropsychological tests used for treatment development in schizophrenia is Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS), (see http://cntrics.ucdavis.edu)[22].A full discussion of issues in experimental design in clinical and preclinical cognitive neuroscience research relevant to schizophrenia is beyond the scope of this review. The reader is referred to the tasks and relevant literature listed at the CNTRICS website (http://cntrics.ucdavis.edu) and an excellent recent review by Barnett et al.[61] The key features of the rodent behavioral tasks used to measure schizophrenia-relevant neurocognitive and neurobehavioral constructs have also been reviewed.[50,60,63] Bringing construct validity to ethologically based phenotyping or analysis of spontaneous or psychostimulant-induced activity is discussed in a number of review articles.[50,54,63,64] The major challenge will be to apply paradigms with high construct validity to pharmacological, developmental neuropathology and risk factor models of schizophrenia. This will require clinical neuroscience research in schizophrenia to more precisely identify the neurocognitive and neurobehavioral constructs that are most reliably and severely affected in schizophrenia.

Summary and Considerations

In summary, treatments for schizophrenia have, thus far, been discovered primarily through serendipity and back-translational psychopharmacology strategies applied to animal models. A significant number of novel treatment targets are beginning to be yielded from more recently developed hybrid pharmacological models of pathophysiology, and there is an enormous potential for more candidate targets to be generated through the study of developmental neuropathology and risk factor models. Whereas the back-translational psychopharmacology strategy constrained research too much with its focus on the pharmacology of known antipsychotic drugs, the newer models may lead to an unmanageable rate of false positives if not properly constrained by etiologic or pathogenic theories and cognitive neuroscience theories as applied to the psychopathology of schizophrenia. Thus, in the next phase of preclinical research in schizophrenia, it is imperative that we improve our disease pathogenesis models so that they more faithfully model the known risk factors and/or the structural and functional neuropathology of schizophrenia. It is equally important for us to implement behavioral tasks with high construct validity in measuring the cognitive, affective, and motivational abnormalities exhibited by schizophrenia patients. With this integrative strategy, we have the opportunity to discover the neurobiological mechanisms underlying both the neuropathology and the psychopathology of schizophrenia and, ultimately, develop treatments that may prevent or treat the disease with drugs that target these mechanisms.

Funding

New York State Office of Mental Health; Lieber Center for Schizophrenia Research at Columbia University; Public Health Service Award (RC1MH088740 and P50MH086404) to H.M.

Acknowledgments

The author declares that there is no conflict of interest in relation to the subject of this article.

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