Developing Predictive Animal Models and Establishing a Preclinical Trials Network for Assessing Treatment Effects on Cognition in Schizophrenia

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Animal models are an essential initial phase in the discovery of novel drugs to treat psychiatric disorders. At the sixth Measurement and Treatment Research to Improve Cognition in Schizophrenia conference, “New Approaches to Assessing and Improving Cognition in Schizophrenia,” a discussion group was formed to address issues related to the development of predictive animal models of cognition that may be used as preclinical assays for putative cognitive enhancers. We identified 2 complementary approaches used to model cognitive impairments in animals. First, basic lesion/pharmacological models provide information about the particular neural substrates that may underlie different types of cognitive deficits found in schizophrenia. Findings from these studies can be mapped onto the second, more elaborate and etiologically relevant neurodevelopmental models of the disorder to ascertain which cognitive systems may be altered by early developmental insults. Particular attention must be given to the types of animal tasks used, in order to relate directly to the cognitive domains that are affected in schizophrenia patients. Importantly, the validation and standardization of the methodologies used in these preclinical assays would require the establishment of a preclinical trials network, serving as a counterpart to the recently established Treatment Units for Research on Neurocognition and Schizophrenia. The need to validate specific approaches to assess cognitive functions relevant to schizophrenia could be satisfied by a concerted effort enabled by a new funding directive from the National Institute of Mental Health with the explicit purpose of facilitating research on these models and assessing novel drug therapies that may be used to ameliorate the cognitive deficits in schizophrenia.

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Introduction

Schizophrenia is known to be a heterogeneous disorder, characterized by positive symptoms, negative symptoms, disorganized states, and cognitive deficits. Even though the cognitive deficits have been recognized since initial description as central to this disorder (i.e., as “dementia praecox”), the therapeutic management of these symptoms has not been a focus since the discovery of the antipsychotic properties of dopamine-antagonist drugs. Nevertheless, it is becoming increasingly apparent that the disruptions in cognitive functioning observed in schizophrenia represent some of the core features of the disorder, as opposed to merely a result of the symptoms.\textsuperscript{1–3} In order to facilitate the development of novel pharmacotherapeutic approaches for the treatment of the cognitive deficits in schizophrenia, the National Institute of Mental Health (NIMH) established the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (www.matrics.ucla.edu). The objective of MATRICS is to bring together representatives of academia, government, and industry in a consensus process to address obstacles that are likely to interfere with the development of pharmacological agents for treating cognition in schizophrenia. Two major accomplishments of this initiative thus far are the identification of the 7 primary cognitive domains that are affected in schizophrenia—attention/vigilance, speed of processing, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition\textsuperscript{3}—and the development of a consensus regarding a standardized cognitive test battery for use in clinical trials to assess the potential benefit to cognitive functioning of novel drug treatments. One of the primary long-term goals of the NIMH-MATRICS program is to facilitate the development of more effective pharmacotherapeutic approaches to treating the cognitive deficits in schizophrenia. Such development would be strongly dependent on the validation of appropriate preclinical drug screens for compounds designed to ameliorate cognitive dysfunction observed in schizophrenia.
Developing Predictive Animal Models of the Cognitive Deficits in Schizophrenia

A primary issue of importance is the question, What is the most appropriate approach to model the deficits seen in schizophrenia in animals? It is apparent that traditional models used to assess the efficacy of traditional antipsychotic medication are not likely to be as valid for use in understanding the mechanisms that underlie cognitive dysfunction in schizophrenia. Simply put, whereas conventional neuroleptic treatments are effective in treating the positive symptoms of the disorder (i.e., psychosis), they have not proven to be effective in alleviating the cognitive symptoms observed in schizophrenia patients. Indeed, the recognition that both the first and the second generations of antipsychotic treatments are largely ineffective in ameliorating these cognitive deficits was a fundamental driver for the MATRICS initiative. Furthermore, it is likely that the pathophysiological abnormalities that underlie psychotic symptoms are distinctively different from the neurobiological disturbances responsible for the cognitive deficits found in these disorders. Thus, in the short-term at least, treatment strategies designed to improve the psychotic and cognitive symptoms in patients with schizophrenia probably will entail a combination of drug therapies, combining classic antipsychotic medication with other co-treatments designed specifically to improve cognitive functioning.

Rather than focus on the benefit of any 1 of the 7 cognitive domains that could potentially be modeled in animals, our group focused on more general issues related to what is needed to drive the field forward and to identify the particular approaches that may be most predictive of the clinical benefit for putative cognitive enhancers. There are 2 potential approaches to developing such a model; 1 would be to identify specific systems that may underlie cognitive deficits related to the cognitive domains referenced above and via lesion, inactivation, or pharmacological analyses, identify how these systems may respond to restorative treatment. The other approach would be to identify as comprehensive a model of the disorder as is possible and then identify which cognitive domains are disrupted and how these effects may be reversed. An important consideration concerns the relationship between tests, operationally defined as paradigms or assays, and models that tend to recapitulate aspects of the disease related to etiology, genetics, neurochemistry, and/or phenotype. Tests can be used to characterize performance in normal animals under conditions where an imposed behavioral challenge may induce impaired performance. Tests can also be used to characterize a performance deficit exhibited in an animal model that utilizes an intervention (lesion, stress, etc.). Both tests and models can be validated pharmacologically by evaluating the effects of potential therapeutics and/or neuropharmacological probe agents. Because we are still working to understand how deficits in specific domains of cognition relate to clinical dysfunction and treatment response, feedback from ongoing clinical studies will be critical to further refine the nonclinical tests and models (figure 1). The lack of an approved drug to use for validation of animal models remains an obstacle.

Clearly, any experimental approach intending to model the deficits found in schizophrenia in animals must reproduce at least 1 of the symptoms or signs found in the patient population. We have identified 3 fundamental issues that should be considered when devising preclinical assays to evaluate the benefit that a particular drug may have in improving cognition in schizophrenia.

Pharmacological/Lesion Models Versus Neurodevelopmental Models

We made note of 2 basic approaches that have been used to induce a particular type of cognitive deficit in animals that may have relevance to schizophrenia. One approach entails using data obtained from clinical imaging and infarct studies to derive specific pharmacological or lesion manipulations that can be mapped onto a specific cognitive domain of schizophrenia pathology. For example, cognitive and imaging studies have reported that schizophrenia patients present working memory impairments that are correlated with alterations in D1 receptor activity in the prefrontal cortex. A potential animal model of this phenomenon could entail assessing the impact of local administration of D1 receptor agents or neurotoxic lesions of the mesocortical dopamine system on tests of working memory in animals and, in turn, investigating whether a potential cognitive enhancer may alleviate deficits induced by such a manipulation. An
The apparent advantage of using such an approach is that the experimental control provides information about the specific alterations in transmitter systems and neural circuits that may be an underlying cause of the deficits observed in schizophrenia. However, the main disadvantage that comes with this method is that it may lack etiological validity. Inducing a particular manipulation in an otherwise normal animal would not be expected to approximate the combined genetic, developmental, and environmental factors that lead to the neural pathology of the disease; nor would it be expected to model the subtle changes in numerous neural systems that underlie the disorder (although see 12). Moreover, there is the danger that a pharmacotherapeutic approach that is dependent on a specific pharmacological manipulation may be limited to reversing the pharmacological treatment itself rather than what may be disrupted in the patient (e.g., an N methyl D aspartate [NMDA] agonist to reverse deficits induced by an NMDA antagonist).

To address the issue of etiological validity, neurodevelopmental disruptions have been used as an alternative approach to developing animal models of schizophrenia that may better approximate the pathophysiology that occurs in the disease. Here, cellular or neural insults are induced early in development (either in utero or in neonatal animals) that are designed to better approximate particular etiologies of schizophrenia. Such approaches have met with some success. Some of these models include inducing lesions to the ventral hippocampus in neonatal rats, disrupting mitosis in utero using antimitotic compounds such as methylazoxymethanol acetate, isolating animals post-weaning, and others. These manipulations typically cause postpubertal behavioral and cognitive disruptions that resemble those observed in schizophrenia and are associated with neuroanatomical and cellular alterations in numerous cortical and subcortical systems that have been implicated in the pathology of the disease. Such models have several attractive features: (1) they may at least approach replicating developmentally driven genetic predisposition to the disorder, and (2) they may cause deficits in cognitive symptoms secondary to early pathological processes, thereby mimicking the delayed onset of symptoms of the disorder. However, even though these models may be more accurate in terms of etiological validity and may better approximate the multiple neural abnormalities associated with the disease, identifying the particular neural disruptions that are responsible for an observed deficit in 1 of the cognitive domains becomes problematic. Any particular cognitive process (to use the example again, working memory) is mediated by interactions involving multiple brain regions, including the prefrontal and other cortical regions, and thalamic, striatal, and midbrain nuclei. The diffuse neural pathology that occurs following a particular neurodevelopmental disruption can make it difficult to determine whether deficits in cognition are due specifically to disruptions of 1 particular brain region or are due to a combination of multiple brain abnormalities that all contribute to an impairment in functioning.

Based on the specific advantages and disadvantages of each of the above-mentioned methodologies, we propose a 2-pronged approach to better understand the mechanisms and develop predictive models of the specific cognitive impairments in schizophrenia. Initially studies should utilize manipulations founded on pharmacologically specific interventions or on disruption of selective neural systems. In turn, the data garnered from these more selective models can then be tested in more etiologically relevant manipulations (neurodevelopmental, genetic) in order to evaluate their validity. Ultimately, this type of combined research effort requires give-and-take between the 2 approaches; the use of more selective pharmacological or neural manipulations can assess the specific neural systems that regulate cognition in 1 domain and identify distinct types of impairments that may occur with these manipulations (e.g., attentional, perseverative, temporally graded memory deficits, etc.). In turn, the information from these studies can be
mapped onto data obtained from more general models in order to ascertain which neural system(s) may be involved in a particular type of deficit. In this regard, it is important to note that any animal “model” of the cognitive deficits in schizophrenia must be viewed as a combination of a particular manipulation and the dependent variable that is being studied. The establishment of the etiological validity of a particular manipulation and the construct validity of the dependent measures, vis-à-vis the neural and behavioral alterations that are observed in schizophrenia, clearly are important parts of the process. However, in order for it to be a truly predictive model, equal concern must be given to the particular tasks that are used to assess specific cognitive domains that are affected by the manipulation, to ensure that any beneficial effects that a potential treatment may have on a cognitive domain in animals will yield similar improvements in schizophrenia patients.

To Disrupt or Not to Disrupt?

An ancillary issue that arose from discussion of the validity of different types of animal models is whether an assessment of the therapeutic benefit produced by putative cognitive enhancers or antipsychotic medication necessitates any type of experimental disruption. There are numerous examples in the literature where the administration of a variety of compounds can improve cognition in normal animals, including the domains that are affected in schizophrenia. These domains include working memory, reasoning/problem solving (set shifting), and attention/vigilance. However, the cognition-enhancing effects of a number of drugs are only observed in perturbed subjects and may provide no benefit or even exert detrimental effects on cognition in normal animals. For example, atypical antipsychotics such as sulpiride or clozapine alleviate attentional or working memory impairments that occur following disruptions in prefrontal cortical function, but these same drugs impair performance when administered to intact control subjects (see 19–20; see also 21). Indeed, numerous groups have shown that D1 receptor stimulation can have biphasic effects, improving working memory function in animals with decreased frontal cortical dopamine but disrupting working memory in animals with a normal complement of frontal cortical dopamine. Thus, although testing the effects of a particular drug on cognition in intact animals may be a useful initial screen for its use in treating the cognitive deficits in schizophrenia, a lack of effect from a particular treatment does not necessarily imply that it would have no beneficial effects on a perturbed system. Therefore, truly comprehensive and predictive models will ultimately need to look at the effects of promising compounds in both normal animals and those that have received some sort of neural insult in order to better evaluate how these drugs can affect cognition in schizophrenia.

Combined Administration of Cognition Enhancers and Classic Antipsychotic Drugs

Given the heterogeneous nature of the symptomatology and pathology that occur in schizophrenia, it is unlikely that we will see the development of a single “magic bullet” treatment that can alleviate both the psychotic and the cognitive disruptions of the disease in the near future. The general consensus is that, for the time being, treatment regimens designed to improve both psychotic and cognitive symptoms will need to consist of administration of traditional antipsychotic medications combined with cognition-enhancing treatments. This being the case, the development of truly comprehensive animal models to test the potential benefit of novel cognition-enhancing compounds will need to take this issue into account. To improve the predictive validity of these assays, it will be insufficient to merely look at the cognitive effects of a particular compound in intact or perturbed animals. Rather, subsequent studies will require testing the effects of the putative cognitive enhancers using particular neural or pharmacological disruptions in combination with chronic treatment with a number of standard neuroleptic medications, in order to better approximate the way such treatments would likely be used in a clinical setting. Of course, this approach adds a further complication to the process, as chronic antipsychotic treatment can have a detrimental effect on learning (e.g., 24). Although it is labor-intensive, it is essential that when designing these studies, appropriate controls are used to ensure that any improvement in performance induced by a particular compound is not due simply to an alleviation of an antipsychotic-induced disruption of cognition. Furthermore, the use of this combined approach will provide important information about which drug combinations may be most effective for treating particular cognitive deficits in the disorder, which in turn can be used to guide treatment approaches in the clinic.

Implementation of a Preclinical Trials Network

Based on the issues reviewed above, it quickly became apparent that any concerted research effort implementing large-scale preclinical assays of the numerous potential cognition-enhancing compounds could not be conducted effectively by a small group of research laboratories working independently. Studies attempting to model the neuropathology of schizophrenia in animals, particularly those using neurodevelopmental insults, take many months to reach their end point. The use of more sophisticated cognitive tests that tap into the identified cognitive domains affected in schizophrenia (attention/vigilance, working memory, reasoning/problem solving,
speed of processing, social cognition) can also be particularly labor-intensive. Some, though not all, of these paradigms require weeks to months of training before animals reach an acceptable level of criterion performance and, hence, are not easily implemented as “high-throughput” types of screens. Despite these costs, the need for more predictive preclinical models for assessing the efficacy of potential cognitive enhancers cannot be understated. One of the major challenges for drug development research is to improve the success rate for clinical trials of new drug candidates; only 10% of candidate compounds that reach clinical trials eventually receive Food and Drug Administration approval. The use of more stringent and comprehensive drug screens for treatment, though time-consuming, has the potential to facilitate substantially the identification of a greater number of promising drugs in the preclinical stages while at the same time allowing for an early elimination of drug candidates that do not yield acceptable levels of improvements. This approach, in turn, would increase the probability that a particular compound that reaches the clinical trial stage would prove beneficial for treating specific cognitive deficits in schizophrenia patients and be brought to market. Thus, even though implementing more stringent preclinical assays may appear to be a long, slow endeavor, the possibility that they may increase the efficiency of the human clinical trial process suggests that the potential benefits of these initial screens far outweigh their costs. Ultimately, spending a bit more time testing the potential benefit of drugs using animal models will still be substantially cheaper than having a drug fail in human clinical trials.

In light of the large-scale effort that would be required to establish effective preclinical assays for the cognitive deficits in schizophrenia, 1 of our primary conclusions is that there is an essential need to implement a preclinical trials research network, for the specific purpose of developing and evaluating the construct and predictive validity of these assays. We envision such a network as being made up primarily of academic laboratories (at least initially), working in collaboration with the pharmaceutical industry and government funding agencies. A particular advantage of such a network would be to circumvent needless duplication of work directed at reinventing cognitive tests and the therapeutic potential of nonproprietary compounds in such trials. The specific research goals of this network would include (1) developing comprehensive and predictive preclinical animal models to be used in the assessment of novel compounds designed specifically for the treatment of cognitive dysfunction in schizophrenia; (2) identifying compounds that are known to have cognitive-enhancing properties in schizophrenia patients to serve as positive control compounds in the validation and conduct of new preclinical models; (3) providing the infrastructure to allow for a coordinated exchange of ideas and data between academic research groups, as well as to facilitate communication between basic scientists and industry; and (4) facilitating 2-way communication between basic and clinical scientists to both enhance the development of these preclinical models and provide information that may be used in a clinical setting. Suggestions on how to implement this network follow.

Several pharmaceutical company representatives in the discussion group noted that soon after the initial MATRICS consensus conferences established the relevant cognitive domains, a number of different groups independently evaluated each of the cognitive domains with respect to appropriate animal tests and evaluated an array of classical and atypical antipsychotic drugs on these models, as well as prototypical nonproprietary selective agents. In general, a hierarchical testing scheme is employed that involves testing some general or higher-throughput cognition models initially and then progressively more specific/labor-intensive models with subsequent tests. Although the findings garnered from these (mostly unpublished) studies provide important information that would further the development of more comprehensive models, as noted above, this duplication of effort reduces the efficiency of the drug discovery process. As such, an initial step in establishing a preclinical trials network would be to make these nonproprietary data available to all researchers in the field in the form of a general-access database. This database might include a listing of the particular drugs that have been tested, along with the pharmacokinetic data and receptor specificity data for each of these compounds. In addition, it was suggested that some of the proprietary compounds that are not suitable for further development could be made available to academic research laboratories, along with their pharmacokinetic and receptor specificity data. Many of these compounds may have failed toxicology tests but would still provide valuable research tools to the basic scientist because of their selectivity and specificity, which would facilitate the advancement of the field. It is hoped that an initiative can be advanced to construct and implement this database in a manner that is easily accessible and searchable by any individual or organization in order to more efficiently advance drug development for the amelioration of cognitive dysfunction in schizophrenia.

Although extremely useful, the formation of a database would only represent part of the solution. The essential long-term goal of this effort would be to establish a network of research groups whose principal goals would be (1) developing and validating animal models of cognition to be used as preclinical and translational tests for candidate compounds and (2) using these paradigms to evaluate the potential benefits of already established and experimental cognition enhancers, in collaboration with the pharmaceutical industry. In essence, this network would serve as a preclinical counterpart to the recently established Treatment Units for Research on
Neurocognition and Schizophrenia, funded by NIMH (www.turns.ucla.edu). The first step in this process would be to develop a coordinated research plan for work that could lead to the establishment of a hierarchy of drug screens of increasing selectivity that can be used to evaluate compounds for efficacy in selective cognitive domains. The goal would be to develop a battery of tests that would be analogous to that achieved by the first 5 MATRICS meetings for the clinical assessment of the 7 cognitive domains relevant to schizophrenia. This process could begin with a 2- or 3-day workshop dedicated to elaborating a research agenda, somewhat akin to an abbreviated “basic sciences” MATRICS process. We would recommend that this be an open meeting and that academia, industry, and government colleagues be well represented. The discussion group recognized some considerable urgency to initiate this process, as industrial, academic, and government labs are already moving forward independently in a manner that is likely to be redundant and less effective than the cooperative organized approach recommended here. In the long run, scientists from academic and pharmaceutical company research laboratories as well as those from the clinical sector would formulate a consensus on particular tests and approaches that most effectively assess animal cognition related to the cognitive domains established by the MATRICS process and institute standardized experimental protocols to be used by research groups involved in drug discovery and validation. In addition, a parallel mandate of this commission should be to facilitate the interactions between basic and clinical scientists for the explicit purpose of developing translational paradigms and measures that could be used in both preclinical studies and Phase II clinical trials.

Once consensus on the best approaches to studying these phenomena has been achieved, formal implementation of a preclinical trials network would benefit from a new funding directive put forth by NIMH. In practice, this effort would likely take the form of a series of new programs specifically designed to fund research dedicated to developing tools for drug discovery in treatments for cognition in schizophrenia. Initially, it might be expected that research programs assessing the validity of these models using currently available cognition-enhancing treatments and novel compounds in development would be the main recipients of these funds. The need to identify positive control compounds that can be used to validate novel models for the identification of pharmacological treatments for the specific cognitive domains of concern in schizophrenia is a specific imperative requiring the combined efforts of clinical and basic scientists. Hence, particular emphasis would be placed on collaborative and interdisciplinary programs that would foster basic–clinical science interactions to promote translational research, whereby certain treatment approaches could be assessed in both preclinical models and clinical settings concurrently. The exchange of information that would result from using this approach not only will further efforts to develop more predictive animal models of the disorder but will likely provide useful information that may be used in clinical applications.

To summarize, we believe that the establishment of a preclinical trials network designed to assess treatments for the cognitive deficits in schizophrenia is an essential part of the endeavor to better understand, discover, and develop treatments for the pathophysiology that underlies this component of the disorder and to develop revolutionary new treatments for these symptoms. We have identified a number of issues that need to be considered when developing these models, as well as proposed an approach for implementing this network. The fact remains that we are only now beginning to address the cognitive deficits in schizophrenia as core components of this disorder and that preclinical testing of novel therapeutic drugs is an integral and essential part of the drug discovery process. Therefore it is apparent that a concerted research effort, entailing collaborative interactions between basic and clinical scientists from academic, industrial, and government sectors, is required to model these impairments and devise effective treatments if we are to move the field beyond the current methods for treating these symptoms of the disease.

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