THE ROLE OF PRECLINICAL MODELS IN THE DEVELOPMENT OF PSYCHOTROPIC DRUGS

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This chapter critically discusses how preclinical models, primarily animal models, can be used in neurobiological research to promote the development of psychotropic drugs as therapeutics for psychiatric disorders. The authors' previous chapter in *Neuropsychopharmacology: The Fourth Generation of Progress* (1) extensively discussed the process of developing, validating, and working with animal models relevant to psychiatric disorders. Various approaches to model development and validation criteria for animal models were defined and evaluated. These basic principles of model development and validation were further elaborated in the context of reviewing animal models of depression and schizophrenia. The present chapter is intended as a continuation and addition to the previous chapter. Thus, assuming the fundamental principles of model development and validation established in the previous chapter and briefly reviewed here, the present chapter focuses on additional aspects of model development, validation, and use that need to be taken into consideration when using models as aids to the development of *therapeutic approaches* for psychiatric disorders. These principles are clarified further by discussing a few exemplary issues relating to animal models used in the study of depression, schizophrenia, and anxiety. Although the development of pharmacologic treatments for psychiatric disorders is typically the major focus, the same basic principles of model use also can be applied in the development of nonpharmacologic therapeutics for these disorders.

DEFINITION OF A PRECLINICAL MODEL

A model is defined as any experimental preparation developed for the purpose of studying a condition in the same

or different species. A model is comprised of both the independent variable (i.e., inducing manipulation) and the dependent variable (i.e., the measure[s] used to assess the effects of the manipulation). The choice of the inducing manipulation is usually based on hypotheses about the etiology of the disorder of interest or nontheoretic exploratory attempts to induce the abnormality (as reflected in the dependent measures) that is considered relevant to the psychiatric disorder of interest. Pathologies having homology with those in humans can be induced in animals more readily if the etiology of the disease is known. Unfortunately, the etiologies of psychiatric diseases are largely unknown, making the choice of the independent variable particularly difficult. The choice of the dependent measures is usually based on operational definitions of abnormalities believed to be pathognomonic, or at least symptomatic, of the disorder of interest. As with the inducing manipulations, the selection of diagnostic criteria and determination of the core features of a psychiatric disorder are also debatable. Thus, the selection of both the inducing manipulations and dependent measures that comprise a model of a psychiatric disorder are based largely on theoretic arguments regarding both the etiology and core aspects of the disorder. The choice of dependent variables is somewhat easier than the choice of the inducing manipulation because it can be based on operational definitions of observable aspects of the disease, even if the chosen measure is not a core symptom of the disorder.

Preclinical models could involve either human or nonhuman experimental preparations. Typically, models are nonhuman animal preparations that attempt to mimic a human condition, including human psychopathology. Nevertheless, as implied in the definition of a model provided above, preclinical models could also be human experimental preparations. Whether a human or a nonhuman model should be used depends largely on the purpose of the model and the experimental question of interest (see the following). The vast majority of preclinical models in use are nonhuman because such models provide two distinct advantages over

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human preclinical models. First, nonhuman models enable the investigation of the neurobiology of the phenomena of interest using invasive techniques that cannot be used in humans. Second, if used properly, nonhuman animal models can significantly reduce the cost of drug development by increasing (or decreasing) the degree of confidence in a particular pharmacologic approach before undertaking expensive and time-consuming clinical trials in the psychiatric population of interest. Nevertheless, it should be clarified that human preclinical models can also contribute importantly to this latter goal, if used properly (see the following).

PURPOSES OF A PRECLINICAL MODEL

In developing and assessing an animal model, it is imperative to consider the *explicit* purpose intended for the model (2), because the intended purpose determines the criteria that the model must satisfy to establish its validity and utility. For example, is the purpose of the experimental system to model specific signs and symptoms or to model the entire diagnostic syndrome? Is the purpose of the model to promote our basic understanding of the neurobiological, genetic, environmental, and other factors that contribute to a mental disorder or the development of therapeutic agents for this disorder? Is the purpose of the model to rapidly and efficiently screen compounds to identify drugs that may have similar therapeutic properties to an existing class of compounds, or the identification of therapeutic targets that may lead to the development of compounds having novel mechanisms of action? The preceding are just a few general examples of the various purposes that a model may be intended to fulfill. Such purposes and uses explicitly guide the development and validation process for a particular model. Following, the necessary and sufficient criteria for evaluating preclinical models are reviewed briefly. (See refs. 1 and 3–7 for more extensive discussions.) Then, some general issues about preclinical models are discussed that also relate to the premise that the intended purpose of a model determines the validation criteria that the model must satisfy.

NECESSARY AND SUFFICIENT CRITERIA FOR EVALUATING PRECLINICAL MODELS

The validity of a model refers to the extent to which a model is useful for a given purpose. Thus, depending on the desired purpose of the test that one wishes to validate, different types of validity are relevant. Further, in considering the validity of a model, both the independent and dependent variables need to be evaluated. The reliability and predictive validity of the model system are relevant to both the independent variable and dependent measures and are the most important criteria to satisfy. (See refs. 1 and 8–10 for definitions of the various types of validity.) The additional criteria

relevant to the independent variable (i.e., inducing manipulation) include etiologic, construct, and face validity, with etiologic validity being the most relevant. The criteria relevant to the dependent variable include construct, convergent, discriminant, and face validity. Undoubtedly, the more types of validity a model satisfies, the greater its value, utility, and relevance to the human condition. Nevertheless, it could be considered circular logic if a model was required to satisfy all types of validity before being considered useful. Hence, it has been argued previously that predictive validity and reliability are the only *necessary and sufficient* criteria for the *initial* evaluation of any animal model (1).

Predictive validity of a model is broadly defined as the ability to make accurate predictions about the human phenomenon of interest based on the performance of the model (1,9). In reference to animal models of human psychopathology, the term predictive validity is often used in a narrow sense to refer to the model's ability to identify drugs with potential therapeutic value in humans (i.e., pharmacologic isomorphism) (2). Although correct, this use of the term is limited because it ignores other important ways in which a model can lead to successful predictions (7). For example, the identification of any variables that have similar influences in both the experimental preparation and modeled phenomenon can demonstrate predictive value of the experimental preparation and enhance one's understanding of the phenomenon.

Reliability refers to the consistency and stability with which the variables of interest are observed, and is relevant to both the independent and dependent variables (1,5).

APPROACHES AND ISSUES RELATED TO MODEL DEVELOPMENT

Modeling Specific Signs or Symptoms Versus Modeling Diagnostic Syndromes

As discussed previously (1), early attempts at model development focused on reproducing in animals a psychiatric syndrome in its entirety. Such an approach, although useful in advancing the field at the time, has been largely abandoned because of increasing awareness that such an approach is typically impractical, unrealistic, and fruitless for the following reasons. (a) The defining symptoms of psychiatric disorders and even the diagnostic categories themselves are being revised and redefined continuously. (b) One would not expect homology on *all* aspects of a disorder between two species (e.g., one would not expect a rodent to exhibit a complete schizophrenia syndrome). (c) Modeling a syndrome in its entirety would require the validation of multiple endpoints. (d) There is considerable heterogeneity within each of the major diagnostic categories of psychiatric disorders. (e) The validation process for such a model needs to be extensive, thorough, and all-inclusive, and thus not different from the scientific process aimed at elucidating

the neurobiological and behavioral mechanisms mediating a psychiatric disorder.

Most recent approaches to the development of animal models rely on mimicking only specific signs or symptoms associated with psychopathologic conditions, rather than mimicking an entire syndrome. These specific signs or symptoms may be: (a) observables that have been identified in psychiatric populations that may or may not be pathognomonic for or even diagnostic symptoms of the disorder, but can be defined objectively and measured reliably; or (b) more theoretically based measures of psychological constructs that are believed to be relevant to the psychiatric disorder under investigation (2,7). The latter approach involves the definition of a hypothetical construct and subsequent establishment of operational definitions suitable for the experimental testing of the validity of the construct in both human and nonhuman animals. The narrow focus of this approach generally leads to pragmatic advantages in the conduct of mechanistic studies addressing the neurobiological substrates of the specific behavior under study. Furthermore, the study of putatively homologous behaviors in both human and nonhuman subjects effectively addresses and bypasses the nonconstructive criticism that complex mental disorders cannot possibly be modeled in nonhuman animals. (See ref. 1 for a more extensive discussion comparing these two approaches to modeling.)

An illustrative example of this approach is provided by some of the models now being used to identify antipsychotic drugs, based on the hypothesis that schizophrenia involves deficits in attentional filtering or gating (i.e., the psychological construct). Theoretically, schizophrenia patients suffer from impairments in filtering or gating of sensory stimuli that lead to an inundation of information and consequent cognitive fragmentation. The hypothetical construct of attentional filtering has been defined operationally and explored in multiple paradigms and in both human and animal studies. For example, numerous studies of schizophrenia patients have demonstrated deficits in behavioral habituation, which is a prerequisite to selective attention, prepulse inhibition (PPI) of startle, a preattentional sensorimotor gating phenomenon, and the gating of auditory P50 event-related potentials (ERPs) (11–13) (see Chapter 51). Each of these operational measures is potentially relevant to the construct of deficient filtering of incoming information, hypothesized to be a common element in the schizophrenia disorders (14,15). Each of these operational measures is also amenable to cross-species studies of analogous or homologous behaviors. (See the following for a discussion of these terms.) The fact that schizophrenia patients exhibit deficits in all three measures provides converging support for the hypothesis that schizophrenia involves disturbances in the filtering of sensory and cognitive information (i.e., construct validity). Nevertheless, a recent study explicitly testing the convergent validity of this hypothetical construct has prompted some further refinements

in our thinking. Specifically, in a group of normal subjects, P50 gating was strongly correlated with the amount of startle habituation and only weakly with PPI (16), despite the fact that P50 gating appears to be more similar phenomenologically to PPI than habituation. Similar findings have been reported in the parallel animal paradigms using the same operational measures (17). This situation illustrates how phenomenologic similarity (i.e., face validity) can sometimes lead to erroneous conclusions until further detailed behavioral investigations of the construct(s) are undertaken. Furthermore, as reviewed elsewhere (see Chapter 50), habituation, PPI, and P50 gating exhibit some differences as well as similarities in their sensitivity to pharmacologic manipulations used to mimic schizophrenia-like changes in animals. Of critical importance is the relationship, if any, between these experimental measures of filtering deficits and clinical complaints of sensory overload or signs of thought disorder that prompted the original hypothetical construct (i.e., extrapolation from animals to humans). Surprisingly, within a cohort of schizophrenia patients (19), those with deficient P50 sensory gating reported fewer complaints of sensory overload than did patients with normal P50 gating (i.e., the opposite of the predicted relationship). With regard to the PPI sensorimotor gating measure, however, significant correlations have been observed between deficient PPI, and both distractibility (20) and measures of thought disorder based on an abstract problem-solving task (21) in schizophrenia patients. Hence, it appears that the three main operational measures of deficient attentional filtering do not all measure the same hypothetical construct. Thus, in parallel with the heterogeneous group of schizophrenia-like disorders, the construct of deficient filtering may not be a unitary construct, although it could still represent a phenomenologically common outcome of differing etiologies in different forms of schizophrenia. It is important to recognize that each of these measures is demonstrably affected in (presumably heterogeneous) groups of schizophrenia patients and each has engendered animal models that have varying degrees of predictive validity for the identification of antipsychotic treatments. It remains to be seen whether different subgroups of schizophrenia patients will exhibit only one or another of these deficits. If so, the parsing of the original hypothetical construct may lead to empirical distinctions among patient subgroups that could have important implications for the application of specific treatment approaches.

Discovery of Novel Versus ''Me-Too'' Treatments

Another extreme approach to model development and use relates to the limited purpose of systematically and efficiently screening and identifying potential therapeutic treatments without explicitly assessing the mode of action that leads to the therapeutic effect. In such a case, the model may or may not mimic the actual psychiatric disorder.

Rather, the model is only intended to reflect the efficacy of known therapeutic agents, and consequently lead to the discovery of new pharmacotherapies. Thus, the principle guiding this approach has been termed "pharmacologic isomorphism" (2). As discussed elsewhere (2,7), the fact that such models are developed and validated by reference to the effects of known therapeutic drugs frequently limits their ability to identify new drugs having novel mechanisms of action. Accordingly, an inherent limitation of this approach is that it is not designed to identify new therapeutics that may treat either the symptoms of the disorder that are refractory to current treatments, or patient populations that are resistant to current treatments. An example of such a limitation is found in the use of drug-discrimination paradigms used to identify new treatment compounds. In these paradigms, the animal is trained to recognize the drug state induced by a prototypical drug. Typically, the animal is required to press either the right or left of two levers, depending on whether it had been treated with the vehicle or training drug. Potential new therapeutics are then identified by their ability to substitute for the prototypical drug on which the animal was trained. Because these paradigms rely only on the subjective drug-induced cue to which each animal responds and not on an endpoint that can be validated by reference to other behaviors in animals or humans, such procedures can only identify drugs having a similar effect on some unknowable dimension. If the screening involves several paradigms, the profile of the drug can be compared qualitatively and quantitatively to the profiles of known compounds. Such profiles, when combined with "a special kind of flair for the problem" (22), may lead to reasonable predictions about the potential of the compound in the clinic. The ability to rapidly and efficiently identify treatments that may be shown clinically to have some advantages over the older treatments is an advantage of this approach. Nevertheless, these screening paradigms do not provide ways to predict whether the "me-too" drug will have any clinical advantages (e.g., fewer side effects, treatment of refractory symptoms or patient populations) over the "prototypes," other than in relation to potency.

Modeling Specific Aspects of Treatment Effects: Chronic Versus Acute Drug Treatments

Because both the etiologies and core features of psychiatric disorders are still poorly understood, much research addressing the neurobiology of these disorders has focused on the study of the mode of action of known therapeutics. The targets of clinically effective therapeutics have provided excellent starting points in the investigation of the neurobiology of psychiatric disorders. When taking this approach, it is important that specific aspects of the treatment effects are taken into consideration and incorporated into the paradigms used. For example, it is recognized that chronic treat-

ment with antidepressants is required before a therapeutic effect is observed. This therapeutic delay is not only a severe limitation of current antidepressant treatments but also a hurdle in determining the mechanisms through which antidepressants produce their beneficial effects. Because of this delay in the emergence of the therapeutic effects, it is assumed that these effects are mediated by neuroadaptations that develop as a result of the chronic drug administration. Much research has focused on these neuroadaptations in order to understand the neurobiology of depression; because the therapeutic effect may be produced through "normalization" of the specific abnormalities characterizing depression. It is possible, however, that the therapeutic effect may be produced by separate systems or mechanisms that counteract the abnormalities that are etiologic in depression.

The preceding discussion is relevant, not only to approaches that may be taken in studying psychiatric disorders, but also to the question of whether animal paradigms that demonstrate positive results after acute administration of an established antidepressant are indeed valid models of depression rather than just screening paradigms. It could be argued that with acute drug administration the mechanisms leading to the reversal of the behavioral deficit are not the same as the ones leading to the clinical therapeutic effect. Such arguments certainly have merit. An animal paradigm that not only indicates therapeutic efficacy but also the time-course of such effects is a powerful tool for both neurobiological investigations and drug discovery. The vast majority of animal models of depression do not readily satisfy this criterion despite extensive efforts over decades. Thus, the question is how to best design and interpret data from paradigms that appear to reveal primarily acute therapeutic effects. In many of the animal studies, the acute drug doses are much higher than doses that would be tolerated by humans, especially on the first drug administration. Higher doses may be more likely to produce an acute effect. This argument is supported by data with the forced swim model where it was shown that either high doses of antidepressant drugs or chronic treatment with low doses of antidepressants, ineffective when administered acutely, reversed immobility in the swim test (23). Further, it has been argued that antidepressants may produce immediate improvement of *some* symptoms in humans, but this acute effect may be hard to detect statistically because the initial improvement may be small and seen only in some, but not all, symptoms (23,24). Thus, it is possible that reversal of a specific behavioral deficit in a model after acute treatment may indeed be consistent with the clinical reality about a specific symptom. This experimental question is an example of a case in which preclinical animal data could guide the design of clinical investigations that would help assess and improve animal models. Finally, animal models that can only detect acute effects, when guided by good working hypotheses, can be used for target identification by investigating the mecha-

nisms that lead to reversal or exacerbation of the deficit of interest.

Issues Regarding the Use of ''Normal'' (Healthy) Versus Perturbed Animals

Although most animal models rely on an explicit inducing manipulation, some models test the effects of putative therapeutic compounds under baseline conditions, that is, without first inducing a deficit in the subjects. Even if such an animal model has predictive validity, it may not be useful in furthering our understanding of the pathophysiology underlying the disorder if the effects of therapeutic treatments depend on an interaction with the underlying pathophysiology. Specifically, the mechanisms through which drugs produce their effects in "normal" versus perturbed animals may differ, even if the primary neurochemical effect may be the same (25,26). Indeed, antidepressant drugs have been shown in some studies to have no effects in "normal" human or nonhuman subjects, whereas inducing "therapeutic" effects in patients or perturbed subjects. For example, fluoxetine, a selective serotonin reuptake inhibitor (SSRI) with antidepressant properties, does not induce euphoria or elevate mood in nondepressed healthy individuals even after chronic treatment (27,28). Similarly, treatment with tricyclic antidepressants or SSRIs has no effect on behaviors assessing reward function in unperturbed animals. More specifically, treatments with desmethylimipramine, a tricyclic antidepressant, or low doses of fluoxetine typically have no effect on intracranial self-stimulation reward thresholds (29–37), whereas reversing reward deficits observed after drug withdrawal or during chronic mild stress (31,32, 38). Moreover, recent findings indicated that the coadministration of fluoxetine together with a relatively selective serotonin 1A receptor antagonist had *opposite* effects in "normal" rats (i.e., decreased reward), whereas reversing reward deficits (i.e., increased reward) in perturbed animals in which a reward deficit had been induced (34). Recent clinical and preclinical findings have suggested that the coadministration of a SSRI together with a serotonin 1A receptor antagonist leads to accelerated or augmented antidepressant effects compared to those seen after treatment with the SSRI alone, presumably by enhancing serotonergic neurotransmission to levels above those seen with the SSRI alone (39–41). In conclusion, the study of animals that exhibit a deficit that is pathognomonic of depression, rather than "normal" healthy animals, may be critical to the study of both the underlying pathophysiology and its treatment.

In other situations, however, it may be advantageous to utilize animal models that examine baseline behaviors. For example, known antipsychotic drugs can be identified with reasonable predictive power using the conditioned avoidance response paradigm (42). The conditioned avoidance response paradigm has then been applied to the testing of potentially novel mechanisms that may have efficacy in the treatment of psychosis (43). Latent inhibition is another paradigm in which antipsychotics produce changes in baseline behavior that are relevant to schizophrenia. Acutely ill schizophrenia patients exhibit deficits in latent inhibition that are reduced by antipsychotic treatment (44). Similarly, when the appropriate testing parameters are used in the analogous animal paradigm, both typical and atypical antipsychotics improve measures of latent inhibition under baseline conditions (45). In contrast to pharmacologically induced models (see the following), models such as the conditioned avoidance response and latent inhibition, in which known antipsychotics influence behaviors under baseline conditions, may be more effective in identifying new therapeutic targets for antipsychotic effects. As discussed elsewhere (see Chapter 50), most of the schizophrenia animal models used historically to identify antipsychotic agents have relied on the induction of abnormal behaviors by the administration of a dopaminergic agonist and then define an antipsychotic as a drug that reverses the agonist effect. Hence, most such models are primarily and perhaps exclusively sensitive to drugs that block dopamine receptors and may not detect novel mechanisms that could have efficacy without involving dopamine receptor blockade. Ultimately, only further research with each class of psychiatric treatments will determine the relative utility of models that use an explicit inducing condition versus models that rely on changes in baseline behavior.

Inducing Conditions: Drug-Induced Versus Nonpharmacologic and Genetic Models

With the exception of paradigms assessing treatment effects in nonperturbed animals, the inducing manipulations constitute a critical aspect of a model. The selection of inducing conditions for animal models of psychiatric disorders is difficult because the etiologies of psychiatric disorders are generally unknown and are likely to be heterogeneous within each diagnostic category. Inducing conditions could be environmental manipulations, drug manipulations, lesions, genetic manipulations, or combinations of the preceding. Further, all of the preceding manipulations could be implemented during development or combined with developmental manipulations or factors. An inducing condition may be selected: (a) based on theoretic arguments about the environmental and/or neurobiological factors that lead to the disorder; (b) because it induces a deficit that is considered pathognomonic of the disorder of interest, even though no theoretic arguments are made about the etiology of the disorder; or (c) based on purely practical considerations about the predictive value of the model without theoretic arguments about either the etiology of the disorder or the relevance of the dependent measure to aspects of the symptomatology characterizing the disorder. The selection of

each inducing condition has advantages and disadvantages and is often based on the following considerations.

Acute or chronic drug manipulations have the advantage of probing the function of a specific receptor or neurotransmitter system that either is implicated in the etiology of the disorder or produces the desired deficit. The main disadvantage of an acute drug manipulation, and often of chronic drug manipulations, is that it readily leads to "receptor" or "neurotransmitter tautology." For example, a deficit induced by a specific receptor agonist is very likely to be reversed most effectively by a receptor antagonist at the same receptor, as in the case of dopamine agonist–antagonist interactions in most animal models of antipsychotic action. The same applies to neurotransmitter systems. Nevertheless, reversal of a drug-induced deficit by a compound acting on a different neurotransmitter system is a powerful indication of system interactions that may be relevant to the pathophysiology and/or treatment of the disorder. Chronic drug manipulations offer additional advantages and disadvantages. Chronic drug administration is likely to lead to compensatory adaptations to the acute effects of the drug that are likely to be longer lasting than the effects of a single drug administration and to involve additional systems that are not involved in the acute drug effects. Nevertheless, the resulting neuroadaptations may be irrelevant to the disorder unless there is a relationship between the deficits induced by the drug and etiology of the psychiatric symptoms.

An example of a pharmacologic model is the use of the reward deficits seen during withdrawal from a variety of drugs of abuse as a model of the core symptom of "diminished interest or pleasure" in rewarding stimuli that characterizes depression (46). In rats, converging evidence indicates that withdrawal from psychostimulant drugs is associated with reward deficits expressed as elevations in brain reward thresholds (33,47), decreased breaking-points under a progressive ratio schedule for a sucrose reinforcer (48), and decrements in motivation for sexual reinforcement (49). The advantage of this model is the induction of deficits in reward and motivational processes that are hypothesized to be, not only pathognomonic of depression, but also deficits expressed as negative symptoms of schizophrenia. Thus, these paradigms focus on the study of a hypothetical construct that may have relevance to core symptoms seen in multiple diagnostic categories. These deficits are most likely homologous to similar deficits seen in people abusing these drugs because the etiology of the deficit is the same in both the animal model and humans. Nevertheless, it is not known whether pharmacologically induced deficits in reward and motivational processes are homologous, or just analogous, to similar deficits seen in nondrug abusing psychiatric populations. That treatments with clinically effective antidepressants reverse the drug-induced reward deficits in both rats and humans suggests that the deficits may be homologous across species (32,34,38,50).

Environmental manipulations often induce only short-lasting deficits in healthy subjects because a healthy system is able to "bounce back" readily once the inducing conditions have been removed. Potential interactions, however, between the environmental manipulation and a genetic predisposition may lead to long-lasting behavioral or neurobiological changes having relevance to the disorder of interest. Finally, environmental manipulations are important to use and incorporate into animal models because it appears that psychiatric disorders often result from interactions between "nature" and "nurture" to a larger extent than most nonpsychiatric diseases. Another advantage of environmental manipulations is that such manipulations are likely to affect integrated brain functions rather than a single component of a system.

Lesion manipulations offer different advantages and disadvantages compared to environmental and drug manipulations. An advantage of lesion manipulations over chronic drug manipulations is that lesions may lead to deficits and/or neuroadaptations in a variety of brain systems rather than just the one or few affected by a drug. A disadvantage of traditional lesion manipulations is that the initial lesion manipulation in most cases is a rather large insult to a specific brain site. Thus, the circuitry affected is dependent on the interconnections of this specific brain site. Nevertheless, recent advances in genetic techniques are allowing very precise "lesions" (knockouts) or increased expression (knockins) of specific proteins in selected brain sites in adult animals. Such technological advances, when combined with more traditional behavioral and pharmacologic aspects of well-developed models, are likely to advance our understanding of psychiatric disorders.

Developmental manipulations are gaining in popularity primarily because there is increased awareness that many psychiatric disorders develop gradually through childhood and adolescence and are lifelong. In some cases, investigators combine one of the previously discussed inducing manipulations with a developmental manipulation (e.g., applying the inducing manipulations during development or in a genetically altered animal). For example, decreases in PPI of startle, an operational measure of sensorimotor gating deficits that are evident in patients with schizophrenia, have been demonstrated to result from socially isolating rats from weaning until after puberty (51). Social isolation of rats in early stages of development has been used to produce a variety of behavioral abnormalities that have been related to both schizophrenia and depression. Recent studies have shown that 6 to 8 weeks of social isolation during development, but not during adulthood (52), produces deficits in PPI that are at least partially reversible by the administration of neuroleptic dopamine antagonists (51) or by clinically effective atypical antipsychotics having antagonist activity at multiple receptors (53,54). Furthermore, postweaning isolation rearing of rats also results in deficits in the gating of the N40 event-related potential, that are analogous to the deficits in P50 gating observed in schizophrenia (55).

Because schizophrenia commonly emerges in early adulthood, developmental factors have provided the basis for some etiologic hypotheses (56,57). Hence, further study of the gating deficits produced by isolation rearing of rats may establish a nonpharmacologic and developmentally relevant animal model of the gating deficits observed in patients with schizophrenia. Potentially, in contrast to the drug-induced models of gating deficits, such a model might have etiologic validity and might be sensitive to antipsychotic drugs having novel mechanisms of action.

Genetic manipulations are popular because of the recent surge of interest in genetic contributions to psychiatric disorders. Such interest promises to enable the development of a class of animal models based on hypothesized etiologic validity. As specific genes and gene products become linked to specific disorders, molecular biologists will be able to generate mutant or transgenic animals having genetic abnormalities that are potentially homologous to those seen in humans. Behavioral and pharmacologic studies of these genetically engineered animals will then be important in identifying the phenotypic changes associated with the mutation, testing hypotheses about the etiology of the disease, and exploring potential therapeutic treatments. The combination of genetic and molecular biological approaches with behavioral and pharmacologic approaches may well revitalize interest in etiologically based models of psychiatric disorders. It is important to recognize that genetic manipulations necessarily begin with the fetus and often lead to compensatory adaptations throughout the course of development. Hence, developmental factors must be taken into account and studied when working with such an early genetic alteration. The latter is an example of a case where a technological limitation can lead to new creative ways of studying the function of a system and how it may contribute to our understanding of the processes mediating a disease.

The increased use of strain differences and genetically engineered mutants in drug discovery programs will necessitate both practical and conceptual modifications to the development and validation of animal models. Among the most fundamental differences between these genetic models and most previous models involves the distinction between trait and state measures. Most of the traditional models used to explore psychiatric treatments have relied on relatively short-term changes in the state of the animal, as modified by inducing manipulations such as stressors or drugs. In contrast, by definition, genetically based models rely on traits rather than states. For example, it has become commonplace to use approach/avoidance conflict tests to examine the possibility that gene knockout mice exhibit alterations in what is called "anxiety." Approach/avoidance conflict tests, such as the elevated plus-maze or the light/dark box, have been widely used in rodent studies of anxiolytic drugs. Anxiolytic drugs increase approach behavior in such paradigms, presumably because they reduce the anxiety that competes with the animal's tendency to explore novel

stimuli and environments. Such an observation with an unknown drug could as readily be interpreted as an increase in novelty seeking (i.e., approach) rather than a decrease in anxiety (i.e., avoidance). The fact that known anxiolytic drugs increase approach behavior has provided substantive validation of approach/avoidance conflict tests for the identification of changes in state anxiety. Accordingly, such conflict tests are now being used widely in the characterization of mutant mice in attempts to identify changes in trait anxiety. It should be recognized, however, that the validation of a measure as predictive of a change in state may or may not validate the measure as reflective of a change in the conceptually related trait. That is, the observation of a shift in approach/avoidance behavior in a mutant mouse that is similar to that produced by an anxiolytic drug cannot readily support the conclusion that the mutant mouse exhibits low levels of trait anxiety rather than high levels of approach behavior, as in the trait of high novelty seeking. Only by examining approach/avoidance behavior across a range of contexts can one determine which pole of the approach/avoidance conflict is altered in the mutant animal (58).

Dependent Measures: Value of Analogous and Homologous Measures Across Species

As with the choice of inducing manipulations, the choice of dependent measures is not simple when developing animal models of psychiatric disorders, primarily because the major and core features of human psychopathology are still poorly understood and still debatable. Thus, what should be considered an adequate or appropriate endpoint for a model in psychiatry is not always clear. Whenever possible, it is preferable to work with homologous rather than analogous endpoints. The terms analogy and homology originated in comparative anatomy and refer to the morphology and function of a structure. Structures or behaviors across species that are similar in origin (i.e., neurosubstrates), form, and function are termed homologous, whereas structures or behaviors that have different origins or neurosubstrates, superficially similar form, and have similar function are termed analogous (59). Another term that has been used to refer to analogous endpoints is isomorphism (60). Thus, in some sense, the terms homology and analogy refer to both the symptomatology and the underlying substrates that relate to the etiology. Although homologous measures are preferable, they are rare. Fortunately, analogous measures can also be valuable. It is because of the assumption of homology, or at least analogy, among the physiological and behavioral characteristics of various species that extrapolations can be made from nonhuman animals to humans (61). The establishment of multiple forms of validation for a particular model provides convergent evidence in support of the postulate of cross-species homology.

When developing an animal model related to a psychiat-

ric disorder, it is important to determine what features of the disorder(s) the experimental preparation is intended to model. Investigators often begin by attempting to identify the core features of the particular disorder of interest. Nevertheless, it is clear that appreciable diversity of both etiologies and symptom profiles exists within each of the major psychiatric diagnostic categories. Furthermore, very few specific symptoms are unique to any specific diagnosis, but occur in multiple diagnostic categories. Hence, it is most productive to focus on specific features observed in patients as endpoints for use in the development of animal models, rather than on clusters of symptoms. A related implication of this reasoning is that multiple different animal models, in terms of the endpoint used, may all be useful in parallel. Thus, it is advantageous to utilize an array of models rather than rely too heavily on any one model. The endpoints used in such models could be *in vivo* behaviors, biological markers, or *in vitro* behaviors of biological systems or preparations. Operational definitions, especially of *in vivo* behavioral measures, assist in determining the theoretic relationship between the observable and the construct of interest (62,63). Finally, the observables should be measured objectively and reliably.

Human Preclinical Models: Relationship between Animal and Human Phenomena

Human preclinical models can also contribute significantly to drug development. Unfortunately, such human models appear to be underutilized, and relatively little effort is focused on the development of such human models. An advantage of using human preclinical models is that one would not have to be concerned about cross-species generalizations. Nevertheless, even with human models, questions regarding the etiology of the disorder or the relationship between the dependent measure and the symptoms still need to be addressed using the same principles as when extrapolating across species. Relative to animal models, human preclinical models are necessarily more constrained by the additional ethical considerations regarding the use of humans in research.

The most typical example of a human preclinical model is when a drug-induced state is used in healthy volunteers to mimic some aspects of a disorder of interest. For example, the glutamate antagonist ketamine is used to induce a state that mimics some aspects of acute schizophrenia in healthy volunteers (64,65). Then, using brain imaging, psychological assessments, and pharmacologic interactions, the neurobiology of this drug-induced state can be studied to gain insight into the possible substrates underlying the psychotic state in schizophrenia patients. Such a human preclinical model can also play an important role in assessing novel treatments. For example, it has been found that the atypical antipsychotic clozapine reduces the exacerbation of symptoms in schizophrenic patients given ketamine (66). In contrast, typical antipsychotics such as haloperidol are ineffective in treating psychotic episodes induced by drugs such as ketamine or phencyclidine (PCP). Hence, studies of ketamine effects in either human or animal preclinical models may aid in the identification of additional atypical antipsychotics having efficacy in the treatment of patients who are nonresponsive to typical antipsychotics. Indeed, in the PPI models of schizophrenia, the disruptive effects of glutamate antagonists on PPI of startle are reversed by atypical, but not by most typical, antipsychotics (67). Interestingly, this effect of clozapine-like antipsychotics is mimicked by the putative antipsychotic M100907, a selective serotonin-2A antagonist (68). In general, one goal of translational research is to utilize the knowledge gained from human preclinical and clinical studies to guide invasive neurobiological studies in animals, which in turn can be translated back to the human clinical studies. In the present example, this strategy would suggest that further studies could now determine whether M100907 reverses disruptions in PPI produced by ketamine in healthy human volunteers. Furthermore, clinical trials of the efficacy of M100907 in schizophrenia could be designed to test the hypothesis that only schizophrenic patients whose deficits in PPI are reversed acutely by M100907 would respond clinically to prolonged treatment with M100907. This admittedly speculative example illustrates some of the potential advantages derived from the use of homologous, or at least analogous, measures in animal and human preclinical models as well as in clinical trials. Such translational research is needed in the field of psychiatric disorders in order to guide both the refinement of the animal models and the development of new drugs.

DRUG DISCOVERY AND DEVELOPMENT: PRECLINICAL MODELS AND CLINICAL TRIALS

An emerging belief is that animal preclinical models represent a bottleneck in psychotropic drug discovery (69). Compared to high-speed chemical synthesis, high-throughput screening of libraries of compounds, and rapid gene seeking and sequencing techniques, the use of preclinical models as screening techniques appears slow. Nevertheless, such preclinical models of human psychopathology are required to provide initial assessments of the functional effects of novel compounds in the integrated organism. Only such *in vivo* functional measures can confirm predictions about the potential effects of psychotropic drugs in patients. It is unrealistic to attempt to go from the "test tube" to the clinic when attempting to treat complex mental, cognitive, and emotional disturbances that do not yet have clearly defined neurobiological substrates, or even correlates. The "relative paucity of preclinical behavioral models predictive of clinical efficacy" (69) reflects the paucity of our quantitative measures of the human phenomena related to psychiatric

disorders, as well as the limited investment in the development of animal behavioral models over the past few decades. Despite the excitement in the field of neuroscience about the recent progress made in understanding brain function (70), there is also an appreciation of how little is known about the neurobiology of psychiatric disorders compared to advances in other fields of medicine (71). Given the rapidity of techniques available to target discovery and drug screening efforts relative to the limited state of our knowledge about psychiatric disorders, the role of *in vivo* preclinical models as the intermediary between these extremes needs to be considered carefully. Some preclinical models, such as the tail suspension or swim tests for antidepressants and the prepulse inhibition test for antipsychotics, are amenable to relatively rapid screening without knowledge or understanding of the compounds' mechanism of action. Paradigms that are far more laborious can be used in the identification of new targets through the investigation of the interacting systems that contribute to the disorder's symptomatology or the therapeutic effects of established drug treatments. After identification of such novel targets, drug development efforts can be focused in identifying a compound with the desired mechanism of action and other desired properties, such as no toxicity and limited actions at systems that would produce side effects. Converging evidence from other basic research efforts would be crucial in such an undertaking. Even though the previously described process is time consuming and requires well-integrated multidisciplinary research efforts, this process may lead to the breakthroughs in psychiatric drug development that have been long awaited.

After a candidate drug has been identified through the use of both animal and human preclinical models and safety issues have been addressed, then the therapeutic efficacy of the compound is tested in the clinical population. Unfortunately, such clinical trials often do not have sufficient power, in the statistical and experimental design meaning of the term, to detect potentially beneficial effects of novel candidate compounds. Because of the high cost of drug development, pharmaceutical companies are interested in pursuing drugs that have the potential to be used in a large market that is often a broadly defined diagnostic category. This situation is aggravated by the fact that diagnostic categories in psychiatry are still rather crudely defined by rating scales rather than by objective and quantitative measures. For example, it is often assumed, at least implicitly, that there is diagnostic homogeneity within a particular patient population. It is also assumed that the boundaries of psychiatric categories as currently defined are rather absolute. In fact, most psychiatric disorders do not have clear pathological or biological markers and are defined as constellations of symptoms that are on a continuum with normality (71). Even though such diagnostic issues are constantly discussed and debated among psychiatrists, such issues are often put aside in clinical trials. Typically, the main focus in clinical

trials is on the global measures of remission that are acceptable to regulatory agencies. Unfortunately, the reliance on rating scales in clinical trials provides little specific information that is useful in guiding either human or animal preclinical studies. Although understandable in view of economic forces, the infrequent use of a selected battery of scientifically established objective measures even in the early phases of clinical trials limits the further development of translational research involving cross-species comparisons and model validation. Hence, clinical trials do not benefit sufficiently from the scientific information provided by academic research and seldom provide the kind of empiric measures that are needed to adequately validate related animal models. Emphasis on multiple biological or psychological measures of disease progression with or without treatment with the drug of interest could potentially provide valuable information about the mechanisms that underlie various aspects or symptoms of the disease and thus lead to pragmatic advances in our understanding of the neurobiology of psychiatric disorders. Communication from the clinic back to the preclinical behavioral laboratory will enable the refinement of established models and the creation of new ones. In turn, understanding of the disorder could benefit if clinical trials included measures suggested to be relevant from preclinical research in either human or animal models. Another situation that limits progress in drug development is a recent movement to discourage clinical trials that include a placebo control group. Instead, the new compounds are expected to show greater efficacy compared to established therapeutics for the particular disorder. Overall, this state of affairs significantly limits the potential to identify new drugs that may: (a) be more beneficial than established treatments to a subpopulation of patients; or (b) produce global improvement through amelioration of symptoms that are not adequately assessed by the established measures of efficacy. Thus, it is difficult to make real advances in the development of new drugs because the current system encourages a circular logic and approach.

Another limitation of clinical trials that contributes to this circular approach is the absence of use of well validated, objective, and reliable measures of psychopathology in addition to the available clinical measures. As with animal models, clinical trials also need to incorporate measures that objectively and reliably assess specific psychological constructs or processes that appear to be altered in the population of interest. The validation of any animal model can be only as sound as the information available in the relevant preclinical human literature and the clinical literature (7). It is very fruitful when conceptually related experiments are undertaken in both the relevant patient population and the putative preclinical human and animal models. That is, studies of appropriate patients are needed to establish the operational definitions of the hypothetical construct, and the construct's relevance to the particular disorder. In concert, parallel studies of the theoretically homologous con-

struct, process, or dimension are required to determine the similarity of the animal model to the human phenomenon. Development of animal models requires parallel development of clinical measures that allow meaningful comparisons. Clinical studies need to be informed by results from animal studies as much as the reverse is true. An important and advantageous aspect of the approach described herein is that the validation of the hypothetical construct and its cross-species homology can be established by studies of normal humans and animals, in addition to psychiatrically disordered patients or experimentally manipulated animals. Thus, this approach adds to and benefits from the psychological and neurobiological literature relevant to the hypothetical construct upon which the model is based. In a sense, this approach explicitly recognizes that the experimental study of the disorder in humans involves as much of a modeling process as does the study of the disorder in an animal model. Thus, more translational science is needed to relate animal findings to humans and vice versa.

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