

## ANIMAL MODELS RELEVANT TO SCHIZOPHRENIA DISORDERS

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Animal models used to study schizophrenia include both models of the full syndrome and models of specific signs or symptoms. As reviewed elsewhere (1), models are commonly explored initially because of indications of so-called face validity, but they are evaluated scientifically in terms of their construct and etiologic and predictive validity with respect to both clinical phenomena and responsiveness to antipsychotic drugs. Here, models are organized by the manipulations used to mimic the clinical phenomena. Thus, in some of these models, only specific dependent measures are utilized, whereas others are evaluated by using a range of dependent measures.

A model is defined as any experimental preparation developed to study a particular condition or phenomenon in the same or different species. Typically, models are animal preparations that attempt to mimic a human condition, in our case the human psychopathology associated with the group of schizophrenia disorders. In developing and assessing an animal model, it is important to specify the purpose intended for the model because the intended purpose determines the criteria that the model must satisfy to establish its validity. At one extreme, one can attempt to develop an animal model that mimics the schizophrenia syndrome in its entirety. In the early years of psychopharmacology, the term *animal model* often denoted such an attempt to reproduce a psychiatric disorder in a laboratory animal. Unfortunately, the group of schizophrenia disorders is characterized by considerable heterogeneity and a complex clinical course that reflects many factors that cannot be reproduced readily in animals. Thus, the frequent attempts to model the syndromes of schizophrenia in animals usually met with failure and so prompted skepticism regarding this entire approach.

At the other extreme, a more limited use of an animal model related to schizophrenia is to study systematically the

effects of antipsychotic treatments. Here, the behavior of the model is intended to reflect only the efficacy of known therapeutic agents and so lead to the discovery of related pharmacotherapies. Because the explicit purpose of the model is to predict treatment efficacy, the principle guiding this approach has been termed *pharmacologic isomorphism* (2). 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 with novel mechanisms of action. Similarly, an important limitation inherent in this approach is that it is not designed to identify new antipsychotic agents that might better treat the symptoms of schizophrenia refractory to current treatments.

Because of the complexity of schizophrenia, another approach to the development of relevant animal models relies on focusing on specific signs or symptoms associated with schizophrenia, rather than mimicking the entire syndrome. In such cases, specific observables that have been identified in schizophrenic patients provide a focus for study in experimental animals. The particular behavior being studied may or may not be pathognomonic for or even symptomatic of schizophrenia, but it must be defined objectively and observed reliably. It is important to emphasize that the reliance of such a model on specific observables minimizes a fundamental problem plaguing animal models of the syndrome of schizophrenia. Specifically, the difficulties inherent in conducting experimental studies of schizophrenic patients have limited the number of definitive clinical findings with which one can validate an animal model of schizophrenia. The validation of any animal model can only be as sound as the information available in the relevant clinical literature (3). By focusing on specific signs or symptoms rather than syndromes, one can increase the confidence in the cross-species validity of the model. The narrow focus of this approach generally leads to pragmatic advantages in the conduct of mechanistic studies addressing the neurobiological substrates of the behavior in question. By contrast, in models intended to reproduce the entire syndrome of schizophrenia, the need for multiple simultaneous endpoints

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makes it relatively difficult to apply the invasive experimental manipulations required to establish underlying mechanisms.

Another approach to the development of animal models is based more theoretically on psychological constructs believed to be affected in schizophrenia. Such identification of underlying psychological processes or behavioral dimensions (2,3) involves the definition of a hypothetical construct and the subsequent establishment of operational definitions suitable for experimental testing of the validity of the construct. Constructs such as selective attention, perseveration, sensorimotor gating, and working memory have been used in this manner in schizophrenia research. This approach is most fruitful when conceptually or procedurally related experiments are undertaken in both the relevant patient population and the putative animal model. In other words, studies of appropriate patients are needed to establish the operational definitions of the hypothetical construct and the relevance of the construct to schizophrenia. In concert, parallel studies of the potentially homologous construct, process, or dimension are required to determine the similarity of the animal model to the human phenomena. An important and advantageous aspect of this approach 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 studies of schizophrenic patients and experimentally manipulated animals. Thus, this approach benefits from the existing literature relevant to the hypothetical construct on which the model is based. In a sense, this approach explicitly recognizes that the experimental study of schizophrenia in humans involves as much of a modeling process as does the study of the disorder in animals.

## PHENOTYPIC CHARACTERIZATION OF ANIMAL MODELS

Behavioral measures have been used extensively for establishing the validity of animal models of schizophrenia. Some of these measures, such as horizontal locomotion, do not correspond to schizophrenic symptomatology and have been primarily useful for providing a functional measure of the antidopaminergic activity of neuroleptics. Other behavioral measures, such as disruption of prepulse inhibition or impaired attentional set shifting, resemble characteristics of schizophrenia. These measures are useful for establishing the construct and predictive validity of putative animal models.

In addition to behavioral assessments, cellular and molecular markers that are based on described changes in human postmortem and imaging studies are potentially useful measures for establishing the validity of animal models. Furthermore, because of the inherent limitations of modeling in laboratory animals some of the most prominent behavioral abnormalities of schizophrenia, such as delusions and hallu-

cinations, cellular and molecular characterizations can complement behavioral investigations in evaluating developmental and genetic models of schizophrenia.

## Behavioral Phenotypes

### *Locomotor and Stereotypy*

Changes in locomotor activity in rodents have often been used to assess both models of schizophrenia and the effects of antipsychotic treatments. The original impetus for the use of locomotor activity measures was derived from the psychostimulant models based on the dopamine hypothesis of schizophrenia, as reviewed elsewhere (3–5). These models arose because of the apparent similarity (i.e., “face validity”) between the symptoms of schizophrenia and the effects of high doses of amphetamine in presumably normal humans (6). Cross-species studies in animals treated with psychostimulants revealed both locomotor hyperactivity and, at higher doses, striking stereotyped or perseverative behaviors, which were seen as having face validity for the stereotyped behavior induced by amphetamine in humans (4,6,7). Measures of locomotor hyperactivity have been used extensively to characterize the effects of both dopaminergic psychostimulants and *N*-methyl-D-aspartate (NMDA) antagonists, such as phencyclidine (PCP), although PCP-induced hyperactivity differs markedly in qualitative features from that produced by dopaminergic psychostimulants. Although patients with schizophrenia are not typically hyperactive, they often exhibit perseverative or stereotyped behaviors. Hence, many studies in rodents have focused on the forms of stereotypy produced by psychostimulants.

### *Gating Measures*

Clinical observations in schizophrenic patients have identified deficiencies in the processing of information, including an inability automatically to filter or “gate” irrelevant thoughts and sensory stimuli to prevent them from intruding on conscious awareness. Hence, theories of schizophrenic disorders often conceptualize the common aspect of these disorders as involving one or more deficits in the multiple mechanisms that enable normal persons to filter or gate most of the sensory stimuli they receive (8–10). In the most classic measure of filtering deficits, numerous studies have observed deficits in the habituation of startle responses in schizophrenic patients (e.g., 12,31,102), which may reflect failures of sensory filtering leading to disorders of cognition. A more specific class of such mechanisms is referred to as *sensory* or *sensorimotor gating*. Theoretically, impairments in either filtering or gating lead to sensory overload and cognitive fragmentation. It is also possible that the mechanisms that subserve experimental examples of filtering or gating are also responsible for the gating of cognitive information. The hypothetical construct of sensorimo-

tor gating has been operationalized and explored in both human and animal studies. The validity of this gating construct has been assessed most thoroughly by means of an operational measure based on cross-species homologies in the startle reflex—namely, the prepulse inhibition (PPI) of startle paradigm. In a conceptually related approach, analogous measures of event-related potentials are used across species to study sensory gating in the P50 event-related potential condition–test paradigm.

### Habituation

*Habituation* refers to the decrement in responding when the same unimportant stimuli or cognitions occur repeatedly in the absence of any contingencies. Habituation is considered to be the simplest form of learning and is essential for the development of selective attention. Although habituation can be assessed with a variety of behavioral measures, the most common approach has been to study the gradual decrease in the startle response elicited by a series of tactile or acoustic stimuli in humans, rats, or mice. In patients with schizophrenia or schizotypy, deficits in startle habituation have been reported with the use of either modality of startling stimuli (9,11–13). A striking advantage of the startle habituation measure is the fact that extremely similar behavioral tests can be conducted in both humans and experimental animals.

### Prepulse Inhibition

The PPI paradigm is based on the fact that a weak prestimulus presented 30 to 500 milliseconds before a startling stimulus reduces, or gates, the amplitude of the startle response. The generality and reliability of this robust phenomenon is clear; PPI is observed in many species, PPI is evident both within and between multiple sensory modalities when a variety of stimulus parameters are used, and PPI does not require learning or comprehension of instructions. Virtually all the evidence available supports the belief that PPI is homologous from rodents to humans, unlike most other cross-species comparisons based on often dubious arguments of similarity or, at best, analogy. As reviewed elsewhere (14,15), several laboratories have reported significant deficits in PPI in schizophrenic, schizotypal, and presumably psychosis-prone subjects with the use of a variety of testing procedures and stimulus parameters. Nevertheless, PPI deficits are not unique to patients in whom schizophrenia has been diagnosed; they are also observed in other psychiatric disorders involving abnormalities of gating in the sensory, motor, or cognitive domains.

### P50 Gating

In the P50 sensory gating paradigm, two acoustic clicks are presented in rapid succession, usually 500 milliseconds apart. In normal persons, the P50 event-related potential to the second click is reduced or gated relative to the event-related potential to the first click. Schizophrenic patients

and their first-degree relatives exhibit less sensory gating (16). An analogous form of sensory gating is studied in rodents based on the N40 event-related potential generated from the hippocampus (17).

### Latent Inhibition

Latent inhibition is a relatively complex paradigm that is conceptually related to the gating theories of schizophrenic disorders. *Latent inhibition* refers to the observation that repeated exposures to a sensory stimulus (i.e., habituation) retard the rate at which a subject subsequently acquires a stimulus–response association based on this stimulus (18). Deficits in latent inhibition have been reported in schizophrenic patients (19), although it appears that such deficits may be limited to acute episodes of schizophrenia (19,20). This limitation has diminished interest in latent inhibition as a model for schizophrenia.

### Social Behavior

Social withdrawal is included among the negative symptoms of schizophrenia and is often one of the earliest symptoms to occur. Models of social isolation have been studied in both monkeys (21) and rats (22). Naturally, given the importance of language in human social interactions, the species-specific differences in social behavior limit the direct comparisons that can be made across species.

### Cognitive Measures

Cognitive deficiencies played a prominent role in the original description of schizophrenia by Kraepelin and distinguish the diagnosis of schizophrenia from manic-depressive and other forms of psychosis. Cognitive deficits are reported across all subtypes of schizophrenia and include impairments of attention, working memory, verbal memory, set shifting, and abstraction. Severe cognitive deficits appear to be a major factor contributing to impaired social and vocational functioning and treatment outcome (23). Current modes of therapy for schizophrenia (i.e., dopamine D2 or dopamine D2/serotonin 5-HT<sub>2</sub> antagonists, which effectively reduce the positive symptoms of schizophrenia in the majority of patients) have minimal beneficial effects on cognitive functioning. Typical antipsychotic drugs (e.g., haloperidol, chlorpromazine) may in fact lead to a deterioration in cognitive functions in schizophrenia patients (24) by producing so-called secondary deficit symptoms. Although some reports suggest that the atypical antipsychotic drug clozapine and the new generation of antipsychotics (e.g., olanzapine and risperidone, which target several subtypes of dopamine and serotonin receptors) may improve cognitive function, this effect is relatively small and has not been reproducible across laboratories (25–27). Thus, an important future direction of preclinical research relating to schiz-

izophrenia is the design of animal models and novel treatments that target cognitive dysfunctions associated with this disorder. However, establishing the validity of animal models of cognitive deficits of schizophrenia and designing new pharmacologic approaches to the treatment of symptoms depends on appropriate behavioral paradigms for laboratory animals. These must provide as good an analogy as possible to the empiric measures on which schizophrenic patients are impaired. Unfortunately, the ratings of symptoms commonly assessed in clinical studies are of little value in this context.

The limited cognitive capacity of laboratory animals hinders the design of cognitive tasks that can be considered entirely “analogous” to relevant experimental paradigms, such as the Wisconsin Card Sorting Test and Continuous Performance Test. Therefore, most of the research involving cognitive tasks that are relevant to schizophrenia has been conducted in monkeys. Nevertheless, it is possible to design behavioral paradigms in rodents that can evaluate cognitive constructs “comparable” with those measured in many human experimental paradigms (40–42).

Among the most common of animal cognitive tasks are those with a working memory component (i.e., the ability to guide behavior by forming internal representations of stimuli that are no longer present in the environment). Human psychological tests of working memory, such as the “*n*-back” task (28), on which patients with schizophrenia exhibit an impairment (29), provide a measure of delay-dependent retention of mental representation. Several rodent tasks of working memory, such as delayed matching or nonmatching to sample (30) and discrete trial delayed alternation (31), contain important elements of human experimental paradigms and are used routinely to understand the cellular basis of working memory.

Schizophrenic patients, like patients with overt frontal lobe damage, display profound deficits in tasks that require behavioral flexibility, strategy shifting, and response to environmental feedback. These tasks include the Wisconsin Card Sorting Test (32), the Category Test (33), and the Tower of Hanoi Task (34), all of which involve an ability to utilize knowledge or feedback to change or shape behavior. Several interesting tasks have been characterized for evaluating behavioral flexibility and strategy-shifting ability in the rat. Of note is a maze-based strategy-shift task described by Ragozzino et al. (35). This task requires rats first to learn either a response strategy (unidirectional turn) or a visually cued place-discrimination strategy (black vs. white maze arm) to obtain a food reward. Following acquisition of the initial strategy, the rats are required to shift to the alternative strategy (e.g., response strategy to visual cue strategy) or to reverse the reward contingency within a strategy (e.g., right turn response to left turn response) to receive the food reward. This task is particularly useful in that it allows the experimenter to assess task acquisition, behavioral flexibility within and between strategies, and perseverative behavior,

all of which appear to be relevant to the cognitive deficits associated with schizophrenia.

Attentional deficits are among the hallmarks of the clinical phenomenology of schizophrenia (36,37). One of the best characterized rodent attentional tasks is the Five-Choice Serial Reaction Time task, which was designed by Robbins and co-workers (38) based on the human Continuous Performance Test of Attention (39). The basic form of this task requires the rat to detect brief flashes of light occurring in one of five holes and provides a steady-state procedure in which the effect of manipulations can be determined against a baseline of stable performance. One advantage of this task is that it allows for a number of manipulations that test several variables on which patients with schizophrenia show deficits during the Continuous Performance Test, such as perseverative responding and omission errors.

The behavioral tests outlined here, albeit not without limitations, provide important tools for establishing the construct validity of animal models of schizophrenia. Although relatively few studies (e.g., 19,75,87) have utilized these measures to characterize animal models, their use may be important for defining novel pharmacologic approaches for the treatment of cognitive deficits associated with schizophrenia.

## Cellular and Molecular Phenotypes

Cellular and molecular markers, identified by morphologic findings from postmortem studies, are being used increasingly to establish the validity of animal models of schizophrenia. Although a review of the schizophrenia postmortem literature is beyond the scope of this chapter, some of the findings relevant to animal models include abnormalities in the neuronal organization of the prefrontal cortex, such as a reduction in cortical volume (e.g., 7,43), altered laminar distribution of neurons that contain the enzyme nicotinamide adenine dinucleotide phosphate diaphorase (44), and reduced neuropil and elevated neuronal density (45). In addition to cytoarchitectural findings, postmortem evidence of abnormalities in cortical neurotransmitter function has also been demonstrated. These abnormalities include alterations in  $\gamma$ -aminobutyric acid (GABA) neurons or other indices related to GABA-mediated neurotransmission (46–48), decreased density of tyrosine hydroxylase immunoreactive axons (49), and changes in gene expression of the NR<sub>2B</sub> and NR<sub>1</sub> subunits of the NMDA receptor (50, 51). These markers have been used primarily in validating developmental animal models. Examples include alterations in cortical cell migration and neurogenesis in the gestational malnutrition model (52) and reduced thickness of neocortex and hippocampus after prenatal exposure to the influenza virus (53) or the antimetabolic agent methyazoxymethanol (54).

Functional findings from imaging studies performed on patients with schizophrenia also have the potential of help-

ing to establish the predictive and construct validity of animal models. Of note are studies demonstrating an exaggerated dopamine release in response to amphetamine in patients with schizophrenia (55,56). These findings have been suggested to support the validity of the amphetamine sensitization model of schizophrenia (57).

## PHARMACOLOGIC MODELS

The most common approach for developing animal models has been to exploit pharmacologic treatments or “drug-induced states” that produce schizophrenia-like symptoms in nonschizophrenic humans. These models generally have some predictive or construct validity and have been instrumental in establishing three of the most prominent theories of schizophrenia: the dopamine hypothesis, serotonin (or serotonin–dopamine) hypothesis, and glutamate hypothesis.

### Dopamine-Agonist Models

The most widely studied class of drug-induced models of schizophrenia is based on the behavioral effects of psychostimulant drugs such as amphetamine. Although the models that evolved from this approach have demonstrated considerable predictive validity in terms of pharmacologic isomorphism, current thinking now indicates that the original appearance of face validity was actually somewhat misleading. In recent years, the dopamine hypothesis of schizophrenia has evolved into the narrower hypothesis that the mesolimbic dopamine system, distinct from the nigrostriatal dopamine system, is most relevant to schizophrenia. The nigrostriatal dopamine system is now seen as most relevant to the dyskinesia side effects of antipsychotic treatments. The mesolimbic system appears to mediate the locomotor-activating effects of lower doses of amphetamine, whereas the nigrostriatal system mediates the stereotypies that predominate at higher doses (4). Thus, the stereotypies originally proposed to have the most face validity for the human condition now appear to be more closely linked neurobiologically to phenomena that are considered side effects of the clinical treatments. Because schizophrenic patients are not generally considered to be motorically hyperactive, the amphetamine-induced hyperactivity that is mediated by what is believed to be the most relevant neurobiological substrate has seldom been considered to mimic the human disorder. Note that the failure of the model to have face validity has in no way weakened its utility in neurobiological research, which is based on the etiologic and predictive validity of the model. In fact, virtually any of the behavioral effects of amphetamine in rodents, including either locomotor hyperactivity or stereotypy, have a high degree of pharmacologic isomorphism as models for the efficacy of dopamine-antagonist treatments for schizophrenia (4,5); thus,

the predictive validity of these models appears limited to dopaminergic treatments.

Both dopamine agonists and antagonists have been studied in rat paradigms used to assess latent inhibition. Most of these paradigms utilize three distinct stages: preexposure, conditioning, and expression. Drugs are typically given during the preexposure or conditioning stages, or both. Hence, different drugs can produce different profiles depending on the stage at which they exert their effect. Such complexity does not arise in the testing of latent inhibition in patients with schizophrenia, in whom the condition being tested is necessarily present at all stages of the test paradigm. In both rats and healthy humans, amphetamine disrupts latent inhibition in a haloperidol-sensitive manner (18). In contrast, direct dopamine agonists, such as apomorphine, do not alter latent inhibition. One of the most interesting aspects of the latent inhibition paradigm is that both typical and atypical antipsychotics can actually improve latent inhibition in rats when testing parameters are adjusted to yield low levels of latent inhibition in control animals. Hence, the latent inhibition paradigm differs from most other models in rats in that it is possible to assess the effects of a putative antipsychotic drug in a latent inhibition paradigm without first having to disrupt performance by the administration of a drug or some other manipulation.

As reviewed in detail elsewhere (14,15), the sensorimotor gating deficits assessed by measures of PPI of startle in schizophrenia-spectrum patients are mimicked in rats by the activation of dopamine systems. Thus, drugs such as the direct dopamine agonist apomorphine and the indirect dopamine agonists D-amphetamine and cocaine impair PPI in rodents. As in patients with schizophrenia (58), the apomorphine-induced disruption of PPI in rats is not modality-specific, being seen when acoustic prepulses are used to inhibit either acoustic or tactile startle (59). The D2-receptor family appears to mediate the apomorphine disruption of PPI in rats because it is blocked by D2 antagonists, largely insensitive to D1 antagonists, and reproduced by the D2 agonist quinpirole, but not by the D1 agonist SKF 38393. Within the D2 family of receptors, the D2 subtype appears to be the most relevant to these effects. In comparisons of knockout mice lacking either D2, D3, or D4 dopamine receptors, the effects of amphetamine on PPI were absent only in the D2-subtype knockouts (60). In addition to being blocked by typical antipsychotics, the apomorphine-induced disruption of PPI is reversed by the atypical antipsychotics clozapine, olanzapine, and quetiapine (15,61), which lack neuroleptic properties in some behavioral assays. For example, clozapine fails to reverse amphetamine- and apomorphine-induced stereotypy in rats, or apomorphine-induced emesis in dogs (4). The ability of antipsychotics, including atypical antipsychotics, to restore PPI in apomorphine-treated rats strongly correlates with their clinical potency ( $r = .99$ ) (61). In addition to its sensitivity, the specificity of the PPI model for compounds with antipsychotic efficacy is supported by

the fact that it predicts no such efficacy for a wide variety of other psychiatric drugs. Thus, the PPI paradigm appears to be sensitive to both typical and atypical antipsychotics, but—when used with the dopamine agonist apomorphine—this paradigm clearly fails to make the important distinction between these two classes of antipsychotic agents. Thus, converging evidence indicates the important involvement of dopaminergic systems, acting via D2-family receptors, in the control of PPI. These findings in rats parallel the deficits in PPI observed in schizophrenic patients (58), which are also reported to be corrected by both typical and atypical antipsychotics (62,63).

It has been suggested that the increased stereotypy and submissive behavior produced by amphetamine in monkeys may mimic the stereotypy and paranoid ideation in schizophrenic patients. Accordingly, both these behavioral effects can be prevented by pretreatment with the antipsychotics haloperidol and chlorpromazine (21). In contrast, the social isolation induced by amphetamine in monkeys is generally regarded as related to the social withdrawal seen in patients with schizophrenia. As in schizophrenic patients, the animals actively avoid other animals, and these effects cannot be reversed by typical antipsychotic drugs such as haloperidol and chlorpromazine (21). Although few novel antipsychotics have been tested in this model, both clozapine and quetiapine have been shown to reverse amphetamine-induced social isolation in monkeys.

One aspect of the psychostimulant model that has generated considerable interest involves the dosage regimens required for amphetamine or related drugs to produce psychotic-like behavior in psychiatrically healthy humans. Because of the widespread belief that amphetamine-induced psychosis is produced only by repeated exposure to the drug (6,64), many preclinical researchers have directed their attention to the behavioral effects of amphetamine that are augmented or sensitized by repeated administration of the drug. A review of the available clinical literature, however, reveals that chronic exposure is not required and that psychotic episodes can be produced by acute administration of amphetamine or related drugs (5). The complex and limited nature of the clinical data seems to have led to mistaken interpretations that have inordinately influenced a large proportion of the basic research in this area. Although it is clear that tolerance to the psychosis-inducing effects of amphetamine does not occur in humans, it is not clear that sensitization is required for these effects. Hence, although an animal model based on the effects of chronic amphetamine could be invalidated if tolerance were observed, the development of sensitization does not provide evidence supporting the relevance of the model to schizophrenia. Indeed, it appears that the animal models having the greatest amount of predictive validity are those based on the effects of the psychostimulant that are evident after acute administration (4,5).

## Serotonin-Agonist Models

Soon after the initial reports of the behavioral effects of lysergic acid diethylamide (LSD), researchers began to explore the idea that the class of drugs represented by LSD might appropriately be called *psychotomimetics*, or even *psychotogens*. This hypothesis was engendered by the similarities between the effects of LSD on perception and affective lability and the symptoms of the early stages of psychoses such as schizophrenia (65). Recent studies systematically comparing hallucinogen-induced psychotic states with the early stages of psychotic disorders have confirmed substantial overlap in the two syndromes (66). Despite many clear similarities, two major differences prompted the dubious albeit widely accepted conclusion that this class of drugs does not provide a useful model of schizophrenia (67,68). First, tolerance was found to develop rapidly to the subjective effects of LSD-like drugs, whereas the symptoms of schizophrenia persist for a lifetime. Second, the hallucinations produced by LSD and related drugs are typically visual rather than auditory, as is characteristic of schizophrenia. These two observations weaken the predictive validity of the hallucinogen model of the syndrome of schizophrenia.

Initial interest in hallucinogens was spurred by the possibility that abnormalities of biochemistry might lead to the endogenous production of such compounds and hence be responsible for some psychotic symptomatology. For example, the transmethylaton hypothesis posited that serotonin could provide a substrate for the endogenous production of hallucinogens similar to *N,N*-dimethyltryptamine (DMT) (68). Initially, this etiologically based model was dismissed because of the rapid tolerance associated with traditional hallucinogens such as LSD and mescaline. Nevertheless, recent studies indicate that no tolerance occurs to the subjective effects of DMT in humans (69), which suggests that DMT may differ from other hallucinogens and that this model may still be viable. Indeed, different mechanisms may be involved in the various actions of the different hallucinogenic drugs, as suggested by the lack of cross-tolerance to DMT in human subjects made tolerant to LSD (70). Hence, further studies are warranted to provide the objective evidence needed to evaluate adequately the model of psychosis based on the hypothesis of an endogenous psychotogen.

Furthermore, it remains possible that these drugs may be psychotomimetic and therefore have relevance as models of some aspects of psychotic episodes in humans. Recent suggestions of serotonergic abnormalities in schizophrenia (71) and of 5-HT<sub>2A</sub>-receptor contributions to the clinical efficacy of atypical antipsychotics (72) have revitalized interest in this possibility. Hallucinogens are now believed to produce their characteristic subjective effects by acting as 5-HT<sub>2A</sub> agonists (73). Many of the newer atypical antipsychotic drugs are clearly potent 5-HT<sub>2A</sub> antagonists (72). With regard to specific abnormalities exhibited by patients

with schizophrenia, evidence indicates that the study of hallucinogen action may provide useful animal models. For example, both schizophrenic and schizotypal patients exhibit deficits in startle habituation (9,11–13). Hallucinogenic 5-HT<sub>2A</sub> agonists such as LSD and mescaline produce similar deficits in startle habituation in rats (59,74). Conversely, opposite behavioral effects are produced by 5-HT<sub>2A</sub> antagonists (74), including some antipsychotics (72). Similarly, the PPI-disruptive effects of hallucinogenic 5-HT<sub>2</sub>-receptor agonists are blocked by the selective 5-HT<sub>2A</sub> antagonist M100907, but not by the dopamine blocker haloperidol (74). Furthermore, in keeping with the similarities between acute psychotic states and the syndrome induced by hallucinogens, latent inhibition is also disrupted by LSD and other serotonergic hallucinogens (75), as it is in acutely ill schizophrenic patients. These effects can be blocked by the putative antipsychotic M100907 (75). Thus, the effects of hallucinogens on habituation, PPI, and latent inhibition in animals have some predictive validity with regard to both specific abnormalities exhibited by patients in the early stages of schizophrenia and the effects of antipsychotics (74). The construct validity of this model is based on compelling evidence that both the symptoms of schizophrenia and the effects of hallucinogens reflect exaggerated responses to sensory and cognitive stimuli, theoretically resulting from failures in normal filtering or gating processes such as habituation, PPI, or latent inhibition (1,3,9). Accordingly, 5-HT<sub>2A</sub> antagonism by itself might be effective in the treatment of certain forms of schizophrenia. Indeed, a rather selective 5-HT<sub>2A</sub> antagonist, M100907, appears to have efficacy as an antipsychotic in some patients with schizophrenia, despite having negligible affinity for dopamine receptors (76). This finding suggests the possibility of a nondopaminergic mechanism for a treatment of subtypes of schizophrenia and provides important support for the predictive validity of the hallucinogen model of psychosis.

### Glutamatergic Models

Dysfunctional glutamate neurotransmission has been implicated in schizophrenia, primarily because noncompetitive antagonists of the NMDA subtype of glutamate receptors, including PCP and ketamine, produce a behavioral syndrome in healthy humans that closely resembles symptoms of schizophrenia and is frequently misdiagnosed as acute schizophrenia (77,78). The syndrome includes positive symptoms, such as paranoia, agitation, and auditory hallucinations; negative symptoms, such as apathy, poverty of thought, and social withdrawal; and cognitive deficits, such as impaired attention and working memory. The remarkable similarity of PCP-precipitated behaviors with the diverse array of symptoms associated with schizophrenia has prompted the use of PCP (and its analogue ketamine) in pharmacologic models of schizophrenia in both basic and clinical studies. Notably, whereas psychotic episodes are

generally associated with prolonged abuse of amphetamine, a single exposure to PCP or ketamine can produce the cognitive deficits and several symptoms listed above in healthy humans. Thus, acute exposure to these compounds is considered a useful pharmacologic tool for producing some aspects of schizophrenic symptomatology in the laboratory animal.

Several interesting aspects of this model distinguish it from monoamine-based models. For example, the behavioral effects of PCP and related compounds are not, for the most part, mediated by increased dopamine transmission and therefore are not blocked by typical antipsychotics (see below). Similarly, in normal human volunteers, the psychotomimetic effects of ketamine are not blocked by typical antipsychotics, but they are reduced significantly by the prototypal atypical antipsychotic clozapine (79). Therefore, this model may be especially useful for testing the effectiveness of atypical and perhaps even novel antischizophrenia drugs. In fact, the first non-monoaminergic ligands (including a glycine-site agonist and a metabotropic glutamate-receptor agonist), which have recently entered clinical trials, have been based on preclinical PCP models (41,80). Another attractive aspect of the NMDA antagonist model is that, unlike the dopamine-based models, it has strong construct validity for studying the cognitive and attentional deficits in schizophrenia. In laboratory animals, NMDA antagonists impair working memory, set shifting, and other cognitive functions that are related to schizophrenia (31). More importantly, in clinical studies, direct comparison of schizophrenic patients with healthy volunteers receiving subanesthetic doses of ketamine have indicated no significant difference in scores for thought disorder between the two groups (81).

In rats and monkeys, noncompetitive NMDA antagonists, including PCP and ketamine, produce a range of behavioral abnormalities that have important relationships to schizophrenic symptomatology. These drugs produce both locomotor hyperactivity and stereotyped behaviors. Although they also increase dopamine neurotransmission in limbic regions (82), their motor-activating effects appear to be dopamine-independent (83). At rather low doses, PCP retards habituation of the startle response without affecting startle reactivity (84), a pattern similar to that seen in parallel studies in schizophrenic patients (9). Also as in schizophrenia, PCP-treated rats exhibit marked deficits in social behavior. Although typical antipsychotics have no reliable effect on the PCP-induced disturbance in social behavior in rats, the atypical antipsychotics clozapine, sertindole, and olanzapine appear to reverse the effects partially (22). In terms of sensorimotor gating measures, PPI is reduced or eliminated in rats by psychotomimetic noncompetitive NMDA antagonists, including PCP, dizocilpine (MK-801), and ketamine (14,15). As with apomorphine and as in schizophrenia, both intramodal and cross-modal PPI is sensitive to noncompetitive NMDA antagonists (59). In contrast to

the effects of dopamine agonists on PPI, but in keeping with the results of studies of the subjective effects of ketamine in humans, the PPI-disruptive effects of NMDA antagonists are *not* reversed by typical antipsychotics such as haloperidol or selective D1 or D2 antagonists. Importantly, these effects *are* reversed by the atypical antipsychotics clozapine, olanzapine, quetiapine, and remoxipride (14,15). These findings raise the possibility that the PCP-induced disruption of PPI may be a useful model for identifying compounds with atypical antipsychotic potential.

In addition to acute dosing with PCP and ketamine, withdrawal from repeated administration of PCP has been proposed to be a useful model for some aspects of schizophrenia (85). Although this model lacks some of the important characteristics of acute models, such as lack of an effect on PPI, it produces an enduring cognitive impairment that is highly relevant to schizophrenic symptomatology.

## DEVELOPMENTAL MODELS

The best-characterized animal model in this class is that proposed by Lipska and Weinberger (86,87), which involves neonatal excitotoxic lesions of the ventral hippocampus. These lesions produce postpubertal behavioral disturbances, such as increased spontaneous, amphetamine-induced, and NMDA antagonist-induced locomotion. They also produce potentiated apomorphine-induced stereotypies, disruption of PPI, reduced cataleptic response to haloperidol, impaired working memory, and hypersensitivity to stressful stimuli. Furthermore, this manipulation results in alterations in some cellular and molecular markers that may have relevance to schizophrenia (88), such as reduced expression of the glutamate transporter excitatory amino acid transporter 1 (EAAT<sub>1</sub>) and glutamic acid decarboxylase (GAD67). To the limited extent that they have been tested, dopamine antagonists, including classic and atypical antipsychotic drugs, ameliorate the behavioral abnormalities produced by neonatal ventral hippocampal lesions. It will be important in the future to examine the predictive power of this model for the identification of antipsychotic drugs more thoroughly with measures that are not sensitive to the effects of antipsychotic drugs in sham-lesioned rats.

Other strategies that have been used to disrupt early cortical development include systemic exposure to L-nitroarginine, a nitric oxide synthase inhibitor that disrupts neuronal maturation (89), or the antimetabolic agent methyloxymethanol (54,90). These models produce morphologic changes relevant to schizophrenia, such as altered neurogenesis and reduced cortical volume. They also produce some of the behavioral characteristics associated with schizophrenia, such as stereotypy, cognitive impairments, and deficits in PPI. As yet, the predictive validity of this model in terms of sensitivity to antipsychotic treatments remains to be determined.

Isolation rearing of rats has also been used as a manipulation to generate models related to schizophrenia and models of depression and attention-deficit/hyperactivity disorder (ADHD). In the context of schizophrenia, the focus has been on the disruptions of PPI rather than the locomotor hyperactivity observed in isolation-reared rats. Indeed, comparisons among different strains of rats indicate that both effects are strain-dependent but appear in different strains (91–93). Thus, as with a variety of pharmacologic manipulations, locomotor hyperactivity and deficient PPI are readily dissociable behavioral phenomena, even though both have been used in animal models related to schizophrenia. In several laboratories, isolation-reared rats have been shown to exhibit a neuroleptic-reversible deficiency in PPI in comparison with group-reared controls (91,94). This effect of isolation rearing appears to be specific to development; similar isolation of adult rats fails to produce the deficit in PPI observed in isolation-reared rats (95). Furthermore, as in the most common form of schizophrenia, the PPI deficits are not evident before puberty but emerge at about that time (96). Converging evidence for an influence of isolation rearing on gating mechanisms in adulthood stem from the observation that the rat analogue of the P50 sensory gating deficit of schizophrenia is also seen in isolation-reared rats (97). Because these deficits in PPI and P50 gating are not associated with concomitant deficits in latent inhibition (95), which occurs only in acutely ill schizophrenic patients (19), it would appear that the isolation-rearing model is more relevant to chronic than to acute schizophrenia. In addition to reversals by typical antipsychotics (haloperidol, raclopride), reversals of the isolation-induced deficits in PPI by clozapine, risperidone, quetiapine, olanzapine, and the putative antipsychotic M100907 have been observed (94, 98). Thus, PPI deficits in isolation-reared rats may be a valuable paradigm that—like the apomorphine-induced disruption of PPI—is sensitive, but not specific, in its ability to identify compounds with atypical antipsychotic properties. The potential advantage of the isolation-rearing model, as of other models involving developmental perturbations, is that it does not rely on the administration of a drug or the introduction of an artificial lesion to produce the behavior of interest. When the behavior studied in the model is induced by a drug, such as a dopamine or serotonin agonist, the model is typically effective in identifying the corresponding antagonist. Indeed, most of the animal models of schizophrenia have relied on dopaminergic psychostimulants and have proved to be largely limited to the detection of dopamine antagonists. The major message of the fact that clozapine is effective, even at doses that achieve low levels of dopamine receptor occupancy, is that new treatments can be identified for patients with schizophrenia, and that these novel treatments may not involve dopamine antagonism. The isolation-rearing manipulation presumably produces a deficit in PPI by virtue of a substantial reorganization of neural circuits through the course of development.



Hence, such a model has the potential to identify completely novel antipsychotic treatments simply because it does not require the administration of a drug.

## GENETIC MODELS

Genetic contributions to schizophrenia have been clearly established in family studies. Although the focus of considerable research, the application of linkage analyses to schizophrenia has not generally proved successful, perhaps because schizophrenia does not represent a single phenotype. Nevertheless, it remains possible that genetic approaches will lead to etiologically based models

### Strain Differences

Genetic factors appear to be critical determinants of both sensory and sensorimotor gating in rats. For example, some inbred strains of mice are deficient in gating of the N40 event-related potential (17), which is the rodent analogue of the P50 gating deficit seen in schizophrenia. Indeed, a linkage between the P50 gating deficit in patients with schizophrenia and a specific chromosomal marker associated with the gene for the  $\alpha_7$  subunit of the nicotinic acetylcholine receptor has been demonstrated in a series of elegant studies (16). The potential power of cross-species studies of specific behavioral abnormalities in psychiatric disorders is exemplified by the parallel between these human linkage studies and the observation that the strain of mice that is most deficient in gating of the N40 event-related potential is also the most deficient in  $\alpha_7$ -nicotinic receptors (17). Such parallel investigations in patients and animals provide an exemplar for the application of modern molecular biological techniques to the generation and validation of animal models of psychiatric disorders. However, this genetically related deficit in sensory gating does not extend to studies of sensorimotor gating as measured by PPI of the startle response. Thus, mice in which the  $\alpha_7$ -nicotinic receptors have been deleted by genetic engineering exhibit normal levels of PPI (99). Nevertheless, other evidence indicates that PPI is regulated by genetic factors. For example, strain-related differences in the dopaminergic modulation of PPI have been reported (100). More relevant to the recent indications that PPI deficits are evident in family members of schizophrenia patients (101), Ellenbroek et al. (102) utilized pharmacogenetic selective breeding to produce strains of rats that were either sensitive (APO-SUS) or insensitive (APO-UNSUS) to the effects of apomorphine on gnawing behavior. Within either a single generation or after many generations of selective breeding, APO-SUS rats and their offspring exhibited significantly less PPI and latent inhibition than did APO-UNSUS rats. Apparently, the physiologic substrates that regulate behavioral sensitivity to apomorphine (presumably some feature related to dopamine-

receptor transduction) are associated with substrates that regulate both PPI and latent inhibition, which are transmitted genetically. In another approach, comparisons of several inbred strains of rats identified some strains that exhibit deficits in PPI (103). Because these strains did not exhibit hearing impairments, the genetically determined deficit in PPI likely represents a deficit in sensorimotor gating processes.

### Genetically Modified Animals

Other examples of nonpharmacologically based models relevant to schizophrenia are emerging from the field of molecular biology, in which genetic engineering is being used to generate transgenic and knockout animals. In the absence of established candidate genes, the use of mutant animals in models of schizophrenia has focused on the identification of phenotypic differences in behaviors considered relevant to the clinical disorder (i.e., validity has been sought primarily in the dependent measure rather than in the independent variable). For example, schizophrenia-like deficits in PPI of startle have been observed in specific strains of mice (104) and in “knockout” mice in which specific genes have been deleted (105). The focus of genetic engineering in the mouse is beginning to prompt extensions of pharmacologic studies from the rat to the mouse. Although much more such work is needed, it is already abundantly clear that species differences in pharmacologic effects between mice and rats will complicate the application of some schizophrenia-related rat models to mice. For example, in rats, antipsychotic drugs by themselves have minimal effects on PPI, in contrast to their marked suppression of locomotor activity and ability to improve latent inhibition. Hence, rat PPI models can identify antipsychotic effects only if a drug reverses the effects of a disruption in PPI produced by another drug, a lesion, or a developmental manipulation such as isolation rearing. In mice, however, it appears that antipsychotics improve PPI in mice that have not been manipulated (106). This important difference means that it may be easier to detect antipsychotic effects in mice, but also that it will be much more difficult to demonstrate a reversal of a PPI deficit produced by an experimental manipulation.

In an approach that is distinctly different from the candidate gene approach, genetically modified mice have been used to test specific hypotheses of relevance to animal models of schizophrenia. For example, although most pharmacologic evidence in rat had implicated the D2 subtype of the family of dopamine receptors in the PPI-disruptive effects of dopamine agonists, gene knockout mice proved useful in testing this conclusion more definitively. Ralph et al. (60) tested the effects of amphetamine on PPI in D2-, D3-, and D4-receptor knockout mice and corresponding wild-type mice. Only the mice lacking the D2 subtype of receptor failed to show the normal effect of amphetamine on PPI. Although knockout manipulations are confounded

by developmental adaptations, such a study takes advantage of the specificity that represents the fundamental strength of the knockout technology, as no dose of a drug can ever inactivate all of a given receptor without interacting with other receptors at the same time.

Another model with relevance to the etiology and pathophysiology of schizophrenia involves the NMDAR<sub>1</sub> (NR<sub>1</sub>) “knock-down” line of mutant mice (107). These animals display exaggerated spontaneous locomotion and stereotypy in addition to deficits in social and sexual interactions. Interestingly, preliminary studies indicate that some of these behavioral abnormalities may be ameliorated with a single dose of haloperidol or clozapine. This is an intriguing model that, with further characterization, may advance our understanding of the long-term effects of congenital NMDA-receptor hypofunction. Nevertheless, its relevance to schizophrenia may be questioned by the fact that no evidence has been found in schizophrenia for abnormalities in genes that express subunits of the NMDA receptor (108). Furthermore, these animals, as would be expected, show no behavioral reaction to the NMDA antagonists PCP and dizocilpine. Schizophrenic patients, on the other hand, exhibit a profound exacerbation of preexisting symptoms after exposure to a single dose of PCP (109) or ketamine (110).

## CONCLUSIONS

Establishing the construct, etiologic, and predictive validity of animal models relevant to schizophrenia-related disorders is limited by the paucity of rigorous experimental data derived from clinical studies. The major source of validation remains the ability of established antipsychotic drugs to demonstrate efficacy, measured by broadly defined clinical scales in heterogeneous groups of patients. Specific measures of clinical subtypes, clinical course, and symptom-specific treatment effects that can be translated into relevant animal models are needed to overcome the limitations inherent in relying on global assessments of treatment efficacy for validity assessment. The objective study of such measures in translational research is critical for the eventual identification of new antipsychotic treatments. Such treatments not only could help patients who are resistant to treatment with typical antipsychotics but also could help in the treatment of the negative and cognitive symptoms that do not appear to be treated adequately even by the newest generation of atypical antipsychotics.

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