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PERSPECTIVES

To Model a Psychiatric Disorder in Animals: Schizophrenia As a Reality Test

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Animal modeling has been instrumental in dissecting pathophysiological mechanisms and designing more effective therapies in many areas of medicine but not so in psychiatry. The critical obstacle in modeling psychiatric disorders has been limited information about their origin and underlying neural mechanisms. Recently, with rapidly growing knowledge about the neurobiology and genetics of psychiatric disorders, animal models of these diseases are gaining popularity in psychiatric research. New models of schizophrenia mimic biological phenomena associated with the clinical condition, particularly developmental changes in the cortex, abnormalities of glutamate neurotransmission, and genetic characteristics of selected behavioral traits. The biological fidelity of some aspects of these new models suggests that they will be useful in the development of new therapies, in identifying candidate genes, and in providing new insights about pathophysiology and etiology.
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Animal models are important developments in investigations of the mechanisms underlying a human disease and the design of new treatments. This is true for many diseases, but generally not for mental disorders, whose modeling in experimental animals has often been regarded as a highly controversial or outright heretic idea. An example of a particularly formidable challenge for animal modeling is schizophrenia, a complex disorder of unknown origin, characterized by abnormalities of uniquely human behaviors in the realms of perception, thinking and the experience of emotions, and whose onset is virtually restricted to young adulthood. Schizophrenia is such an inherently human disease that reproducing its most prominent symptoms—hallucinations, delusions and thought disorder—in a rodent or even in a non-human primate seems doomed. However, recent new evidence about the neurobiology of the condition has generated new avenues of animal research. In this perspective article, we highlight recent achievements in the efforts to model the neurobiology of schizophrenia in animals, consider limitations inherent in any heuristic animal model of this and probably other psychiatric disorders, and discuss the usefulness of a new generation of animal models for testing particular hypotheses about etiology and pathophysiology of schizophrenia.

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TRADITIONAL DOPAMINE-BASED ANIMAL MODELS

An animal model may represent a disease on three different levels: (1) it may reproduce inducing factor(s) (e.g., a genetic defect and the subsequent pathological processes underlying the disease); (2) it may mimic phenomenology (e.g., an array of symptoms of schizophrenia); and (3) it may predict responsiveness to already available treatments (e.g., antipsychotic drugs).

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Thus, the characteristics of an animal model and its faithfulness vary according to the aspects that it aspires to represent. Models that reconstruct the etiology and pathophysiological mechanisms of the disease are of the highest order of fidelity; they have so-called "construct validity." Models with construct validity usually, though not invariably (see below), possess some degree of face and predictive validity (Kornetsky and Markowitz 1978; McKinney and Moran 1981; Ellenbroek and Cools 1990; Rupniak and Iversen 1993; Costall and Naylor 1995). A good illustration of valid and useful models of complex diseases are genetic models of diabetes and hypertension; for instance, the db/db mice model of diabetes (Kobayashi et al. 2000) and the spontaneously hypertensive rat (SHR) (Patel et al. 2000). Unlike these models which faithfully reproduce relatively clear-cut physiological characteristics (e.g., high blood sugar levels or high blood pressure), models of psychiatric disorders face the unique difficulty of simulating much more complex and less easily defined pathophysiology. Traditionally, most animal models of schizophrenia have focused primarily on phenomena linked to dopamine, because the dopaminergic system has been strongly implicated in this disorder, as all effective antipsychotic drugs are antagonists of dopamine receptors, and dopamine agonists induce symptoms that resemble psychosis (Kornetsky and Markowitz 1978; McKinney and Moran 1981; Ellenbroek and Cools 1990; Costall and Naylor 1995, see Table 1).

Some dopamine-based models involve behavioral paradigms that were inspired by antipsychotic (i.e., antidopaminergic) pharmacology but bear no resemblance to schizophrenia (e.g., antagonism of apomorphine-induced emesis). Others reproduce phenomena isomorphic with selected characteristics of schizophrenia such as motor behaviors (e.g., dopamimetic drugs-induced stereotypies) and information processing deficits (e.g., apomorphine-induced prepulse inhibition of startle (PPI) abnormalities) (Braff and Geyer 1990; Costall and Naylor 1995). These dopamine-linked behaviors, although not specific for or uniquely prominent in schizophrenia, can be at least detected and precisely quantified in non-human species and have been useful in screening drugs with a predicted mechanism of action (e.g., dopamine blockade). Thus, models based on perturbing dopamine have no construct validity, limited face validity and relatively good predictive validity. The predictive validity was to be expected given that the models were based on changing dopamine function. However, as "dopamine-in, dopamine-out" models (i.e., models based on direct pharmacological manipulation of the dopaminergic system and tests of behavioral outcome related to dopamine function), they precluded exploring other than dopamine-based mechanisms of the disease and discovering novel antipsychotic therapies; to wit, drugs that emerged as a result of such models all exerted antidopaminergic efficacy. Antidopaminergic drugs, however, although ameliorative of some of the symptoms of schizophrenia, do not cure the disease. It has become increasingly clear that models based on direct manipulations of the dopamine system may have exhausted their heuristic potential and that new strategies need to be developed to provide novel targets for the development of more effective therapeutic agents.

THE SEARCH FOR A HEURISTIC MODEL

In the context of our current knowledge about schizophrenia, heuristic (i.e., "serving to discover," innovative) models have several goals: (1) to test the plausibility of theories derived from the emerging research data about the disorder; (2) to probe the explanatory power of new biological findings about the disorder; (3) to uncover mechanisms of schizophrenia-like phenomena; and (4) to suggest potential new treatments. Thus, a heuristic model, in contrast to a traditional dopamine-based model, needs to evince other schizophrenia-like abnormalities besides the feature that it directly manipulates. For instance, a model based on hippocampal injury would be heuristic if it triggered behavioral and/

Table 1. Clinical Aspects of Schizophrenia and Relevant Behavioral Changes in Animals

Schizophrenia: Clinical Phenomena	Animal Models: Behavioral Changes
1. Psychotic symptoms	Behaviors related to increased dopaminergic transmission: Dopamimetic-induced hyperlocomotion Reduced haloperidol-induced catalepsy
2. Stereotypic behaviors	Dopamimetic-induced stereotypies
3. Worsening of psychotic symptoms by NMDA-antagonists	NMDA antagonists-induced locomotion
4. Vulnerability to stress	Stress-induced hyperlocomotion
5. Information processing deficits	Sensorimotor gating (PPI, P50) deficits
6. Attentional deficits	Deficits in latent inhibition
7. Cognitive deficits	Impaired performance in delayed alternation and spatial memory tests
8. Social withdrawal	Reduced contacts with unfamiliar partners

or molecular changes outside the hippocampus that are associated with schizophrenia, enabled testing the mechanisms underlying the ensuing changes, and predicted novel therapies based on newly discovered mechanisms.

Recently, as interest in schizophrenia research has shifted from a principal focus on dopamine to theories of abnormal neurodevelopment, dysfunction of cortical glutamatergic neurons, and genetic susceptibility, animal models have followed a similar trend. The novel models considered below are either non-pharmacological or based on pharmacological manipulation of a neurotransmitter other than dopamine. Thus, they have ventured off the beaten path of "dopamine-in, dopamine-out" models, and offer the potential of elucidating non-dopamine mechanisms of disease and treatment. All animal models of schizophrenia, however, whether new or old, suffer from a generic problem—lack of a straightforward "litmus test" of fidelity. This is because there is no valid genotype, cellular phenotype or other biological marker that is characteristic of the disorder, and no animal model can fully reproduce the perceptual, cognitive and emotional features of the human illness. In the absence of a pathognomonic marker, a faithful model is expected to reproduce a constellation of behavioral and biological phenomena relevant to schizophrenia. If a model addresses a cluster of relevant changes ranging from anatomical and neurochemical to behavioral and cognitive features, rather than a single or a few non-specific phenomena, then there is a higher probability that the model is heuristic and isomorphic with biological processes related to the human disorder. As new findings about the pathophysiology of schizophrenia emerge, new models increasingly focus on certain cell or tissue phenotypes and a variety of complex behavioral characteristics, in addition to time-honored effects on dopamine related function (see Tables 1 and 2); unfortunately, as shown in the examples below, rarely are multiple phenomena addressed in a single model.

In the following discussion, we examine three approaches to creating animal models related to schizophrenia: (1) neurodevelopmental models, (2) glutamatergic hypofunction models and (3) genetic models. The first approach is based on experimentally induced disruption of brain development that becomes evident in an adult animal in the form of altered brain neurochemistry and aberrant behavior (neurodevelopmental models). These models test hypotheses that schizophrenia is caused by a defect in cerebral development (Lillrank et al. 1995), and in some instances, test whether the effects of early brain damage could remain inconspicuous until after a considerable delay, as appears to be the case in the human condition (Weinberger 1986, 1987; Murray and Lewis 1987; Bloom 1993). Another popular modeling approach involves pharmacological disruption of brain function and behavior via N-methyl-D-aspartate (NMDA) antagonists. These models test the hypothesis that dysfunction of glutamate neurotransmission accounts for a variety of schizophrenic phenomena (Javitt and Zukin 1991). Still another effort focuses on the search for susceptibility genes employing modern technologies of genetic engineering (genetic models, see Erickson 1996). These models test the clinical evidence that susceptibility genes account for risk for illness and, together with epigenetic/environmental factors, for phenotypic variation. Characteristically, a majority of these new models, despite the diversity of

Table 2. The Neonatal Ventral Hippocampal Lesion Model: Schizophrenia-like Phenomena

	Neonatal VH Lesion Model	Schizophrenia
Behavioral changes:		
	Hyperlocomotion to stress	Stress vulnerability
	PPI deficits	PPI deficits
	LI deficits	LI deficits
	Deficits in delayed alternation tests	Working memory deficits
	Reduced social contacts	Social withdrawal
Pharmacological responses:		
	Amphetamine-induced hyperactivity }	Enhanced symptomatic response to dopamimetics
	Apomorphine-induced stereotypies }	
	Reduced catalepsy to haloperidol	Neuroleptic tolerance
	MK-801 and PCP-induced hyperactivity	Enhanced symptomatic response to ketamine
Molecular changes in the prefrontal cortex:		
	NAA levels↓	NAA levels ↓
	GAD67 mRNA↓	GAD67 mRNA↓
	BDNF mRNA↓	BDNF mRNA↓

Abbreviations: BDNF, Brain derived neurotrophic factor; GAD-67, Glutamate decarboxylase-67; LI, Latent inhibition; NAA, N-acetylaspartate; PCP, phencyclidine; PPI, prepulse inhibition of startle; ↓ reduced vs. controls.

their origins, target components of a common neural circuitry implicated in schizophrenia (i.e., the temporolimbic cortices – nucleus accumbens/striatal complex – thalamus – prefrontal cortex. The involvement of this circuitry may account for the overlap in "schizophrenia-like" phenomena at the anatomical, neurochemical or behavioral level that are common to these various models.

NEURODEVELOPMENTAL MODELS

Testing Etiologic Theories

Many epidemiological and clinical correlational studies have been carried out in search of early developmental factors that may predispose to schizophrenia. There have been reports linking schizophrenia to obstetrical complications (Woerner et al. 1973; DeLisi et al. 1988; McNiel 1988; Hultman et al. 1997; Dalman et al. 1999), in utero exposure to alcohol (Lohr and Bracha 1989) and severe malnutrition (Susser and Lin 1992). Although many of these data are controversial (for review, see Weinberger 1995), a number of animal models have been designed to test the plausibility that specific gestational factors play a role in the origin of this disorder. These "etiological" models, none of which directly manipulates dopamine, aspire to construct validity and heuristic value because they reproduce putative causes of the disease and theoretically model putative primary pathological mechanisms.

For instance, a gestational malnutrition model (or more precisely, prenatal protein deprivation that begins prior to and continues throughout pregnancy) results in severe permanent changes in the development of the rat brain (for reviews, see Morgane et al. 1993; Brown et al. 1996). Malnutrition affects neurogenesis, cell migration and differentiation, and leads to deviations in normal brain development, including disrupted formation of neural circuits and neurotransmitter systems (Lewis et al. 1979; Cintra et al. 1997). Not suprisingly, malnutrition has been shown to have debilitating effects on cognitive function and learning abilities (Tonkiss and Galler 1990). Thus, to some degree these models mimic certain "face" features of schizophrenia. In contrast to schizophrenia, however, morphological abnormalities are severe and widespread, and the behavioral consequences are varied and inconsistent, perhaps, at least in part, because the impact of malnutrition on brain development is likely to be quite variable and depend on many factors, which have only been explored to a small degree. As a test of the plausibility of the malnutrition theory of schizophrenia this model has limited validity.

Prenatal exposure to influenza virus, another predisposing factor implicated in schizophrenia by several large epidemiological studies (Mednick et al. 1988; Kendell and Kemp 1989; O'Callaghan et al. 1991; Adams et al. 1993), has been shown to induce pyramidal cell disarray in a small subgroup of mice whose mothers were inoculated with the virus (Cotter et al. 1995). This developmental defect is somewhat similar to that reported in two studies in the hippocampi of schizophrenic patients (Conrad et al. 1991; Scheibel and Kovelman 1981). Another recent report indicates that infection with human influenza of day 9 pregnant mice results in defective corticogenesis as indicated by reduced thickness of the neocortex and hippocampus and by significant reductions of cortical Reelin immunoreactivity in the offspring (Fatemi et al. 1999). This model thus reproduces a hypothetical causative factor in schizophrenia and has face validity at least at the level of reduced Reelin expression, a neurobiological finding recently explored in brains of patients with schizophrenia (Impagnatiello et al. 1998). These are intriguing observations, but more conclusive data on the involvement of Reelin in schizophrenia and on the behavioral phenotype of the animal model are required before conclusions about the relevance of this model for schizophrenia can be made.

The plausibility that other, less common, viruses may induce schizophrenia-like changes has also been investigated (Rott et al. 1985; Waltrip et al. 1995). In utero Borna disease virus (BDV), a neurotropic virus with limbic selectivity, damages the hippocampus and prefrontal cortex, and results in complex changes in regional dopamine in rats (Solbrig et al. 1994, 1996a, 1996b; Hornig et al. 1999). While this model may invite further research into the mechanisms involved, notwithstanding convincing evidence of BDV infection in schizophrenia, its relevance to the pathophysiology of schizophrenia seems remote. Another example of a viral model is neonatal infection with lymphocytic choriomeningitis virus (LCMV) which disrupts in adult rats the integrity of γ-aminobutyric acid (GABA)-ergic neurons and excitatory amino acid systems, both implicated in schizophrenia (Pearce et al. 1996, 1999). The potential face validity of this model at a cellular level makes it particularly attractive because it addresses two theories about the pathophysiology of schizophrenia, vulnerability of GABAergic interneurons to developmental insult and adolescent vulnerability to excitotoxic injury (Benes et al. 1991, 1992; Olney and Farber 1995). Although conceptually appealing, it has yet to address a broader spectrum of aspects of the disorder, and its basic construct, LCMV infection, is of dubious relevance to schizophrenia.

The plausibility of obstetrical and birth complications are difficult to explore in animals because their causes in schizophrenia are unknown. Nevertheless, studies of models of Cesarean birth and of anoxia during birth in rats, report changes in limbic dopamine function of adult animals consistent with hyperresponsiveness of the dopamine system to stimulants (Brake et

al. 1997a, 1997b; El-Khodor and Boksa 1997, 1998). Surprisingly though, animals born by C-section and not subject to anoxia seem to be even more affected than anoxic rats (El-Khodor and Boksa 1997). If this has bearing on schizophrenia, it would suggest that C-section constitutes a greater risk factor than the more dramatic birth trauma of anoxia. In humans, C-section is generally assumed to involve less stress to the fetus and has not been noted as one of the obstetrical complications linked to schizophrenia. Clearly, more studies are needed to elucidate the mechanisms underlying the C-section-related phenomena in animals.

Until a broader array of schizophrenia-related phenomena is assessed in each of these etiologic models, it is premature to draw firm conclusions about whether any reproduce mechanisms underlying the human disorder. Moreover, the validity of these models is tempered by the lack of convincing evidence for the role of any of these various causative factors in schizophrenia, with the possible exception of influenza. These models illustrate, however, that certain early developmental insults may permanently disrupt brain function in ways that are similar to some of the phenomena reported in schizophrenia.

Testing the Impact of Disrupted Neurogenesis

Several post mortem studies of schizophrenia have reported variations in cortical cytoarchitecture (Akbarian et al., 1993a, 1993b; Arnold et al. 1991; Kirkpatrick et al. 1999), possibly of developmental nature. These reports have inspired models based on disrupted neurogenesis. These models do not attempt to reproduce specific putative causative factors implicated in schizophrenia, but aspire to face validity at the anatomical level by mimicking cellular aberrations that presumably would follow a disruption of early cortical development analogous to what has been described in some of the human post mortem studies. The heuristic framework of these models is that specific prenatal interruptions of cell maturation would result in relevant biological and behavioral changes as the animal matures. Examples include cortical dysgenesis induced by gestational X-ray irradiation (Rakic 1996; Mintz et al. 1997), in-utero exposure to a mitotic toxin, methylazoxymethanol acetate (MAM), which destroys populations of rapidly dividing neurons (Johnston et al. 1988; Talamini et al. 1998), and systemic administration of nitric oxide synthase (NOS) inhibitors, which interfere with maturation of neurons and synaptogenesis (Black et al. 1999). Animals that have undergone X-ray or MAM manipulations exhibit morphological changes in a broad array of brain structures implicated in schizophrenia, particularly the hippocampus, and frontal and entorhinal cortices. These animals also demonstrate a variety of behavioral alterations such as locomotor hyperactivity, stereotypies, cognitive impairments, and disruption of latent inhibition and PPI, and show electrophysiological abnormalities posited to underlie psychomotor disturbances in schizophrenia (Johnston et al. 1988; Talamini et al. 1998; Moore et al. 1998). Male rats exposed to an NOS inhibitor (L-nitroarginine) between 3–5 days of life show in adulthood locomotor hypersensitivity to amphetamine and deficits in PPI, but similarly treated females were not found to be affected on tese measures (Black et al. 1999). These preliminary results are provocative and invite further research.

Models of aberrant neurogenesis, though the data are limited at this time, appear to have potential heuristic value in discovering mechanisms of specific neural circuit disruptions caused by elimination of maturing neurons. There are a number of areas to be pursued including characterizing critical risk periods (specifically a period corresponding to the second trimester of gestation in humans), critical neuronal populations, molecular adaptations in remaining neurons, etc. These models demonstrate again that perturbation in cortical development can reproduce some of the behavioral characteristics associated with schizophrenia, including those linked to dopamine systems.

Testing the Relevance of Early Stressful Experience

This group of models focuses on the long-lasting consequences of stress for brain development and for shaping adult behavioral responses. They have been variably used as models of depression, anxiety, and schizophrenia, diseases in which stress has long been thought to play some role. Stress has been postulated as a factor in so called "two hit" models of schizophrenia in which two independent insults (e.g., aberrant genetic trait and stressful experience) are thought to be necessary for the occurrence of the disorder. In rodents, early life exposure to experiential stressors such as maternal separation (Liu et al. 1997) and social isolation (Jones et al. 1992; Geyer et al. 1993; Wilkinson et al. 1994) produce numerous hormonal, neurochemical and behavioral changes, including locomotor hyperactivity in a novel environment, maze learning impairments, anxiety, latent inhibition and sensorimotor gating deficits. Of particular interest is that some of these alterations emerge in adult life and can be restored by a wide range of antipsychotics, including various typical and atypical drugs (Varty and Higgins 1995; Ellenbroek et al. 1998; Bakshi et al. 1998). Importantly, the effects of adverse early life events (e.g., maternal separation) on adult reactivity are strongly influenced by genetic as well as non-genomic factors (Zaharia et al. 1996; Anisman et al. 1998; Francis et al. 1999).

These models provide important evidence for an interaction between genetic predisposition and early life experiences and demonstrate that both are involved in

shaping the adult stress response system and adult patterns of behavior. They might thus represent an interesting approach to study the interactions of these variables in schizophrenia.

Neonatal Brain Lesions

Another series of studies have focused on neonatal damage of restricted brain regions in rats (Lipska et al. 1993; Flores et al. 1996a; Chambers et al. 1996; Wan et al. 1996, 1998; Wan and Corbett 1997; Brake et al. 1999, Black et al. 1998; Becker et al. 1999; Grecksch et al. 1999; Schroeder et al. 1999) and in monkeys (Beauregard and Bachevalier 1996; Bertolino et al. 1997; Saunders et al. 1998; Bachevalier et al. 1999). The main objective of many of these studies is to disrupt development of the hippocampus, a brain area consistently implicated in human schizophrenia (Falkai and Bogerts 1986; Jeste and Lohr 1989; Bogerts et al. 1990; Suddath et al. 1990; Eastwood et al. 1995, 1997; Eastwood and Harrison 1995, 1998; Weinberger 1999), and thus disrupt development of the widespread cortical and subcortical circuitry in which the hippocampus participates. The lesions were intended to involve regions of the hippocampus that directly project to the prefrontal cortex, i.e., ventral hippocampus and ventral subiculum (Jay et al. 1989; Carr and Sesack 1996), and that correspond to the anterior hippocampus in humans, a region that shows anatomical abnormalities in schizophrenia (Suddath et al. 1990).

Neonatal excitotoxic lesions of the rat ventral hippocampus (VH) lead in adolescence or early adulthood to the emergence of abnormalities in a number of dopamine-related behaviors, which bear close resemblance to behaviors seen in animals sensitized to psychostimulants. When tested as juveniles (postnatal day 35), rats with the neonatal VH lesions are less social than controls (Sams-Dodd et al. 1997), but otherwise behave normally in motor tests involving exposure to stress and dopamine agonists. In adolescence and adulthood (postnatal day 56 and older), lesioned animals display markedly changed behaviors thought to be primarily linked to increased mesolimbic/nigrostriatal dopamine transmission (motor hyperresponsiveness to stress and stimulants, enhanced stereotypies). They also show enhanced sensitivity to glutamate antagonists (MK-801 and PCP), deficits in PPI and latent inhibition, impaired social behaviors and working memory problems (Lipska and Weinberger 1993, 1994a, 1994b; Lipska et al. 1995a; Becker et al. 1999; Grecksch et al. 1999; Al-Amin et al. in press; Hori et al. 1999), phenomena showing many parallels with schizophrenia.

Emergence of the behavioral changes in adolescence appears not to be related to the surge of gonadal hormones during puberty because a similar temporal pattern of abnormalities is observed in animals depleted of gonadal hormones prior to puberty (Lipska and Weinberger 1994b). Notably, removal of prefrontal neurons in adult animals with the earlier hippocampal lesion restores some of the behaviors (i.e., these modulated by but not critically dependent on the prefrontal cortex, such as hyperlocomotion after amphetamine), suggesting that aberrant development of the prefrontal cortex in the context of early damage to the hippocampus may be a critical factor in the onset of the syndrome (Lipska et al. 1998a). In this context, it is important to emphasize that anatomical findings from post mortem studies and neuropsychological and neuroimaging studies of brain function in patients with schizophrenia have implicated prefrontal cortical maldevelopment and a developmental "dysconnection" of the temporolimbic and prefrontal cortices (for review, see Weinberger 1995). Although the exact mechanisms of a seemingly similar "dysconnection" and malfunction of the prefrontal cortex in the VH lesioned rats need to be elucidated, preliminary findings from molecular and electrophysiological studies (such as reduced cortical levels of N-acetylaspartate (NAA), attenuated stress-induced cortical dopamine release, attenuated cortical expression of a membrane glutamate transporter EAAC1 and of a synthetic enzyme for γ-aminobutyric acid (GABA), glutamate decarboxylase-67 (GAD67), reduced BDNF expression, altered cortical expression of transcription factors, c-fos and ΔfosB, as well as altered firing pattern of cortical pyramidal neurons in response to ventral tegmental area (VTA) stimulation) suggest that aberrant cortical dopamine/glutamate/GABA interactions may underlie cortical dysfunction in the neonatally VH lesioned rats (Lipska et al. 1995b; Bertolino et al. 1999; Lee et al. 1998; Ashe et al. 1999; O'Donnell et al. 1999). We have recently reported that excitotoxic prefrontal cortical lesions in adult animals cause downstream striatal NAA losses and reduced GAD-67 mRNA expression, and suggested that both changes might reflect transsynaptic pathology (Roffman et al. 2000). It is possible that similar transsynaptic events occur in response to the neonatal VH lesion but further work is required to determine if and by what mechanisms molecular changes in prefrontal neurons are linked. It is interesting to note that many of these changes have been reported in stress- and psychostimulant-sensitization models (Vanderschuren et al. 1999; Gambarana et al. 1999; Feldpausch et al. 1998), as well as in patients with schizophrenia (Akbarian et al. 1995; Bertolino et al. 1998). Subcortical function in the neonatally lesioned rats is also altered in a fashion consistent with at least some reports on behavioral sensitization (Imperato et al. 1996; Castner et al. 2000; Steiner and Gerfen 1998; Nestler and Aghajanian 1997), i.e., striatal dopamine release is attenuated in response to stress and amphetamine, midbrain expression of the membrane dopamine transporter (DAT) mRNA is reduced, striatal

expression of dynorphin (an opioid peptide co-localized with D1 receptors) and of ΔfosB (a transcription factor sensitive to persistent stimulation) are enhanced (Lipska et al. 1998b; Lee et al. 1998). It should be noted, however, that enhanced rather than attenuated striatal dopamine release has been observed in other paradigms of sensitization to psychostimulants (for review, see Spanagel and Weiss 1999) as well as in a subgroup of schizophrenics as evidenced by recent SPECT studies (Abi-Dargham et al. 1998; Laruelle et al. 1996; Breier et al. 1997). Nevertheless, an array of behavioral and molecular changes associated with this model suggest that early developmental insult of the ventral hippocampus may facilitate sensitization of the dopamine system, and thereby account for the adult onset of a maladaptive condition characterized by a vriety of dopamine-related abnormalities. Similar pathophysiological mechanisms have been hypothesized to underlie schizophrenia (Lieberman et al. 1997; Meng et al. 1998; Duncan et al. 1999). Unlike psychostimulant sensitization models, however, the neonatal lesion model does not target the dopamine system directly and similar sensitization-like phenomena are not seen following an analogous hippocampal lesion in adult animals. It may be of considerable heuristic interest to determine how the developmental lesion initiates the subsequent behavioral and molecular phenomena associated with sensitization.

In terms of the predictive validity of the neonatal VH lesion model, antipsychotic drugs normalize some lesion-induced behaviors (Lipska and Weinberger 1994a; Sams-Dodd et al. 1997). Drugs targeting the glutamate system may also prove beneficial; LY293558, an AMPA antagonist, is highly efficient in blocking hyperlocomotion in the neonatally lesioned rats at doses that do not affect locomotor activity in controls (Al-Amin et al. in press). Thus, this model may have predictive validity and heuristic potential to identify drugs with new mechanisms of action. The model also appears to mimic a spectrum of neurobiological and behavioral features of schizophrenia, including functional pathology in presumably critical brain regions interconnected with the hippocampal formation and targeted by antipsychotic drugs—the striatum/nucleus accumbens and the prefrontal cortex (see Table 2). It is noteworthy that in the non-human primate, early postnatal damage of the hippocampal region also alters development of the dorsal prefrontal cortex and the mechanisms whereby the dorsal prefrontal cortex regulates subcortical dopamine function, phenomena similar to those described in patients with schizophrenia (Saunders et al. 1998; Bertolino et al. 1997, 2000). Thus, neonatal damage to the hippocampus of the rat appears to reproduce a broad spectrum of schizophrenia related phenomena, and establishes the neurobiological plausibility of early damage having a delayed impact on neural functions implicated in schizophrenia.

Developmental lesions of other brain structures implicated in schizophrenia and components of a limbic-neocortical circuit (e.g., thalamus, prefrontal cortex) also have been considered as models. For instance, thalamic excitotoxic lesions in PD7 rats result in adult expression of apomorphine- and amphetamine-induced hyperlocomotion (Rajakumar et al. 1996). Intracerebroventricular infusions of kainic acid into neonatal (PD7) rats lead in adulthood to a reduction in neural numbers in the dorsal hippocampus, and are associated with changes in the expression of subpopulations of glutamate receptors and immediate early genes (Csernansky et al. 1998; Montgomery et al. 1999). Neonatal (PD7) excitotoxic damage of the medial prefrontal cortex was reported to produce delayed behavioral effects accompanied by dopamine receptor changes (Flores et al. 1996b), although others did not confirm these data (Lipska et al. 1998a). The spectrum of behavioral and cellular parameters examined in these models is rather limited at this time.

Another neonatal insult with intriguing implications is selective depletion of serotonin in neonatal rats (by tryptophan hydroxylase inhibitor parachlorophenylalanine, PCPA) that decreases markers of synaptic density in the adult brain, and results in cognitive deficits (Mazer et al. 1997). These effects are somewhat similar to those reported in the post mortem schizophrenic brain (Weinberger 1999), but other schizophrenia-relevant aspects need to be tested in this model.

Although developmental lesion models represent a rather crude technique to study the role of particular brain regions, transmitter systems or the connections between them, they have confirmed the plausibility of neurodevelopmental damage having selected deleterious effects after a prolonged period of relative normalcy. In this respect, they appear to have face validity not just in terms of behavioral, cellular and pharmacological phenomena, but also in terms of the temporal course of the clinical disorder. As models of developmental pathology, they certainly lack construct validity, as the schizophrenic brain does not manifest a "lesion" analogous to any of these models; but they may have heuristic value in discovering molecular consequences of early brain damage, and new treatment prospects.

N-METHYL-D-ASPARTATE (NMDA) RECEPTOR BLOCKADE

In addition to the non-pharmacological, non-dopaminergic approaches described above, pharmacological blockade of NMDA receptors in adult animals has gained popularity as a model of schizophrenia. Observations that noncompetitive NMDA antagonists, such as phencyclidine (PCP) and ketamine, exacerbate some psychotic symptoms in schizophrenic patients and

have psychotomimetic effects in normal humans (Krystal et al. 1994; Lahti et al. 1995) have encouraged speculation that some aspects of schizophrenia may relate to abnormal glutamatergic function. This has been further supported by post mortem studies in schizophrenia showing a variety of changes in the glutamate system, including altered glutamate metabolism and expression of various glutamate receptors (Javitt and Zukin 1991; Akbarian et al. 1996; Jentsch and Roth 1999; Weinberger 1999).

In rodents and monkeys, acute sub-anesthetic doses of NMDA antagonists produce a constellation of phenomena potentially relevant to schizophrenic symptomatology, including hyperlocomotion, enhanced stereotyped behaviors, cognitive and sensorimotor gating deficits, and impaired social interactions. PCP as well as other NMDA antagonists acutely increase extracellular levels of dopamine and glutamate (as well as norepinephrine and acetylcholine) in the prefrontal cortex, and alter firing patterns of dopaminergic and nucleus accumbens neurons (Verma and Moghaddam 1996; O'Donnell and Grace 1998). Repeated administration of PCP can also induce robust behavioral and neurochemical changes even after long-term withdrawal (Jentsch et al. 1997, 1998a, 1998b). Of particular interest is differential dysregulation of the firing patterns of mesolimbic and mesocortical dopaminergic neurons by low, behaviorally relevant doses of NMDA antagonists. These changes in dopamine cell firing may render them unresponsive or inappropriately responsive to salient environmental stimuli such as stress and reward (Murase et al. 1993; Mathe et al. 1998). If a similar process underlies psychotic symptoms and cognitive deficits in schizophrenia, the NMDA antagonist model may offer novel treatment strategies targeting glutamate rather than dopamine. Recently, experimental approaches to reverse NMDA antagonist-induced abnormalities have included pharmacological enhancement of NMDA receptor activity, enhancement of metabotropic glutamate receptor (mGluR2) activity, and blockade of AMPA receptors (Moghaddam et al. 1997; Moghaddam and Adams 1998), the latter approach shown to be also effective in the neonatal hippocampal lesion model (see above). Thus, a model based on a primary glutamatergic abnormality appears to show important heuristic properties in terms of identifying potential novel therapies. This model may offer insight into molecular adaptations that follow chronic NMDA blockade, and identify new therapeutic targets. Notably, the repeated no-competitive NMDA blockade model, which had also been intensely investigated from the perspective of behavioral sensitization and its role in drug addiction and reward mechanisms (Wolf et al. 1993), shares certain behavioral and neurochemical similarities with the neonatal hippocampal lesion model, including cognitive deficits (in particular, in working memory tasks), reduced frontal dopamine transmission (Jentsch et al. 1997, 1998a) and reduced GABA activity as indicated by reduced levels of GAD67 (Qin et al. 1994; Yonezawa et al. 1998), and disrupted social behaviors and augmented locomotor responses to stress and amphetamine (Jentsch et al. 1998b). The similarities between the models may reflect a common disruption of cortical glutamate/GABA function which may converge toward a common underlying process of behavioral sensitization. Unlike the etiological or neonatal lesions models, the NMDA antagonist approach does not, however, address the developmental component of schizophrenia.

GENETIC PREDISPOSITION

Schizophrenia is a highly heritable disorder that probably involves multiple genes with small effects across large populations (Kendler et al. 1996). Elucidating the roles of the susceptibility genes for this clinically diverse and probably genetically heterogeneous disorder will require considerable effort and is unlikely to be fully resolved soon. Modern technologies, involving targeted gene deletions or gene transfer techniques that have revolutionized experimental medicine, may provide a new generation of animal models for schizophrenia that may help in this daunting task.

Some genetic models for neurological diseases are almost perfect in terms of construct validity because transgenic animals may be, in a sense, "humanized" by the introduction of human genes involved in the disease or the mutated animal homologues of such genes (Loring et al. 1996). However, transgenic models also illustrate that even a highly accurate model in terms of construct validity may fail the test of face validity in terms of a phenotype analogous to the disorder. For instance, the Duchenne's muscular dystrophy mdx mutation mouse model is hardly symptomatic (Erickson 1996), the PDAPP transgenic mouse model of Alzheimer's disease which overexpresses human amyloid precursor protein (Johnson-Wood et al. 1997), does not have an isomorphic behavioral phenotype, and the hypoxanthine-guanine phosphoribosyl-transferase (HPRT) knock-out mouse has no recognizable phenotype analogous to Lesch-Nyhan Disease (Wu and Melton 1993). Behavioral phenotypes of these models are not isomorphic with the disease, because genetic mutation can have remarkably different phenotypes when placed on different genetic backgrounds. Despite phenotypic dissimilarity, however, such models are faithful in terms of certain cellular characteristics and can be very useful in illuminating molecular mechanisms leading to pathological changes and in discovering new treatments. This approach is, of course, possible only if the disease can be attributed to specific human genes, and thus seems to

have limited application in studying schizophrenia or other psychiatric illnesses at the present time.

In an attempt to test the possibility of involvement of various neurotransmitter receptors relevant to schizophrenia (D1-D5 subtypes of dopamine receptors, adenosine A2A receptors, α2-adrenergic receptors and NMDA receptors) and to elucidate their functional roles, investigators have used genetically altered mice in which expression of these receptors was selectively and usually completely suppressed (Sibley 1999). Probably the most intriguing is a recent attempt at targeting the NR1 subunit of the NMDA receptor in a genetic mouse model (Mohn et al. 1999), despite lack of direct evidence that an NMDA receptor gene is abnormal in schizophrenia. Mutant mice expressing only 5% of essential NR1 receptors show increased spontaneous hyperlocomotion that attenuates after a single injection of haloperidol and clozapine, and deficits in social and sexual behaviors that respond to acute clozapine treatment. Although some of these behavioral changes suggest increased dopaminergic tone, dopamine release and turnover are not altered in these animals. However, somewhat contrary to the phenotype expected in a schizophrenia model, NR1 mutant mice do not exhibit enhanced responsiveness to the NMDA antagonists, MK-801 or PCP. Continued studies of these mice will provide more information about the consequences of dramatic congenital hypofunction of the glutamatergic system and will shed light on interactions of the glutamatergic system with other neurotransmitter systems, but the relevance of this model to schizophrenia is yet unclear. This example underscores a unique problem of modeling the schizophrenic phenotype in animals that even a genetic model cannot escape—lack of pathognomonic neurobiological markers and unequivocal validation criteria.

Another promising genetic strategy is identification of predisposing candidate genes by selecting rodent lines or strains for particular behavioral traits. Such candidate genes may then be used to identify homologous human genes potentially involved in the etiology of schizophrenia. For instance, studies in inbred mice strains with deficits in sensory inhibition have indicated that altered expression and function of the α7nicotinic cholinergic receptor may be responsible for some auditory sensory gating deficits (Stevens et al. 1998). A defect in the so-called "P50 auditory–evoked response" is found in patients with schizophrenia and in their unaffected relatives (Freedman et al. 1987). This evoked potential defect (but not schizophrenia itself because many individuals showing P50 deficits are clinically unaffected) was subsequently linked to a chromosome 15 locus, near the site of the α7-nicotinic cholinergic receptor gene (Freedman et al. 1997). This linkage finding, which echoed data from the earlier mice experiments, suggested that a genetic defect in the α7-nicotinic cholinergic receptor might be a predisposing factor in schizophrenia. Sequencing of the α7-nicotinic cholinergic receptor gene in individuals with this phenotype is currently in progress. Another example involves animals bred for high susceptibility to apomorphine-induced stereotypic behaviors (APO-SUS rats). These animals, in contrast to apomorphine nonresponsive (APO-UNSUS) rats, demonstrate various behavioral (e.g., prepulse inhibition and latent inhibition deficits), biochemical (e.g., elevated levels of tyrosine hydroxylase mRNA in the substantia nigra and D2 receptor binding in the dorsal striatum), and immunological (e.g., reduced sensitivity for rheumatoid arthritis) features implicated in schizophrenia (Ellenbroek et al. 1995, 2000). Thus, such behavioral trait-selected animals may be used as models of schizophrenia-prone individuals and provide material for novel gene identification and for candidate gene analyses.

Another model has combined neurodevelopmental and genetic predisposition approaches. Fisher344 rats, a highly stress-responsive inbred strain, show particularly high susceptibility to the behavioral effects of neonatal hippocampal damage. Lewis rats, on the other hand, bred for low stress responsiveness, appear to be resistant to the behavioral consequences of identical lesions (Lipska and Weinberger 1995). This lesion-genetic model may be used for identification of candidate genes that mediate behavioral responses to a neonatal hippocampal insult, and that, by extension, might predispose to or modify the expression of schizophrenia. These studies are currently under way.

Because recent data suggest a significant role for neurodevelopmental processes in schizophrenia, another approach to genetic modeling of schizophrenia may focus on manipulating in animals genes that play a role in neurodevelopment, maintenance of cell–cell connections, and trophic factors (Weickert and Weinberger 1998) (see Table 3). For instance, in an attempt to alter genes involved in neural migration, neural cell adhesion molecule isoform 180 (NCAM-180) gene was deleted in mice. Mice with this selective gene deletion display a marked reduction in the levels of PSA-NCAM (polysialic acid rich NCAM), a molecule involved in neuronal regeneration and plasticity, which has also been reported as reduced in the hippocampus of patients with schizophrenia (Barbeau et al. 1995). N-CAM-180 depleted mice are characterized by abnormal migration of neurons within the subventricular zone, altered cytoarchitecture of multiple brain regions, including olfactory bulb, hippocampus and cerebellum, enlarged ventricles and changes in behavior (PPI deficits) (Tomasiewicz et al. 1993; Wood et al. 1998). Although some of these changes resemble abnormalities observed in schizophrenia, more thorough phenotypic characterization is needed.

Because the early hippocampal damage models have demonstrated the plausibility of developmental defects

Table 3. Potential Animal Models Based on Genetic Manipulation of Cellular Phenotype

Molecular Changes in Schizophrenia	Brain Region	Molecular Targets for Genetic Manipulations in Animals
Trophic/ECM molecules↓	Cortex, Hippocampus	BDNF, LAMP, PSA-NCAM, Reelin[a]
Glutamate function↓	Cortex, Hippocampus	GluR1-4, GluR5-7, NR1-2, KA1-2, GCP II, EAAC1, GLT1 GLAST[b]
GABA function↓	Cortex, Hippocampus	GAD67, GABA(A)[c]
Synaptic markers↓	Cortex, Hippocampus	Synapsin, Synaptophysin, SNAP-25, GAT1,3, Complexin[d]
Other Cellular markers↓	Cortex, Hippocampus	GAP-43, MAPs[e]

Abbreviations: BDNF, Brain derived neurotrophic factor; ECM, Extracellular matrix; EAAC1, Neuronal glutamate transporter; GABA(A), γ; aminobutyric acid A receptors; GAP-43, Neuronal growth-associated protein; GAD-67, Glutamate decarboxylase-67; GAT1,3, GABA transporters; GCP II, Glutamate carboxypeptidase II; GLT1, GLAST, glial glutamate transporters; GluR1-4, Subunits of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor; GluR5-7 and KA1-2, Subunits of kainate receptor; LAMP, Limbic system-associated membrane protein, MAP, Microtubule-associated protein; NR1-2, Subunits of NMDA (N-methyl-D-aspartate) receptor; PSA-NCAM, Polysialylated neural cell adhesion molecule; SNAP-25, Synaptosomal-associated protein of 25 kDa.

↓Decreased expression or compromised function.

Selected references:

[a]Vawter et al. 1998; Barbeau et al. 1995; Impagnatiello et al. 1998; Fatemi et al. 1999.

[b]Ohnuma et al. 1998; Eastwood et al. 1995, 1997.

[c]Benes et al. 1996, 1997; Huntsman et al. 1998; Dean et al. 1999.

[d]Eastwood and Harrison 1995; Glantz and Lewis 1997; Young et al. 1998; Harrison and Eastwood 1998; Karson et al. 1999.

[e]Perrone-Bizzozero et al. 1996; Eastwood and Harrison 1998.

in the hippocampus having a delayed impact on other neural circuits and systems (e.g., prefrontal cortex), transgenic models that selectively disrupt development of hippocampal circuitry may turn out to be especially heuristic. In a recent attempt to alter development of the hippocampus, the LIM homeobox Lhx5 gene, was deleted in mice. The Lhx5 homozygous mutant embryos showed dramatic defects in hippocampal morphology; however, most of the homozygotes died within a few days after birth. Somewhat less severe changes in hippocampal development, but still often lethal or too damaging to be considered relevant to schizophrenia, have been reported in mice with null deletions of other homeobox genes [e.g., Emx2 (Pellegrini et al. 1996) and Lhx2 (Porter et al. 1997)] as well as genes involved in neural migration during development [e.g., β subunit of platelet-activating factor acetylhydrolase Pafah1b1 (or Lis1) (Hirotsune et al. 1998), cycline-dependent kinase 5 (Cdk5) (Ohshima et al. 1996), mdab1 (Sheldon et al. 1997) and reeler]. A more promising strategy might involve conditional reduction (or enhancement) of expression of certain genes restricted to critical periods in development, an approach that has recently been used in a drug addiction model that inducibly overexpresses ΔfosB (Kelz et al. 1999). Table 3 contains other suggestions for novel models based on transgenic approaches to reproduce specific cellular abnormalities that have been implicated in certain brain regions in schizophrenia; not all of these findings, however, have been independently replicated. Such developmental genetic models may provide new candidate genes for assessment in clinical studies and help to model the cell biology of this complex disorder. Candidate genes selected from their chromosomal position near genetic loci linked to schizophrenia might also be future targets for transgenic modes.

CONCLUDING REMARKS

The approach to studying the etiology and pathophysiology of schizophrenia at the level of animal neurobiology has become much more sophisticated. Schizophrenia had long been regarded as a social or psychological illness, not a brain disorder with a particular neurobiological cause. This situation is changing rapidly in light of mounting evidence linking schizophrenia to certain neuropathological processes in the brain, although their origin is still unclear. Heuristic animal models may prove to be important tools in testing new theories about the origin and mechanisms of this disorder. In particular, some of the recent models have confirmed the plausibility of neurodevelopmental insults having prolonged effects on the dopamine system and behaviors relevant to schizophrenia, and supported the notion that disruption of glutamatergic neurotransmission may lead to new approaches to treatment. The neonatal lesion model has suggested that the effects of an early ventral hippocampal insult, rather than being compensated for, precipitate a state remarkably similar to stress- or psychostimulant-induced sensitization, associated with long lasting maladaptive cellular changes

that lead to delayed onset of abnormal behaviors. Mechanisms underlying sensitization to either stress, amphetamine, cocaine, opioids or non-competitive NMDA antagonists are not well understood and seem to involve complex changes in multiple neurotransmitter systems, including dopamine, glutamate and GABA. If the effects of sensitization following developmental abnormalities of the cortex are, indeed, involved in the adolescent/adult onset of schizophrenia-like changes in this model, and by extension in schizophrenia, this may underscore the importance of preventive treatment strategies directed at reducing the impact of experiential stressors in predisposed individuals. Findings from the neonatal stress models discussed above might provide clues about the mechanisms of such potential interventions.

Modern technologies that have been successfully applied to animal modeling of genetic neurological diseases may one day also open the door to our understanding of the mechanisms underlying psychiatric disorders. The transgenic murine models, in which mutations homologous to mutations in humans are inserted by transgenesis or by stem cell knockouts, may seem superior to any pharmacological, surgical or experiential models, but they have their own limitations. It is clear that most psychiatric disorders, including schizophrenia, are multifactorial, [i.e., multiple genes interact with multiple environmental factors to create a particular phenotype (Egan and Weinberger 1997)]. Theoretically at least, by choosing the right combination of the mutation and modifier genes as well as appropriate environmental influences on their expression, one might be able to create at the cellular level a high fidelity animal model of such a complex human disease as schizophrenia.

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