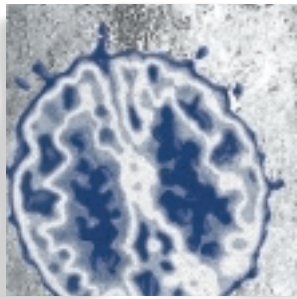


Neonatal disconnection of the rat hippocampus: a neurodevelopmental model of schizophrenia

Barbara K. Lipska, PhD



In the context of our current knowledge about schizophrenia, heuristic models of psychiatric disorders may be used to test the plausibility of theories developed on the basis of new emerging biological findings, explore mechanisms of schizophrenia-like phenomena, and develop potential new treatments. In a series of studies, we have shown that neonatal excitotoxic lesions of the rat ventral hippocampus (VH) may serve as a heuristic model. The model 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), and leads in adolescence or early adulthood to the emergence of abnormalities in a number of dopamine-related behaviors. Moreover, our data show that even transient inactivation of the VH during a critical period of development, which produces subtle, if any, anatomical changes in the hippocampus, may be sufficient to disrupt normal maturation of the prefrontal cortex (and perhaps, other interconnected late-maturing regions) and trigger behavioral changes similar to those observed in animals with the permanent excitotoxic lesion. These results represent a potential new model of aspects of schizophrenia without a gross anatomical lesion.

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Animal models are important in investigating the origin and the mechanisms underlying a human disease and designing new therapies, and have been widely used in various areas of medical research. Animal models have not been, however, very popular in psychiatric research. Reproducing psychiatric disorders in animals has often been considered difficult, if not impossible. Modeling schizophrenia is an example of a particularly difficult task, because it is a uniquely human disease, and its most prominent symptoms—hallucinations, delusions, and thought disorder—cannot be reproduced in an animal. Recent new evidence about the neurobiology of this disease has opened new possibilities of animal research. In particular, abnormalities in the neural circuitry involving the hippocampus, prefrontal cortex, and the dorsomedial thalamus have been reported recently, in addition to previously recognized abnormal function of the dopaminergic system. Cytoarchitectural and molecular studies of the brain, as well as neuropsychological studies showing that schizophrenia symptoms emerge in young adulthood but subtle motor and behavioral abnormalities are present early in life, suggest a neurodevelopmental origin of the disease.

To address a neurodevelopmental origin of schizophrenia, numerous studies modeling schizophrenia in animals have focused on neonatal damage of restricted brain regions in rats¹⁻¹¹ and in monkeys.¹²⁻¹⁵ The main objective of many of these studies is to disrupt development of the hippocampus, a brain area consistently implicated in human schizophrenia,¹⁶⁻²⁵ and thus disrupt development of the wide-

Keywords: animal model; schizophrenia; hippocampus; prefrontal cortex; neurodevelopment; neonate; locomotion; dopamine

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Basic research

Selected abbreviations and acronyms

BDNF	<i>brain-derived neurotrophic factor</i>
DAT	<i>dopamine transporter</i>
GABA	<i>γ-aminobutyric acid</i>
GAD67	<i>glutamate decarboxylase-67</i>
NAA	<i>N-acetylaspartate</i>
PD	<i>postnatal day</i>
PPI	<i>prepulse inhibition</i>
TTX	<i>tetrodotoxin</i>
VH	<i>ventral hippocampus</i>
VTA	<i>ventral tegmental area</i>

spread 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, ie, ventral hippocampus (VH) and ventral subiculum,^{26,27} and that correspond to the anterior hippocampus in humans, a region that shows anatomical abnormalities in schizophrenia.²¹ Valid models would be expected to mimic a wide array of behavioral aspects of the human disorder (*Table I*).

Neonatal excitotoxic VH lesions alter development of prefrontal cortex

In a series of studies, we have shown that neonatal excitotoxic lesions of the rat VH lead in adolescence to the emergence of abnormalities in a number of dopamine-related behaviors.²⁸ When tested as juveniles (postnatal day 35 [PD35]), rats with the neonatal VH lesions are less social than controls,²⁹ but otherwise behave normally in motor tests involving exposure to stress and dopamine agonists. In adolescence and adulthood (PD56 and older), lesioned animals display marked 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 phencyclidine [PCP]), deficits in prepulse inhibition (PPI) and latent inhibition, impaired social behaviors, and working memory problems,^{9,10,30-38} phenomena showing many parallels with schizophrenia (*Figure 1*).³⁷

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.³² Notably, removal of prefrontal neurons in adult animals with the earlier hippocampal lesion restores some of the behaviors (ie, those 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 expression of the syndrome.³⁹ In this context, it is important to emphasize that anatomical findings from postmortem studies and neuropsychological and neuroimaging studies of brain function in patients with schizophrenia have implicated prefrontal cortical maldevelopment and a developmental disconnection of the temporolimbic and prefrontal cortices.⁴⁰ Although the exact mechanisms of a seemingly similar disconnection 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

Schizophrenia	Animal model
Psychotic symptoms	Behaviors related to increased DA transmission
Stereotypic behaviors	Dopamimetic-induced stereotypy
Worsening of symptoms by NMDA antagonists	NMDA antagonist-induced hyperlocomotion
Vulnerability to stress	Stress-induced hyperlocomotion
Improvement of psychotic symptoms by neuroleptics	Reduction of hyperlocomotion by neuroleptics
Information-processing deficits	Sensorimotor gating (PPI) deficits
Attention deficits	Deficits in latent inhibition
Cognitive deficits	Impaired performance in delayed alternation and spatial memory tasks
Social withdrawal	Reduced contacts with unfamiliar partners
Anhedonia	Diminished sensitivity to rewarding stimuli

Table I. Clinical aspects of schizophrenia and relevant behavioral changes in an animal model. DA, dopamine; NMDA, *N*-methyl-D-aspartate; PPI, prepulse inhibition.

membrane glutamate transporter EAAC1 and of a synthetic enzyme for γ -aminobutyric acid [GABA], glutamate decarboxylase-67 [GAD67], reduced brain-derived neurotrophic factor [BDNF] expression, altered cortical expression of transcription factors, c-fos and Δ fosB, 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 neonatally VH-lesioned rats.^{34,41-44}

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.⁴⁵ 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.

Neonatal VH lesions mimic aspects of psychostimulant sensitization

It is interesting to note that many of these changes have been reported in stress- and psychostimulant-sensitization

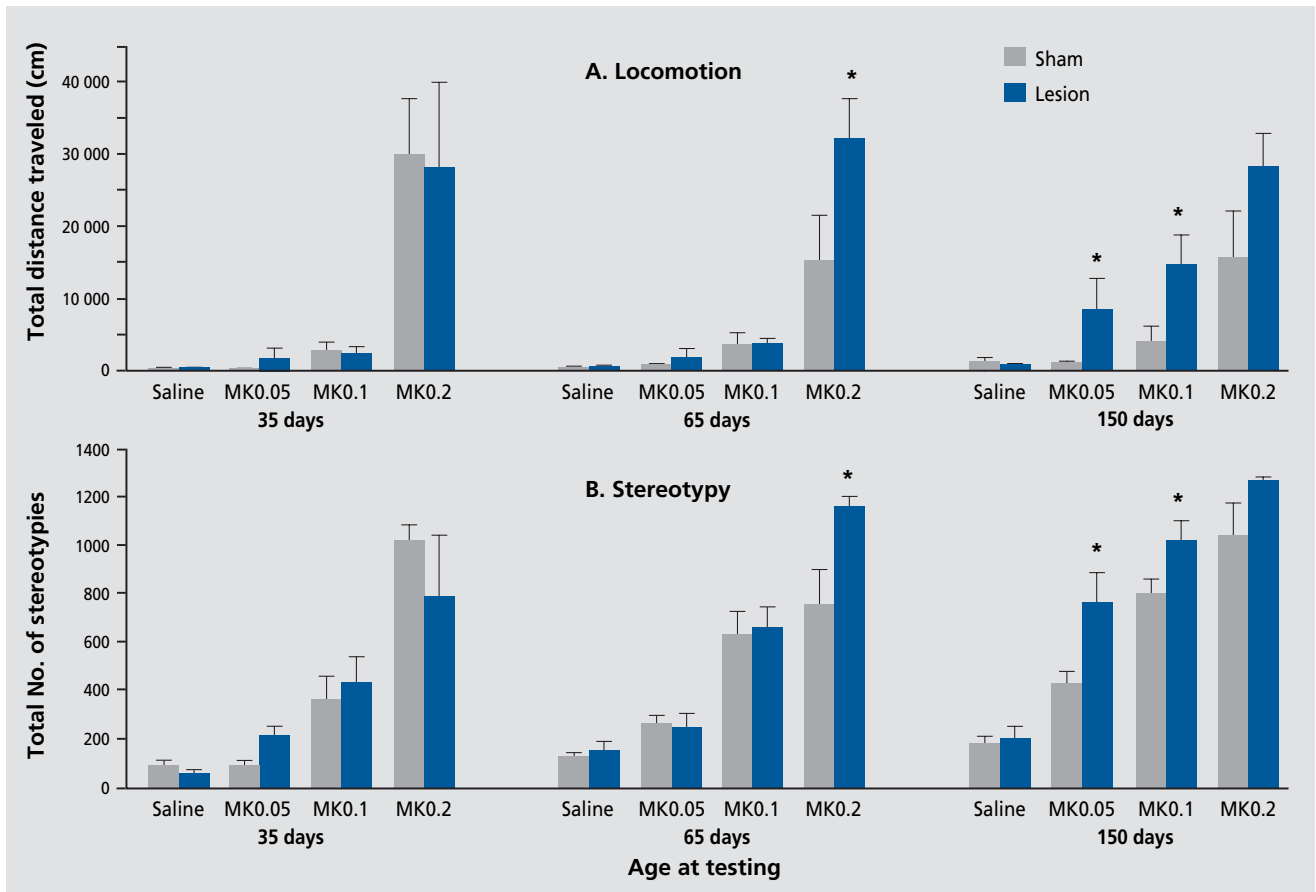


Figure 1. Effects of the glutamate antagonist MK-801 (0.05 [MK0.05], 0.1 [MK0.1], and 0.2 [MK0.2] mg/kg) on locomotion (A) and stereotypy (B) in sham and ventral hippocampus (VH)-lesioned rats. Rats were lesioned as neonates at postnatal day 7 and tested at three ages: 35, 65, and 150 days. At all ages tested, only the highest dose of MK-801 (0.2 mg/kg) significantly increased locomotion (total distance traveled in cm) in the sham-operated rats as compared with the saline injection. In the lesioned rats, only 0.2 mg/kg MK-801 significantly increased locomotion at postnatal days 35 and 65, but all three doses were effective at 150 days of age as compared with saline. Neonatally lesioned animals showed significantly more locomotion and stereotypies than controls at days 65 and 150, but not at day 35. *Significantly higher than controls that received the same dose of MK-801 ($P < 0.05$); sham $n = 5$ per dose group; lesion $n = 6$ per dose group.

Reproduced from reference 37: Al-Amin HA, Weickert CS, Lillrank SM, Weinberger DR, Lipska BK. Delayed onset of enhanced MK-801-induced motor hyperactivity after neonatal lesions of the rat ventral hippocampus. *Biol Psychiatry*. 2001;49:528-539. Copyright © 2001, Elsevier Science.

Basic research

models,⁴⁶⁻⁴⁸ as well as in patients with schizophrenia.^{49,50} Subcortical function in the neonatally lesioned rats is also altered in a fashion consistent with at least some reports on behavioral sensitization,⁵¹⁻⁵⁴ ie, striatal dopamine release is attenuated in response to stress and amphetamine, mid-brain expression of the membrane dopamine transporter (DAT) mRNA is reduced, striatal expression of dynorphin (an opioid peptide colocalized with dopamine D₁ receptors) and Δ fosB (a transcription factor sensitive to persistent stimulation) is enhanced.^{42,55} It should be noted, however, that enhanced rather than attenuated striatal dopamine release has been observed in other paradigms of sensitization to psychostimulants,⁵⁶ as well as in a subgroup of patients with schizophrenia as evidenced by recent single-photon emission computed tomography (SPECT) studies.⁵⁷⁻⁵⁹ Similarly discrepant are the findings of synaptic morphology: increased synaptic densities, number of branches, and dendritic length are reported in prefrontal cortex in sensitization models,⁶⁰ whereas these dendritic parameters are decreased in schizophrenia⁶¹ and in the neonatal hippocampal lesion model.⁶² Nevertheless, an array of behavioral and molecular changes associated with this model suggest that early developmental insult of the VH may facilitate sensitization of the dopamine system, and thereby account for the adult onset of a maladaptive condition characterized by a variety of dopamine-related abnormalities. Similar pathophysiological mechanisms have been hypothesized to underlie schizophrenia.⁶³⁻⁶⁵ 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.^{29,31} Drugs targeting the glutamate system may also prove beneficial; LY293558, an aminoisopropyl propionic acid (AMPA) antagonist, is highly efficient in blocking hyperlocomotion in the neonatally lesioned rats at doses that do not affect locomotor activity in controls,³⁶ as is the glycine transporter inhibitor.⁶⁶ 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, includ-

ing 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. It is noteworthy that in the nonhuman 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.^{13,14,67} Thus, neonatal damage to the hippocampus of the rat appears to reproduce a broad spectrum of schizophrenia-related phenomena (*Table I*), and establishes the neurobiological plausibility of early damage having a delayed impact on neural functions implicated in schizophrenia.

Transient VH inactivation 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 strategies.

In the next series of studies, we hypothesized that transient inactivation of the VH during a critical period of development, that produces subtle, if any, anatomical changes in the hippocampus, may be sufficient to disrupt normal maturation of the prefrontal cortex (and perhaps, other interconnected late maturing regions). We explored whether this developmental disruption would, in turn, trigger behavioral changes similar to those observed in animals with the permanent excitotoxic lesion. We used tetrodotoxin (TTX), a potent and specific blocker of the voltage-gated sodium channels, whose action is fully reversible, to inactivate VH on PD7, an important time for refinement of intracortical connections, and then assessed behavioral changes that this infusion might have evoked later in life, in juvenile (PD35) and young adult (PD56)

rats.⁶⁸ The overall characteristics of behavioral changes and their temporal pattern were reminiscent of the disturbances associated with the permanent excitotoxic lesion of the VH produced at the same neonatal age (Figure 2).^{40,68} Neonatally TTX-infused rats displayed adulthood motor hyperactivity upon pharmacological stimulation (amphetamine and MK-801) and after stress of novelty and a saline injection as compared with sham controls. The magnitude of TTX-induced behavioral disruptions was smaller, however, than those observed after the excitotoxic lesion (eg, ibotenic acid lesions of the VH increased spontaneous and amphetamine-induced locomotor activity by approximately 50% as compared with controls,^{30,33,34} whereas TTX produced increases by about 15% to 20%). Moreover, in contrast to the permanent lesion, TTX infusions did not significantly affect social behaviors, although a trend for reduced social interactions mimicked again a pattern seen after the permanent lesions. Analogous TTX infusions in adult animals did not alter these behaviors later in life. It is unclear how such a transient and restricted blockade of ventral hippocampal activity in neonatal life can permanently alter brain function. One possibility is that neonatal blockade impacts on the development of neurons in the hippocampal formation and interconnected systems that also undergo important maturational changes at this time. These data suggest that transient loss of VH function during a critical time in maturation of intracor-

tical connections permanently changes development of neural circuits mediating certain dopamine- and *N*-methyl-D-aspartate (NMDA)-related behaviors. These results represent a potential new model of aspects of schizophrenia without a gross anatomical lesion. □

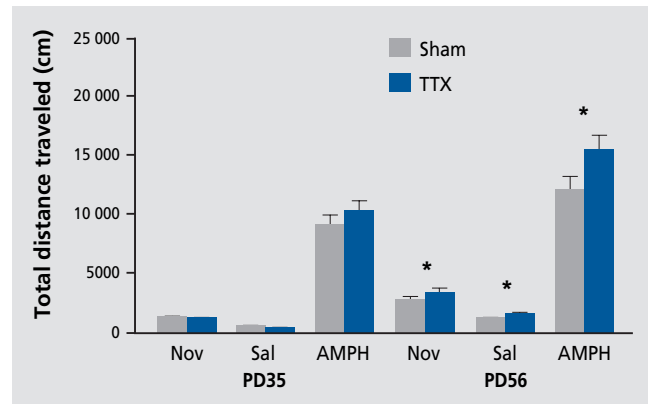


Figure 2. Locomotor activity (total distance traveled) in rats with neonatal tetrodotoxin (TTX) infusions. Rats were tested in photocell monitors at postnatal day 35 (PD35) and 56 (PD56) after exposure to novelty (Nov), after saline injection (Sal), and amphetamine administration (AMPH, 1.5 mg/kg, IP). TTX-infused rats were significantly more active than sham rats (* $P < 0.05$; $n = 13$ to 16 per group).

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Desconexión neonatal del hipocampo de la rata: un modelo de neurodesarrollo en la esquizofrenia

En el contexto de nuestro conocimiento actual acerca de la esquizofrenia, los modelos heurísticos de los trastornos mentales pueden ser utilizados para probar la plausibilidad de las teorías desarrolladas a partir de los nuevos hallazgos biológicos que están emergiendo, para explorar los mecanismos de los fenómenos tipo-esquizofrenia y para desarrollar potenciales nuevos tratamientos. En una serie de estudios, nosotros hemos mostrado que las lesiones excitotóxicas neonatales del hipocampo ventral (HV) de la rata pueden servir como modelo heurístico. El modelo parece semejar un espectro de características neurobiológicas y conductuales de la esquizofrenia, incluyendo patología funcional en regiones cerebrales presumiblemente críticas, interconectadas con la formación del hipocampo y blancos de fármacos antipsicóticos (el estriado/núcleo accumbens y la corteza prefrontal), y conduce en la adolescencia o inicio de la adultez a la aparición de anomalías en diversas conductas que se relacionan con la dopamina. Sin embargo, nuestros datos muestran que incluso una inactivación transitoria del HV durante un período crítico del desarrollo, la cual puede producir cambios anatómicos sutiles del hipocampo, puede ser suficiente para alterar la maduración normal de la corteza prefrontal (y tal vez otras regiones interconectadas de maduración tardía) y provocar cambios conductuales similares a los observados en animales con lesiones excitotóxicas permanentes. Estos resultados representan un potencial nuevo modelo de aspectos de la esquizofrenia sin una gran lesión anatómica.

Déconnexion néonatale de l'hippocampe de rat : un modèle de développement neurologique de la schizophrénie

Dans le contexte de nos connaissances actuelles sur la schizophrénie, des modèles heuristiques des troubles psychiatriques peuvent être utilisés pour vérifier que les théories fondées sur la base des nouvelles découvertes biologiques sont plausibles, explorer les mécanismes de manifestations analogues à la schizophrénie et développer de nouveaux traitements potentiels. Dans une série d'études, nous avons montré que les lésions excitotoxiques néonatales de l'hippocampe ventral du rat (HV) peuvent servir de modèle heuristique. Ce modèle semble mimer un faisceau de particularités neurobiologiques et comportementales de la schizophrénie, y compris la pathologie fonctionnelle dans des régions cérébrales sans doute cruciales, interconnectées avec la formation hippocampique et ciblées par les médicaments antipsychotiques (le striatum/noyau accumbens et le cortex préfrontal), conduisant dans l'adolescence ou au début de l'âge adulte à l'apparition d'anomalies dans un certain nombre de comportements en relation avec la dopamine. De plus, nos données montrent que même une inactivation transitoire de l'HV pendant une période-clé du développement, qui produit des changements anatomiques subtils de l'hippocampe, s'il y en a, peut être suffisante pour interrompre la maturation normale du cortex préfrontal (et peut-être d'autres régions interconnectées à maturation tardive) et entraîner des changements comportementaux semblables à ceux observés chez l'animal ayant une lésion excitotoxique permanente. Ces résultats constituent un nouveau modèle potentiel des aspects de la schizophrénie sans lésion anatomique marquée.

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