Using animal models to test a neurodevelopmental hypothesis of schizophrenia

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A series of studies has shown that neonatal excitotoxic disconnection of the rat ventral hippocampus may serve as a heuristic model of schizophrenia. The model mimics a spectrum of neurobiologic and behavioural features of schizophrenia. It produces functional pathology in critical brain regions implicated in schizophrenia and connected with the hippocampal formation, namely, the striatum, nucleus accumbens and the prefrontal cortex. These brain regions are also targeted by antipsychotic drugs. Neonatal insult leads in young adulthood to the emergence of abnormalities in a number of dopamine-related behaviours. It also models some of the negative aspects of schizophrenia, such as social impairments and working memory deficits. Moreover, our data show that even transient inactivation of the ventral hippocampus during a critical period of development that produces subtle anatomical changes in the hippocampus may be sufficient to trigger behavioural changes similar to those observed in animals with the permanent excitotoxic lesion. The results of bromodeoxyuridine (BrdU) incorporation studies show that this transient disconnection in the CA1 and CA2 area of the hippocampus may have long-lasting consequences for neurogenesis in the dentate gyrus. Our data suggest that neonatal disconnection of the ventral hippocampus alters development and plasticity of prefrontal cortical circuitry and produces a constellation of behavioural and cellular changes that mimic many aspects of schizophrenia. The neonatal hippocampal disconnection model represents a potential new model of schizophrenia without a gross anatomical lesion.

Une série d'études ont démontré que la déconnexion excitotoxique néonatale de l'hippocampe ventral du rat peut servir de modèle heuristique de la schizophrénie. Le modèle imite un éventail de caractéristiques neurobiologiques et comportementales de la schizophrénie. Il produit une pathologie fonctionnelle dans des régions critiques du cerveau incriminées dans la schizophrénie et reliées à la formation de l'hippocampe, soit le néostriatum, le noyau accumbens et le cortex préfrontal. Ces régions du cerveau sont aussi visées par les antipsychotiques. Les atteintes néonatales entraînent chez le jeune adulte l'apparition d'anomalies dans un certain nombre de comportements reliés à la dopamine. Elles produisent aussi certains aspects négatifs de la schizophrénie, comme les déficiences sociales et les déficits de la mémoire de travail. Nos données montrent de plus que même l'inactivation transitoire de l'hippocampe ventral pendant une période critique du développement qui produit des changements anatomiques subtils dans l'hippocampe peut suffire pour déclencher des changements de comportements semblables à ceux qu'on a observés chez des animaux où la lésion excitotoxique est permanente. Les résultats d'études d'incorporation de la bromodéoxyuridine (BrdU) montrent que cette déconnexion transitoire dans la région CA1 et CA2 de l'hippocampe peut avoir des répercussions de longue durée sur la neurogénèse dans le gyrus denté. Nos données indiquent que la déconnexion néonatale de l'hippocampe ventral modifie le développement et la plasticité des circuits du cortex préfrontal et produit une constellation de changements comportementaux et cellulaires qui imitent de nombreux aspects de la schizophrénie. Le modèle de déconnexion de l'hippocampe néonatal peut offrir un nouveau modèle possible de schizophrénie sans lésion anatomique macroscopique.

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Introduction

Animal models are important in the investigation of the mechanisms underlying human disease and in designing new therapies. For example, these models may be used to test the plausibility of theories about the origin of schizophrenia; explore the mechanisms of schizophrenia-like phenomena; test the effects of confounding factors, such as medication and postmortem interval, or time since death; investigate therapeutic and adverse effects of the drugs used for the treatment of schizophrenia and develop potential new treatments.

Most conventional animal models of schizophrenia have focused on phenomena linked to dopamine, because the dopaminergic system has been strongly implicated in this disorder. All effective antipsychotic drugs are antagonists of dopamine receptors, and dopamine agonists induce symptoms that resemble psychosis.[1] It has become clear, however, that models based on direct manipulations of the dopamine system have a limited heuristic potential and that new strategies need to be developed to provide novel targets for the development of more effective therapeutic agents.

Neonatal excitotoxic hippocampal lesion

Numerous studies have focused on neonatal damage of the hippocampus in rats[2–12] and in monkeys[13–16] as a potential model of schizophrenia, because various functional and structural changes in the hippocampus have been consistently implicated in human schizophrenia.[17] It was hypothesized that neonatal insult of the hippocampus may 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, namely, the ventral hippocampus (VH) and ventral subiculum.[18,19] These regions correspond to the anterior hippocampus in humans that shows anatomical abnormalities in schizophrenia.[20]

A series of studies has shown that neonatal excitotoxic lesions of the rat VH lead in young adulthood to the emergence of abnormalities in a number of dopamine-related behaviours, which show some similarities to abnormal behaviours seen in animals sensitized to psychostimulants. When tested as juveniles (postnatal day [PD] 35), rats with the neonatal VH lesions are less social than controls[21] but otherwise behave normally in motor tests involving exposure to stress and dopamine agonists. In adolescence and adulthood (PD 56 and older), animals with lesions display markedly changed behaviours that are thought to be primarily linked to increased mesolimbic and nigrostriatal dopamine transmission (e.g., 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 of startle (PPI) and latent inhibition, impaired social behaviours and working memory problems.[2,10–11,22–28] Recent studies have demonstrated that adult rats with neonatal hippocampal lesions show enhanced sensitivity to drugs of abuse and deficits in reward mechanisms.[29,30] These phenomena show many parallels with schizophrenia (Box 1). Emergence of the behavioural changes in adolescence appears not to be related to the surge of gonadal hormones during puberty, because these abnormalities are also observed in animals depleted of gonadal hormones before puberty.[23] Notably, removal of prefrontal neurons in adult animals with the earlier hippocampal lesion restores some of the behaviours (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 expression of the syndrome.[31] 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

Box 1: Behavioural changes in an animal model with face validity for schizophrenia

1. Cellular, molecular and morphological changes in the brain
2. Increased responses to stress, *N*-methyl-D-aspartate antagonists and dopamine agonists
3. Sensorimotor gating (prepulse inhibition of startle [PPI]) and latent inhibition deficits
4. Diminished sensitivity to rewarding stimuli
5. Responsiveness to neuroleptic drugs
6. Impaired working memory
7. Vulnerability to drug abuse
8. Social deficits

cortices.[32] Although the exact mechanisms of a seemingly similar disconnection and malfunction of the prefrontal cortex in the rats with VH lesions need to be elucidated, findings from molecular and electrophysiologic studies suggest that aberrant cortical dopamine–glutamate–γ-aminobutyric acid (GABA) interactions may underlie cortical dysfunction in the neonatally VH-lesioned rats (Box 2). These findings include reduced cortical levels of *N*-acetylaspartate (NAA) and glycogen synthase kinase-3β (GSK-3β); attenuated stress-induced cortical dopamine release; attenuated cortical expression of a membrane glutamate transporter EAAC1 and of a synthetic enzyme for GABA, glutamate decarboxylase-67 (GAD-67); reduced brain-derived neurotrophic factor (BDNF) expression; altered cortical expression of transcription factors c-fos mRNA and ΔfosB; as well as an altered firing pattern of cortical pyramidal neurons in response to ventral tegmental area stimulation.[33–38] Many of these molecular changes have also been reported in schizophrenia.

Subcortical function in the neonatally lesioned rats is also altered. The pattern of changes is reminiscent of alterations reported in behavioural sensitization models, namely, striatal dopamine release is attenuated in response to stress and amphetamine, midbrain expression of the membrane dopamine transporter (DAT) mRNA is reduced and striatal expression of dynorphin (an opioid peptide co-localized with dopamine D_1 receptors) and of ΔfosB (a transcription factor sensitive to persistent stimulation) are enhanced.[35,39,40] It should be noted, however, that enhanced rather than attenuated striatal dopamine release has been observed in other paradigms of sensitization to psychostimulants,[41] as well as in a subgroup of patients with schizophrenia as evidenced by single-photon emission computed tomography studies.[42,43] Similarly discrepant are the findings of synaptic morphology, namely, increased synaptic densities, number of branches and dendritic length are reported in prefrontal cortex in sensitization models,[44] whereas these dendritic parameters are decreased in schizophrenia[45] and in the neonatal hippocampal lesion model.[46] Nevertheless, an array of behavioural 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. It has been suggested that similar pathophysiologic mechanisms underlie schizophrenia.[47] 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 behavioural and molecular phenomena associated with sensitization.

In terms of the predictive validity of the neonatal VH lesion model, antipsychotic drugs normalize some lesion-induced behaviours.[21,22,48] Drugs that target the glutamate system may also prove beneficial: LY293558, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist, is highly efficient in blocking hyperlocomotion in neonatally lesioned rats at doses that do not affect locomotor activity in controls,[26] as is the glycine transporter inhibitor.[49] 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 neurobiologic and behavioural features of schizophrenia, including functional pathology in presumably critical brain regions interconnected with the hippocampal formation and targeted by antipsychotic drugs, that is, 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.[14,15,34] Thus, neonatal damage to rat hippocampus appears to reproduce a broad spectrum of schizophrenia-related

Box 2: Evidence that the prefrontal cortex is compromised in rats with a neonatal ventral hippocampal lesion

1. Complex behaviours are disrupted
2. Neuronal function is compromised (levels of *N*-acetylaspartate [NAA] and glycogen synthase kinase-3β [GSK-3β] and expression of glutamate receptor GluR3, membrane glutamate transporter EAAC1, brain-derived neurotrophic factor [BDNF] and glutamate decarboxylase-67 [GAD-67] mRNAs are reduced)
3. Patterns of firing of pyramidal neurons in response to ventral tegmental area stimulation are altered
4. Neuronal morphology is changed

phenomena and establishes the neurobiologic plausibility of early damage having a delayed impact on neural functions implicated in schizophrenia.

Neonatal reversible hippocampal disconnection

In a further 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 behavioural 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 the VH on PD7, an important time for refinement of intracortical connections, and then assessed behavioural changes that this infusion might have evoked later in life in juvenile (PD35) and young adult (PD56) rats.[50] The results of bromodeoxyuridine (BrdU) incorporation studies show that this transient disconnection in the CA1 and CA2 area of the hippocampus may have long-lasting consequences for neurogenesis in the dentate gyrus. The overall characteristics of behavioural 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.[51] Neonatally TTX-infused rats displayed in adulthood motor hyperactivity upon pharmacologic stimulation (amphetamine and MK-801) and in response to stress, novelty and a saline injection compared with sham controls. The magnitude of TTX-induced behavioural disruptions was smaller, however, compared with those observed after the excitotoxic lesion (e.g., ibotenic acid lesions of the VH increased spontaneous and amphetamine-induced locomotor activity by about 50% compared with controls,[2,52] whereas TTX produced increases of about 15%–20%). Moreover, in contrast with the permanent lesion, TTX infusions did not significantly affect social behaviours, although a trend for reduced social interactions again mimicked a pattern seen after the permanent lesions. Analogous TTX infusions in adult animals did not alter these behaviours 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 affects 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 ventral hippocampal function during a critical time in maturation of intracortical connections permanently changes the development of neural circuits mediating certain dopamine-related and *N*-methyl-D-aspartate-related behaviours. These results represent a potential new model of aspects of schizophrenia without a gross anatomical lesion.

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