Discussion of Bogerts' Temporolimbic System Theory of Paranoid Schizophrenia

by John W. Olney and Nuri B. Farber

Abstract

Olney and Farber present their work with N-methyl-D-aspartate (NMDA) antagonists, which are psychotogens, and propose that the structural changes described by Bogerts could be accounted for by a two-stage process. The first stage of the process would occur early in life and would culminate in the selective loss of NMDA-receptor bearing gamma-aminobutyric acid (GABA)ergic neurons and thus render the brain into a NMDA receptor hypofunctional (NRH) state. Such a loss would set the foundation for the second stage in which the neural circuits that have been altered by the loss of these GABAergic interneurons would become activated in late adolescence but would be dysfunctional. Dysfunction of this circuit would lead to the psychopathology of schizophrenia and potentially, if severe enough, to neuronal degeneration. Thus, the changes described by Bogerts could originate partially in early life and partially in adulthood. Based on their animal model, the authors suggest studies that should be carried out in humans.


In his article, the temporolimbic system theory of paranoid schizophrenia, Bogerts (1997, this issue) presents evidence for the hypothesis that specific patterns of structural brain changes correspond with, and can explain, certain clinical syndromes of schizophrenia. This interesting hypothesis can be further strengthened by studies aimed at identifying specific neurons and neurotransmitter networks that are responsible for generating and transmitting abnormal signals. While the dopaminergic transmitter system has been the main focus of the schizophrenologist’s attention for several decades, we propose that the glutamatergic system, which heretofore has been underemphasized, may be an important contributor to the pathophysiology of schizophrenia.

Glutamate, the predominant excitatory neurotransmitter in the mammalian brain, activates two general classes of receptors (ionotropic and metabotropic); within the first are three subclasses (N-methyl-D-aspartate [NMDA], alpha-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid [AMPA], and kainate). The NMDA subclass of glutamate receptor has recently aroused interest among schizophrenia researchers because antagonist drugs that block this receptor, including phencyclidine and ketamine, trigger a psychotic reaction in adult humans that mimics many of the cardinal symptoms of schizophrenia. In addition, researchers recently learned (Olney et al. 1989, 1991; Fix et al. 1995b; Corso et al. 1997) that blockade of NMDA receptors can injure or kill pyramidal and multipolar neurons in various cerebrocortical and limbic regions of the rat brain.

We have proposed (Olney and Farber 1995) that NMDA receptor hypofunction (NRH), the condition induced in the human or animal brain by an NMDA antagonist drug, might also be viewed as a disease mechanism which, if present in the schizophrenia brain, could explain the symptoms of this disorder. Our NRH hypothesis is consistent with the proposal of Bogerts (1997, this issue) that structural brain changes may be related to schizophrenia symptom formation, and it also addresses the important question of whether the structural changes occur during development or as an ongoing process in adulthood. The NRH hypothesis holds that a certain type of pathological event (either genetically or environmentally determined) occurs early in life and involves subtle structural changes that instill in the developing brain a latent NRH potential.

One type of pathological event we have in mind is the situation where certain NMDA receptor-bearing gamma-aminobutyric acid (GABA)ergic neurons are
killed or rendered permanently impaired. Loss of these neurons, and their NMDA receptors, would leave the NMDA receptor system in a hypofunctional (NRH) state that can give rise to psychosis and ongoing structural brain changes. Of course, if the NRH state is already present in the brain during infancy and childhood, we must explain why it does not begin to trigger psychotic symptoms until early adulthood. This fundamental enigma of schizophrenia is readily explained by the nature of the NRH mechanism. It can trigger neurotoxic and psychotic reactions only in the adult brain, apparently because certain maturational events must take place in late adolescence for the brain to become sensitive to this mechanism. Evidence supporting this conclusion is as follows: (1) administration of NMDA antagonists in doses that induce a profound NRH state in the brain causes cerebrotocortical neuronal injury in adult animals but not in fetal, infant, or juvenile animals (Farber et al. 1995b); (2) administering NMDA antagonists in anesthetizing doses triggers psychotic reactions in human adults but not in children (Karp et al. 1980; Welch and Correa 1980; White et al. 1982; Reich and Silvay 1989; Baldridge and Bessen 1990).

In adulthood, the NRH mechanism would initially cause psychotic manifestations; if the NRH process is particularly severe, it could eventually cause the neuronal degeneration and cognitive deterioration known to occur in some schizophrenia patients. These degenerative (structural) changes would not be accompanied by a detectable gliosis, in that conspicuous or enduring gliosis is not a characteristic feature of the neurodegenerative reaction induced by the NRH mechanism (Fix et al. 1995a). Thus, the NRH hypothesis holds that structural damage in the brain of schizophrenia subjects may be of two kinds: it may include a developmental component and also one of ongoing degeneration in adulthood. Neither component would be expected to cause conspicuous scarring.

How might this hypothesis be tested? For the developmental component, immunohistochemical studies should be undertaken to determine whether small GABAergic interneurons and accompanying NMDA receptors are missing from certain regions of the brains of schizophrenia subjects, including the cerebral cortex, thalamus, and basal forebrain (Benes et al. 1991; Ikonomidou et al. 1995). For the adult component, evidence should be sought for loss of pyramidal or multipolar neurons from a variety of corticolimbic regions—including the cingulate/retrosplenial, temporoparietal, perirhinal, entorhinal, and prefrontal cortices; the amygdala; and the hippocampus (Corso et al. 1997).

Using NMDA antagonist drugs as tools for inducing an NRH state in the animal brain, we have learned that many classes of drugs, including those that ameliorate the symptoms of schizophrenia (Farber et al. 1993, 1996), arrest the mechanism by which NRH damages the brain. This finding has provided insight into the transmitter receptor mechanisms and neural circuitry that mediate this neurotoxic process (for a detailed review, see Olney and Farber 1995). It also has led to an important new realization—that glutamate functions not only as a straightforward excitant in the brain, but as a major regulator of inhibitory tone. Glutamate achieves this by tonically activating NMDA receptors on GABAergic neurons, driving them to inhibit the activity of major excitatory pathways (both glutamatergic and cholinergic) that convergently innervate primary neurons in the cerebrocortical and limbic brain regions. When the NMDA receptors in this system are blocked or impaired, the result is a syndrome in which the excitatory pathways are blocked from inhibition, which causes them to hyperstimulate corticolimbic neurons in an erratic manner.

The time-honored filter concept is applicable. The GABAergic neurons are the modulatory filter, but this dynamic filter works only if driven by glutamate acting through NMDA receptors. The NRH state, in essence, is a faulty filter syndrome in which disinhibited (unfiltered) messages chaotically bombard cerebrotocortical and limbic neurons.

The neural network that we believe mediates NRH psychotic symptom formation and neuronal injury includes transmitter receptors of at least seven different types: NMDA glutamate, kainate glutamate, m1 muscarinic, alpha2-adrenergic, GABA_A, sigma, and 5-HT_2A serotonin (Olney et al. 1991; Farber et al. 1993, 1995a; Price et al. 1994; Farber and Olney 1996). In addition, we postulate that in some schizophrenia patients, the NRH state is maintained by a genetic defect causing hyperactivity of the dopamine system, which leads to NRH by excessive inhibition of the release of glutamate at NMDA receptors (Olney and Farber 1995).

In summary, we propose that the structural changes described by Bogerts (1997, this issue) may be the result of a two-stage pathological mechanism: A subtle structural change early in life instills a latent NRH state in the developing brain that is subsequently activated by maturational events in early adulthood. The activated NRH mechanism, if severe, can cause not only psychosis but ongoing structural brain changes in adulthood, resulting eventually in cognitive deterioration. Thus, the structural changes discussed by Bogerts may originate partially in early life and partially in adulthood.

According to the NRH hypothesis, schizophrenia symptom formation results from defective function of a GABA-inhibitory filtering mechanism that normally is driven by glutamate acting through NMDA receptors.
Malfunction of the filter results in disinhibited excitatory activity that floods corticolimbic neurons with erratic unmodulated messages. Receptors for nearly all of the major transmitter systems participate as functional (dysfunctional) elements in the circuitry through which symptom formation occurs.

Can a focus on these elements lead to rational pharmacotherapy to prevent symptom formation in schizophrenia? This is the ultimate test of the hypothesis.

References


Acknowledgments

This research was supported by grants AG-11355 from the National Institute of Aging, DA-05072 from the National Institute on Drug Abuse, and a Research Scientist Award MH-38894 from the National Institute of Mental Health to John W. Olney and a Scientist Development Award for Clinicians DA-00290 from the National Institute of Drug Abuse to Nuri B. Farber.

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Erratum

The article by Lynn E. DeLisi et al. entitled “Anomalous Cerebral Asymmetry and Language Processing in Schizophrenia (Schizophrenia Bulletin, 23(2):255-271, 1997) contains the following errors: In table 4 (page 260), under the “DMS-III-R diagnosis” column for “Controls,” the diagnosis should have read “normal”; for “Siblings,” the diagnoses were as follows: 16 chronic schizophrenia, 11 schizoaffective, and 1 schizotypal personality disorder. In table 7 (page 263), under the heading “Patients,” the subheading should read: males (n = 52); females (n = 35) for a total of 87 patients.