

Changing Concepts in the Neurochemistry of Schizophrenia

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Its receptors and associated proteins are likely to be located on every neuron in the brain. Thus, glutamatergic transmission may affect every central neuron and is critical to all mental, sensory, motor, and affective function. For this reason alone, the glutamatergic transmitter system should receive attention in examinations of schizophrenia. In addition, there is cogent pharmacologic evidence that dysfunction of the *N*-methyl-D-aspartate (NMDA)-sensitive glutamate receptor may play a role in mediating psychosis (Goff and Coyle, this issue). Neurobiologists are now looking for specific pathologic evidence of glutamatergic dysfunction in schizophrenia.

Glutamatergic signaling is more than simply the critical step in excitatory neurotransmission. The spatial and temporal distribution of electrical activity is a key modulator of the constructive and destructive processes that determine neuronal form and sculpt the pattern of neural circuitry during ontogeny (1). Because glutamatergic signaling is one of the major sources of excitatory drive in the CNS, glutamate is obligatorily implicated in these developmental processes. Neuronal depolarization caused by glutamate binding to its receptors activates critical intra- and intercellular signaling molecules, such as calcium, nitric oxide, and neurotrophins.

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These molecules, in turn, trigger a variety of intracellular signaling cascades that modulate the developmental processes just mentioned. In addition, the glutamatergic transmission system has reciprocal interactions with other neurotransmission systems—most notably the dopaminergic and γ -aminobutyric acid (GABA)-ergic systems—which are also important determinants of neural activity.

Multiple lines of evidence suggest that although the psychotic phase of schizophrenia usually does not appear until adolescence, there may be a significant developmental component of the disease. Because glutamatergic signaling is an important influence on the development of neural circuitry, altered glutamate function, either primarily or as a downstream consequence of some other event, may be part of the pathogenic mechanism leading to psychosis. More research is required to establish definitively the role of glutamatergic signaling in the mechanistic sequence leading to schizophrenia.

In the mature brain, as in the developing one, neural circuits undergo constant rearrangement. This may take the form of structural changes or modulation of the efficacy of synapses, both of which alter the functional properties of neural networks. The spatiotemporal pattern of electrical activity—and, by extension, glutamatergic function—is a crucial determinant of these changes. This plasticity of neural circuits is necessary for many normal functions of the mature brain, most notably learning and memory (2). However, in the brains of individuals with schizophrenia, glutamatergic signaling may well contribute to the functional changes in neural networks that account for the progression of the disease through its various stages, as well as for temporal variations in the severity of symptoms at each stage. Some studies pertaining to this topic are included in this issue.

Glutamate is also part of the mechanism of various neurotoxic processes. Excessive glutamate release as a consequence of injury or hypoxia can, by its effects on glutamate

receptors, cause excitotoxic cellular death (3). In addition, altered glutamate metabolism leading to the formation of free radicals is likely to be a significant cause of cellular death in some neurodegenerative diseases and in response to toxic agents, including some drugs of abuse. Thus, neurotoxic processes are another potential pathway for glutamate to contribute to the pathophysiology of schizophrenia.

It is satisfying to see in the current literature the development of a timely, organizing glutamate hypothesis of schizophrenia and its testing with critical experimental data (4). These investigators sought to identify the biologic determinants of schizophrenia using sensitive and selective technologies. Their results will be the basis not only for understanding the pathophysiology of schizophrenia, but also for postulating novel drug targets. It was not long ago that studies of schizophrenia were encumbered with too many confounds to allow clear interpretation. Investigators despaired over finding meaningful data. Now, improved technology and experimental design are producing credible results. Smith et al. (this issue), using postmortem tissue to analyze the expression of several newly cloned glutamate transporter proteins, have obtained data suggesting that synaptic glutamate reuptake may be abnormal in the thalamus of schizophrenia subjects. Also, Dracheva et al. (this issue) report abnormalities in multiple postsynaptic measures of glutamatergic transmission in schizophrenia. The expression of certain subunits of NMDA-sensitive glutamate receptors in the dorsolateral frontal cortex in elderly schizophrenia subjects and the expression of an associated postsynaptic protein involved in NMDA-receptor signaling were found to be elevated. Lewis et al. (this issue) found a putative marker for thalamocortical neurons from the mediodorsal thalamus to the frontal cortex in lower amounts in schizophrenia. These neurons are glutamate containing, suggesting a reduction of glutamatergic transmission in the dorsolateral frontal cortex in schizophrenia. Thus, in two interrelated brain regions in schizophrenia, elements of glutamatergic transmission are altered. These studies illustrate the application to schizophrenia research of new neurobiologic tools and experimental designs and demonstrate the strength of the results. The data provide hope for improved understanding of the pathology of schizophrenia and the development of rational therapies.

References

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