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CME Objective

After studying this article, you should be able to:

- Compare and contrast the dopamine and glutamate hypotheses of schizophrenia

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Financial Disclosure

All individuals in a position to influence the content of this activity were asked to complete a statement regarding all relevant personal financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. In the past year, Alan J. Gelenberg, MD, Editor in Chief, has been a consultant for Allergan, Forest, and Zynx Health; has received grant/research support from Pfizer; and has been a stock shareholder of Healthcare Technology Systems. No member of the CME Institute staff reported any relevant personal financial relationships. **Faculty financial disclosure appears at the end of the article.**

This COMMENTARY section of The Journal of Clinical Psychiatry presents the highlights of the planning teleconference series “Making Connections Between Science and Symptoms in Schizophrenia,” which was held in January and February 2014. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Genentech.

The opinions expressed herein are those of the faculty and do not necessarily reflect the opinions of the CME provider and publisher or Genentech.

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Schizophrenia: The Role of Dopamine and Glutamate

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Although antipsychotics are effective in treating schizophrenia, they primarily address positive symptoms of the disorder, while disabling negative and cognitive symptoms can persist. This Commentary series explains the neuroscience behind schizophrenia in order to identify novel treatment targets. The following section focuses on the dopamine dysfunction and glutamate hypothesis underlying the pathophysiology of this condition.

DOPAMINE DYSFUNCTION IN SCHIZOPHRENIA

Information processing and motivational behavior are mediated by cortico-striatal-pallidal-thalamo-cortical loops. These circuits consist of glutamatergic projections from cortical regions such as the orbitofrontal, dorsolateral, and sensorimotor cortices to the striatum; the striatum sends inhibitory GABAergic projections to the pallidum, which itself projects to the thalamus. The thalamus then sends glutamatergic projections back to the cortex. In summary, the striatum receives projections from the cortex, processes this information, and feeds it back to the cortex via the thalamus. Dopamine provides an important modulatory input to these cortico-striatal-pallidal-thalamo-cortical loops.

Dopaminergic projections from midbrain dopamine cells are divided in nigrostriatal, mesolimbic, and mesocortical systems. The nigrostriatal system projects from the substantia nigra in the midbrain to the dorsal striatum and has been classically involved in cognitive integration and habituation (associative striatum) and sensorimotor coordination and initiation of movement (sensorimotor striatum). The mesolimbic system projects from the ventral tegmental area (VTA) to limbic structures such as the ventral striatum (VST), hippocampus, and amygdala. The VST includes the nucleus accumbens and the ventral parts of the caudate and putamen and is involved in processing emotions. The mesocortical system projects from the VTA to most cortical regions and is involved in cognition.

Striatal dopamine alterations in schizophrenia include increased dopamine synthesis, dopamine release, and D₂ receptor density.¹ Excess presynaptic dopamine in the dorsal striatum or abnormal postsynaptic D₂ receptor sensitivity has been shown to relate to positive psychotic symptoms.¹ Additionally, excess striatal dopamine release predicts the therapeutic response of psychotic symptoms to antipsychotics.¹ In summary, enhanced dopamine leads to psychosis, which in turn, is alleviated by D₂ antagonism (the main effect of antipsychotics).

Dopamine dysregulation begins early in the disease course and can be detected during the prodromal phases of schizophrenia. For example, the dopamine synthesis rate is elevated in patients with prodromal symptoms of schizophrenia and this excess is related to the severity of prodromal symptoms and cognitive deficits.² Prodromal patients also have elevated cerebral blood volume (CBV) in the ventral hippocampus as measured with fMRI, indicating increased neural activity and thought to be an index of excess glutamatergic transmission in the ventral hippocampus. Both increased dopamine synthesis rate and

increased CBV in the hippocampus have been shown to predict conversion to schizophrenia.³ Preclinical animal models suggest that these observations may be linked, as hippocampal glutamatergic overdrive may disinhibit dopamine midbrain cells' firing activity.

Dopamine levels in the ventral limbic striatum are elevated in schizophrenia, although not to the extent seen in the associative striatum. However, in relation to schizophrenia symptoms, low dopamine release in this area directly impacts the severity of negative symptoms (the lower the dopamine levels, the more negative symptoms).⁴ A dopamine deficit, as well as alterations in glutamate and GABA, in the cortical regions are thought to contribute to negative symptoms and cognitive impairments in schizophrenia.

Although dopamine has a role in the pathophysiology of schizophrenia, dopamine dysfunction does not adequately describe all aspects of schizophrenia, especially the underlying pathology of negative or cognitive symptoms, hence the need for a better understanding of alterations affecting other systems.

THE GLUTAMATE HYPOTHESIS

The glutamate hypothesis of schizophrenia posits that the disorder may be caused by deficient activity at glutamate synapses, specifically the *N*-methyl-D-aspartate (NMDA) receptor subtype of glutamate receptors. The evidence for this hypothesis comes from exposure data, which revealed that NMDA glutamate receptor antagonists elicit schizophrenia-like symptoms (auditory hallucinations, delusions, cognitive dysfunction) in both animal studies^{5,6} and human studies.^{7,8}

Glutamate is the primary excitatory neurotransmitter and is used by all pyramidal cortical cells. Glutamate receptors are classified as ionotropic (NMDA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA], and kainate) or metabotropic (3 large groups of mGlu receptors).⁹ Ionotropic receptors comprise a series of ion channels located around a central pore that controls the flow of calcium, sodium, and potassium ions in and out of the cell; once activated, they cause rapid ion flow. Metabotropic receptors are connected to G protein-coupled receptors (GPCR); neurotransmission is slow, requiring the GPCR to interact with a G-protein to either increase or decrease the level of a second messenger (eg, cyclic AMP).

Each of the glutamate receptors has its own properties, gene families, and preferred agonists. The 3 ionotropic receptors are colocalized on the postsynaptic neuron and are part of a complex interaction for NMDA-mediated neurotransmission. For the NMDA receptor to fully open, the coagonist glycine must bind with glutamate at distinct sites on the NMDA receptor, allowing for transmission of both sodium and calcium. NMDA also has another coagonist, D-serine, at the glycinergic (but not glutamatergic) site. The glycine sites, with their 2 coagonists, provide potential targets for pharmacologic manipulation through inhibition of reuptake pumps for glycine, or inhibition of the enzyme that metabolizes D-serine.

The glutamate hypothesis, thus, provides possible new targets for pharmacotherapy and serves as a reminder that,

- Excess dopamine can explain the psychotic symptoms of schizophrenia, but it does not explain the negative and cognitive symptoms.
- Understanding the glutamate hypothesis allows broader insight into the possible causes of and potential treatments for schizophrenia.

although dopamine may be intimately involved in schizophrenia, other receptor systems may be implicated in both the pathogenesis and possible treatment of this illness. An understanding of actions at the receptor level is helpful in developing new understandings of psychosis and schizophrenia, but gaps still exist in how receptor level dysfunction might translate to more global issues with the circuits that they impact.

Part 2 of this Commentary will present information on the mechanism of action of antipsychotic medications and the specific role of NMDA receptors in schizophrenia.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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POSTTEST

To obtain credit, go to PSYCHIATRIST.COM (Keyword: March) to take this Posttest and complete the Evaluation.

1. A limitation of the finding that excess striatal dopamine is a core feature of schizophrenia is that it only addresses which of the following symptom domains:
 - a. Positive symptoms
 - b. Negative symptoms
 - c. Cognitive symptoms