Natural Antiviral Cellular Defense in Relation to Positive and Negative Symptoms of Schizophrenia?

TO THE EDITOR: The review article by Alan S. Brown, M.D., M.P.H., and Elena J. Derkits, B.A. (1), published in the March 2010 issue of the *Journal,* provided further evidence of a possible role of prenatal infection and maternal immune response in the etiology of schizophrenia. The authors also emphasized the importance of gene-environment interplay in neurodevelopmental disturbance leading to schizophrenia. However, the hypothesis of the single prenatal viral or immunological effect on the developing brain as a predisposing factor to schizophrenia cannot explain the variable long-term course of the illness.

A recent discovery of intracellular RNA-based gene inactivation machinery (short interfering RNA-induced silencing complex) (2) suggested a mechanism of the natural defense against neurotropic viruses. RNA-induced silencing complex is the natural mechanism that prevents viruses from producing functional proteins. Such cellular defense can inhibit production of HIV and poliovirus (2–3). In some cases, the viral infection can be cleared; in other cases a virus can escape (4).

A hypothetical genetic variation in RNA-induced silencing complex may explain a variability of illness progression in schizophrenia: in some affected individuals, RNA-induced silencing complex controls an expression of schizovirus, while in others genetic polymorphism in RNA-induced silencing complex may lead to overstimulation of the cellular defense with temporary silencing of both schizoviral RNA and some host cell RNAs. Such dysregulation in the RNA-induced silencing complex response may increase dopamine production in affected neurons and lead to transient positive symptoms of schizophrenia, a clinical presentation consistent with "cycloid psychosis"(5). In some other patients, the underresponsive defense leads to a fast progression of neuronal damage and early development of deficit schizophrenia (6). In a majority of cases, overstimulation of RNA-induced silencing complex and eventual viral escape from the short interfering RNA inhibition is represented by often intermittent positive psychotic symptoms and progression of negative symptoms. Thus, suggested polymorphisms in the RNA-induced silencing complex genes may be related to genetic vulnerability to schizophrenia and a progression of the disease.

There is a lack of studies of RNA-induced silencing complex activity in humans. It is tempting, however, to suggest that a study of intracellular RNA defense may help to identify infectious agents, predisposing to schizophrenia, and that a development of short interfering RNA therapy may potentially cure some schizophrenia spectrum disorders.

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Response to Vedeniapin Letter

TO THE EDITOR: We appreciate the comments of Dr. Vedeniapin, which call attention to the fact that it is unlikely that a prenatal infection alone can account for the fluctuations in the clinical state of schizophrenia over the long-term course of the illness.

He also introduces a mechanism for potential effects of infection in patients with schizophrenia: the small interfering RNA-induced silencing complex. Such a mechanism may not only account for changes in the expression of the illness over time but also introduces a target to be investigated for genetic polymorphisms that may interact with infectious exposures.

It should be acknowledged, however, that while such a mechanism might relate to an infectious process in the brain of a patient with schizophrenia, it probably would not explain the effect of most prenatal infectious exposures that have been associated with schizophrenia, since, as noted in our review article, most of these infections do not appear to infect the fetal brain.

Regardless, this could represent an important new lead in the discovery of pathogenic microbes that might predispose an individual to schizophrenia.

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CACNA1C Risk Allele for Psychotic Disorders Is Related to the Activation of the AKT-Pathway

TO THE EDITOR: Genome-wide association studies have revealed a significant relationship between mood disorders, schizophrenia, and a variant in the *CACNA1C* gene (rs1006737, A/G) (1). This gene encodes the alpha subunit of the L-type voltage-dependent calcium channel (CAv1.2), and the risk variant is related to gray matter volume (2) and brain activation (3) in healthy individuals. However, the molecular correlates of the polymorphism are unknown. Recent evidence suggests that signals stemming from calcium channels modulate the activation of the phosphatidylinositol 3 kinase-