The Cytokine Model of Schizophrenia: Emerging Therapeutic Strategies

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We discuss the rationale for a trial of a novel biological immunotherapy in schizophrenia (SCZ). Available antipsychotic treatments for SCZ are often limited by partial effectiveness and significant side effects. The search for novel medications is of high priority. All current antipsychotics function primarily by blocking D2-type dopamine receptors. An emerging theory of SCZ postulates disturbances of cytokines and inflammatory mediators (i.e., the cytokine model), possibly originating in part from infectious exposures. Cytokines are one of the most important components of the immune system that orchestrate the response to infectious and other exogenous insults. Preclinical models of SCZ support a convergence between a role for certain cytokines in the pathophysiology of SCZ and major neurochemical postulates of the disorder, including the dopamine and glutamate hypotheses. Several cytokines are elevated in plasma in SCZ, and positron emission tomography studies have shown active inflammation in the brains of patients with psychosis. Treatment studies of anti-inflammatory agents, such as celecoxib and aspirin, in patients with SCZ have provided further support for neuroinflammation in this disorder. The development of approved biological therapies for autoimmune diseases provides new opportunities to target cytokine signaling directly as a novel treatment strategy in SCZ. In addition, advances in imaging, immunology, and psychopharmacology have paved the way for using measures of target engagement of neuroimmune components that would facilitate the identification of patient subgroups who are most likely to benefit from cytokine modulation.

Key Words: Cytokine, inflammation, interleukin, microbial, neuroimmune, schizophrenia

All current antipsychotic medications for schizophrenia (SCZ) function primarily by blocking D2-type dopamine receptors (1), although many individuals are only partially responsive to these medications (2). In addition, their effects on negative symptoms (3–6) and cognitive deficits (1,7–14) are limited. There is a great need for new psychopharmacologic agents for SCZ. An emerging theory of SCZ derives from a body of literature (15–17) that postulates disturbances of neuroimmunity in this disorder. Spurred by advances in infectious disease and immunologic research, there has been a renewed interest in microbial pathology, neuroinflammation, and SCZ.

This article reviews the rationale and treatment strategies for biological immunotherapy for SCZ. In particular, the focus is on medications aimed at modulating cytokine function, and key issues in the development and implementation of these approaches are discussed. Throughout this article, we refer to this rationale and approach as the "cytokine model of SCZ" (Figure 1). First, we summarize the epidemiologic and preclinical evidence for early life infection in the etiology of SCZ, links between cytokine dysfunction and the dopamine and glutamate hypotheses, and clinical and imaging studies of inflammation and cytokine disturbances in SCZ. Next, we review investigations of treatment approaches involving anti-inflammatory medications conducted to date. Finally, we discuss how these findings can be translated into novel therapeutic strategies, such as medications that directly target cytokines, including the identification of patients most likely to benefit from these medications and challenges of these approaches.

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Infection in SCZ

Emerging literature suggests that prenatal exposure to pathogenic microbes may contribute to the etiopathogenesis of SCZ (17). Although earlier studies, primarily on influenza, were based on ecologic data, more recent investigations have capitalized on birth cohorts with prospectively acquired data from serum bioassays on infectious exposures during the prenatal period. These infections include influenza (18), *Toxoplasma (T.) gondii* (19,20), genital reproductive infections (21), and herpes simplex virus type 2 (22,23). Although not all studies have yielded evidence of associations (24), most suggest an increased risk of SCZ in offspring of mothers with prenatal infection. Evidence suggests that exposure to *T. gondii* during periods other than pregnancy also may be related to SCZ (25–28).

Further epidemiologic evidence has supported infections and autoimmune dysfunction as risk factors for SCZ. In a prospective, nationwide study, hospital contacts for infections and autoimmune diseases before onset of SCZ were associated with an elevated risk of the disorder (29). These associations increased with the number of infections in a dose-response manner, and there was synergy between autoimmune diseases and infections. The risk of SCZ was greater if the infection occurred closer to the onset of SCZ, although associations were observed 15 years before the diagnosis.

Several models have attempted to explain how prenatal infections increase the risk of SCZ in offspring of infected mothers (17). The most parsimonious model suggests that cytokines mediate the effects of infection (17,30). Cytokines are a family of soluble proteins that play an important role as the systemic mediators of the host response to infection (17), are critically involved in the inflammatory response to noninfectious agents and insults, and are contributors to normal development and function of the central nervous system (17). Cytokines have been categorized into those that initiate proinflammatory versus anti-inflammatory processes (Table 1). Proinflammatory cytokines, such as interleukin (IL)-6 (which in certain circumstances also has anti-inflammatory effects) or tumor necrosis factor (TNF)-α, may play roles in cytotoxicity as well as influence dopaminergic and glutamatergic pathways and cognitive processes that are

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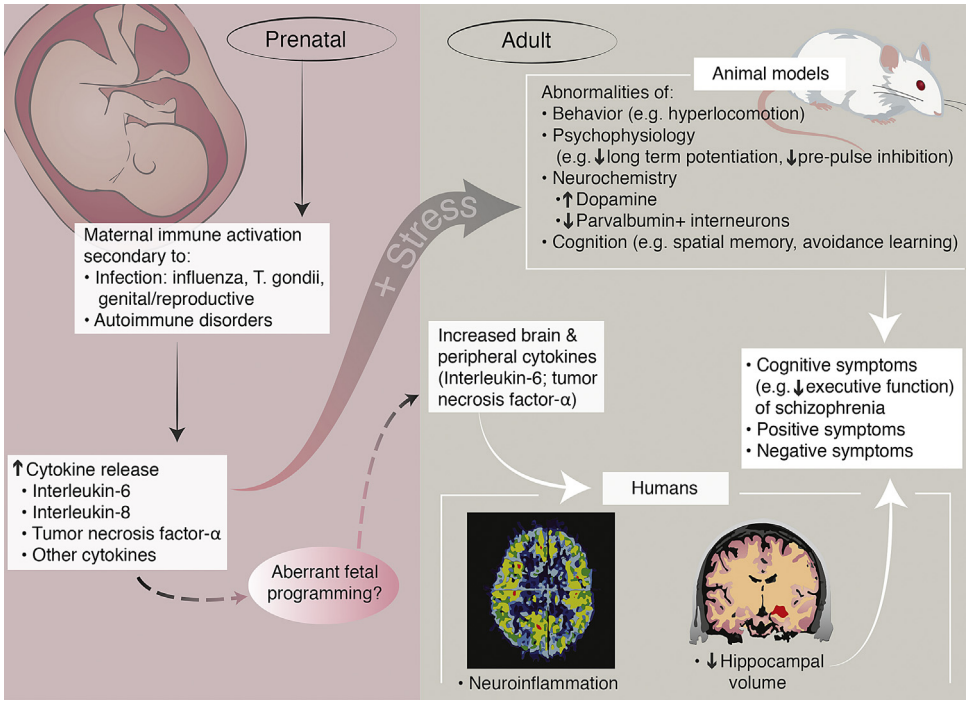

Figure 1. The cytokine model of schizophrenia. Artwork by Applied Art, LLC.

implicated in the pathophysiology of SCZ (see section on Cytokines and the Dopamine and Glutamate Hypotheses of SCZ). Cytokine activity also can trigger other biological events, such as activation of the hypothalamic-pituitary-adrenal axis (31), and is associated with increases in oxidative stress (32). Maternally generated cytokines may cross the placenta (33) and blood-brain barrier (34). In this review, we focus mainly on the proinflammatory cytokine IL-6 because the preclinical and clinical literature on a role of IL-6 in SCZ is robust, although other cytokines, such as TNF-α and IL-2, may be involved.

Maternal Immune Activation Model

The maternal immune activation (MIA) model of SCZ has provided a wealth of data on the potential connections between prenatal infection, cytokines, and SCZ. We focus here on select studies [Patterson (35) and Meyer *et al.* (36) provide comprehensive reviews], including studies involving administration of the double-stranded RNA polyinosinic:polycytidylic acid (poly I:C) and of lipopolysaccharide, both of which induce strong innate immune responses to pregnant rodents and, more recently, primates. Offspring of these pregnancies evidenced behavioral, neurochemical, psychophysiologic, and histologic abnormalities found in patients with SCZ. Of particular relevance to the dopaminergic hypothesis of SCZ, administration of poly I:C to pregnant rodents causes an increased number of mesencephalic dopamine neurons in the fetal brain during mid to late gestation, accompanied by changes in fetal expression of several genes involved in dopamine neuron development (37).

Table 1. Cytokines Putatively Implicated in Schizophrenia

Proinflammatory	Anti-inflammatory
IL-1	IL-10
IL-2	
IL-8	
IL-6	
TNF-α	

IL, interleukin; TNF, tumor necrosis factor.

The cytokine IL-6 appears to play an especially important role. Smith *et al.* (38) investigated the potential contribution of several cytokines to the abnormalities observed in MIA models of SCZ. The authors found that injection of poly I:C into pregnant mice produced offspring with prepulse inhibition abnormalities and social interaction deficits, analogous to observations in SCZ. Coadministration of anti-IL-6 antibodies neutralized these abnormalities. Similarly, offspring of IL-6 knockout mice given poly I:C did not exhibit these deficits (38). Samuelsson *et al.* (39) injected pregnant rats directly with IL-6 and found that adult offspring exhibited increased IL-6 levels, increased hippocampal IL-6 messenger RNA (mRNA), hippocampal astrogliosis and neuronal loss, and impaired spatial learning. These data suggest that IL-6 is required for detrimental effects of MIA on the fetal brain. Downstream of the IL-6 receptor, activation of IL-6 response genes was found both in the placenta and in the fetal brain of MIA-exposed offspring, and IL-6 mRNA was induced as well (40–42).

Evidence also suggests that MIA is associated with elevations of cytokines in offspring at homologous ages to the usual age of onset of SCZ (43,44). Prenatal exposure to lipopolysaccharide caused an increase in serum proinflammatory cytokine levels, including IL-2, IL-6, and TNF-α, during this stage of life. These effects were reversed by haloperidol. These findings and the above-noted findings on hyperdopaminergia in MIA-exposed mice provide support for aberrant fetal programming of adult immune hyperactivity and its relationship with dopamine dysfunction in SCZ and antipsychotic treatment effects coincident