Inflammation, Immune Function, and Schizophrenia: An Overview

May 19, 2017 | CME [1]
By Erin Walling, MSIV [2] and Phebe Tucker, MD [3]

Current research investigates new pathophysiologic mechanisms and lays the groundwork for redefining schizophrenia based on distinct medical subclasses—which may lead to more targeted and effective treatments. Details here.

Premiere Date: May 20, 2017
Expiration Date: November 20, 2018
This activity offers CE credits for:
1. Physicians (CME)
2. Other
All other clinicians either will receive a CME Attendance Certificate or may choose any of the types of CE credit being offered.

ACTIVITY GOAL
To understand the role of inflammation and immune function in the risk of schizophrenia.

LEARNING OBJECTIVES
At the end of this CE activity, participants should be able to:
• Define the mechanisms responsible for a healthy immune system
• Describe the effects of higher levels of inflammation on the CNS to promote mood disturbances and psychosis
• Describe variable responses to antipsychotics and the connection to the anti-inflammatory properties of these medications
• Recognize anti-inflammatory treatments that might be used as adjunctive therapy to mitigate symptoms

TARGET AUDIENCE
This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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Positive emission tomography (PET) studies of patients with schizophrenia have shown increases in only indicate astrocyte overactivity, but S100B also causes microglial cells to be more active. In support of this, researchers have identified an astrocyte-specific protein, S100B, found to be ultimately leads to cognitive dysfunction.

peripheral stimulation, too much activity within this system can damage healthy host tissues, which protecting the CNS from infection and buildup of unwanted cellular debris. However, as with cells of the CNS. Astrocytes exhibit stimulatory effects on microglia, which act as macrophages within the brain, consuming damaged cells and infectious agents. This process is essential to protecting the CNS from infection and buildup of unwanted cellular debris. However, as with peripheral stimulation, too much activity within this system can damage healthy host tissues, which ultimately leads to cognitive dysfunction.

In support of this, researchers have identified an astrocyte-specific protein, S100B, found to be elevated in cerebrospinal fluid samples of patients with schizophrenia. Elevations of this protein not only indicate astrocyte overactivity, but S100B also causes microglial cells to be more active. Positive emission tomography (PET) studies of patients with schizophrenia have shown increases in

An introduction to immunological theory
The association between autoimmunity, chronic inflammation, and psychosis is not new. It was first postulated by German neuropsychiatrist Hermann Lehmann-Facius in 1937 and further expanded by P.R.J. Burch in the early 1960s. More recently, scientists have expanded this theory, prompted by repeated findings of elevated inflammatory markers in patients with schizophrenia (Figure). Elevated serum levels of nonspecific proinflammatory markers such as prostaglandin E2 and C-reactive protein have been noted across multiple studies, in addition to elevated inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α).1 Within a healthy immune system, these factors are essential in promoting immunological responses through febrile reactions, phagocyte activation, leukocyte recruitment, and activation of the complement system in response to physiological insult. However, over-activation of this protective mechanism can damage host tissues with excessive production of nitrogen monoxide and superoxide anion, which are toxic to healthy proteins, mitochondria, and DNA. Increased levels of proinflammatory mediators can also cross the blood-brain barrier, where they damage polyunsaturated fatty acids that comprise the neuronal membrane. They are known to disturb brain function and to affect cognition, perception, mood, and behavior.

Higher levels of inflammatory markers have also been linked to increased catabolism of tryptophan, an essential amino acid required for the production of serotonin.2 Furthermore, over-activation of proinflammatory CNS cells can produce a kynurenic acid by-product, a substance known as a potent glutamatergic antagonist associated with both positive and negative symptoms of schizophrenia. Hence, increased inflammation can directly contribute to decreased serotonin levels and increased glutamatergic activity in the CNS, factors associated with both mood disturbances and symptoms of schizophrenia in previous studies.3 In addition to known peripheral effects of proinflammatory proteins, other changes noted in the CNS involve actions of astrocytes and microglial cells. These 2 cell types serve as the immunocompetent cells of the CNS. Astrocytes exhibit stimulatory effects on microglia, which act as macrophages within the brain, consuming damaged cells and infectious agents. This process is essential to protecting the CNS from infection and buildup of unwanted cellular debris. However, as with peripheral stimulation, too much activity within this system can damage healthy host tissues, which ultimately leads to cognitive dysfunction.

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Schizophrenia affects an estimated 1% of the population worldwide. Its prominent positive and negative psychotic symptoms and adverse effects on cognitive functioning lead to low levels of global functioning and increased morbidity and mortality.

Historically, research has focused on dopaminergic theories to explain the pathophysiology of schizophrenia, supported by years of clinical evidence that typical and atypical antipsychotic drugs can benefit patients. In practice, however, limitations of the clinical efficacy of antipsychotic medications suggest that the dopaminergic theory is not an entirely adequate explanation. Current research investigates new pathophysiologic mechanisms and lays the groundwork for redefining schizophrenia based on distinct medical subclasses—which may lead to more targeted and effective treatments.
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microglial cell activity, which lends further support to the link between dysfunctional immunomodulation of the CNS and the pathophysiology of schizophrenia.\(^4\)

Note, however, that additional research using PET has produced vastly diverse results; therefore, this area requires further exploration and analysis.

**Genetics**

Schizophrenia has a strong genetic component—studies of monozygotic twins show concordance rates of up to 48% to 50%.\(^5\) Use of advanced technologies such as genome-wide association studies have enabled researchers to examine precise heritable biomarkers in schizophrenia. In addition to others, the major histocompatibility complex region has been most strongly associated with schizophrenia.\(^6\) This complex is considered one of the key regulators of immune function, contributing to HLA genes, TNF production, and production of components of the complement cascade.

The association between major histocompatibility complex and schizophrenia is composed, in large part, by the complement component 4 (C4) alleles that produce increased levels of C4A and C4B in the CNS. In mice, C4 has been credited with postnatal synapse destruction, implicating the role of C4 in the reduced number of synapses found in patients with schizophrenia.\(^7\) This finding clarifies both the heritability of mental disorders like schizophrenia and a possible genetic link between this disorder and excessive activation of the immune system.

Epidemiological studies support a link between overt autoimmune disorders and schizophrenia. In one study, the presence of an autoimmune disorder indicated a 45% increase in the risk of schizophrenia, with strong associations of this mental disorder with rheumatoid arthritis, intestinal malabsorption, autoimmune thyroid disease, dermatomyositis, acquired hemolytic anemia, interstitial cystitis, and Sjögren syndrome.\(^8\) The same study also found an overall increase in the presence of familial autoimmune disease in patients with schizophrenia, which suggests that in many cases schizophrenia shares a genetic diathesis with familial autoimmune disorders. Overall, this evidence implies a heritable link between these disease processes, but further research is needed to identify specific genes or loci.

**Immune priming and neurodevelopmental insults**

Immune priming refers to a theory that specific environmental factors that take effect during formative prenatal or early postnatal developmental windows can cause permanent changes to physiological, emotional, or physical functionality later in life. Recent studies suggest that early exposure to infection may induce sensitizing or preconditioning effects that lead to intensified reactions to infectious or noninfectious insults as an adult. One study showed that prenatal increases in the proinflammatory cytokine IL-8 were associated with an increased risk of schizophrenia in the offspring.\(^9\) This link could not only explain early susceptibility to mental illness but also illuminate the disruption during formative developmental periods that can change lifelong physiology.

Other theories of developmental predisposition to psychosis suggest that early prenatal insults can disrupt neurodevelopment, which leads to permanent changes in neuroanatomy, cognitive processing, and behavior—thus predisposing individuals to psychiatric disorders.\(^10\) Although it is difficult to make a direct correlation between a prenatal or early postnatal insult and a disease that typically is not diagnosed until the second or third decade of life, more extensive studies are needed to explore additional risk factors or environmental insults that could produce such neurodevelopmental differences.

**NMDA dysregulation**

\(N\)-methyl-\(d\)-aspartate (NMDA) glutamate receptor involvement has long been suspected in the pathophysiology of psychosis. In one study, autoantibodies to the NMDA receptor caused decreased rates of glutamate transmission, resulting in psychotic symptoms secondary to encephalitis.\(^11\) This supports not only the premise of glutamatergic modulation as a possible contributor to psychosis in schizophrenia, but also that the modulation can be provoked by atypical immunological function. Moreover, animal studies have found that excessive activation of proinflammatory cells of the CNS such as astrocytes and microglia can produce a kynurenic acid by-product, a substance that serves as a potent antagonist of glutamatergic NMDA receptors.\(^3\) Therefore, the possibility of multiple pathways of immunological disruption could contribute to an NMDA receptor component of schizophrenia.

**Inflammatory cells and receptors**

Recent research into the increased numbers of inflammatory cells in patients with schizophrenia offers additional support for inflammatory theories. In one study, cell lines in affected patients were
compared with those of healthy, matched participants. Patients with schizophrenia had higher levels of natural killer cells, monocytes, naive B cells, and memory T cells than healthy controls. These differences were particularly prominent in patients with primarily negative and cognitive symptoms, and in those with treatment-resistant disease. The results demonstrate a link between immune dysregulation and schizophrenia, and suggest that such dysregulation may contribute to symptoms that may not be easily treated by traditional dopamine antagonists.

Furthermore, the immune system’s monocytes and macrophages, controlled by toll-like receptors (TLRs) that mediate inflammatory responses, have been implicated. In a double-blind study, patients with schizophrenia and matched, healthy controls were exposed to a lipopolysaccharide to mimic bacterial infections and to polyI:C to mimic viral infections. Patients with schizophrenia showed an increase in TLR-3 and TLR-4 on flow cytometry and increased overall numbers of monocytes. These findings support the hypothesis of an increased inflammatory response and an abnormal response to normal environmental insults.

**Anti-inflammatory properties of antipsychotics**

One potential explanation for variable responsiveness to antipsychotics could be differences in the anti-inflammatory properties of these medications. Research on this topic shows variable results. Some studies have found increased levels of inflammatory markers with antipsychotic treatment, while others have found decreased levels or no change in levels. Findings suggest that antipsychotic drugs may have both direct anti-inflammatory and indirect inflammatory effects, depending on the weight gain associated with treatment.

A longitudinal study of patients treated with risperidone noted an initial decrease in IL-1β and IL-6 in the first 6 weeks, followed by a subsequent increase in levels, which mimics patients’ weight gain patterns. This could explain discrepancies among previous studies and demonstrates the importance of measuring timing of metabolic dysfunction when inflammatory markers and immune dysregulation are evaluated. Future studies should incorporate this information when investigating anti-inflammatory properties of medications that are currently first-line treatments for schizophrenia.

**Other anti-inflammatory treatments**

**COX-2 inhibitors**

Cyclooxygenase (COX) is a critical-step enzyme in the inflammatory process, which results in the direct production of inflammatory mediators. Specifically, COX-2 is responsible for the conversion of arachidonic acid to active prostaglandins that are direct mediators of fever, leukocyte recruitment, and vascular permeability.

In a double-blind, randomized trial, patients treated with COX-2 inhibitors (celecoxib) in conjunction with amisulpride (an atypical antipsychotic available in Europe) showed statistically significant improvement in both positive and negative symptoms of schizophrenia compared with patients treated with amisulpride and placebo. In another double-blind, randomized trial, patients with first-episode schizophrenic psychosis were treated with risperidone plus celecoxib or risperidone plus placebo. Those treated with the combination of an antipsychotic and a COX-2 inhibitor benefited particularly in negative and cognitive symptoms.

Studies that used other atypical antipsychotics have replicated these results, which supports the utility of this treatment with a variety of antipsychotics. However, one meta-analysis that compared NSAIDs with placebo for adjunctive treatment of schizophrenia showed only minimal and/or small effect size for positive symptoms. Although this finding suggests that NSAIDs adjunctive to first-line antipsychotics may not benefit patients with schizophrenia, further controlled studies are needed.

**Minocycline**

Minocycline is a second-generation tetracycline with both anti-inflammatory and antimicrobial effects through its inhibition of protein synthesis. In a double-blind, placebo-controlled trial, patients treated with antipsychotics in combination with minocycline showed statistically significant improvement in both negative symptoms and cognitive symptoms of schizophrenia, compared with patients who received antipsychotics plus placebo.

Specific anti-inflammatory benefits in the treatment of schizophrenia may involve decreased activation and proliferation of microglia, which mediate CNS inflammation and subsequent cytokine production. Other theories propose that minocycline as an adjunctive therapy could benefit patients with schizophrenia because of its inhibition of nitric oxide synthase in the glutamatergic system.

**Omega-3 fatty acids**

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the 2 principal omega-3 fatty acids found in fish oil. They are thought to exhibit anti-inflammatory properties through proteins known as resolvins, which bind to G-protein–coupled receptors on the surface of leukocytes and block their
production of inflammatory substances. Resolvins also prevent migration of leukocytes and block expression of inflammatory mediators on microglial cells.

A double-blind, randomized, controlled trial compared EPA, DHA, and placebo treatment in patients who were receiving antipsychotics but had residual symptoms. The results showed that EPA combined with antipsychotics was more beneficial than antipsychotic treatment combined with either placebo or DHA.20

Additional studies with other antipsychotics are needed to further define possible benefits of such combined treatments.

Conclusions
Old theories of schizophrenia, although widely accepted, do not completely explain its pathophysiology or effective treatments. With decades of antipsychotic treatment still associated with persistence of symptoms or subsequent relapse into psychosis, clinical research strives to increase novel treatment options. Although research into autoimmune and inflammatory theories of schizophrenia is in its infancy, it shows some promise in addressing more resistant problems, such as negative symptoms and cognitive deficits.

Future research should expand on pioneer studies of anti-inflammatory treatments, with a focus on efficacy in treating symptom types, first-onset psychosis, and treatment-resistant disease. Medications that block inflammatory pathways are safe and currently available to treat other disorders; thus, they offer the potential to treat mentally ill patients in desperate need of new options.

As evidenced by patients’ variable response rates to current antipsychotic treatments, the pathophysiology of schizophrenia should be reconsidered and broadened. The field of psychiatry has recognized for decades that mental illness is multifactorial in nature. It is time that we think beyond the traditional genetics, physiology, and social history of a patient.

There is strong evidence that a multitude of different pathways or combinations of pathways in schizophrenia could produce distinct subclasses of patients who respond variably to different therapeutic modalities. In the distant future, we may be further classifying schizophrenia into subtypes such as inflammatory, dopaminergic, glutamatergic, or genetically mediated. Identifying these subtypes could serve to create specialized treatment plans that reduce the rates of relapse and persistence of symptoms. Moreover, it could allow for earlier diagnosis of disease and identification of high-risk individuals, which could provide opportunities for earlier intervention and better patient outcomes.

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Disclosures:

Erin Walling is a fourth-year medical student at the University of Oklahoma College of Medicine, Oklahoma City; Dr. Tucker is Professor and Vice Chair of Education, Department of Psychiatry, University of Oklahoma Health Sciences Center, Oklahoma City.

References:


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