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Inflammation and Schizophrenia

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An association between inflammatory abnormalities and schizophrenia has been found repeatedly. The purposes of this special feature are to clarify the key findings on inflammation in schizophrenia, identify major gaps in the literature, and suggest priorities for research in this area.

What Is Inflammation?

Inflammation is one of the body's first lines of defense in response to injury or infection, and increased inflammation is found in many diseases. Acute inflammation is a nonspecific response characterized by warmth, pain, and swelling. Leukocytes migrate to the area of injury and become activated, the blood supply to the area increases, and blood vessels become more permeable, allowing cells and molecules to leave blood vessels and enter the injured tissue. The inflammatory response also involves the complement system, a group of proteins that, when activated, combine to form a complex molecular structure that kills cells, usually bacteria and parasites.

Cytokines are key molecules that regulate inflammation; they also have important roles in the immune system. They are produced by a wide variety of immune cells and cells outside of the immune system. The term cytokine derives from their ability to influence the movement of inflammatory cells, but they also have other functions.

Chronic inflammation is usually a lower grade response, lacks the grossly visible signs of acute inflammation, and may be systemic rather than localized. Chronic inflammation plays a role in the pathophysiology of many chronic diseases, including cardiovascular and cerebrovascular disease, diabetes, Alzheimer's disease, and some cancers.

The characteristics of chronic inflammation differ somewhat in the brain from what occurs in other tissues. An important component of neuroinflammation is the microglial activation. The brain contains relatively few of the inflammatory cells that are found outside the brain. Microglia, which are related to the peripheral inflammatory cells, serve some of the protective functions such cells play in the rest of the body. Microglia are involved in other brain functions, including the pruning and maintenance of synapses, trafficking of neurotransmitters, and devouring—phagocytosis—of cell fragments and damaged cells. Activated microglia produce inflammatory cytokines and the phagocytose cells or proteins that provoke the inflammatory response. Microglial activation and subsequent proinflammatory cytokine production may disrupt the blood-brain barrier (BBB). An intact BBB usually tightly controls the entry of cytokines and leukocytes into brain tissue. Damage to the BBB impairs its ability to control which inflammatory cells and molecules enter the brain; other substances leak into brain tissue, and the brain is unable to function normally.

Findings in Schizophrenia

A discussion of prenatal inflammation as a risk factor for schizophrenia is beyond the scope of the present special feature, and the reader is referred to previous reviews of human[1,2] and animal studies.[3–6]

Numerous studies have found that people with schizophrenia have increased blood concentrations of inflammatory cytokines.[7] Two important themes emerge from these studies. First, inflammatory abnormalities are present in subjects with first-episode, drug-naive psychosis (FEP) compared with controls, suggesting an association that may be independent of the effects of antipsychotic medications. Second, the concentrations of some inflammatory molecules may vary with the clinical status of patients: ie, there appear to be separate groups of state and trait markers. The state-related markers include interleukin (IL) 1-beta, IL-6, and transforming growth factor-beta. People

with schizophrenia have higher concentrations of these cytokines than controls during an exacerbation of symptoms, but there is no difference during periods of clinical stability. IL-12, interferon-gamma, and tumor necrosis factor-alpha (TNF-alpha) appear to be trait markers. Concentrations of these cytokines are higher in patients with FEP than in controls, and in patients with chronic illness, during both periods of symptomatic worsening, than in controls. C-reactive protein (CRP), another proinflammatory molecule, also appears to be a state marker,[8] and specific lymphocyte populations may also segregate into state and trait markers.[9] Additional evidence for potential state-related markers in schizophrenia has been reviewed elsewhere.[10] Two studies suggest that inflammatory molecules may predict subsequent relapse.[11,12]

Other studies have found abnormal levels of inflammatory parameters in the central nervous system (CNS) in schizophrenia, including cerebrospinal fluid (CSF) cytokine[11] and leukocyte levels,[13,14] CNS microglia and lymphocytes,[15–19] CSF and CNS oxidative stress,[20,21] and anti-*N*-methyl-*D*-aspartate receptor autoantibodies.[22] There is also evidence suggesting that infections may be associated with illness relapse.[23] Within schizophrenia, blood cytokine abnormalities have been associated with poorer cognitive function and measures of regional brain volume[24–26] and negative symptoms.[27–30]

Anti-inflammatory Treatment in Schizophrenia

There are several randomized clinical trials of the nonsteroidal anti-inflammatory drugs (NSAIDs) celecoxib and aspirin as adjuncts to antipsychotics.[31] Interpretation of this evidence is complex, as these studies have not consistently distinguished relapsed from clinically stable patients. Furthermore, if inflammation plays a role in psychotic relapse, the efficacy of anti-inflammatory treatments may "disappear" in a lengthy trial because the treatment would not have any effect once patients have returned to their clinical baseline. However, an adjunctive agent that accelerates a patient's antipsychotic response would be valuable.

Agents other than NSAIDs that have anti-inflammatory properties, used in adjunct to antipsychotics, have been found to be superior to placebo. There have been two trials of minocycline,[32,33] a second-generation tetracycline with anti-inflammatory and antimicrobial effects, that were superior to placebo. The efficacy of minocycline may have "disappeared" over the course of one trial,[33] raising the possibility of an effect restricted to relapsed patient and not in those at a stable baseline. Adenosine is a purine nucleoside that modulates many physiological processes and has anti-inflammatory effects. A meta-analysis found that adjunctive treatment with adenosine-modulating drugs is superior to the effects of placebo.[34] These drugs were associated with significant symptomatic improvement in inpatients, but not in outpatients, supporting the concept that state/trait differences may be an important predictor of antipsychotic response to adjunctive agents.

Oxidative stress refers to an increase in free radicals, highly reactive molecules generated from metabolism and environmental exposures that can damage cell membranes. Inflammation and oxidative stress strongly influence each other.[35] Antioxidant drugs decrease oxidative stress. One trial found that adjunctive treatment with the antioxidant *N*-acetylcysteine significantly reduced psychopathology in schizophrenia.[36] A trial of fish oil, which also has significant anti-inflammatory effects, was conducted in adolescents and young adults with subthreshold psychotic symptoms,[37] ie, "prodromal" patients. Patients receiving fish oil were significantly less likely to progress to a psychotic disorder than subjects receiving a placebo. Interestingly, fish oil was prescribed for 12 weeks, but the protective benefits with regards to transition to psychosis remained significant for 40 weeks after cessation of treatment.

Why Would People With Schizophrenia Have Increased Inflammation?

Inflammation may be a common mediator of diverse prenatal risk factors for schizophrenia, including preterm labor; preeclampsia (pregnancy-induced hypertension); neonatal birth asphyxia; and maternal gestational diabetes, stress, and depression.[2] Maternal serum concentrations of the cytokines IL-8[38] and TNF-alpha[39] during pregnancy were associated with an increased risk of schizophrenia in the offspring. Animal studies suggest that inflammation during critical periods of neurodevelopment may permanently alter the "set-point" of the inflammatory system, with increased inflammation in adult offspring.[40–45]

Meta-analyses have confirmed the presence of other abnormalities in schizophrenia that are associated with inflammation: increased autoantibodies,[22] oxidative stress,[46] CRP,[8] and circulating lymphocytes.[9] Antibodies are crucial "weapons" the immune system uses against foreign proteins. Autoantibodies, antibodies against a person's own proteins, are associated with cytokine abnormalities.[47] Lymphocytes, a group of white blood cells that combat infections, produce antibodies, and are an important source of cytokines, are increased in schizophrenia.[9] Some subsets of lymphocytes may be state markers for acute psychosis, whereas others may be trait markers.[9] CRP is a protein synthesized by the liver in response to inflammation, particularly IL-6 and other cytokines. Inflammation and oxidative stress may contribute to the decreased blood and CNS membrane levels of polyunsaturated fatty acids observed in schizophrenia.[48]

Is Peripheral Inflammation Related to Brain Function?

There are other disorders outside of schizophrenia in which peripheral inflammation appears to impact brain function. Inflammation is a risk factor for Alzheimer's

disease and mild cognitive impairment,[49] rheumatoid arthritis is a risk factor for dementia,[50] and "sickness behavior" is induced by peripheral cytokines.[51,52] Depression is also associated with increased inflammation.[53] The effects in depressed patients of an antibody against the cytokine TNF-alpha[54] support the concept that brain function is impacted by peripheral cytokines.

There are other mechanisms by which peripheral inflammation might cause or reflect brain dysfunction in schizophrenia. Cytokines may directly modulate dopaminergic neurotransmission[55–57] or indirectly modulate glutamatergic neurotransmission through tryptophan metabolism.[58–61] There is also some movement of peripheral leukocytes into the brain parenchyma, and the interaction of cytokines with the vagus nerve influences brain function.[62] Blood cytokines induce cytokine production in the cells that form the BBB, and cytokines may move into the brain via the circumventricular organs, which lack a BBB.[62] Inflammation may also disrupt the BBB, resulting in abnormal trafficking of cells and inflammatory molecules between blood and brain. Some have suggested that the increase in blood concentrations of the protein S100-beta in schizophrenia[63] is consistent with abnormal function of the BBB in people with schizophrenia, resulting in abnormal trafficking of cells and inflammatory molecules between blood and brain. However, circulating S100-beta has sources other than the brain.[64,65]

Potentially Confounding Variables

Several potentially confounding variables are important to consider in studies of inflammation. Antipsychotics increase the risk of weight gain and diabetes, which are associated with inflammation. However, there is evidence from meta-analyses of abnormal inflammatory parameters in FEP,[8,9,22,46] suggesting that the association between schizophrenia and inflammation is not solely due to antipsychotics. Antipsychotic-naïve relatives of people with schizophrenia also have increased inflammation compared with controls.[66–68] Other potentially confounding variables include body mass index, age, gender, smoking, alcohol and illicit drug use, and whether patients are fasting at the time of sampling.[69] The proportion of studies that either matched patients and controls, or statistically controlled for many of these potential confounders, has been low.[8,9,22,46]

Inflammation is comorbid with other physiological abnormalities, including hypertension, impaired glucose tolerance (fasting blood glucose [FBG] 100–126 mg/dl), diabetes (FBG > 126, or a random blood glucose >200 mg/dl), and increased oxidative stress. The associations with these other conditions also support the plausibility of increased inflammation in schizophrenia. However, the comorbidity of these physiological measures in schizophrenia complicates the interpretation of adjunctive treatment trials: what is the best therapeutic target?

Another complicating issue is the relationship of inflammation to neurotropic viruses. One study found that treatment of patients with antibodies to herpes simplex 1 virus with a herpes-specific antiviral drug improved cognition with impressive effect sizes, suggesting the presence of an ongoing problem related to the virus.[70] The association of other infectious agents with schizophrenia also raises the question of what relationship might exist between inflammation and either chronic infections or the expression of genes derived from an infectious agent and integrated into human DNA.

Implications for Schizophrenia Research

The background presented above can be used to guide future research.

1. Attempts to replicate current findings in well-matched patients and controls would be helpful.
2. Cytokine levels in subjects with prodromal psychosis have not been investigated. We would hypothesize that these subjects should have abnormal trait markers compared with controls; within prodromal subjects, those who develop clinical psychosis should have abnormal state markers compared with high-risk subjects who do not. The effects of fish oil in preventing conversion to psychosis in high-risk subjects should be investigated in relationship to its effects on inflammation.
3. The therapeutic anti-inflammatory agents that have been studied to date, such as aspirin, celecoxib, and fish oil, have multiple actions. Specific antibodies against individual cytokines are used in the treatment of rheumatoid arthritis and have been studied in depression.[54] A change in symptoms or cognition in response to these antibodies would directly implicate inflammation in the pathophysiology of schizophrenia.
4. More longitudinal studies with serial measurement of inflammatory parameters across the clinical course of illness are needed.
5. It would be useful to test the hypothesis that patients with treatment-resistant schizophrenia have a different inflammatory profile than other patients with schizophrenia.[7]
6. Although it seems likely that there is increased inflammation in the brain when there are cytokine increases in the peripheral blood, the response might not be exactly the same in these two compartments. For instance, the inflammatory cytokines with altered levels in the brain might not be the same as those that change in the blood. More studies of markers of inflammation in the CNS—including CSF, postmortem analyses, and imaging studies—are needed.
7. Two strategies may increase the signal-to-noise ratio for adjunctive trials of anti-inflammatory agents.

First, inflammation may play a role in some patients with schizophrenia but not others. Patients with evidence of inflammation in the peripheral blood may be more likely to respond to an anti-inflammatory treatment strategy than those without inflammation and should be the ones included in treatment studies. Second, acutely ill and stable patients should be studied in separate trials and considered separately in meta-analyses. Furthermore, baseline-to-end-point analyses may not appropriate for studies of relapsed patients because there may be faster improvement with the use of adjunctive anti-inflammatories but not a greater total improvement by the end of the study.

8. Studies of inflammation in schizophrenia should assess possible relationships of inflammatory cells and molecules to symptoms and cognition. To date, few studies have considered these measures.[8,9,22,46]
9. The comorbidity of inflammation, oxidative stress, hypertension, and abnormal glucose concentrations raise the issue what is the most appropriate treatment target in schizophrenia. As a first step in understanding this issue, it would be helpful to investigate relationships between inflammation, oxidative stress, hypertension, and glucose intolerance on the one hand, and clinical variables on the other.
10. Several studies found that first-degree relatives of people with schizophrenia have increased inflammation and oxidative stress.[66–68] It would advance the field to test the hypothesis that relatives have abnormal concentrations of the trait markers for schizophrenia but not of the state markers associated with relapse.
11. Inflammatory molecules do not work in isolation but have complex interactions among themselves and with other systems. Most previous studies have measured only a small number of molecules. Concurrent measurement of cytokines, leukocytes, oxidative stress, and related parameters would increase the ability to make broader inferences regarding inflammation. Furthermore, if groups or clusters of covarying molecules—ie, molecules that change simultaneously—could be defined within schizophrenia, investigation of these groups is likely to yield better signal-to-noise ratios than individual molecules and should have more biological validity.
12. Does increased inflammation due to infections or physical trauma increase the risk of relapse? If so, do preventive measures (eg, antibiotic prophylaxis for recurrent urinary tract infections)[23] decrease that risk?
13. What is the relationship between inflammation and the presence of antibodies to herpes viruses, toxoplasmosis, etc?

Although the evidence on inflammation in schizophrenia is provocative, the number of studies in some areas is small, and increased methodological rigor is needed. Nonetheless, the evidence from FEP and first-degree relatives of patients with schizophrenia supports the idea that increased inflammation is truly associated with schizophrenia. This research raises the possibility that further study of inflammation will lead to greater understanding of the etiology and pathophysiology of schizophrenia.

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