HARVARD MEDICAL SCHOOL

Harvard Mental Health Letter

VOLUME 26 • NUMBER 4 | OCTOBER 2009

Infection, inflammation, and mental illness

The body's immune response to infectious agents may imperil the brain.

For more than a century, researchers have explored whether infectious agents might trigger some types of mental illness, particularly schizophrenia. For the most part, however, these theories rested on studies that proved only an association between certain infections and mental disorders, not cause and effect.

But in the past decade, researchers have produced a growing body of observational and biological evidence suggesting that the body's defensive immune response, rather than the infection itself, may be what damages the brain. Further, chronic stress may activate a harmful immune response, even in the absence of infection. Although the research remains preliminary, the findings could suggest a new approach to treatment.

Immune privileged—or influenced?

The immune system functions in part by unleashing inflammatory cells that identify and destroy viruses, bacteria, and other causes of disease. But this formidable firepower may kill healthy tissue along with foreign invaders.

In the brain, this would be devastating, because brain cells do not regenerate as well as cells located elsewhere in the body. The traditional view has been that the brain is "immune privileged," or protected in various ways from inflammation's onslaught.

But this view has been challenged on two fronts. First, consensus now exists that the brain's immune privilege is not absolute, but rather a regulatory system that sometimes malfunctions. One example is the neurodegeneration evident in multiple sclerosis, in which the immune system attacks the myelin sheath around nerve extensions.

Second, a growing body of research suggests that the immune system may support brain health in several ways. One study in mice, for example, found that the complement cascade, a biochemical pathway that helps clear disease-causing invaders from the body, may also help to prune synapses in the brain. Other research has found that an immune system enzyme, indoleamine 2,3-dioxygenase (IDO), affects circulating levels of tryptophan, an amino acid that is a precursor to the neurotransmitter serotonin in the brain. Such insights into the immune system's contribution to brain health have renewed interest in how its activation in response to infection or chronic stress might contribute to brain disorders.

KEY POINTS

- Research suggests that the immune system supports brain health in several ways.
- Activation of certain immune system cells in response to an infection, or on an ongoing basis (chronic inflammation), may contribute to mental illness in different ways.
- Studies are under way to evaluate the use of anti-inflammatories in treating depression and schizophrenia.

Sickness behavior and depression

Much of the research has focused on immune system proteins known as cytokines that initiate and orchestrate an inflammatory attack on viral or bacterial invaders. These proteins are also the main instigators of what researchers refer to as "sickness behavior"—loss of appetite, fatigue, sleep disruptions, and depressed mood.

Sickness behavior fosters healing, as it encourages people to slow down and allow the immune system to combat pathogens. ▸▸

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Given the similarity between sickness behavior and symptoms of depression, however, some researchers now think cytokines or other components of the immune system might also trigger at least some cases of this mood disorder.

Evidence. A link between immune system activation and depressed mood would help explain what many observational studies have reported: depression is more common in patients with type 2 diabetes, rheumatoid arthritis, and coronary artery disease—all of which involve chronic inflammation—than it is in people in the general population. It would also explain why interferon alpha, a synthetic cytokine used to ramp up the immune system of patients with cancer or hepatitis C, causes depression in 30% to 50% of patients, depending on the dose used.

Of course, such observational studies document only an association between cytokine elevation and depression, not cause and effect. But a 2006 review identified 17 studies that reported elevated levels of various cytokines or other biological signs of inflammation in the blood or spinal fluid of patients with major depression who were otherwise healthy.

More recently, the Leiden 85-plus Study, a prospective longitudinal study in the Netherlands, measured blood levels of six biological markers of inflammation when each of the 267 participants first entered the study, at age 85. Five years later, the researchers found that elevated baseline levels of three blood markers of inflammation—C-reactive protein (CRP) and two cytokines—preceded the development of depression in participants whose mood had been normal when they entered the study.

Possible mechanisms. Cytokines and other immune system molecules may contribute to depression in several ways. For example, cytokines affect the synthesis, release, or reuptake of dopamine, serotonin, and other neurotransmitters. They stimulate the release of hormones involved in the hypothalamic-pituitary-adrenal axis, which underlies the stress response. They also affect the brain's ability to nourish and support neurons and the synaptic connections between these brain cells, which enables learning and memory.

Treatment implications. About one in three patients with depression experiences only partial relief of symptoms from current drug therapies—or does not respond at all (see *Harvard Mental Health Letter,* August 2008). Researchers now think that understanding the role of inflammation in depression may help them improve treatment.

Preliminary research suggests that patients with increased blood levels of inflammatory cells are less responsive than other patients to antidepressant treatment. Likewise, a handful of early studies suggest that some anti-inflammatory drugs might help treat depression.

For instance, two small studies have found that combining an antidepressant with some type of anti-inflammatory drug improves mood in patients with major depression more than an antidepressant alone. Larger and better-controlled studies are necessary, however, before clinicians will know whether this is something to recommend for their patients.

Inflammation and schizophrenia

Over the years, researchers have linked many infectious agents to an increased risk of schizophrenia and other psychotic disorders. But it's never been clear which infectious agents were the most important, or how they might cause psychosis and other symptoms of schizophrenia.

A review of five studies, for example, showed that individuals with newly diagnosed schizophrenia were more likely than controls to have antibodies to Cytomegalovirus, which spreads through breast milk, saliva, and other bodily fluids. And multiple reports have implicated the influenza virus.

Meanwhile, a meta-analysis of 23 studies found that patients with schizophrenia were nearly three times as likely as controls to be infected with *Toxoplasma gondii*, a parasite transmitted through

cat feces or contaminated soil or water. More recently, scientists at the Walter Reed Army Institute of Research examined blood samples collected from soldiers both before and after a diagnosis of schizophrenia and compared them with blood samples from controls. Although they looked for evidence of nine types of infections, only a pre-diagnosis infection with *T. gondii* increased the chance of developing schizophrenia.

Common pathology. Because multiple pathogens have been implicated in schizophrenia, researchers started trying to identify a common pathological process that might occur in response to infection. As with depression, the focus has turned to inflammation.

One body of evidence suggests that prenatal exposure to maternal infection may activate cytokines and other elements of inflammation—in either the fetus or the mother. This short-term or "acute" inflammatory response has long-term consequences for the fetal brain, which is actively developing. Although the exact mechanism of damage is not known, one theory is that acute inflammation causes abnormalities in apoptosis, a form of programmed cell death that prunes unnecessary nerve cells, making brain functioning more efficient. The result could be the type of abnormal thinking seen in schizophrenia.

A separate body of evidence implicates chronic inflammation later in life, based on studies that have found that patients with schizophrenia have higher blood levels of inflammatory chemicals than controls do. The thinking is that chronic inflammation may contribute to symptoms of schizophrenia—particularly the difficulties in thinking that tend to emerge as the disease progresses—in one of two ways. Inflammation causes irregularities in blood flow (a condition known as vascular dysregulation), so that the brain may be deprived of sufficient oxygen and nutrients. Another leading theory is that inflammation causes insulin resistance and other metabolic problems, so that the brain cannot adequately metabolize blood sugar for energy.

However, the research on the impact of chronic inflammation later in life has been inconsistent, with some studies finding no difference in inflammatory biomarkers that would differentiate patients from controls. This may reflect the heterogeneity of schizophrenia. And because inflammatory cells and proteins may become activated at times of mental distress, it's possible that elevated levels of inflammatory biomarkers are a consequence rather than the cause of schizophrenia.

It's also likely that some individuals are more vulnerable than others to damage from inflammation. A recent large genetic study found that patients with schizophrenia had alterations in the area of chromosome 6 that contains genes important for normal immune system functioning.

Therapeutic implications. Although it's not yet clear if chronic inflammation contributes to symptoms of schizophrenia, there is evidence that it may affect response to treatment. Preliminary studies in patients with schizophrenia have suggested that elevated markers of inflammation predict poorer response to medication and more severe symptoms.

For example, a study of 79 patients with schizophrenia found that those with higher baseline spinal fluid levels of a biological marker of inflammation, interleukin-2 (IL-2), were more likely than other patients to experience a worsening of psychotic symptoms after they temporarily stopped treatment with haloperidol (Haldol). Another study followed 78 patients with schizophrenia who were treated with risperidone (Risperdal) or haloperidol for 12 weeks. Patients whose baseline blood levels of IL-2 were lower were more likely to improve with drug treatment than those whose baseline levels were higher. In another study, researchers found that patients whose blood levels of CRP were above the normal range had worse psychotic symptoms than those whose CRP levels were normal.

Because so much evidence suggests some type of role for inflammation in schizophrenia, several research teams are currently exploring whether it's possible to improve treatment response by adding various anti-inflammatory drugs to antipsychotic therapy. So far, the results of preliminary studies have been mixed—but the research continues and may produce a clearer answer in the next few years.

Other mental disorders

In the wake of the growing evidence of the role of infection and the immune response in depression and schizophrenia, scientists are also investigating the potential link with other mental disorders, including autism spectrum disorders and bipolar disorder. Whether a connection exists remains to be seen, but the question about the potential role of microbes in mental illness remains as provocative today as it was more than a century ago.

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For more references, please see www.health.harvard.edu/mentalextra.