

“Imagine what happens when instead of protecting our cells, the immune system attacks our own cells...”

Schizophrenia and the Immune System

By Kathleen Jacobs

We commonly think of the immune system as protecting us from the cold, flu, or bacterial infections. But imagine what happens when instead of protecting our cells, the immune system attacks our own cells: autoimmune disease. Common examples include lupus, rheumatoid arthritis and diabetes; all these diseases are characterized by attack on and degeneration of specific native tissues (1).

Schizophrenia is a devastating mental illness, characterized by debilitating hallucinations, paranoia, and delusions, that affects one percent of the world's population (2). Current research primarily focuses on the neurochemical and biological pathology of schizophrenia. But a subset of research has taken a decidedly different approach. This research postulates that, in at least some cases, the immune system causes the disastrous psychotic symptoms of schizophrenia. This autoimmune hypothesis describes that somehow the immune system is triggered to attack the brain, producing neurodegeneration and inflammation. For nearly a century, an autoimmune basis for schizophrenia onset and progression has been proposed. This hypothesis continues to grow stronger as more

markers of immune dysfunction are linked to schizophrenia.

Beginning to Describe Schizophrenia

Schizophrenia has long perplexed scientists and non-scientists alike. Accounts of schizophrenia are found throughout history, but it was not until the late 1800s that the illness was identified as separate from other psychoses. In

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1911, Eugene Bleuler gave it the name “schizophrenia,” meaning “split mind,” though this should not to be mistaken for the notion of a split personality (3). Symptoms of schizophrenia are

classified according to a Negative and Positive Symptom scale. Negative symptoms are characterized by the loss of motivation, impaired concentration, and the inability to express emotions, while positive symptoms include hallucinations, anxiousness, and distorted perceptions of reality (3,4).

Physicians rely upon the recognition of these symptoms to diagnose schizophrenia since there is no biochemical test that can identify the disease (5). Researchers are still in the beginning stages of understanding the biological basis of schizophrenia. Much of our current understanding of the disease is thanks to the accidental discovery of antipsychotic drugs. The observation that a class of dopamine receptor inhibitors effectively treats positive systems led to the classic “dopamine hypothesis,” which states that schizophrenia is caused by an excess of dopamine in the brain. While dopamine modulates a number of brain functions, it is commonly associated with the ‘pleasure system.’ Addictive drugs cause increased dopamine release, producing a pleasurable reward that encourages continued drug use (6). In fact, the observation that some amphetamine addicts eventually develop psychotic

symptoms similar to schizophrenia reinforces the dopamine hypothesis. However, this postulation is weakened by the fact that other drugs that do not act at dopamine receptors are equally or often more effective. It is now thought that the excess dopamine must be interrelated with a decreased activity of the excitatory neurotransmitter glutamate at NMDA receptors in the brain (5).

But the presence of neurotransmitter imbalances is only one facet of schizophrenia. It does not explain the strange observations of the immune system in schizophrenic patients.

Linking Schizophrenia to Autoimmunity

Schizophrenia as an autoimmune disease was first theorized based on observed commonalities between the

onset and progression of well-known autoimmune diseases and that of schizophrenia. They both usually begin in late adolescence or early adulthood, and can be triggered by stress or viral infection (3). They also tend to have chronic, but episodic disease progression characterized by periods of apparent intermission and periods of disease 'flare-ups' (7). Of course, this alone cannot categorize schizophrenia as an autoimmune disease. An autoimmune disease occurs when the body overgenerates antibodies for its own tissues, or so-called autoantibodies. Antibodies are produced by B cell lymphocytes in response to infection by a foreign substance, or antigen, including bacteria and viruses. They act as a kind of memory bank by storing information about past infections, allowing the body

to quickly recognize and attack an antigen should it reappear (8). Everyone has a certain level of autoantibodies; but in an autoimmune disease, this level increases to a pathogenic level.

Researchers reason that if high levels of autoantibodies are found in schizophrenic patients, then it must be an autoimmune disease. In support of this, elevated autoantibodies have been found in the blood and cerebral spinal fluid (CSF), which bathes the brain and spinal cord, of schizophrenia patients (9). Even specific autoantibodies have been identified in the blood. Antibodies have been found against the hippocampus (memory consolidation), amygdala (fear and emotion), and frontal cortex (movement and olfaction) (10). In addition, antineuronal and anti-myelin antibodies have been identified (2). The

latter is important because myelin acts as support for neurons and accelerates neuronal messaging; without myelin, neurons cannot survive and cognitive functioning declines (10). However, researchers have not consistently found high levels of autoantibodies across patients, and some have not been able to duplicate past findings of specific antibodies. Schizophrenia as an autoimmune disease could be clearly proved by taking the autoantibodies of a schizophrenia patient and injecting it into a mouse or other test animal. If that animal subsequently manifests symptoms of schizophrenia, then it is indeed an autoimmune disease (3).

Although no such direct evidence has yet been found, there is strong evidence of a connection between the immune system and the brain. Systemic lupus erythematosus, an autoimmune disease that has a clear connection with pathological autoantibodies, can produce psychiatric complications including dementia and seizures (11); conversely,

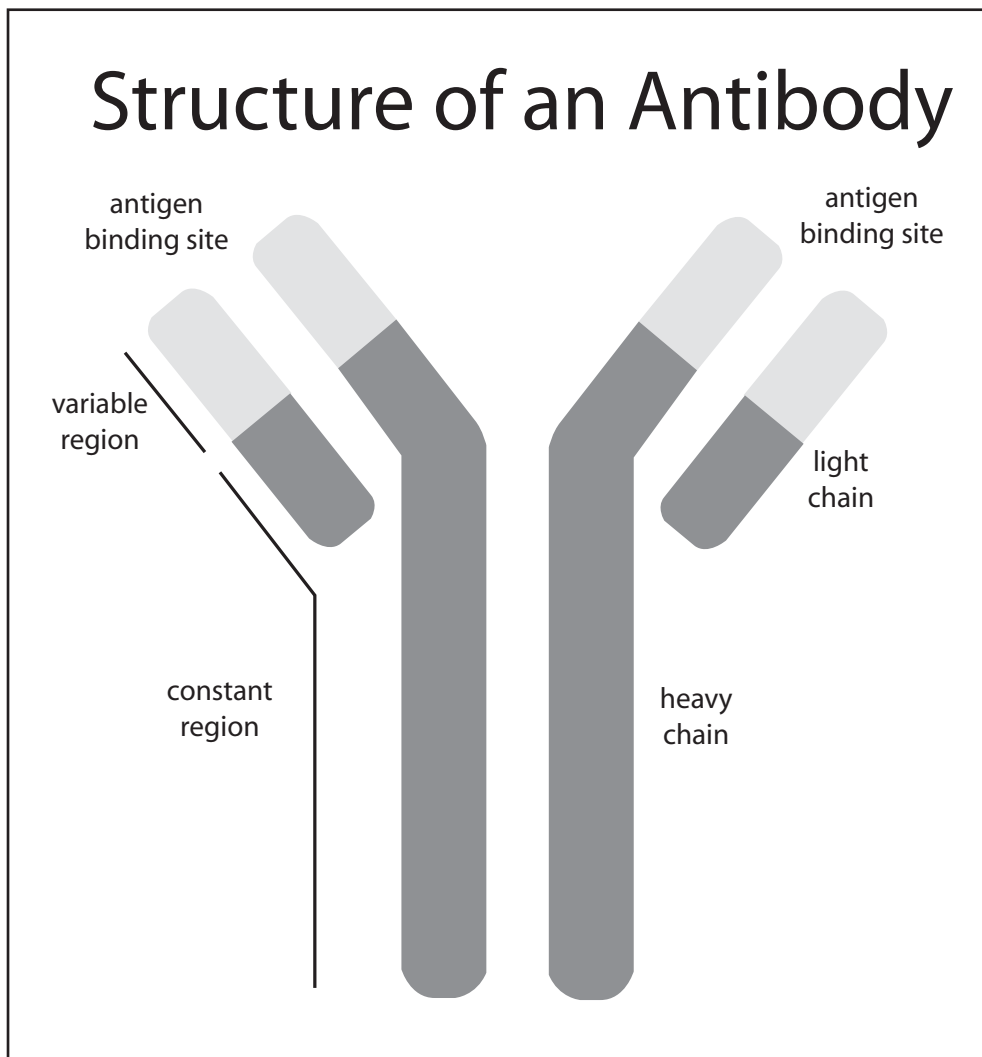


Figure 1. Diagram depicting characteristics of antibody structure.

schizophrenic patients are susceptible to developing lupus (3). It has also been shown that anti-DNA antibodies, the marker of lupus, can associate with NMDA receptors and induce neuronal apoptosis, or cell death. This association between lupus and schizophrenia suggests that there is a common immune dysfunction that predisposes patients to develop schizophrenia, given lupus, or vice versa (11).

A link between immune deficiency and cognitive dysfunction has also been observed in mice. When mice were deprived of mature T cell lymphocytes, which promote immune response, they performed poorly on standard cognitive tests including the water maze, a test of memory. When the T cells were replenished, normal performance slowly returned (4). An explanation for how T cells could interact with the brain to produce such effects remains unknown.

Breaking the Blood Brain Barrier

The above evidence of autoantibodies and a link between cognitive abilities and the immune system suggests that the blood brain barrier (BBB) can be infiltrated by the immune system. This presents a problem for the autoimmune hypothesis. The BBB, which protects the central nervous system (CNS), is impermeable to lipid-soluble compounds, but allows passage of water-soluble compounds. This means antibodies are generally excluded from the CNS and a disturbance of the BBB would be required for penetration by autoantibodies or most other factors of the immune system (12).

There has been recent evidence which shows disruption of the BBB in schizophrenic patients. Activated lymphocytes have been found in the CNS.

These cells have dispersed chromatin and enlarged nuclei, which are morphological indicators of lymphocytes that have been stimulated in response to an infection (13). In addition, Muller reported that schizophrenia patients with lymphocytes in the CNS have higher levels of sICAM-1, a cell adhesion protein that aids infiltration of lymphocytes through vessel walls (12). Therefore, in those patients with active immune components in the brain, there must also be other proteins

abnormally expressed to assist with the attacking of the brain.

A common marker of active infection is inflammation produced by cytokines, which are released by macrophages that have been activated by an antigen. In some schizophrenic patients, there are elevated levels

of interleukin-6 (IL-6), a cytokine that activates B cell lymphocytes, promoting antibody production and the release of other proteins that contribute to an inflammatory response. These elevations were found in both the blood and the CSF. Patients on antipsychotic medication versus non-medicated patients tended to have variable levels of IL-6 in the blood, but the levels remained elevated in the CSF independent of medication (7). This leads to the conclusion that inflammatory factors can pass the BBB. These observations of activated lymphocytes and BBB penetration by cytokines are curious because even though blood tests and lymphocyte morphology support the presence of an infection, schizophrenic patients do not show any clinical signs of active inflammation.

Conclusion

The current problem with the autoimmune hypothesis is that the battery of evidence is mostly circumstantial: observations of inflammatory mark-

ers and increased autoantibodies in a certain group of patients do not equal autoimmune disease. However, even if schizophrenia may not be classified as an autoimmune disease, it is clear that the biochemical consequences of schizophrenia are not exclusive to neurotransmitter depletion or neurological morphology. We can conclude that schizophrenia can either affect the immune system, or immune dysfunction can manifest schizophrenic symptoms. The effects of our immune system are not limited to fighting infections, even though this is its evolutionary purpose—malfunctions can have extensive destructive consequences in our tissues, including the brain. **H**

—Kathleen Jacobs '08 is a Biochemical Sciences concentrator in Pforzheimer House.

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