The blood-brain barrier (BBB) is an essential barrier of closely spaced cells that regulates entry into the CNS. What passes should be highly regulated to protect the brain from potentially harmful peripheral cells or molecules from the rest of the body. However, research has revealed that the BBB is pathologically permeable in several disease states, including schizophrenia, epilepsy, traumatic brain injury, autism, and DiGeorge syndrome (22q11.2 deletion syndrome, which often presents with symptoms of schizophrenia). In this article, we discuss potential markers of BBB dysfunction, the consequences of a porous BBB, the effect of BBB permeability on microglial activation, and possible treatment implications.

Detecting a BBB leak

The BBB is composed of microvascular endothelial cell units. Adherens junctions, astrocyte endfeet, and pericytes are all part of these units, but tight junctions have the most significant role in BBB barrier function. Tight junction protein composition varies depending on the location of the endothelium. In the BBB, they are primarily composed of claudin-5, occludin, zonulin, and junction adhesion molecules (JAMs) (Figure, page 29). Claudins and occludins are especially important components of the tight junction because they span plasma membranes.

Researchers began to suspect tight junction permeability in schizophrenia while searching for schizophrenia biomarkers. For example, S100B is a marker of astrocytic reactivity to damage. It is increased in schizophrenia, major depressive disorder, and bipolar disorder. Studies found elevated S100B specifically in drug-free patients with schizophrenia, which prompted research suggesting it could predict the severity of negative symptoms. The accuracy of S100B as a biomarker was later complicated by the finding that adipose tissue also secretes S100B. This is problematic due to the high rates of comorbid obesity in psychiatric populations.

Perhaps a better biomarker is the ratio of albumin in the CSF vs that in peripheral serum. The CSF-to-blood albumin ratio (Q-Alb) is widely considered an acceptable marker of BBB dysfunction because albumin must cross the BBB to alter the ratio. Studies have found a high Q-Alb in neurodegenerative disorders such as multiple sclerosis as well as in schizophrenia, which suggests that some level of BBB dysfunction is occurring. Although the Q-Alb may change slightly when confounded by antipsychotic use or with CSF flow changes, both S100B and Q-Alb elevation are sufficient for further investigation into tight junction alteration in schizophrenia.

Claudin-5 is a promising factor in detecting BBB permeability. Claudin-5 is deleted in...
DiGeorge syndrome, which is highly comorbid with schizophrenia and psychosis. Mouse knockdown studies show that full suppression of claudin-5 results in psychotic symptoms before fatal seizures, but a partial absence may enable psychotic symptoms. The same study showed that normally continuous claudin-5 was patchy along blood vessels in the affected sample. Follow-up experiments suggest that loss of claudin-5 in schizophrenia is especially prominent in the hippocampus, and there is mixed evidence of a decrease in the prefrontal cortex.

Outside of claudin-5 alone, JAM-A plays a more regulatory role. It is upstream from an enhancer protein gene that serves as a transcription factor for the claudin-5 promoter, so when JAM-A is deleted, there is less claudin-5. However, while this decrease in claudin-5 may be pathological, there could still be various upstream changes that lead to schizophrenia.

What are the consequences of a porous BBB?

Although it is well established that the BBB passes small molecules and solutes, there is significant evidence of inflammatory trafficking in disease states. The BBB moves proinflammatory cytokines, alters transporters, and may even let white blood cells (WBCs) pass through. Immune cell infiltration has different requirements depending on the cell type. T cells rely on integrins, vascular cell adhesion molecule 1 (vCAM1), and intercellular adhesion molecule 1 (iCAM1) for binding, rolling, adhering, crossing, and migration to sites of inflammation. Both iCAM1 and vCAM1 are elevated in schizophrenia compared to other psychiatric disorders (such as unipolar depression) and correlate with other biomarkers. For example, vCAM1, responsible for recruitment and crossing, is correlated with a high Q-Alb. Primarily produced by astrocytes and endothelial cells, iCAM1 plays the largest role in crossing the BBB and migration. Postmortem tissue demonstrates that cytokines upregulate iCAM1 mRNA at the BBB in schizophrenia. Increased cytokines are well documented in the inflammatory model of schizophrenia. Interestingly, decreasing claudin-5 also upregulates iCAM1 production. Therefore, low baseline claudin-5 may contribute to additional inflammation and symptoms.

BBB permeability also results in a certain pattern of leukocyte and cytokine activity. Interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha can all cross the BBB during neuroimmune inflammation, but there are abnormal heightened and sustained...
responses of these molecules in schizophrenia. IL-6 is a proinflammatory cytokine in both acute and chronic inflammation that is expressed by astrocytes, endothelial cells, and microglia. IL-6 and its soluble receptor are both elevated in schizophrenia and are associated with white matter degeneration and an increase in vCAM1. This implies that while neuroinflammation in schizophrenia is occurring, additional leukocytes are being recruited and secreting their own cytokines in a chronic destructive positive feedback loop. Meanwhile, atypical IL-10 levels can no longer maintain balanced levels of inflammatory molecules, which leads to reduced control of inflammation.

Genetics and immunohistochemistry suggest that the BBB allows the passage of excess B cells and T cells in schizophrenia. Cytokines from WBCs or the BBB during inflammation recruit these additional infiltrating lymphocytes. In gene-wide association studies, there are several genes in schizophrenia important for B cells and T cells in addition to inflammation that interact in a proinflammatory network. These cells are also diffusely found in the white matter and hippocampal tissue of patients with schizophrenia. Taken together, an increased access to cytokines in schizophrenia and increased migration across the BBB may keep the TRegs hypofunctional in schizophrenia and promote T cell conversion to inflammatory cell types. Experimentally, TReg induction reversed some psychotic symptoms, and greater TReg expression was associated with fewer negative symptoms. In an already insufficient BBB, more access to cytokines and leukocytes would sustain inflammation and microglial secretions.

In addition to the issues described regarding the BBB, the blood-CSF barrier at the choroid plexus may also be insufficient in schizophrenia.

Caveats about this research
There are 3 important points to note about the current research concerning abnormal BBB permeability:

1. BBB dysfunction may exist only in a subset of people diagnosed with schizophrenia. In most human studies, only some patients with schizophrenia demonstrated alterations that suggested pathological BBB permeability. In addition, even when there is BBB dysfunction, it could be a secondary phenomenon, rather than a primary etiologic process.

2. Patient demographics across studies have not always been adequately...
The choroid plexus’ primary role is to make CSF, but it also secretes cytokines and to some extent serves as a barrier. Unlike the blood-brain barrier (BBB), the blood-CSF barrier is composed of endothelial cells with fenestrations as well as tight junctions, which make the blood-CSF barrier overall more permeable. The most unusual finding regarding the choroid plexus in schizophrenia is size. The choroid plexus is physically larger in patients with schizophrenia, and to a lesser extent, in their first-degree relatives. A larger choroid plexus is correlated with more severe cognitive symptoms, increased risk for psychosis via biological stress, and neurosteroids, N-acetylcysteine, statins, and estrogen—show replicable improvement in symptoms of schizophrenia, but we know these abnormalities are not universal and currently there is no marker for determining which individuals might benefit from one of these treatments over another. Antipsychotics have also been found to alter adhesion molecules, claudin-5, and cytokine levels, but more research must be conducted to tease out the differential effects of first- vs second-generation antipsychotics.

### Treatment implications

One of the first treatment directions that comes to mind is managing the gaps in the BBB via tight junctions. Presently, there are no FDA-approved medications for altering tight junction proteins, but researchers are exploring potential agents that can induce claudin-5 and reduce inflammation. While we wait for such a medication, patients may benefit from existing anti-inflammatory treatments to control immune infiltration and its products. Various anti-inflammatory agents—including cyclooxygenase inhibitors, minocycline, and cytokine levels, but we know these abnormalities are not universal and currently there is no marker for determining which individuals might benefit from one of these treatments over another. Antipsychotics have also been found to alter adhesion molecules, claudin-5, and cytokine levels, but more research must be conducted to tease out the differential effects of first- vs second-generation antipsychotics.

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### References


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**Box**

**Choroid plexus permeability in schizophrenia**

The choroid plexus’ primary role is to make CSF, but it also secretes cytokines and to some extent serves as a barrier. Unlike the blood-brain barrier (BBB), the blood-CSF barrier is composed of endothelial cells with fenestrations as well as tight junctions, which make the blood-CSF barrier overall more permeable. The most unusual finding regarding the choroid plexus in schizophrenia is size. The choroid plexus is physically larger in patients with schizophrenia, and to a lesser extent, in their first-degree relatives. A larger choroid plexus is correlated with more severe cognitive symptoms, increased risk for psychosis via biological stress, and significantly higher interleukin-6 (IL-6). The increased thickness could be an attempt to compensate for hyperactivity and toxic processes in a permeable environment. More circulating cytokines such as IL-6 and tumor necrosis factor-alpha from microglia can trigger an increase in intercellular adhesion molecule 1, resulting in leukocyte attachment and entry. Less claudin-5 at the choroid plexus in schizophrenia implicates similar permissive effects as seen at the BBB. Although the contribution of blood-CSF barrier dysfunction to schizophrenia requires further study, reduced barrier function outside the BBB is a viable line of inquiry.
Clinical Neuroscience

Patients may benefit from existing anti-inflammatory treatments to control immune infiltration and its products

Related Resources


Drug Brand Names

Minocycline - Dynacin, Minocin


Bottom Line

Recent research has revealed that the blood-brain barrier (BBB) is pathologically permeable in several disease states, including schizophrenia. Better characterization of the leaky BBB in schizophrenia has enormous potential in helping us understand how current theories fit together and could serve as a missing puzzle piece in treating schizophrenia.