BLOOD-BRAIN BARRIER DYSFUNCTION IN SCHIZOPHRENIA: A REVIEW OF THE EVIDENCE

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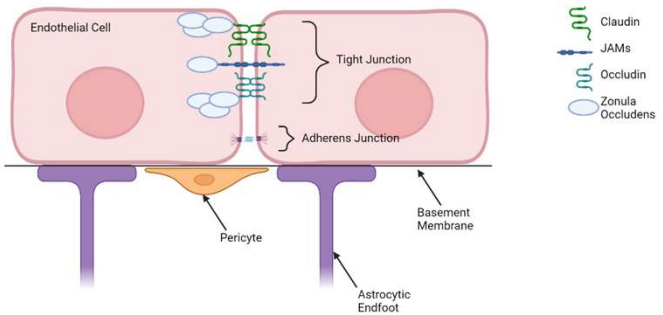
Background

- The blood-brain barrier (BBB) selectively allows molecules into the brain to promote homeostasis[1]. This is largely accomplished through tight junctions (TJ) located in the vasculature and choroid plexus (CP). In the BBB, TJs are composed of claudin-5, occludin, zonulin, and junction adhesion molecules (Figure 1).
- However, rather than being completely impermeable, recent studies show that the BBB may be dysfunctional in several neuropsychiatric disorders including schizophrenia (SZ) spectrum disorders[2].
- Here, we present potential markers of BBB dysfunction, immune involvement, the relationship with microglia, changes in the choroid plexus, and possible treatment implications.

Figure 1



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Methods

A PubMed literature search was performed using the key terms BBB, schizophrenia, psychosis, tight junctions, astrocytes, claudin, occludin, JAM, choroid plexus, CSF markers, immune markers, and microglia. We included peer-reviewed PubMed controlled studies and reviews published in English. There were no restrictions on date of publication.

Results

- 31 studies met our criteria.
- 16 included sources are presented (Tables 1-4), grouped by where BBB dysfunction could have impact.
- Studies included imaging, animal, cross sectional correlation, cell culture, and clinical research.
- All studies featured either the blood-CSF barrier of the CP or the BBB, with most identifying a relationship to aspects of schizophrenia or psychosis.

Table 1: Biomarkers

Study Design	Major Findings	Selected Sources
Meta-Analysis	S100B is increased in SZ spectrum disorders, MDD, BPD, and obesity.	Futtrup 2020
Review	S100B is a calcium binding peptide from astrocytes and is normally undetectable in healthy people. It is found in the blood and CSF of SZ spectrum disorders. CSF albumin:blood ratio adequately measures BBB function but fluctuates with antipsychotic use and alterations in CSF flow.	Kealy 2020
Cross Sectional	The logS100B level could predict severity of negative symptoms.	Wu 2018
Controlled Animal Study	Claudin-5 is decreased in SZ and 22q deletion syndrome. Li+, haloperidol, and chlorpromazine treatment increased claudin-5, and suppression resulted in BBB disruption and behavior changes. However, complete absence is lethal.	Greene 2018
Postmortem	Immunohistochemistry and PCR showed reduced claudin-5 in hippocampus of SZ spectrum disorders. Decreasing claudin-5 increases iCAM1, as does IL1B.	Greene 2020
Controlled Animal Study	JAM-A is a protein with barrier function in TJs. There is a reduction in claudin-5 when JAM-A is deleted. It is upstream from an enhancer region for a claudin-5 promoter.	Kakogianos 2020

Table 2: Immune Activity

Study Design	Major Findings	Selected Sources
Cross Sectional	iCAM1 allows migration of leukocyte, while vCAM1 is expressed by the BBB for leukocyte recruitment and moving through the endothelium. Soluble iCAM1 and vCAM1 were higher in SZ spectrum than unipolar depression, and vCAM correlated with blood CSF albumin.	Meixensberger 2021
Cell Culture	Postmortem mRNA for iCAM1 was localized to blood brain barrier vessels and I L1-B cytokines upregulated iCAM1 in culture.	Cai 2020
Controlled Animal Study	Decreasing claudin-5 via KO mice model upregulated production of iCAM1.	Greene 2003
Review	IL-6 and its soluble receptor are both elevated in SZ and are associated with white matter degeneration. IL-10 levels can no longer reduce the inflammatory state.	Pong 2020
Postmortem	CD3 and CD 20 cells were seen in the hippocampus of patients with SX spectrum disorders.	Busse 2012

Table 3: Microglia

Study Design	Major Findings	Selected Sources
Imaging	Translocator protein (TPSO) was more expressed when microglia were activated and secreting cytokines. PET showed reduced or inconsistent binding in SZ.	Conen 2021
Review	T regulatory cell hypofunction in SZ may disrupt mediation between astrocytes and microglia. Microglial PET markers showed no change or decreased microglial expression in gene studies. Soluble IL-6 receptors may sustain hypofunction. T regulatory cell induction has shown some reversal of symptoms of experimental autoimmune mouse models.	Corsi-Zuelli 2021

Table 4: Choroid Plexus

Study Design	Major Findings	Selected Sources
Review	In addition to increased heritable thickness of the CP in SZ, there is a high concentration of mitochondria, less claudin-5, more matrix metallopeptidase 9, and more ROS.	Bitanihirwe 2022
Review	Larger CP correlated with worse cognition, less grey matter, and high IL-6.	Bannai 2020
Imaging	Larger CP associated with smaller amygdala and high IL-6.	Lizano 2019

Discussion

- S100B is elevated in SZ but may be confounded by obesity. CSF albumin:blood ratio is also compromised by changes in CSF and antipsychotics. However, the logS100B level could be a more accurate marker of permeability.
- There is a marked decrease in claudin-5 in SZ that could be intertwined with altered levels of JAM-A.
- Elevated iCAM correlates with an increase in IL-6 and a decrease in claudin-5. Elevated vCAM correlates with an increased CSF albumin:blood ratio, which could signify leukocyte recruitment and crossing.
- TPSO is an unreliable method of imaging microglial activity. Moreover, T regulatory cell hypofunction may play a larger role in sustained neuroinflammation.
- A larger and thicker choroid plexus in SZ disorders may be heritable and correlates with declines in BBB integrity as demonstrated by a reduction in claudin-5 and increases in inflammatory IL-6.

Limitations:

- BBB dysfunction may only be pathologic in a subset of patients with SZ.
- Patient demographics like smoking, antipsychotics, and obesity are not consistently reported.
- There is not yet a single definitive direct marker of BBB dysfunction.

Clinical Implications

According to this research, there may be several avenues for future treatment that targets the BBB including:

- Addressing the claudin-5 deficiency in TJs.
- Reversing inflammation via agents such as cyclooxygenase inhibitors, minocycline, neurosteroids, N-acetylcysteine, statins, and estrogen[3, 4].
- Investigating how current antipsychotic treatments affect TJ molecules, adhesion molecules, and cytokine levels.

References

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