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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

The role of the blood–brain barrier in psychiatric disorders

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SUMMARY
The blood–brain barrier (BBB) is formed by continuous, closely connected endothelial cells, enveloped in the basal lamina, pericytes, and foot extensions of astrocytes. BBB has a vital role in brain metabolism and protects the brain parenchyma from harmful agents present in the systemic circulation. Damage to the BBB and an increase in its permeability have an important role in many neurodegenerative diseases. This paper aims to review the literature on the impact of the BBB damage on psychiatric illness, a largely neglected and under-researched area. Links between BBB impairment and specific neuropsychiatric disorders are described including schizophrenia, affective disorders, dementias with behavioral disorders, and alcohol use disorder, with comparison to typical hereditary small vessel diseases affecting the BBB such as cerebral autosomal dominant arteriopathy with subcortical infarction and leukoencephalopathy and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. The authors critically summarize possible pathogenic mechanisms linking BBB damage and these common disorders.
Keywords: blood–brain barrier; schizophrenia; affective disorders; alcohol use disorder; dementia; hereditary small vessel disease

INTRODUCTION

Current research has shown that various neurological diseases occur due to the structural and/or functional disorder of the blood–brain barrier (BBB) [1]. Most frequently studied entities include multiple sclerosis, infectious or inflammatory brain diseases, certain vascular as well as degenerative disease such as Alzheimer's (AD), Parkinson's disease, and amyotrophic lateral sclerosis [2]. The pathogenesis of these conditions includes damage to the occludent endothelial junction and subsequently increased BBB permeability, expression of a procoagulant endothelial phenotype, as well as the production of free radicals and other mediators of inflammation [3]. Changes in the structure of the BBB can be transient and mild corresponding to the opening of the tight junctions, but also chronic with permanent damage to the BBB leading to alterations in protein and enzyme transport. The consequent activation of microglia and infiltration of the brain parenchyma with plasma proteins and immune cells induce the disruption of the central nervous system (CNS) homeostasis and damage to the surrounding brain tissue [1].

Interestingly, data in the literature on the impact of the BBB damage on psychiatric illnesses are mostly lacking. One intriguing contemporary hypothesis states that the BBB dysfunction and subsequent increase in its permeability may be the basis for the development of certain psychiatric disorders [4]. Previous research on experimental models indicated that the development of psychiatric conditions as well as the co-existence or overlap between certain neurological and psychiatric diseases may be explained by BBB disruption, which may widen the therapeutic approach [4]. Therefore, our paper aims to review possible pathogenetic mechanisms linking BBB disruption to the main psychiatric conditions.

THE STRUCTURE OF THE BBB

The BBB is a very complex cellular system consisting of endothelial cells, pericytes, perivascular microglia, astrocytes, and continuous basal laminae made of pericytes and foot extensions of astrocytes [2]. These components configure a very restrictive wall named BBB as its main role is to maintain a safe extracellular environment for CNS neurons [2]. The impermeability of the BBB is mostly achieved through the specific structure of the endothelium [3]. The BBB protects the brain from toxins in the blood and controls the transport of glucose and other nutrients to the CNS, but also manages the removal of various metabolites from the brain tissue.

The vascular wall lining the brain capillaries is characteristically formed by uninterrupted endothelial cells surrounded by branching

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cytoplasmatic extension of astrocytes and pericytes [3]. The endothelium of the BBB is continuous, and endothelial cells form an inner sheath of capillaries. These cells secrete numerous vasoactive substances that have a role in the regulation of the vascular tone [1]. Nitric monoxide (NO) is one of the most important vasodilators secreted by these cells, and its deficiency is an important indicator of endothelial dysfunction [5]. Endothelial cells are interconnected, predominantly by occluding (tight) junctions, the most important components of BBB, as well as with adherent compounds that provide mechanical stability [3]. Occluding compounds form a selective barrier that regulates and restricts the transport of certain metabolites, ions, macromolecules, toxic substances, pathogenic microorganisms, erythrocytes, and leukocytes from blood to the brain tissue [3]. Various nutrients including glucose and amino acids enter the brain tissue through the transporters, while the introduction of large molecules such as insulin, leptin, transferrin, and low-density lipoprotein is carried out by receptor endocytosis [2]. Recent research has shown that claudins (CLDNs), a family of 24 members, are the main structural and functional elements of the occluding compounds [4]. Specifically, claudin-5 (CLDN5) is the most expressed occluding compound in the BBB, and its suppression leads to BBB damage and the emergence of a schizophrenia-like phenotype in experimental animals (mice) [4, 6]. In addition, important integral proteins of occluding compounds are CLDN-12 [2]. The transmembrane claudin and occluding proteins are linked by the Zonula Occludens-1 (ZO-1) protein to the actin filaments of the endothelial cell cytoskeleton, making ZO-1 essential for maintaining the integrity and functioning of the occluding compound [2]. The function of the occluding compound is regulated by a number of factors, including vascular endothelial growth factor, G-proteins, tyrosine kinases, Ca++, cAMP, proteases, TNF- α (tumor necrosis factor-α) [7].

The characteristic feature of pericytes is contractile, branched cytoplasmatic extensions surrounding endothelial cells. They express receptors for vasoactive mediators, such as catecholamines, endothelin-1, and angiotensin II [1]. All these molecules play a vital role in regulating cerebral blood flow through capillaries [1]. The pericytes are critical in the maintenance, stability, and selectivity of the BBB. The most important factor for the functioning and homeostasis of pericytes and BBB itself, is the platelet-derived growth factor [3]. The role of pericytes have been evidenced in the cerebral autosomal dominant arteriopathy with subcortical infarction and leukoencephalopathy (CADASIL), AD, Huntington's disease and amyotrophic lateral sclerosis [3].

The foot extensions of astrocytes are interconnected by junctions that communicate with each other (Gap Junctions; nexus) and form a perivascular glial membrane that envelops the outer surface of the brain capillaries [2]. Astrocytes regulate endothelial vasodynamic, proliferative and phenotypic activities as well as their capacity for the formation of occluding compounds within the BBB [1]. Astrocytes synthesize factors such as glial neurotrophic factor, TGF-β-growth basal fibroblast growth factor, and angiopoietin-1, all acting as stimulants for the endothelial cells [8]. They also contain aquaporins (AQP), and water transport channels, with AQP4 being specific for astrocyte foot extensions [9]. Changes in the BBB stability, as well as changes in the secretion of antioxidative compounds of glutathione and superoxide dismutase, are implied in the pathogenesis of many neurodegenerative diseases [2].

Perivascular microglia is positioned between the endothelial basal lamina and cytoplasmatic extensions of astrocytes, making an interconnected web of brain macrophages [10]. These macrophages have significant phagocytic activity, by which they internalize proteins and other substances, thus reducing the detritus from the brain parenchyma. Moreover, these cells can secrete specific cytokines enhancing the inflammatory response [11]. Perivascular microglia have a significant role in the presentation of antigens in the CNS. This has been demonstrated in experimental allergic encephalomyelitis and studied in animal models of multiple sclerosis [12]. Microglial cells can quickly reduce inflammation and eliminate infectious agents before they damage brain tissue [11].

In recent years several studies identified BBB dysfunction and its increased permeability as potentially important factor in the development of psychiatric disorders [4, 13, 14]. Numerous control mechanisms can become disrupted due to infiltration of brain parenchyma with neurotoxic substances, resulting in inflammation and oxidative stress. Our previous work has shown that oxidative stress has a significant role in the development and progression of psychiatric disorders, including major depressive disorder (MDD) and bipolar affective disorder (BAD) [15, 16]. In addition to affective disorders, current literature recognizes the role of BBB dysfunction in schizophrenia, dementia, and addictive disorders such as alcohol abuse.

BBB AND SCHIZOPHRENIA

Schizophrenia is a heterogeneous clinical syndrome characterized by a constellation of symptoms divided into positive, negative, and cognitive, often severely impacting individual functionality [17]. The pathogenesis of schizophrenia is still poorly understood, and the variability of its clinical manifestations indicates several distinct pathophysiological processes in play [17]. The roles of neurotransmission disturbances, immune response, and low-grade inflammation ("low-grade encephalitis") have been all implied [18, 19]. Recent data indicate that the oxidative stress associated with neuroinflammation and neurovascular endotheliopathy can lead to impairment of BBB integrity and decreased cerebral perfusion and disruption of neuronal homeostasis in patients with schizophrenia [13, 19]. The damage to occluding compounds between endothelial cells of continuous BBB capillaries (i.e., decreased CLDN5 expression in the hippocampus) has been demonstrated in schizophrenia [20]. Decreased levels of mRNA in charge of the synthesis of occluding compounds such as CLDN5, CLDN12, and ZO-1 appear to be associated with schizophrenia [20]. In addition, 5-HT

regulates the functioning of the BBB by increasing the expression of CLDN5, potentially playing an important role in the pathogenesis of schizophrenia. [6].

The plasma levels of astrocyte protein S100B are elevated in schizophrenia, making 100B protein levels a putative treatment marker particularly in patients with predominantly negative symptoms [14, 20]. Since S100B is a calcium-binding protein, specifically found in the astrocytes, its elevation indicates astrocyte activation with increased permeability of the BBB, which may lead to neurodegeneration [21]. Moreover, S100B synthesis induces oxidative stress, potentially resulting in the promotion of NO synthesis and an increase of pro-inflammatory cytokines which has a detrimental effect on neuronal integrity [1, 20]. There are also data indicating beneficial effects of psychotropic medications by reducing the oxidative stress in the CNS [22].

BBB ROLE IN AFFECTIVE DISORDERS

There is an increasing body of evidence linking major affective disorders (MDD and BAD) to BBB dysfunction [23–26]. Both functional and structural abnormalities are heterogenous and widespread in schizophrenia [27]. Similarly to schizophrenia, elevated values of S100B have been observed in the serum of patients with affective disorders, and are also associated with the severity of symptoms in depression [28]. Moreover, the elevation of S100B is a predictor of a successful response to antidepressant therapy in MDD [29]. In addition, chronic social stress can have an effect on CLDN5 levels, potentially affecting the BBB integrity [26]. The most intense passage of proinflammatory cytokines through the dysfunctional BBB has been observed in the region of nucleus accumbens, which is a brain region important for mood regulation [29].

Recent data indicate an association between mRNA levels for CLDN5, CLDN12, and ZO-1 and the onset and duration of MDD and BAD [4]. It has been shown that BAD patients with impaired BBB integrity have a more pronounced clinical expression of the disease and its progression [4, 30]. Both acute or chronic BBB damage increases the passage of proinflammatory cytokines such as IL-1, IL-6, TNF-α, and reactive oxygen species (ROS) [15]. This triggers the activation of microglial cells with a central role in the pathway of neuroinflammation, and also promotes local oligodendrocyte and myelin sheath damage, compromising neuronal network integrity [15, 31]. Positron emission tomography imaging revealed increased microglial activity and neuroinflammation in the hippocampus of patients with affective disorders [4]. In addition, oligodendrocyte density is decreased in BAD which indicates potential instability of the neural circuitry [31].

BBB STATUS IN DEMENTIA

Frequently, patients with dementia present with additional psychiatric symptoms such as depression, agitation, anxiety, apathy, or psychosis [32, 33]. The brain endothelium becomes progressively dysfunctional in aging, with corresponding alterations in the BBB [34]. However, in the two most common types of dementia, AD and vascular dementia, the critical role of BBB dysfunction has been documented in the last years [2, 3]. The data is especially robust concerning pericyte degeneration [3]. It has been shown that an influx of immune cells (CD4+ and CD8 T cells, dendritic cells, B cells) via disturbed BBB, lead to damage of multiple efflux transporters (adenosine triphosphate dependent pumps that remove harmful agents out of the brain tissue), and accumulation of molecules prone to aggregation, such as amyloid beta [1, 35]. In AD in particular, amyloid beta as the main component of amyloid plaques is a key pathological feature of the disease [35]. High levels of amyloid beta and oligopeptides lead to activation of microglial cells and astrocytes, resulting in increased production of toxic molecules, and consequent synaptic and neuronal damage [1]. Microglia activated in relation to amyloid beta plaques leads to the activation of astrocytes which results in the release of cytokines such as IL-1, TNF-β, TNF-α, TGF-β, NGF, bNGF, and ROS [1]. In addition, the amyloid beta has been shown to stimulate the nuclear kappaB transcription factor (NF- κB) which in turn also induces the transcription of TNF-α, IL-1, IL-6, MCP-1 (monocyte chemotaxis-1 protein), and NO synthase [34]. Activation and migration of immune cells, as well as the release of cytokines, damage the integrity of the BBB [1]. The dysfunction of BBB is reflected in the impaired functioning of the amyloid beta transporter whose role is to transport these peptides from brain tissue to the blood, via BBB [1, 36]. Dysfunction of the amyloid beta transporter could be the precipitant in the cascade of events leading to the damage of neurons, synapses, and glial cells [36].

The pathophysiology of the subcortical small-vessel disease, the most frequent type of vascular cognitive impairment, is also characterized by endothelial damage and BBB dysfunction [32, 33, 37, 38]. Cerebral hypoxia due to vascular damage leads to increased levels of inflammatory molecules causing apoptosis [34]. The inflammatory molecules such as IL-1, IL-6, MMPs (MMP-2, MMP-9), TNFα, and TLR4 (toll-like receptor 4) cause demyelination and damage to the axons and oligodendrocytes associated with the white matter lesions [33, 37]. Besides risk factors, the clinical presentation including cognitive decline and behavioral changes, AD and vascular dementia also share several aspects of brain pathology, such as increased oxidative stress, disturbed amyloid beta clearance, and BBB disruption [33, 36].

BBB IN ALCOHOL USE DISORDER

Cognitive decline is common in patients with alcohol use disorder [38]. Largely, an association between alcohol use and the risk for dementia has been demonstrated in studies with robust methodology [39]. Particularly vulnerable might be the elderly and patients with documented neuroinflammatory conditions. Although the pathophysiological

pathways of neurodegeneration associated with alcohol use are not sufficiently explored, it is clear that dietary deficiencies, such as depletion of vitamin B1 and B12, in combination with alcohol metabolites (such as acetaldehyde) have a neurotoxic effect [40, 41, 42]. In addition, chronic alcohol abuse leads to increased BBB permeability via the inhibition of protein expression such as ZO-1, occludins, VE-cadherins, AQP4), thus stimulating neuroinflammation and oxidative stress, most intensely in the hippocampal region [41]. In vitro studies demonstrated a detrimental effect of alcohol on tight junctions, endoplasmic reticulum, and an increase in ROS production [41, 42].

BBB STATUS IN HEREDITARY CEREBRAL SMALL VESSEL DISEASE

The BBB likely has an important role in the pathogenesis of the CADASIL, the most frequent inherited form of vascular dementia [43]. This clinical phenotype is characterized by four basic manifestations: strokes, migraine with aura, psychiatric symptoms, and cognitive decline that progresses to subcortical vascular dementia [44]. Symptomatology of CADASIL can start with neuropsychiatric symptoms, sometimes delaying the diagnosis, with depression being the most frequent psychiatric manifestation [44, 45]. The main pathological characteristics of CADASIL are damage to smooth muscle cells of small cerebral arteries and arterioles, as well as deposition of granular osmiophilic material in the vascular wall, due to mutation in the Notch3 gene on chromosome 19p13 [46, 47]. Recent data suggest a significant role for BBB in this syndrome, with pronounced destruction of pericytes in the vascular wall of the brain, increasing the permeability of the BBB [48].

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a rare hereditary progressive systemic disease with encephalopathy as a leading clinical feature [45, 49]. Although the most prominent clinical manifestations of the MELAS are neurological, comprising migraine, stroke-like episodes, seizures, and cognitive decline, depressed mood, anxiety, and behavioral changes are often neglected but important clinical features [44, 45, 49]. At the core of this syndrome are 29 specific point mutations documented so far, occurring at the level of various mitochondrial DNA (mtDNA) [45]. The key pathological process is a disorder in the synthesis of intramitochondrial proteins including respiratory chain enzymes and leading to reduced adenosine triphosphate synthesis [49]. Endothelial dysfunction is also evidenced in the pathogenesis of stroke-like episodes since there is a lack of vasodilatation in these patients due to reduction of NO synthesis by the endothelium [49]. There is also the metabolic hypothesis based on a generalized mitochondrial cytopathy, but the neuro-vascular hypothesis merging all potential pathological pathways appears most comprehensive [49].

CONCLUSION

There is evidence of involvement of all elements of the BBB in major psychiatric disorders as well as neurological conditions with behavioral changes. The role of astrocytes seems important since damage to the BBB leads to astrocyte activation and altered gene expression, resulting in disturbances in the extracellular environment of neurons. Activation of astrocytes also increases cytokine synthesis and secretion, thus contributing to local inflammation of brain tissue. Therefore, the "astrocytic hypothesis" of schizophrenia and depression, as well as the "low-grade encephalitis" hypothesis of schizophrenia remain highly relevant today. Importantly, emerging infectious agents, such as SARS-CoV-2 virus infection, might add additional knowledge to the inflammatory processes adding to psychiatric conditions and cognitive disturbances. As taking into account the BBB hypothesis for the development of certain psychiatric disorders seems justified, we advocate for the development of precise molecular markers which would enable clinicians to measure the presence and the degree of BBB damage, as well as markers of brain parenchyma inflammation connected to BBB dysfunction in these entities. Increasing knowledge of these pathogenetic mechanisms may open new frontiers in the therapeutic approach to these chronic and burdening conditions.

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Улога крвно–можданe баријере у психијатријским обољењима

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САЖЕТАК

Крвно–можданa баријера (КМБ) састоји се од континуираних, тесно спојених ендотелних ћелија омотаних базалном ламином, перицитима и стопаластим продужецима астроцита. КМБ има виталну функцију у можданом метаболизму и штити мождани паренхим од штетних фактора присутних у системској циркулацији. Показано је да оштећење КМБ и повећање њене пропустљивости имају значајну улогу у многим неуродегенеративним обољењима.

Циљ овога рада је преглед литературе о значају оштећења КМБ код психијатријских обољења, у великој мери занемареној и недовољно истраженој области. Повезаност између поремећаја КМБ и неуропсихијатријских поремећаја посебно је анализирана за схизофренију, афективне поремећаје, деменције са поремећајима понашања, поремећаје повезане са употребом алкохола, са посебним осврtом на наследне болести малих крвних судова мозга са оштећењем КМБ, као што су церебрална аутозомно доминантна артериопатија са супкортикалним инфарктима и леукоенцефалопатијом и митохондријска енцефаломиопатија са лактатном ацидозом и епизодама налик можданом удару. Аутори критички сумирају могуће патогенетске механизме који повезују оштећења КМБ са овим честим обољењима.

Кључне речи: крвно–можданa баријера; схизофренија; афективни поремећаји; поремећај употребе алкохола; деменција; наследне болести малих крвних судова мозга