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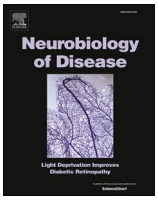

Blood brain barrier and inflammation in depression

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ABSTRACT

The blood brain barrier (BBB) is a vital structure to protect the brain, tightly filtering the passage of nutrients and molecules from the blood to the brain. This is critical for maintaining the proper functioning of the brain, and any disruption in the BBB has detrimental consequences often leading to diseases. It is not clear whether disruption of the BBB occurs first in depression or is the consequence of the disease, however disruption of the BBB has been observed in depressed patients and evidence points to the role of important culprits in depression, stress and inflammation in disrupting the integrity of the BBB. The mechanisms whereby stress, and inflammation affect the BBB remain to be fully understood. Yet, the role of cytokines in regulating tight junction protein expression seems crucial. Altogether, the findings in depression suggest that acting at the BBB level might provide therapeutic benefit in depression.

1. Blood brain barrier

The brain is highly vascularized. The blood provides the oxygen, nutrients to the brain and allows the removal of metabolic waste or carbon dioxide from the brain. In addition, blood vessels carry hormones and inflammatory molecules required for modulating signaling pathways, which have a major impact on brain functions. Therefore, the blood brain barrier (BBB) is an important interface between the brain and the blood and requires stringent properties.

1.1. Characteristics of the blood brain barrier

To understand the characteristics of the BBB, one needs to visualize the complexity of the vascular system. The vascular tree includes: i) arteries and arterioles, which bring blood to the tissues, ii) the capillary bed, which is necessary for gas and nutrient exchange and iii) venules and veins, which drain the blood out of the tissues. Since capillaries have different functions, each portion of the vascular tree has different properties. And this applies to the blood brain barrier, which possesses unique properties as microvasculature of the central nervous system (CNS) and is considered the largest interface for blood-brain exchange (Sukriti and Begley, 2005). The vessels of the CNS are continuous non-fenestrated vessels, like the lungs and skin vessels. They are composed of tight junctions, contain a basement membrane consisting of a dense gel-like structure surrounding the cells, also called glycocalyx and lack fenestrations (or pores) in the plasma membrane limiting the passage of molecules or cells. The endothelial cells are held by tight junctions, which create a high resistance paracellular barrier preventing the passage of ions, polar (water-soluble) molecules >4 nm, or cells (Van Itallie and Anderson, 2006; Van Itallie et al., 2008). Tight junctions are composed of claudins, occludins and junction adhesion molecules (Furuse, 2010). Claudin-5 is highly expressed in the CNS endothelial cells and depletion of claudin-5 in mice is sufficient to increase the permeability of the BBB (Morita et al., 1999; Nitta et al., 2003). Similarly, occludin is highly enriched in CNS endothelial cells. However, occludin-deficient mice do not seem to exhibit changes in BBB permeability or function, except for exhibiting an impaired calcium flux across the BBB (Saitou et al., 2000), suggesting that not all tight junction

Abbreviations: BBB, Blood brain barrier; CNS, Central nervous system; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; LFA, lymphocyte function-associated antigen; VLA, very late antigen; EAE, experimental autoimmune encephalomyelitis; MDD, Major depressive disorder; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; MS, multiple sclerosis; CTE, chronic traumatic encephalopathy; ALS, amyotrophic lateral sclerosis; RUR, relative uptake ratio; NAc, nucleus accumbens; VEGF, Vascular endothelial growth factor; PET, Positron emission tomography; GLUT1, glucose transporter 1; MIP, macrophage inflammatory protein; LPS, Lipopolysaccharide; Th, T helper; GDF-15, Growth/differentiation factor-15.

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proteins exhibit the same role in BBB maintenance.

In addition to the tight junctions, the BBB is characterized by a lack of pinocytic activity and the presence of active transport mechanisms that control the passage of essential molecules (e.g., essential amino acids, glucose, etc.). It also includes efflux transporter such as P-glycoprotein (Cordon-Cardo et al., 1989), which actively pump compounds out of the endothelial cells, back to the circulation. In sum, there is a free diffusion of oxygen and carbon dioxide in opposite direction, and small lipophilic molecules <4 kDa across the endothelium (Pardridge, 2015), whereas all other nutrients such as glucose or amino acids require selective active transporters while larger molecules require endocytosis (Pardridge et al., 1985; Zhang and Pardridge, 2001).

1.2. The blood brain barrier involves different cell types

Besides the permeability properties, the BBB is also constituted of different cell types. Although the endothelial cells form the blood vessel wall, immune cells (e.g., perivascular macrophages), pericytes, astrocyte end-feet and neurons interact at the neurovascular unit to ensure the integrity of the BBB (Fig. 1).

Briefly, pericytes are in close contact with endothelial cells. They are particularly abundant in the CNS (Liebner et al., 2011) and share a basement membrane with endothelial cells (Armulik et al., 2011). They are essential in maintaining BBB integrity and microvascular stability and helping angiogenesis (Armulik et al., 2011), as they exhibit contractile properties sufficient to control vessel diameter and cerebral blood flow (Hall et al., 2014; Peppiatt et al., 2006), multipotent stem cell capabilities (Nakagomi et al., 2015) as well as phagocytic properties to eliminate metabolic waste (Sagare et al., 2013).

The astrocytes are also essential for the BBB as their foot processes represent close to 99% of the surface area of the brain capillary. Astrocytes are the most numerous cells of the brain and therefore provide a crucial physiological support to the neurons as previously reviewed (Sofroniew and Vinters, 2010). Astrocytes have a critical role during the maturation of the BBB since astrocytic end-feet have been considered as key checkpoints of brain metabolism (Wolburg et al., 2009), because a high density of organic anion transporters are present at the interface between astroglial end-feet and the basal lamina of the endothelial cells (Rubin et al., 1991; Wolburg et al., 2011) and astrocytes secrete factors that regulate BBB function.

The blood vessels in the CNS interact with both microglia and perivascular macrophages. The perivascular macrophages are present in the abluminal side of the vessel and are found in the Virchow-Robin space (Hickey and Kimura, 1988; Polfliet et al., 2001). They derive from blood progenitor cells and have a fast turn-over (80% of the cells are replaced in 3 months) (Unger et al., 1993; Vass et al., 1993; Williams et al., 2001). Together with the microglia, which are the CNS resident immune cells, they represent the first line of defense, phagocytosing pathogens or cell debris. Furthermore, other immune cells originating from the blood vessels (e.g., T cells, neutrophils, monocytes etc) after activation, are also able to change the BBB permeability during infection, injury or disease by releasing for example reactive oxygen species (Hudson et al., 2005; Persidsky et al., 1999).

1.3. Function of the blood brain barrier

Because the BBB involves many cell types and controls the passage of molecules and cells from the blood to the brain, the BBB has the critical function of maintaining homeostasis. The BBB is a well-organized network controlling ion, molecule, and cell trafficking between the CNS and the blood (Daneman, 2012; Zlokovic, 2008). It protects the brain parenchyma from blood borne agents and represents a significant obstacle for the entry of drugs or other compounds to the CNS (Ballabh et al., 2004; Pardridge, 2005). It is thought to prevent the entrance of cells and neurotoxic factors into the brain parenchyma to maintain a homeostatic microenvironment. Therefore, in physiological conditions,

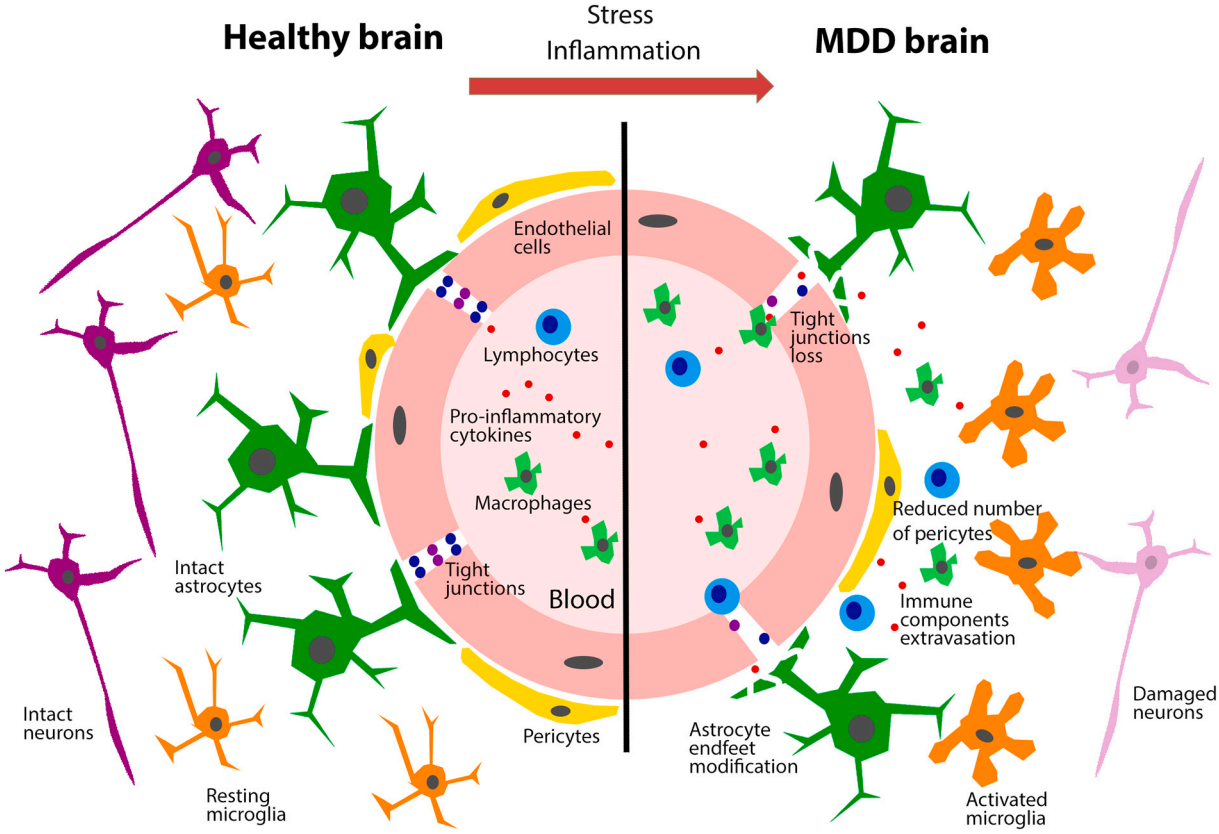

Fig. 1. The structure of the BBB in healthy and MDD conditions.

the BBB permeability is tightly regulated by environmental factors such as nutrition, temperature, aging, or exposure to stressors (reviewed in (Segarra et al., 2021). It is important to note that in order to maintain proper neural and synaptic functions the ionic composition of the CNS has to be stable in contrast to the ionic levels in the plasma that fluctuate with exercise or meal intake for example (Bradbury et al., 1963; Hansen, 1985). This is accomplished by specific ion channels and transporters present on the BBB (Hladky and Barrand, 2016; Sweeney et al., 2019). Similarly, the BBB ensures the separation between the pool of neurotransmitters in the CNS and the ones found in the plasma to protect the CNS from any harmful effects of fluctuant neurotransmitters (Abbott et al., 2006; Bernacki et al., 2008). The BBB prevents the leakage of macromolecules to the CNS. Thus, the production of the cerebrospinal fluid (CSF) is the result of the filtration of plasma at the choroid plexus to remove unneeded molecules (Abbott et al., 2010). It is indeed important to avoid CNS tissue damage, as proteins such as blood albumin, prothrombin and plasminogen cause cellular activation leading to apoptosis once in the brain (Gingrich and Traynelis, 2000; Nadal et al., 1995). Furthermore, the BBB protects against neurotoxins circulating constantly in the blood (Abbott et al., 2010).

Maybe the most intriguing function of the BBB remains the prevention of immune cell entry. For many years the brain was considered immune-privileged because of the low infiltration of neutrophils in the CNS compared to other tissues. It is thought nonetheless that in inflammatory conditions, the tight junctions between endothelial cells are disrupted allowing immune cells to enter the CNS. In a matter of fact, monocytes and leukocytes use transcellular and paracellular routes to enter the CNS (Anthony et al., 1997; Davoust et al., 2008), which is considered a dynamic process involving tethering, crawling, arrest and diapedesis across the endothelial cells (Carman and Martinelli, 2015). Adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1, are indeed upregulated on endothelial cells during inflammation and are responsible for the arrest of $CD4^+$ T cells on the inflamed vessel through lymphocyte function-associated antigen (LFA)-1 and very late antigen (VLA)-4 (Carman and Martinelli, 2015). Other molecules have been shown to regulate the transcellular pathway for immune cells to enter the CNS (Cayrol et al., 2008; Larochelle et al., 2012). The paracellular route involves the disruption of the tight junctions via CD99. It has been shown that blocking CD99 ameliorates experimental autoimmune encephalomyelitis (EAE) and reduces immune cell infiltration to the CNS (Winger et al., 2016).

Altogether, the BBB is a well-organized interface between the periphery and the CNS tightly filtering what crosses the BBB. A question remains as whether the BBB in different brain regions exhibits different properties to support local neuronal function. It is known for example that the circumventricular organs possess continuous fenestrated capillaries, conferring a high permeability of solutes. It has been hypothesized that the BBB was uniformly disrupted in diseases. Yet, accumulating evidence points to localized changes of the BBB in pathology such as depression.

2. Major depressive disorder and BBB disruption

Major depressive disorder (MDD) is a debilitating disease affecting 7.1% of adults and 9.4% of adolescents in the U.S. (NIMH data) (Greenberg et al., 2021). There is a strong sexual dimorphism in MDD, with females being more likely to develop and be affected by depression than males. This sexual dimorphism is in part encoded at the transcriptional level (Labonte et al., 2017).

MDD is associated with BBB disruption, which has been thought to lead to brain homeostasis disturbances and as a result induces detrimental health outcomes (reviewed in (Wu et al., 2021). Besides depression, BBB malfunction is involved in several neurological diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS), HIV-1-associated dementia or chronic traumatic encephalopathy (CTE) (reviewed in (Sweeney et al., 2018), suggesting either a common mechanism of disruption of the BBB (e.g. neuroinflammation) between all these illnesses and/or in contrast that regulation of the BBB is different in different diseases.

In depression, there is accumulating evidence for a disruption of the BBB integrity. The functionality of the endothelial cells can be measured in MDD patients using the relative uptake ratio (RUR) of blood flow in the brachial artery after hyperemic challenge using dynamic nuclear imaging. A low RUR is associated with poorer endothelial functioning, and MDD patients exhibit lower RUR (Lavoie et al., 2010).

Consistent with this, the serum of MDD patients promotes apoptosis of endothelial cells *in vitro* when compared to the serum of non-depressed patients (Politi et al., 2008) and MDD patients also exhibit reduced *Claudin-5* mRNA level in the nucleus accumbens (NAc) (Menard et al., 2017), which is consistent with the strong and bidirectional association found between MDD and development of vascular endothelial pathologies (Serlin et al., 2011). Indeed, MDD is highly comorbid with cardiovascular diseases including both an increased prevalence of MDD in patients with cardiovascular diseases and increased risk for MDD patients to experience cardiovascular issues (Carney and Freedland, 2017; Elderon and Whooley, 2013; Seligman and Nemeroff, 2015). Furthermore, evidence of BBB hyperpermeability in MDD is associated with changes of the cerebrospinal fluid (CSF)-blood ratio of various molecules (detailed below), or reduction of the multidrug efflux transporter P-Glycoprotein expression on endothelial cells (Hawkins et al., 2010). Thus, for example, the CSF/serum ratio of albumin is increased in MDD patients (Bechter et al., 2010; Gudmundsson et al., 2007) and in suicidal patients (Niklasson and Agren, 1984) suggestive of an increase entry of albumin to the brain, which could have detrimental effects in the brain parenchyma. Endothelial P-Glycoprotein expression in contrast is reduced in MDD patients (de Klerk et al., 2010; de Klerk et al., 2009; Wiencken and Casagrande, 1999) leading to less expulsion of molecules outside of the brain and potential harm to the brain. Furthermore, functional polymorphisms of the gene *ABCB1* which encodes P-Glycoprotein confer susceptibility to MDD (Fujii et al., 2012). The presence in the blood of high level in MDD patients of S100B, a calcium-binding protein produced by glial cells is also indicative of an increased BBB leakage (Futtrup et al., 2020). Other plasma markers of endothelial dysfunction such as soluble ICAM-1, soluble VCAM-1, soluble *E*-selectin and von Willebrand factor (vWF)) have been found in depressed patients (Geraets et al., 2020; Lopez-Vilchez et al., 2016; Muller, 2019; Tchalla et al., 2015; van Agtmaal et al., 2017). Tight junction Claudin 5 expression is reduced in the hippocampus of MDD patients, and the expression of Claudin-5, Claudin-12 and ZO-1 correlates with the age of onset and the duration of the depressive episode (Greene et al., 2020). Imaging studies confirm that greater leakage of the BBB in bipolar patients is associated with more severe depression (Kamintsky et al., 2020). All these findings suggest a dysfunction of the various transporters that control the low permeability of the BBB required to maintain homeostasis.

Changes in the expression of these various transporters might also be the result of a cell rearrangement around the blood vessels. Thus, loss and alterations of astrocytes have been observed in humans with MDD (Rajkowska and Stockmeier, 2013), and this has critical structural consequences for the BBB, as the coverage of blood vessels by astrocytic end-feet is reduced by 50% in MDD samples (Rajkowska et al., 2013).

Altogether, there is a disruption of the BBB integrity in depressed patients. However, whether the BBB disruption induces depression or in contrast results from depression remains to be determined in humans.

3. Animal models and BBB disruption

Rodents have been used to model some of the symptoms of depression (for review Nestler and Hyman, 2010). The models are mainly based on exposing rodents to stress. It has been proposed that severe or

persisting stress may result in the maladaptation of the BBB that may contribute to depression (Segarra et al., 2021). Studies in mice subjected to chronic social defeat stress, consisting in the repetitive exposure of a naïve mouse to an aggressor mouse, showed reduced expression of Claudin-5 and abnormal blood vessel morphology in the NAc of stress-susceptible mice compared to resilient mice (Menard et al., 2017). Chronic social defeat stress also induces cerebrovascular microbleeds, indicative of vascular pathology after stress (Lehmann et al., 2020). Vascular endothelial growth factor (VEGF) promotes paracellular and transcellular barrier function, increasing BBB disruption and associated depressive-like behaviors (Matsuno et al., 2022). Furthermore, resilience to chronic social defeat stress has been associated with low endothelium expression of repressive Claudin 5-related transcription factor, foxo1 (Dudek et al., 2020), whereas susceptible mice exhibit increased plasma markers associated with endothelial dysfunction such as soluble *E*-selectin (Dion-Albert et al., 2022). Others have proposed that the reduced production of cAMP by neurons induces damages to the BBB in the nucleus accumbens to promote susceptibility to chronic social defeat (Zhang et al., 2020). Similarly, learned helpless mice exhibit increased BBB permeability, evidenced by the increased brain leakage of peripherally injected sodium fluorescein, and by lower hippocampal levels of the tight junction proteins occludin, ZO-1, and Claudin-5 (Cheng et al., 2018). Positron emission tomography (PET) analyses also revealed decrease of the multidrug efflux transporter P-Glycoprotein function in rats exposed to foot shocks-induced stress whereas this decrease is prevented by antidepressant treatment (de Klerk et al., 2010). Mice subjected to chronic restraint stress exhibit a clear passage of 40-kDa fluorescent dextran into the brain perivascular area as shown with real-time *in vivo* two-photon microscopic imaging (Lee et al., 2018), a reduction of the tight junction proteins Claudin-5, occludin and ZO-1 and of the glucose transporter 1 (GLUT1), which plays a critical role in maintaining BBB integrity, in the rat amygdala (Xu et al., 2019). Furthermore, short-term immobilization of rats causes albumin extravasation in the cerebellum, hippocampus, and hypothalamus (Skultetyova et al., 1998). Maternal separation of rat offspring is sufficient to increase BBB permeability in the dams as revealed by increased Evans blue staining in their brains (Gomez-Gonzalez and Escobar, 2009). Other stress paradigm such as a forced swim also induced increased BBB permeability as exemplified by the entry of non-BBB-penetrant drugs into the brain that enhance neuronal excitability (Friedman et al., 1996).

Like the human findings, pericytes and astrocytes are altered in animal models of stress-induced depression-like-behaviors. For example, the number of $NG2^{+}$ pericytes is altered in the hippocampus of rats subjected to chronic unpredictable stress (Treccani et al., 2021). Furthermore, depletion of aquaporin-4, which is expressed on astrocytes end-feet, and controls BBB permeability, is sufficient to promote depressive-like behaviors in the chronic animal model of subcutaneous injections of corticosterone (Kong et al., 2014). In contrast, the mood stabilizer, lithium, attenuates the decrease of hippocampal aquaporin-4 and upregulates hippocampal Claudin-5 expression in rats subjected to chronic unpredictable stress, restoring the functionality of the BBB and preventing depressive-like behaviors (Taler et al., 2021).

To conclude, depression is associated with a dysfunction of the BBB both in humans and rodents, yet the cause of this disruption remains largely unknown. Inflammation has emerged as an important culprit in depression (Beurel et al., 2020), and neuroinflammation has been proposed to promote the disruption of the BBB.

4. Role of inflammation in the increased permeability of the BBB in depression

Although the contribution of inflammation to depression is not fully understood, there is strong evidence for the presence of increased inflammatory markers as well as dysfunction of the immune cells in depression (reviewed in Beurel et al., 2020; Medina-Rodriguez et al., 2018). Cytokines are known to increase the permeability of the BBB. Thus, TNF disrupts the BBB integrity in mice subjected to the learned helplessness paradigm (Cheng et al., 2018). But other molecules secreted by astrocytes can also affect the BBB integrity (e.g. taurine, glutamate, aspartate, Nitric oxide or macrophage inflammatory protein (MIP)2) (Manley et al., 2000; Yamazaki et al., 2020; Yao et al., 2008). Lipopolysaccharide (LPS) has also been reported to increase BBB permeability. Although this result remains controversial, it has been estimated that LPS affects BBB permeability in ~60% of the studies (Varatharaj and Galea, 2017). Treatment with anti-TNF (etanercept) or Fingolimod (sphingosine-1 receptor agonist) restores the BBB integrity in mice and induces an antidepressant effect (Cheng et al., 2018) confirming the role of TNF in controlling BBB integrity. The mechanism whereby inflammation affects BBB integrity remains largely unknown, but it has been hypothesized that the duration of the inflammation might impact differently the BBB. Thus, various degrees of damage can be found depending on the amplitude and duration of inflammation, including i) changes in signaling, ii) increased cell infiltration, iii) increase passage of molecules and iv) direct damage of the endothelial cell barrier. It has been demonstrated that endothelial cells can transmit the inflammatory signal without affecting solute permeability via activation of various signaling pathways leading to neuronal activation (Gosselin and Rivest, 2008; Herkenham et al., 1998; Quan et al., 2003). Similarly, reduction of P-Glycoprotein expression associated with systemic inflammation is another way by which signaling pathways can mediate inflammatory effects without affecting the BBB integrity. Inflammation also promotes leukocytes passage into the brain (Banks et al., 2012; Bohatschek et al., 2001; He et al., 2016; Thomson et al., 2020), which is consistent with recent post-mortem studies reporting both T- and B-lymphocytes and monocytes in the brain parenchyma of MDD patients (Enache et al., 2019; Schlaaff et al., 2020). In mice, similar findings are observed. Interleukin-17A expressing CD4 cells or T helper (Th)17 cells accumulate in the hippocampus and promote susceptibility to depression-like behaviors (Beurel et al., 2013; Beurel et al., 2018; Medina-Rodriguez et al., 2020). Human Th17 cells induce BBB disruption (Kebir et al., 2007). Chronic social defeat stress induces the recruitment of peripheral monocytes in the NAc of stress-susceptible animals (Menard et al., 2017). Monocyte trafficking into the brain also mediates stress responses (reviewed in Wohleb et al., 2014). This increased infiltration of cells has been hypothesized to be the result of several changes at the BBB occurring to allow leukocytes to enter the brain [e.g. degradation of the basement membrane (Constantinescu et al., 2003; Fitzgerald et al., 2000; Mulivor and Lipowsky, 2009; Wiesinger et al., 2013) and endothelial upregulation of chemokines such as Ccl2 (Chui and Dorovini-Zis, 2010), E/P-selectins required for cell rolling (Barkalow et al., 1996; Carvalho-Tavares et al., 2000; Zhou et al., 2009) and integrin ligands such as ICAM-1 required for cell adhesion (Bohatschek et al., 2001)]. In addition, TNF, IFNγ or IL-17A induce metalloprotease (MMP) activity at the BBB to promote leukocyte migration through the basal membrane (Agrawal et al., 2006; Song et al., 2015). Proinflammatory cytokines such as TNF, IL-17A and IL-23 together with increased BBB permeability have been found increased in the brain of learned helpless mice (Cheng et al., 2018). Analysis of pathways differentially regulated in NAc endothelial cells revealed increased expression of genes associated with the proinflammatory TNF/NF-κB pathway in mice susceptible to chronic social defeat stress (Dudek et al., 2020). MMP induction has also been associated with increased leakage of macromolecules after inflammation due to decreased expression of the endothelial tight junction proteins (Erikson et al., 2020; Qin et al., 2015). The localization of the endothelial tight junctions is also maintained by sphingosine 1-phosphate receptor (Yanagida et al., 2017). Yet sphingosine 1-phosphate receptor is reduced in inflammation (Winkler et al., 2015). And evidence of antidepressant effects in mice of fingolimod (sphingosine 1-phosphate receptor agonist) confirms the importance of this receptor in maintaining the BBB integrity in depression (Cheng et al., 2018). Similarly, hypoxia reduces tight junction protein expression, increasing permeability of the BBB to

sucrose for example (Halder and Milner, 2020; Mark and Davis, 2002). It is also known that TNF and IL-6 diminish occludin/ZO-1 interaction (Rochfort and Cummins, 2015). A direct damage to the BBB is rare and has been observed with anti-CD19 chimeric antigen receptor T-cell immunotherapy for refractory B-cell malignancies (Gust et al., 2017; Rice et al., 2019) by destroying CD19-expressing pericytes which leads to BBB leakage (Parker et al., 2020). In depression, alteration and loss of astrocytes has also been hypothesized to contribute to the loss of permeability of the BBB. It is interesting to note that microglia protect at first against BBB disruption by aggregating around leaky vessels (Halder and Milner, 2020). But overtime, activated microglia have been proposed to phagocytize astrocytic end-feet and promote the impairment of BBB function as observed in a model of depression-like behavior induced by sustained inflammation (Haruwaka et al., 2019). Upregulation of bradykinin activity, a polypeptide that mediates inflammation, vasodilation, and increased capillary permeability, and of bradykinin B1 receptor expression have been also observed in mice models of LPS-induced depression-like behaviors associated with BBB maintenance (Viana et al., 2010). Bradykinin induces inflammation, oxidative injury, and astroglial NF-κB pathway-mediated IL-6 production that may increase BBB permeability (Najjar et al., 2013; Schwaninger et al., 1999; Viana et al., 2010). Growth/differentiation factor-15 (GDF-15), also named macrophage inhibitory cytokine-1, promotes astrocyte remodeling and reverses Claudin-5 reduction, resulting in the reduction of BBB permeability and improvement of depression-like-behaviors in rats selectively bred for high anxiety-related behavior, a model of innate depression (Malik et al., 2020).

Blockade of inflammation has been successful to induce antidepressant actions and reduce BBB permeability (Cheng et al., 2018; Menard et al., 2017). In addition, LPS-induced depressive-like behavior and BBB dysfunction in mice are reversed with Fenretinide, a synthetic retinoid derivative, by downregulating NF-κB activity and subsequently NO, IL-1β, IL-18, IL-6 and TNF in the serum and hippocampus (Li et al., 2020).

5. Potential therapeutic strategies

There is a major paradox in targeting the BBB permeability for therapeutic interventions. On one hand, increasing permeability of the BBB has been the holy grail for decades to cure brain related diseases in order to let drugs enter the brain. On the other hand, reducing BBB permeability in MDD has been suspected to enhance antidepressant effects. Reducing inflammation is sufficient to restore the integrity of the BBB and provides antidepressant actions. Thus, blocking TNF or IL-6 or more generally inflammation (e.g., Fenretinide) restore the BBB integrity and reverse the depressive-like behaviors in mice (Cheng et al., 2018; Menard et al., 2017; Li et al., 2020). Fingolimod, a sphingosine-1 phosphate receptor agonist, promotes BBB integrity (Nishihara et al., 2015). Although the mechanism of action is less clear, fingolimod promotes recovery from learned helplessness (Cheng et al., 2018) offering another antidepressant strategy. Others have proposed treatment with a VEGFR2 inhibitor to restore BBB integrity (Matsuno et al., 2022) or other growth factors (Malik et al., 2020). Overall, the challenge to maintain BBB integrity relies on the large number of cell types constituting the BBB, the relatively localized change in BBB disruption, the wide involvement of the BBB in brain function and of course the degree of cell damage affecting the BBB. Targeting inflammation might be beneficial in treating localized BBB disruption without cell damage, whereas it might not be sufficient to reverse BBB damages associated with cell destruction of the BBB.

6. Conclusion

Much evidence converges on a strong association between depression and BBB dysfunction. The idea that the BBB disruption in depression is the consequence of the chronic low inflammation in MDD patients seems to be favored. Nonetheless disruption of the BBB is also sufficient to promote depressive symptoms in mice suggestive of a bidirectional interaction between the BBB and depression. Nevertheless, the mechanisms underlying these processes remain largely unknown. But promoting BBB integrity might provide novel therapeutic strategy for depression.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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