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REVIEW

Blood-brain barrier dysfunction as a potential therapeutic target for neurodegenerative disorders

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Abstract The blood-brain barrier (BBB) is composed of specific tight junction proteins and transporters expressed on the lining of endothelial cells of the vasculature in the brain. The structural and functional integrity of the BBB is one of the most critical factors for maintaining brain homeostasis and is mainly regulated by complex interactions between various cell types, such as endothelial cells, pericytes, and astrocytes, which are shaped by their differential responses to changes in microenvironments. Alterations in these cellular components have been implicated in neurodegenerative disorders. Although it has long been considered that BBB dysfunction is a mere ramification of pathological phenomena, emerging evidence supports its critical role in the pathogenesis of various disorders. In epilepsy, heightened BBB permeability has been found to be associated with increased occurrence of spontaneous seizures. Additionally, exaggerated inflammatory responses significantly correlate with increased BBB permeability during healthy aging. Furthermore, it has been previously reported that BBB disruption can be an early marker for predicting cognitive impairment in the progression of Alzheimer's disease. We herein review a potential role of the major cellular components of the BBB, with a focus on the contribution of BBB disruption, in neurodegenerative disease progression.

Keywords Epilepsy · Aging · Alzheimer's disease · Neurovascular unit · Neuroglial interaction · Inflammation · Extracellular matrix

Introduction

Capillaries in the brain have a specialized structure, namely the blood-brain barrier (BBB), which consists of tight junction (TJ) proteins, specific transporters, and ion channels that maintain homeostasis in the brain. The BBB establishes selective permeability between the brain parenchyma and blood circulation for tight regulation of the synaptic milieu (Abbott 2002). Given its crucial role in maintaining homeostasis in the brain, emerging evidence has shed light on the importance of the disruption of BBB in the pathophysiology of numerous neurodegenerative disorders. For instance, recent studies have demonstrated that compromised functional integrity of the BBB leads to the presence of pathological markers for Alzheimer's disease (AD) (Bowman et al. 2018; Nation et al. 2019) and the extent of BBB impairment was correlated with cognitive decline (Nation et al. 2019). Furthermore, BBB breakdown has been associated with cognitive decline in aged rodents (Senatorov et al. 2019). Recurrent seizures result in BBB disruption (Marchi et al. 2007; Li et al. 2013). Although previous studies have reported evidence suggesting strong associations between the disrupted functional integrity of the BBB and various neurodegenerative disorders, it remains unclear whether BBB dysfunction plays an active role during pathological processes or whether it is a consequential phenomenon.

Numerous factors can alter the functional and structural integrity of the BBB. For example, systemic infection increases BBB permeability (Hofer et al. 2008). It has been previously established that various cytokines, including

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TNF-α (Tsao et al. 2001; Daniels et al. 2014), IL-1β, and IL-6 (de Vries et al. 1996), in the brain often induce BBB disruption. Given that exaggerated inflammatory responses are associated with a broad range of neurological disorders as precipitating events and/or as complications, it seems reasonable to postulate that compromised BBB integrity may play a role in increasing susceptibility to the development of neurodegeneration. As numerous neurological disorders have aging as a major risk factor (Zlokovic 2008; Zhao et al. 2015), altered BBB integrity might be a precipitating event for instigating a key pathological process in neurodegenerative disorders. Here, we first review how cellular components are involved in the regulation of BBB integrity and then current findings regarding the tight association of BBB dysfunction with various neurodegenerative disorders in order to share our perspectives on the role of the compromised BBB in the pathology of brain disorders in an effort to identify a novel therapeutic target for neurodegeneration.

Cellular components of the blood-brain barrier

Endothelial tight junction

The structural integrity of the BBB is primarily dependent on TJ proteins to establish a physical "barrier" between adjacent endothelial cells in brain capillaries. Among numerous TJ proteins, claudins are known to play a central role in the regulation of BBB permeability (Günzel and Yu 2013). Deficiency of claudin-5, one of the most abundant TJ proteins expressed in the BBB, results in increased BBB permeability in mice, suggesting its importance in barrier function (Nitta et al. 2003). Claudins tightly interact with other TJ proteins, such as occludins and cytoplasmic proteins, including zonular occludens (ZOs) (Poliak et al. 2002). ZO-1, -2, and -3 are expressed in the brain and play critical roles in the assembly of TJ proteins by cross-linking them into actin filaments (Fanning et al. 1998). Indeed, ZO-1 directly binds F-actin and is known to be associated with the regulation of the actomyosin cytoskeleton (Van Itallie et al. 2009). ZO-1 also regulates the mechanical tension of endothelial cell–cell contacts by acting on adherence junctions, and its depletion has been found to result in the loss of other TJ proteins (Tornavaca et al. 2015). In fact, there are numerous proteins on the TJs junctions between endothelial cells and various factors released from and/or bound to other cells in proximity that are involved in the regulation of barrier properties in the neurovascular unit, as summarized in Fig. 1 and Table 1.

Pericytes

Pericytes are vascular mural cells in proximity to the basement membrane of capillaries in the brain (Winkler et al.

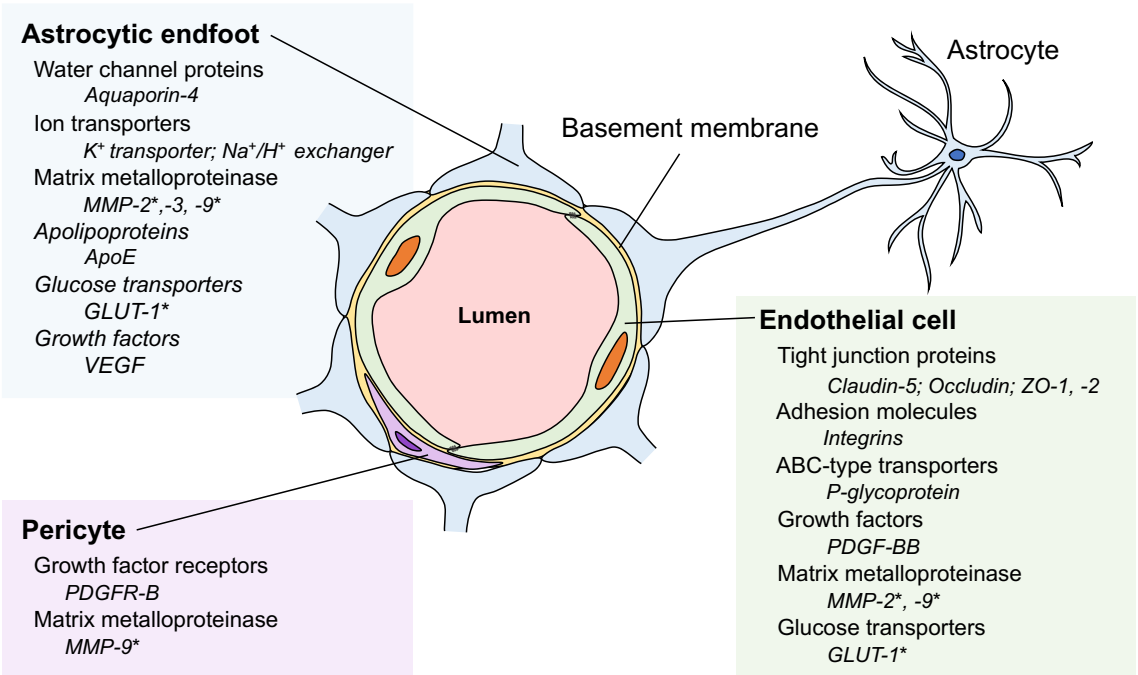

Fig. 1 Schematic illustration of cellular components and molecules involved in the regulation of BBB integrity. Astrocytic end-feet and pericytes encompass blood vessels in the brain and endothelial cell linings are connected by tight junctions (//). Various molecules are released from different cell types and regulate the BBB integrity based on their complex interactions within neurovascular units. * indicates molecules that are abundantly expressed in more than two types of cells

Table 1 Molecules involved in the control of BBB integrity and their responses in neurodegenerative disorders

Molecules	Main cell type	Neurodegenerative disorders		
		Epilepsy	Aging	Alzheimer's disease
AQP4	Astrocytes	Transient downregulation followed by a gradual return to baseline levels (Hubbard et al. 2016)	Altered expression (Zeppenfeld et al. 2017)	Altered expression and loss of perivascular localization (Zeppenfeld et al. 2017)
Kir4.1	Astrocytes	Decreased expression (Ivens et al. 2007; Cacheaux et al. 2009)	Upregulation (Gupta and Kanungo 2013)	Decreased expression (Wilcock et al. 2009)
Claudin 5	Endothelial cells	Transient upregulation (Yan et al. 2018)	No change (Yamazaki et al. 2019)	Decreased expression (Yan et al. 2018; Yamazaki et al. 2019)
ZO1	Endothelial cells	Decreased expression in HS-TLE patients (Castañeda-Cabral et al., 2020) Increased 24 h after kainic acid injection (Yan et al. 2018)	Age-associated loss (Goodall et al. 2018)	Abnormal distribution with disrupted TJ and hypervascularity (Biron et al. 2011)
GLUT1	Astrocytes and endothelial cells	Decreased expression (Pearson et al. 2013; Hildebrand et al. 2014)	Decreased (Hooijmans et al. 2007)	Decreased (Merlini et al. 2011)
PDGFRβ	Pericytes	Re-distribution towards the cerebrovasculature (Milesi et al. 2014)	Increased levels in CSF (Montagne et al. 2015)	Decreased expression in pericytes (Miners et al. 2018; Halliday et al. 2016) Increased levels in CSF (Nation et al. 2019)
EGF	Astrocytes and endothelial cells	Increased (Castañeda-Cabral et al. 2019)	CSF levels correlated with age (Chakraborty et al. 2018)	No change in CSF levels (Chakraborty et al. 2018) Serum levels correlated with severity (Alvarez et al. 2018) Increased transcription (Mahoney et al. 2019)
MMP-2	Astrocytes, pericytes, and endothelial cells	Increased expression and activity (Rempe et al. 2018)	Increased activity (Lee et al. 2012)	Age-specific upregulation (Py et al. 2014)
MMP-9	Astrocytes, pericytes, and endothelial cells	Increased expression (Mizoguchi et al. 2011)	Increased expression/activity (Romero et al. 2010; Lee et al. 2012)	Age-specific upregulation (Py et al. 2014)

AQP aquaporin, *ZO* zonula occludens-1, *GLUT* glucose transporter; *PDGFR* platelet derived growth factor receptor, *EGF* epidermal growth factor, *MMP* matrix metalloproteinase, *HS-TLE* hippocampal sclerosis-temporal lobe epilepsy, *CSF* cerebrospinal fluid

2011). Due to their proximity to endothelial linings, pericytes can regulate BBB permeability by altering the expression of TJ proteins on endothelial cells and directly regulating transcytosis across the BBB (Armulik et al. 2010). Furthermore, such an important role for pericytes in the regulation of BBB permeability makes them one of the critical cells that contribute to the pathological progression of neuroinflammation by controlling the adhesion and migration of leukocytes through endothelial cells, which can result in altered immune responses in the brain (Olson and Soriano 2011). Accordant with the abundance of interactions between pericytes and endothelial cells for maintaining the integrity of the BBB, pericytes express various cell-surface molecules, such as transmembrane chondroitin sulfate proteoglycan NG2 and platelet-derived growth factor receptor β (PDGFRβ), which govern cell–cell and/or cell-extracellular matrix interactions (Sweeney et al. 2016); the expression of such molecules seems to be related to the functional integrity of the BBB. When the BBB is disrupted following circadian rhythm disturbance, the expression of PDGFRβ is downregulated in pericytes, along with increased BBB permeability (Nakazato et al. 2017). Traumatic brain injury (TBI) directly causes PDGFRβ signaling impairment and subsequently decreases the expression of various tight junction-related molecules, including connexin-43, adherent junction proteins, and TJ proteins such as ZO-1, claudin-5, and occludin (Bhowmick et al. 2019). These findings highlight the importance of crosstalk between pericytes and endothelial cells in the maintenance of BBB integrity.

Astrocytes

Astrocytes are one of the most abundant cells in the brain and play a critical role in the regulation of homeostasis within neurovascular units. For instance, astrocytes regulate cerebral blood flow in accordance with changes in neuronal activity by detecting the metabolic state of the brain parenchyma (Gordon et al. 2008). Given their proximity to endothelial cells via their perivascular end-feet (Fig. 1), interactions between astrocytes and endothelial cells can directly determine the integrity of the BBB. The perivascular end-feet of astrocytes have several specialized features that include not only expressing channels for water (e.g., aquaporin 4) and ions (e.g., inwardly rectifying Kir 4.1) but also producing molecules such as agrin (Barber and Lieth 1997; Warth et al. 2004) that regulate barrier properties and other humoral factors, including ATP and endothelin-1 (Paemeleire and Leybaert 2000; Ostrow et al. 2000). In particular, given that astrocytes wrap around synapses and actively regulate neuronal activity (Araque et al. 1998), alterations in astrocytes may affect the physiology of both endothelial cells and neurons in an interactive way.

Implications of BBB dysfunction in neurological disorders

Epilepsy

Epilepsy is a common neurological disorder and is characterized by recurring seizures occurring due to hypersynchronized excitability of neurons. It is known that one-third of patients develop “pharmacoresistant” epilepsy, which refers to a disease state that does not respond effectively to antiepileptic drugs. While neuronal hyperexcitability is a key pathophysiological phenomenon, emerging evidence suggests that not only neural components but also factors rooted in the synaptic milieu that disrupt homeostasis within neurovascular units play a critical role in the pathology of epilepsy (Vezzani and Granata 2005; Eyo et al. 2017). For example, severe astrocytic dysfunction has been reported to occur during the early phase of epileptogenesis, resulting in a dysregulated supply of energy metabolites and impaired clearance of ions and glutamates (reviewed in Patel et al. 2019). It has been recently reported that altered mTOR signaling in microglia results in massive reactive astrocytosis and severe spontaneous recurrent seizures in mice (Zhao et al. 2018), indicating that noninflammatory changes in microglia are likely to underlie the development of epilepsy. Furthermore, it has been suggested that compromised integrity of the BBB is highly associated with the pathological processes occurring in epilepsy. For instance, in various animal models of status epilepticus, chronic BBB dysfunction and increased inflammatory responses have been reported (Heinemann et al. 2012; Van Vliet et al. 2014). Notably, extravasation of blood-borne molecules into the brain parenchyma due to compromised BBB integrity has been found to contribute to the development of pharmacoresistant epilepsy (Salar et al. 2014). BBB dysfunction seems sufficient to result in recurrent seizures in animal models (Seiffert et al. 2004). Furthermore, the occurrence of seizures is heightened in patients with a compromised BBB due to severe chemotherapy (Marchi et al. 2007, 2011).

Seizures often worsen the disruption of BBB integrity. Increased permeability of the BBB has been found in patients with epilepsy and is correlated with disease progression (Van Vliet et al. 2007). In animal models, recurrent seizures have been associated with a decrease in the expression of TJ proteins, including claudin-1 and -5, occludin, and ZO-1 (Rempe et al. 2018), and inducing the expression of proteases, including matrix metalloproteinases, that disrupt the integrity of the BBB (Li et al. 2013; Kim et al. 2015; Rempe et al. 2018). A recent study employing in vivo intravital microscopy analyses demonstrated that recurrent seizures and consequent excessive glutamate release results in disruption of the BBB integrity through the activation of NMDA receptors (Vazana et al. 2016). These findings

suggest that compromised BBB and pathological hyperexcitability can robustly affect disease progression in epilepsy in an interrelated way.

Aging

Aging is one of the main risk factors for various neurodegenerative disorders, including AD, Parkinson's disease (PD), and amyotrophic lateral sclerosis (Hou et al. 2019). Notably, the normal aging process involves BBB disruption (Zlokovic 2008; Zhao et al. 2015). Increased BBB permeability seems to be associated with increased inflammation and reduced expression of TJ proteins in the aged brain (Elahy et al. 2015). A recent study has suggested that the decreased expression of sirtuin-1, which is found in the aged brain, plays a critical role in the development of BBB dysfunction (Stamatovic et al. 2019). Additionally, increased BBB permeability is likely to be linked to deteriorating changes related to aging. As summarized in Table 2, BBB dysfunction is closely associated with network hyperexcitability. Indeed, not only progressive BBB dysfunction and albumin extravasation but also heightened seizure susceptibility has been found during normal aging (Senatorov et al. 2019). Given that network hyperexcitability can also exacerbate neurodegenerative processes (Ping et al. 2015; McMackin et al. 2019), it seems reasonable to postulate that BBB disruption may underlie the role of aging as a precipitating factor for neurodegenerative disorders.

Alzheimer's disease

AD is one of the most common neurodegenerative diseases and is characterized by learning and memory deficits, impaired cognition, mood swings, and changes in behavior. The well-known molecular hallmarks of AD include extracellular aggregates of amyloid beta (Aβ) fibrils and intracellular aggregates of hyperphosphorylated tau, known as neurofibrillary tangles (Elahi and Miller 2017). Numerous previous studies have focused on such neuron-centric phenomena. However, emerging evidence suggests that alterations in BBB integrity play a central role in the pathology of AD. For instance, the degree of BBB disruption is tightly correlated with cognitive dysfunction in humans (Nation et al. 2019). Soluble PDGFR-β (sPDGFR-β), which is

Table 2 BBB dysfunction-related changes in neurodegenerative disorders

Disorders	Changes in neurovascular units	References
Epilepsy	Increases in the BBB permeability are linked to the high frequency of seizures	Vliet et al. 2007
	The dysfunction of astrocytes leads to dysregulated clearance of ions and glutamates in neurovascular units	Patel et al. 2019
	Severe chemotherapy induces both compromised BBB and recurrent seizures in humans	Marchi et al. 2007; Marchi et al. 2011
	Excessive glutamate due to hyperexcitability, excitoxcitiy leads to decreases in the tight junction proteins such as claudin-1,-5 and ZO-1	Rempe et al. 2018
	Hyperexcitability increased MMPs leading to BBB disruption	Kim et al. 2015; Rempe et al. 2018
	Excessive release of the glutamate leads to disrupt BBB integrity via the activation of NMDA receptors in the rat brain	Vazana et al. 2016
	Chronic BBB dysfunction and exaggerated inflammatory responses have been found in various animal model of status epilepticus	Heinemann et al. 2012; Vliet et al. 2014
	Altered mTOR signaling in microglia results in both massive reactive astrocytosis and spontaneous recurrent seizures	Zhao et al. 2018
	Recurrent seizures induce BBB dysfunction, correlated with MMP9 levels in CSF	Li et al. 2013
	Serum albumin extravasation due to BBB dysfunction is associated with the development of pharmacoresistant epilepsy	Salar et al. 2014
Aging	The decline in Sirtuin-1 level triggers BBB dysfunction in aged mice	Stamatovic et al. 2019
	Increases in the network hyperexcitability through the activation of TGFβ signaling contribute to BBB dysfunction in hippocampus of aged mice	Senatorov et al. 2019
	Dysregulated BBB permeability along with the heighted inflammation is found in the brain of aged mice	Elahy et al. 2015
Alzheimer's Disease (AD)	The degree of BBB disruption measured as in the CSF levels of sPDGFRβ is correlated with cognitive dysfunction in humans	Nation et al. 2019
	APOE4 carriers have increased MMP9 activity and BBB breakdown in the hippocampus and medial temporal lobe in human	Montagne et al. 2020
	The deficiency of GLUT1 worsens cerebrovascular degeneration, BBB breakdown, and neuronal dysfunction in a mouse model of AD	Winkler et al. 2015

known to be abundantly expressed in BBB-associated pericytes around brain capillaries (Fig. 1), has been reported as a potential cerebral spinal fluid marker of BBB dysfunction; this marker was correlated with dynamic contract-enhanced magnetic resonance imaging measures of BBB breakdown (Nation et al. 2019). Notably, individuals with cognitive impairment were found to have an increased concentration of sPDGFR-β without any significant surge in aggregates of Aβ and tau protein (Nation et al. 2019). These findings suggest that BBB disruption may be a biomarker of cognitive dysfunction, presumably even in the early stages of AD pathology. A recent study employing the E4 variant of apolipoprotein E (APOE4), a well-known genetic risk factor for AD (Corder et al. 1993; Roses 1998), reported that APOE4 is involved in BBB dysfunction (Montagne et al. 2020). Individuals with APOE4 exhibit BBB breakdown characteristic features, particularly in the hippocampus and medial temporal lobe, that are distinct from those of individuals without such a variant protein, and the degree of cognitive decline in APOE4 carriers is significantly correlated with BBB breakdown markers, including the increased activity of matrix metalloproteinase (MMP)-9, which directly induces BBB disruption (Montagne et al. 2020). These findings suggest that BBB dysfunction is likely to be a precipitating event in the development of cognitive decline during the pathological progression of AD.

Potential factors associated with neurological disorders and their influence on BBB integrity

Inflammation

Inflammation has been implicated in various neurological disorders, including multiple sclerosis (Voet et al. 2019), ischemic stroke (Jin et al. 2013), and AD (Akiyama et al. 2000). It is usually associated with a worse prognosis than that associated with neurodegeneration (Glass et al. 2010; Amor et al. 2014). Notably, inflammation in the brain often leads to drastically compromised functional integrity of the BBB. For instance, increased BBB permeability and decreased expression of major TJ proteins, such as claudin-5, occludin, and ZO-1, have been found in cerebral amyloid angiopathy, for which an exaggerated inflammatory response to amyloid beta accumulation is known to be a major pathological marker (Carrano et al. 2012). Seizure-induced inflammation has been found to worsen BBB disruption, as well as increase the duration and frequency of seizures, via the increased expression of IL-1β (Librizzi et al. 2012). Furthermore, the activation of microglia, a key step in the development of neuroinflammation, has been found to induce BBB dysfunction, concomitantly resulting in the loss of TJ proteins on endothelial cells and pericytes, and the increased release of chemokines and cytokines such as IL-6 and MCP-1 (Shigemoto-Mogami Y et al. 2018).

In addition to structural damage, inflammation can alter the functional integrity of the BBB. Adenosine triphosphate-binding cassette (ABC)-type transport proteins, which are highly expressed on endothelial cells, are known to prevent drugs or unwanted substances from entering the brain (Kooij et al. 2011). P-glycoprotein is an ABC transporter family, and it has been reported that systemic inflammation can directly alter P-glycoprotein trafficking in cerebral endothelial cells (McCaffrey et al. 2012). ABC transporters regulate the secretion of chemokine ligands from reactive astrocytes, which is formed in response to chronic inflammation (Kooij et al. 2011). These findings indicate that inflammation triggered by and/or associated with various etiologies related to neurodegeneration can affect the structural and functional integrity of the BBB.

Extracellular matrix and matrix metalloproteinases

Extracellular matrix (ECM) components in neurovascular units play an active role in regulating the structural and functional integrity of the BBB. While the ECM has long been known to provide the vasculature with structural stability, various ECM components can govern cell–cell and cell–matrix interactions. For instance, the laminin family, which is abundantly expressed in the basement membrane, can interact with endothelial cells via integrins, which is followed by binding with other matrix components such as perlecan and agrin (Reed et al. 2019). Furthermore, emerging evidence suggests that ECM molecules actively regulate synaptic plasticity (Kurshan et al. 2014; Ferrer-Ferrer and Dityatev 2018) and that they are dynamically changed in an activity-dependent manner (Lazarevich et al. 2020).

MMPs are key players in the regulation of ECM remodeling. MMPs are endopeptidases that play critical roles in various physiological and pathological processes, including cell migration (Sternlicht and Werb 2001), angiogenesis and cancer metastasis (Sabeh et al. 2004), and wound healing (Rohani and Parks 2015). In neurovascular units, MMPs can degrade both TJ proteins and the basement membrane of the vasculature in the brain (Feng et al. 2011; Dhanda and Sandhir 2018). Notably, the expression and activity of MMPs dynamically change with disease state. For instance, the transcription levels of MMPs are altered during epileptogenesis (Gorter et al. 2007), neuroinflammation (Chandler et al. 1997), and activation of TGFβ signaling (Kim et al. 2017a, b). Given that TGFβ signaling is activated upon BBB disruption (Cacheaux et al. 2009) and that neuroinflammation is exacerbated by increased infiltration of leukocytes and cytokines through a compromised BBB (Ransohoff et al. 2003), it seems reasonable to postulate that the pathological events initiated by or involved in BBB dysfunction

exacerbate disease progression by worsening BBB disruption via increases in levels of MMPs.

Increased expression or activity of MMPs has been found in various brain neurodegenerative disorders, which are closely associated with BBB dysfunction in its pathology (Table 2). Indeed, the expression and activity levels of MMP-2 and MMP-9 are significantly increased in animal models of status epilepticus (Rempe et al. 2018). Increased MMP-9 levels induced by genetic overexpression have been found to induce epileptogenesis following TBI (Pijet et al. 2018). MMP-9 expression is also significantly increased after stroke or TBI, both of which involve BBB breakdown, and the increased MMP-9 expression is likely to exacerbate the loss of TJ proteins and BBB dysfunction (reviewed in Prakash and Carmichael 2015). In addition, the expression level of MMP-3 was found to be increased in the substantia nigra of rats in an experimental model of PD, in which the degeneration of dopaminergic neurons was induced either by 6-hydroxydopamine (Sung et al. 2005) or lipopolysaccharide-triggered inflammation (McClain et al. 2009). On the other hand, MMP-3 deficiency induced by genetic or pharmacological manipulation ameliorated the degeneration of dopaminergic neurons in an animal model of PD (Kim et al. 2007). Given that BBB disruption has been found in patients with PD (Koretekaas et al. 2005), such increased MMP-3 expression seems to contribute to BBB dysfunction during the pathological progression of neurodegeneration occurring in brain disorders such as PD.

BBB as a critical therapeutic target for neurodegenerative disorders

Due to its lack of disease specificity, BBB dysfunction has long been regarded as a common phenomenon that is merely involved in various types of neurological disorders. However, as reviewed herein, evidence has emerged that BBB disruption occurring in the early disease stages can actively instigate or trigger a key pathological process. Indeed, several studies have investigated whether BBB dysfunction-related signaling pathways can be a therapeutic target. Albumin extravasation through a compromised BBB can induce pathological hyperexcitability, which is mediated by TGFβ signaling (Ivens et al. 2007). Pharmacological inhibition of TGFβ signaling, through the administration of losartan (Bar-Klein et al. 2014) or small synthesized molecules to specifically inhibit the receptor (Senatorov et al. 2019), prevented epileptogenesis and reduced seizure susceptibility, respectively. Furthermore, the previous finding that BBB dysfunction precedes other pathological markers, such as heightened inflammation and amyloid β and/or tau-related pathology in patients with mild cognitive impairment (Nation et al. 2019), corroborates the importance of BBB dysfunction as an early diagnostic marker to enable early intervention in AD. Given that APOE4 variants, a well-known genetic risk factor for AD, also result in BBB disruption (Montagne et al. 2020), altered integrity of the BBB may be a critical pathological point in the progression of AD.

Several studies have suggested therapeutic approaches that are associated with improved structural and functional integrity of the BBB. For example, deep brain stimulation of the anterior thalamic nuclei, which is well known for its anti-seizure effects, has been found to reduce BBB disruption and albumin extravasation (Chen et al. 2017). Vitexin, a naturally derived flavonoid compound, was also found to effectively reduce seizure susceptibility by restoring BBB integrity by increasing the expression of TJ-related proteins (Luo et al. 2018). Furthermore, donepezil, an acetylcholine esterase inhibitor that has been previously shown to attenuate the cognitive and psychiatric symptoms of AD (Kim et al. 2017a), has been reported to reduce injury-induced BBB disruption by elevating the expression of claudin-5 (Ongnok et al. 2021). A recent study has suggested that a combination of etodolac and α-tocopherol can be used as a novel therapeutic strategy for the treatment of AD to enhance BBB integrity and amyloid β clearance, highlighting the important role of compromised BBB integrity in the pathology of AD (Elfakhri et al. 2019). Additionally, altering the activity of MMPs that are tightly associated with the BBB, as noted above, has been proven to exert promising therapeutic effects. For instance, a specific inhibitor of MMP2/9 prevented recurrent seizures in animal models of epilepsy (Broekaart et al. 2021). Rapamycin, a well-known inhibitor of mTOR signaling, has been found to protect the structural integrity of the BBB in animal models of AD and prevent vascular cognitive impairment via the downregulation of MMP9. These previous findings further indicate the active and critical role of a compromised BBB in neurodegenerative disorders. However, it remains unclear whether the reduced BBB disruption is a cause for or a consequence of the observed therapeutic effects.

Given that BBB disruption often occurs as a precipitating event in the pathology of neurogenerative disorders, targeting directly on aftereffects of BBB breakdown can be a potential disease-modifying approach. The TGFβ receptor-mediated signaling pathway, one of the major pathways immediately triggered by the infiltration of blood-borne molecules due to BBB disruption, is likely to be an effective target to dampen the consequences of a compromised BBB, as demonstrated in several studies (Cacheaux et al. 2009; Bar-Klein et al. 2014; Kim et al. 2017a, b; Senatorov et al. 2019). In addition, inhibition of potent factors, such as MMPs, that directly instigate BBB disruption could be another potential therapeutic target for alleviating reciprocal interaction between BBB disruption and neurodegeneration, as suggested by studies using genetic or pharmacological manipulation of MMPs in models of ischemic stroke (Murata et al.

2008; Chaturvedi and Kaczmarek 2014), PD (Kim et al. 2007; Choi et al. 2008), and epilepsy (Pijet et al. 2020). It should be noted, however, that MMPs are also known to play a critical role in the degradation of Aβ (White et al. 2006), as well as the processing of Aβ precursor proteins (García-González et al., 2019), which indicates the complex role of MMPs in the pathology of AD. Further studies are warranted to identify a pathway that can regulate the integrity of the BBB without undermining favorable processes involved the course of disease progression.

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Declarations

Conflict of interest The authors declared that they have no competing interests.

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