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REVIEW ARTICLE

Blood–brain barrier and blood–cerebrospinal fluid barrier in normal and pathological conditions

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Abstract Blood-borne substances can invade into the extracellular spaces of the brain via endothelial cells in sites without the blood–brain barrier (BBB), and can travel through the interstitial fluid (ISF) of the brain parenchyma adjacent to non-BBB sites. It has been shown that cerebrospinal fluid (CSF) drains directly into the blood via the arachnoid villi and also into lymph nodes via the subarachnoid spaces of the brain, while ISF drains into the cervical lymph nodes through perivascular drainage pathways. In addition, the glymphatic pathway of fluids, characterized by para-arterial pathways, aquaporin4-dependent passage through astroglial cytoplasm, interstitial spaces, and paravenous routes, has been established. Meningeal lymphatic vessels along the superior sagittal sinus were very recently discovered. It is known that, in mice, blood-borne substances can be transferred to areas with intact BBB function, such as the medial regions of the hippocampus, presumably through leaky vessels in non-BBB sites. In the present paper, we review the clearance mechanisms of interstitial substances, such as amyloid-β peptides, as well as summarize models of BBB deterioration in response to different types of insults, including acute ischemia followed by reperfusion, hypertension, and chronic hypoperfusion. Lastly, we discuss the relationship between perivascular clearance and brain disorders.

Keywords Blood–brain barrier · Blood–cerebrospinal fluid barrier · Glymphatic pathway · Perivascular drainage pathway

Abbreviations

ABC	ATP-binding cassette
Aβ	Amyloid-β
AD	Alzheimer's disease
BBB	Blood–brain barrier
BCSFB	Blood–cerebrospinal fluid barrier
CAA	Cerebral amyloid angiopathy
CSF	Cerebrospinal fluid
FPRL1	Formylpeptide receptor-like-1
IDE	Insulin-degrading enzyme
ISF	Interstitial fluid
LDLR	Low-density-lipoprotein receptor
LRP	LDLR-related protein
MRI	Magnetic resonance imaging
NMO	Neuromyelitis optica
P-gp	P-glycoprotein
RAGE	Receptor for advanced glycation end product

Blood–brain barrier (BBB) and blood–cerebrospinal fluid (CSF) barrier (BCSFB)

The BBB of cerebral vessels has been well studied and restricts the entry of blood-borne substances into the brain parenchyma [1, 2]. The BBB is composed of a monolayer of endothelial cells with no fenestrations and scarce cytoplasmic vesicles. The endothelial cells are reinforced by pericytes and the basement membrane. The end-feet of the astrocytes cover the abluminal surface of the basement

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membrane. In addition, the BCSFB is also well known, and is mainly composed of a monolayer of epithelial cells of the choroid plexus, that separates blood-borne substances from the CSF [3]. Because the fenestrated endothelial cells of the capillaries in the choroid plexus are permeable to blood-borne substances, the BCSFB in the choroid plexus epithelium has an important role in controlling the entry of these substances into the CSF. In addition, previous studies have reported that the junctions between the ependymal cells surrounding the ventricles are open [2, 4]. The pia mater is known to be a loose tissue with gaps or fenestrations, and allows flow through of fluids [3]. Therefore, two major barriers, the BBB and the BCSFB, likely play significant roles in the maintenance of homeostasis in the brain.

Roles of circumventricular organs in interstitial fluid (ISF) flow

It is known that BBB function is defective or absent in certain periventricular regions of the brain, known as circumventricular organs [3]. It is unclear whether the defective BBB function in the circumventricular organs has an effect on the BBB function in areas close to the organs. It has been demonstrated in mice that blood-borne substances enter the brain parenchyma via endothelial cells of the subfornical organ with defective BBB function, and moves throughout not only the white matter of the corpus callosum [5], but also the hippocampus [6]. In addition, horseradish peroxidase (HRP) injected intravenously was confirmed to be transported throughout the periventricular areas, presumably via leaky vessels in the choroid plexus [7]. A portion of the intravenously injected HRP was also transported throughout medial regions of the amygdala [8]. These reports suggest that, at least in mice, the leaky vessels in the circumventricular organs likely play significant roles in the BBB function in areas close to the organs.

Drainage pathways of CSF and ISF

The drainage pathways of CSF and ISF from the brain have been examined in some studies [9–12]. Three major drainage pathways have been proposed. The first pathway is characterized by: CSF of the subarachnoid space drainage directly into the blood via the arachnoid villi of the superior sagittal sinus. The second pathway is characterized by: CSF of the subarachnoid space drainage into the lymph nodes via the subarachnoid spaces around the olfactory nerves and nasal lymphatics. The third pathway is characterized by: ISF drainage into the cervical lymph nodes through the basement membrane of the walls of the capillaries and the tunica media of the arteries, and then through the vessel walls of the internal carotid artery in the neck [9–12].

The glymphatic pathway and meningeal lymphatic vessels

Recently, Iliff et al. [13] reported that a paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, and proposed this system to be named the glymphatic pathway. The glymphatic pathway includes multiple components. The first is the para-arterial routes of the fluids. The second is the convective bulk ISF flow facilitated by aquaporin4-dependent astroglial water flux. The third is the paravenous routes of fluids. Finally, the solutes and fluids may be dispersed into the subarachnoid CSF or enter the bloodstream across the vasculature [13]. In addition, meningeal lymphatic vessels lining near the dural sinus were recently discovered [14, 15]. A detailed review paper on the glymphatic pathway and the perivascular drainage pathway has been published [16].

These recent studies [10–16] suggest that perivascular clearance comprises both perivascular drainage and glymphatic pathways (Fig. 1). Through the perivascular drainage pathway, ISF flows through the basement membrane in walls of cerebral capillaries, the tunica media of the arteries, and the vessel walls of the internal carotid artery, and then drains into the cervical lymph nodes. This pathway may be affected by cellular uptake or degradation. Through the glymphatic pathway, CSF flows through the para-arterial routes, enters the interstitial space after aquaporin4-dependent transport through the astroglial cytoplasm, drains into the paravenous routes, and then possibly disperses into the subarachnoid CSF or enters the bloodstream across the vasculature. CSF in the subarachnoid space drains directly into the blood via the arachnoid villi of the dural sinus, enters the meningeal lymphatic vessels, or drains into the cervical lymph nodes via the subarachnoid spaces around the olfactory nerves and nasal lymphatics.

Transporters/receptors associated with clearance of Aβ peptides through the BBB and the BCSFB in the human brain

At present, several kinds of transporters or receptors such as low-density-lipoprotein receptor (LDLR) [17], LDLR-related protein 1 (LRP1) [18, 19], LRP2 [20], formylpeptide receptor-like-1 (FPRL1) [21], ATP-binding cassette (ABC) transporter–A1 (ABCA1) [22], ABCC1 [23],

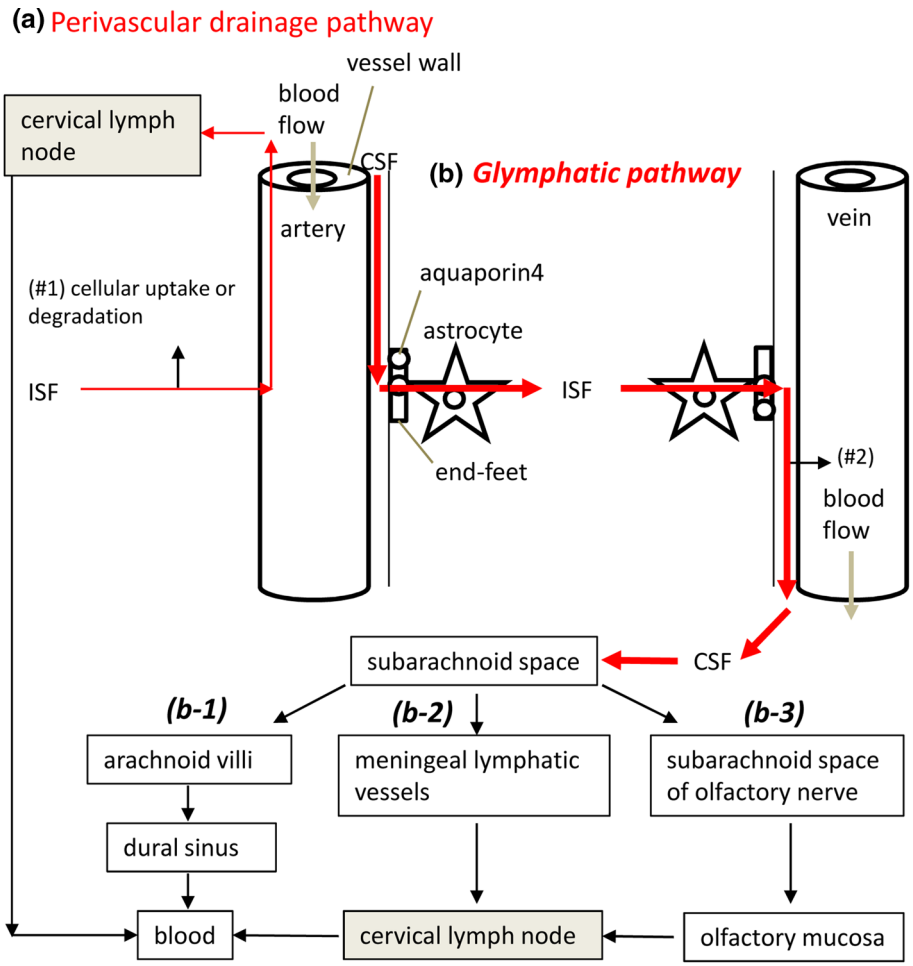

Fig. 1 Recent reports [10–16] suggest that perivascular clearance of ISF (*indicated by lines*) comprises both perivascular drainage and glymphatic pathways. **a** Through the perivascular drainage pathway (*indicated by thin red lines*), ISF flows drains through the basement membrane in walls of cerebral capillaries, the tunica media of arteries, and through the vessel walls of the internal carotid artery, and then drains into the cervical lymph nodes. This may be affected by cellular uptake or degradation (#1). **b** Through the glymphatic pathway (*indicated by thick red lines*), CSF flows through the para-arterial routes, enters the interstitial space through aquaporin4-dependent transport through the astroglial cytoplasm, drains into the paravenous routes, and may be dispersed into the subarachnoid CSF or enter the bloodstream across the vasculature (#2). CSF in the subarachnoid space drains directly into the blood via the arachnoid villi of the dural sinus (b-1), enters into the meningeal lymphatic vessels (b-2), or drains into the cervical lymph nodes via the subarachnoid spaces around the olfactory nerves and nasal lymphatics (b-3)

ABCG4 [24], ABCB1 [25], CD36 [26], insulin-degrading enzyme (IDE) [27], and the receptor for advanced glycation end product (RAGE) [28]) have been reported to be associated with the clearance of Aβ peptides through the BBB and the BCSFB, although it is unclear whether Aβ peptides are transported transendothelially or transepithelially via these transporters. RAGE is known as an influx transporter of Aβ at the BBB [28]. Recently, we reported the immunohistochemical localization of transporters/receptors associated with the clearance of Aβ peptides, using autopsied human brains [29]. We observed immunoreactivity of LDLR (Abnova, Taipei, Taiwan), LDLR-related protein 1 (LRP1) (Santa Cruz, Dalla TX), LRP2 (Gene Tex, Irvine, CA), formylpeptide receptor-like-1 (FPRL1) (Novus, Littleton, CO), ABCA1 (Abcam, Cambridge, UK), ABCC1 (Abcam), and ABCG4 (Bioss, Woburn, MA) in the choroid plexus epithelium of human brains. Immunoreactivity for CD36 (ProteinTech, Chicago IL) as well as LDLR, LRP1, LRP2, FPRL1, ABCA1, ABCC1 and ABCG4 was observed in the ventricular ependymal cells of the brain. In addition, another study reported the immunoreactivity of ABCB1 in the choroid plexus epithelium [25], although Matsumoto et al. [29] reported that no ABCB1 staining using the antibody for ABCB1 (Calbiochem, Darmstadt, Germany) was observed in the choroid plexus epithelium. Weak immunoreactivity for IDE (Abcam) has been frequently observed in the choroid plexus epithelium and ventricular ependymal cells. Clear

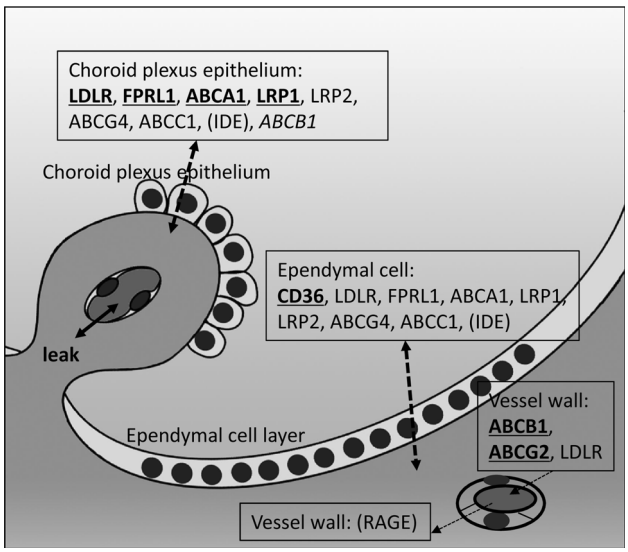

Fig. 2 Recent studies of autopsied human brain [25, 29], have reported the immunohistochemical expression of LDLR, LRP1, LRP2, FPRL1, ABCA1, ABCC1, and ABCG4 in the choroid plexus epithelium. Immunohistochemical expression of CD36 as well as LDLR, LRP1, LRP2, FPRL1, ABCA1, ABCC1, and ABCG4 was also observed in the ventricular ependymal cells. Clear expression of transporters is *indicated by underlined bold type*. In addition, the study [25] reported immunohistochemical expression of ABCB1 (*indicated by italic type*) in the choroid plexus epithelium. Weak expression of IDE (*indicated in parentheses*) was frequently observed in choroid plexus epithelia and ventricular ependymal cells. Clear expression of ABCB1 and ABCG2 (*indicated by underlined bold type*) was observed in the microvessels, as well as LDLR. Weak expression of RAGE (*indicated in parentheses*) was occasionally observed in the microvessels

immunoreactivity for LDLR, ABCB1, and ABCG2 (Abcam) has been reported to be observed in the microvessels. In addition, expression of FPRL1, ABCA1, ABCC1, and RAGE (LSBio, Seattle, WA) has been frequently reported to be observed in the microvessels. Figure 2 shows the supposed localization of these transporters or receptors determined by immunohistochemical studies using human brains. These findings suggest that these transporters/receptors expressed in the BBB and BCSFB complementarily or cooperatively contribute to the clearance of amyloid-β peptides from the brain.

Clearance of tau

The mechanism of tau clearance remains to be clarified. Transporters that specifically transport tau through the BBB have not yet been identified. It is thought that tau does not undergo clearance through the BBB, and is instead cleared from the brain primarily by degradation, ISF flow, and CSF absorption [16, 30, 31]. It is likely that neuronal death and increased intracellular tau concentrations or aggregation trigger the release of tau into the extracellular space, leading to elevated CSF tau levels [16]. Iliff et al. [31] showed that extracellular tau is cleared from the brain through the glymphatic pathways. In mice receiving traumatic brain injury, glymphatic pathway function was reduced by approximately 60 %, with the impairment persisting for at least 1-month post injury, followed by development of neurofibrillary pathology and neurodegeneration. In addition, they showed that genetic knockout of the gene encoding the astroglial water channel aquaporin-4, which plays an important role in paravascular interstitial solute clearance, exacerbated the dysfunction of the glymphatic pathway after the traumatic injury, suggesting the significance of the role of the glymphatic pathway in tau pathology.

BBB damage in pathological conditions of the human brain and in experimental animal models

Many papers have reported the deterioration of the BBB in response to several types of cerebral vasculature insults [32]. In the following sections, we will introduce the response of the BBB against several types of insults that are known to be associated with brain function, including aging, cognitive dysfunction, acute ischemia followed by reperfusion, chronic hypoperfusion, hypertension, and hyperglycemia.

(a) BBB changes with aging

Although it had been controversial whether BBB permeability significantly increases with aging in human brains, a large-scale meta-analysis study including 31 BBB permeability studies demonstrated that BBB permeability, evaluated by CSF/serum albumin ratios, increased with normal aging, and further increased in patients with dementia and with accumulation of white matter lesions [33]. Recently, BBB breakdown was shown to be an early event in the aging brain, beginning in the hippocampus, and may contribute to cognitive impairment [34]. Similarly, in experimental animals, BBB permeability to serum albumin increased with aging in three different strains of mice [35]. This increase in permeability was accelerated in aged mice showing cognitive impairment, such as senescence accelerated prone mice (SAMP8) [36–38].

(b) BBB changes in acute ischemia followed by reperfusion

Increased BBB permeability has been observed in magnetic resonance imaging (MRI) of acute ischemic stroke cases. Some studies have demonstrated that ischemia-modified albumin, which is thought to be formed by

the production of reactive oxygen species and passage through an impaired BBB, is a useful serum marker for the early diagnosis of stroke, particularly with acute ischemia and reperfusion [39, 40]. Thus, it is likely that BBB permeability is increased even in the early stages of acute stroke. The increased BBB permeability to intravenously injected HRP was observed in the hippocampus of a Mongolian gerbil experimental model of acute ischemia followed by reperfusion [41].

(c) BBB changes in chronic hypoperfusion

Alterations of the BBB in white matter lesions presumably due to chronic hypoperfusion, were observed in cerebrovascular and Alzheimer's disease patients [42]. In addition, BBB permeability was confirmed to be increased in the white matter lesions of Binswanger's disease patients by contrast-enhanced MRI [43]. BBB permeability to intravenously injected HRP in a Wistar rat experimental model of chronic cerebral hypoperfusion was observed to be increased in the corpus callosum [44].

(d) BBB changes in hypertension

High blood pressure has been reported to precede the formation of white matter lesions, presumably accompanied by impairment of the BBB [45]. In addition, it has been reported that hypertension, as well as atherosclerosis and cerebral amyloid angiopathy, is the most common causes of BBB lesions [46]. BBB permeability to intravenously injected HRP in animal models of hypertension was increased in the hippocampus of 3-month-old spontaneously hypertensive rats (SHR) and stroke-prone SHR (SHRSP) [47, 48].

(e) BBB changes in hyperglycemia

BBB permeability was reported to be increased in patients with type II diabetes by gadolinium MRI [49]. Although BBB permeability to naïve HRP was not increased in diabetic db/db mice, changes in the endothelial glycocalyx were induced in a hyperglycemic state [50]. In addition, it has been demonstrated that BBB permeability was increased in experimental diabetic animals using sugar derivative tracers such as ^{14}C-labeled sucrose and fluorescein isothiocyanate-labeled dextrans [51, 52].

Biochemical analyses of vessels with BBB damage

Microarray and real-time quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) analyses using vessels located along the hippocampal fissure in the hippocampus of 3-month-old SHRSP with the BBB damage, revealed that the increased gene expression of osteopontin, matrix metalloproteinase-13, and CD36 [53–55].

Dysfunction of perivascular clearance and brain disorders

Obstruction of the passage of fluids through perivascular drainage and glymphatic pathways may induce brain disorders, such as cerebral amyloid angiopathy. Amyloid-β (Aβ) peptides in the brain parenchyma are thought to be eliminated via (1) degradation by peptidases [56–58], (2) cellular uptake [59–63], (3) efflux into the blood via efflux transporters at the BBB [64–67], (4) ISF clearance through the perivascular drainage pathway [68, 69], (5) ISF clearance through the glymphatic pathway, followed by CSF absorption through the arachnoid villi and meningeal lymphatic vessels [16], or (6) efflux into the ventricles via efflux transporters of the BCSFB [70, 71].

Increasing attention has been paid to the effects of interstitial or cerebrospinal fluid obstruction on the pathogenesis of AD, as well as cerebral amyloid angiopathy [12, 72]. It was recently reported that impairment of the glymphatic pathway aggravated glial tau pathology in experimental animals receiving traumatic brain injury [31]. It was also reported that deletion of the *Aqp4* gene suppressed the clearance of soluble Aβ, suggesting that this pathway may remove Aβ from the central nervous system [13]. Expression of AQP-4 in the foot processes of astrocytes was confirmed to be decreased in patients suffering from neuromyelitis optica (NMO) [73], suggesting that the glymphatic pathway is likely to be affected in the brains of NMO. Accordingly, detailed functional image analyses in living bodies, as well as examination of autopsied samples, will be useful to clarify the pathogenesis of various kinds of neurodegenerative disorders.

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Compliance with ethical standards

Conflict of interest None.

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