

Neuroinflammation: A Common Pathway in CNS Diseases as Mediated at the Blood-Brain Barrier

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Key Words

Blood-brain barrier • Neuroinflammation • Cytokines • Transport • Alzheimer's disease • P-glycoprotein • Drug delivery

Abstract

The blood-brain barrier (BBB) is not simply a physical barrier but a regulatory interface between the central nervous system (CNS) and immune system. The BBB both affects and is affected by the immune system and connects at many levels with the CNS, including the following: (1) the BBB transports cytokines and secretes various substances with neuroinflammatory properties; (2) transporters are altered in disease states including traumatic injury, Alzheimer's disease and inflammatory processes; (3) cytokines and other immune secretions from the cells comprising the BBB are both constitutive and inducible; (4) immune cells are transported across the BBB by the highly regulated process termed diapedesis, which involves communication and interactions between the brain endothelial cells and the immune cells; (5) the neuroimmune system has various effects on the BBB, including modulation of important transport systems and in extreme pathological conditions even disruption of the BBB, and (6) the brain-to-blood efflux transporter P-glycoprotein is al-

tered in inflammatory conditions, thus affecting drug delivery to the brain. In summary, the BBB is an interactive interface that regulates and defines many of the ways that the CNS and the immune system communicate with one another.

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Introduction

Inflammatory processes are involved in a wide variety of diseases and conditions that involve the central nervous system (CNS). These range from neurodegenerative diseases such as Alzheimer's disease (AD) to obesity. The study of the interactions between the immune system and CNS has given rise to a rich field often referred to as neuroimmunology or psychoneuroimmunology. The CNS was once felt to be an immune-privileged area. A major rationale for this notion of sequestration was the blood-brain barrier (BBB), which was believed to prevent immune cells and mediators of immunity from accessing the CNS. Currently, the separation of the immune system and the CNS is appreciated to be a qualified one with cross-talk between these two systems occurring both in disease and physiological states. Definition of the role of

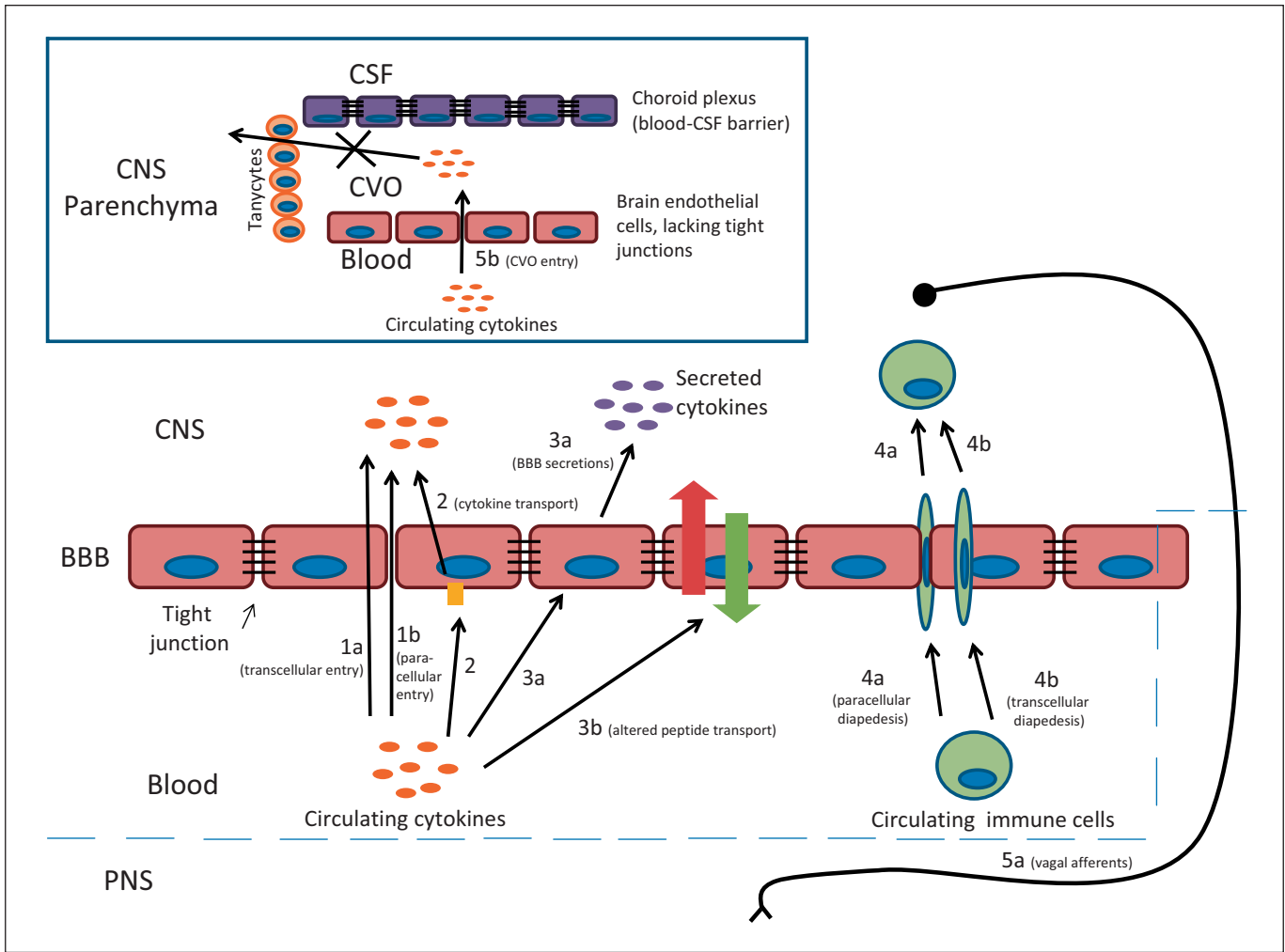


Fig. 1. An endocentric view of neuroinflammation. (1) Disruption of BBB integrity and disassembly of tight junctions permits transcellular (1a) and paracellular (1b) entry of circulating components. (2) Circulating cytokines are transported across the BBB into the brain. (3) BBB endothelial cells are activated by circulating cytokines and other circulating inflammatory mediators, causing secretion of inflammatory mediators including cytokines into the brain parenchyma (3a) and alterations in the

transport of substances across the BBB (3b). (4) Circulating immune cells cross the BBB via diapedesis by paracellular (4a) and transcellular (4b) pathways. (5) Circulating cytokines bypass the BBB by inflammatory activation of vagal afferents (5a) or inflammatory mediators crossing the leaky vasculature into circumventricular organs (CVOs; 5b), which are compartmentalized from the rest of the CNS by tanyctic barriers. PNS = Peripheral nervous system.

the BBB has also shifted in that it is now appreciated to mediate, and in some cases to define, the interactions between the CNS and the immune system.

The ways in which the CNS and the immune system interact are numerous (fig. 1). Having participated in the dichotomy of the neuro- and immune systems by separating the CNS and the circulation, the BBB does not immediately appear to be involved in their interactions. For example, a great deal of communication between the

CNS and immune systems occurs through vagal mediation [1, 2]. However, a number of other mechanisms have been discovered through which the CNS and immune systems communicate, and the BBB is involved in many of them. As examples, immune cell trafficking into the CNS and the exchange of cytokines between the circulation and the CNS each involve the BBB. Additionally, the immune system influences the functioning of the BBB, which in turn affects CNS function in health and disease.

Hence, there is a dynamic interplay between the CNS, the BBB and the immune system. This review will examine in two sections some of the established mechanisms that involve the BBB and neuroimmune interactions. The first section will concentrate on physiologic processes and regulation of those processes, although occasionally disease states will be discussed that help to illustrate underlying physiologic processes. The second section will then examine how these processes can contribute to and even produce diseases.

Overview of Interactions between the BBB and the Neuroimmune System

BBB Disruption

That the BBB can be disrupted during infection and inflammation has long been known [3–7]. BBB disruption can be catastrophic to an organism, removing the protective function that the BBB provides to the CNS. Early studies with cytokines suggested that disruption occurred quite readily, although later studies showed that this in part may have been because solvents such as SDS were not totally removed from the early preparations of cytokines [8, 9]. Treatment with lipopolysaccharide (LPS) can also result in BBB disruption [6]. LPS is derived from the cell wall of Gram-negative bacteria and induces a robust increase in blood and brain levels of many cytokines. Subsequent studies have shown that it can be difficult to consistently disrupt the BBB with individual cytokines and even with LPS [10, 11]. This makes teleological sense as mechanisms would be expected to have evolved under evolutionary pressures to protect the brain by preventing BBB disruption.

The mechanisms by which neuroimmune events disrupt the BBB are not fully understood. It is also increasingly speculated that the restrictive aspects of the BBB are not always maximal, but may be modulated within limits as part of physiological processes. It is clear that some cytokines have effects on brain endothelial cells that could lead to either disruption or modulation of the restrictive aspects of the BBB. These effects include alterations of the actin cytoskeleton and tight junction expression [12, 13].

Immune Cell Trafficking

Leukocytes were once thought to enter the CNS only during disease and as a result of BBB disruption. More recent studies have shown that immune cell surveillance is a physiologic aspect of neuroimmunity [14–16]. The detailed mechanisms by which immune cells enter the CNS

have been extensively described [for a review, see 17, 18] and are beyond the scope of this review. Instead, this section will provide a brief overview of the process of immune cell trafficking under physiological conditions, and later sections will describe how trafficking is altered under neuroinflammatory conditions. Because the rate of leukocytes entering the CNS is relatively low under physiological conditions [15], inflammatory models have been critical in delineating mechanisms by which leukocytes cross the BBB in vivo. One example of such a model is experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis where high levels of leukocyte infiltration into the CNS are observed [14]. In EAE, cross-talk between activated myelin-specific CD4+ T lymphocytes, endothelial cells of a healthy BBB and other components of the neurovascular unit is required both for entry of the activated lymphocytes into the CNS as well as further recruitment of leukocytes from the circulation [17]. In vivo studies following fluorescently labeled encephalitogenic T cells have shown that the capture and subsequent diapedesis of these cells across a noninflamed BBB is dependent on the interaction of α 4-integrin with vascular cell adhesion molecule-1 expressed on brain endothelial cells [19, 20]. Interestingly, these studies showed that the initial capture of immune cells at the BBB in spinal cord and retinal microvessels happens abruptly without rolling, which may be due to a lack of P-selectin in Weibel-Palade bodies of parenchymal endothelial cells [21, 22]. Furthermore, diapedesis in these vessels occurs slowly, requiring between 4 and 16 h for complete passage across the BBB [19, 20]. This delayed response is likely due to further communication between the immune and endothelial cells [23], which is necessary for the recruitment of other factors to facilitate diapedesis, such as intercellular adhesion molecule-1 [17, 24]. Although a small amount of serum protein accompanies immune cells crossing the BBB [25], under the conditions outlined above, the BBB has been shown to remain intact [26]. When the BBB is inflamed, additional interactions occur, which will be discussed in the disease section of this review.

BBB Transporters for Cytokines

Many cytokines are capable of crossing the BBB, thus providing a direct link between the circulating and CNS compartments of the immune system [27, 28]. Many of these cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)- α , fibroblast growth factor, epidermal growth factor and leukemia inhibitory factor [29–34], are transported across the BBB by distinctive unidi-

rectional saturable transport systems. Additionally, cytokines can cross from cerebrospinal fluid into blood with the reabsorption of cerebrospinal fluid; by this mechanism, the CNS can make significant contributions to blood levels of cytokines [35, 36]. Only one cytokine, IL-2, has to date been found to be transported by a saturable system in the brain-to-blood direction [37].

In some cases, the transporter across the BBB has been identified. In the case of TNF, the transporters are known to be the same proteins as its receptors, with both p55 and p75 being involved in a transcytotic (i.e. vesicle-dependent) mechanism [38, 39]. In other cases, such as for epidermal growth factor, the transporter protein is not the same protein as that forming the receptor [31].

Cytokine transporters at the BBB provide one mechanism by which circulating cytokines can affect the CNS. For example, transport of IL-1 α into the posterior division of the septum mediates in large part the cognitive impairments associated with sickness behavior [40, 41]. It is likely that IL-1 α crossing into the brain from the blood both acts directly at receptors at the posterior division of the septum and also stimulates release of IL-1 α and IL-1 β from brain sources [42]. TNF- α transport mediates neurotoxicity at the substantia nigra, providing a pathway by which this cytokine could be involved in promoting Parkinson's disease [43]. The transport of fibroblast growth factor across the BBB explains its ability after peripheral administration to promote neurogenesis and to protect the hippocampus from ischemic injury [44, 45].

Immune Events Affect BBB Transporters

Several of the classic saturable transporters at the BBB are altered or modulated by neuroimmune-related events. For example, tryptophan levels increase in the brain of animals exposed to TNF, likely because of increased transport across the BBB [46]. Insulin transport across the BBB is enhanced in mice treated with LPS and is mediated through induction of nitric oxide synthase [47]. The rate of transport of TNF- α from blood to brain is enhanced in mice with experimental allergic encephalopathy. Although these mice also have disruption of the BBB, the increased entry of TNF- α is caused by an enhancement of its saturable transporter [48]. In contrast, the transport of IL-15 is selectively abolished in the brain but not in the spinal cord of mice with experimental allergic encephalopathy [49].

Another BBB efflux transporter whose expression and function are modulated by inflammatory processes is P-glycoprotein (P-gp), a member of the ATP-binding cassette protein family [50]. P-gp is predominantly located

on the luminal side of brain endothelial cells [50]; this is consistent with its primary function to restrict the passage of circulating amphipathic molecules, including many xenobiotics, into the brain [50, 51]. Multiple studies reporting the effects of proinflammatory cytokines on P-gp expression and function in cultured brain endothelial cells show varying results. For example, increases, decreases or no changes in P-gp mRNA, protein expression and function have been reported for TNF- α , IL-1 β and IL-6 [52–60]. Possible explanations for these disparate findings include the use of brain endothelial cells from different species, the use of primary versus immortalized cells and the time between cytokine application and analysis.

In support of the latter explanation, studies using freshly isolated rat brain capillaries demonstrated that TNF- α induces a time-dependent modulation of P-gp activity. An initial decrease in activity lasting for 3 h is followed by an increase in P-gp activity that doubles control values by 6 h [54, 57, 58]. The effects of TNF mediated directly at brain endothelial cells occur via nuclear factor (NF)- κ B [61, 62]. Interestingly, multiple *in vitro* as well as *in vivo* studies have also found that P-gp activity does not always correlate with protein levels of P-gp [54, 58, 63, 64]. Furthermore, induction of systemic inflammation by intraperitoneal administration of LPS has been found to result in decreased P-gp activity [63], although another group found that this change was only significant in mice lacking the p50 subunit of NF- κ B [64]. In both of these studies, P-gp protein expression was increased, further suggesting that inflammatory regulation of P-gp relies on posttranslational mechanisms. Given that decreases in P-gp activity at the BBB affect the bioavailability of many drugs in the brain [51], a better understanding of inflammatory regulation of P-gp function could have important applications in a clinical setting.

BBB Cell Secretions

Brain endothelial cells form the vascular BBB, and epithelial cells form the cerebrospinal fluid-blood barrier. Both of these cell types secrete cytokines and other substances associated with immune cell activation, such as nitric oxide and prostaglandins [52, 65–67]. Thus, the cells that form the BBB can themselves become activated in a fashion similar to that of circulating immune cells. BBB cells secrete some cytokines constitutively, but secretion can also be induced or modulated. For example, several workers have shown that IL-6 release from brain endothelial cells is stimulated by LPS [65, 67, 68]. Another example is the release of endothelin-1, IL-6 and IL-8 from

brain endothelium in response to HIV-1, its cell surface glycoprotein gp120 and TNF [69, 70]. Release of gp120-induced endothelin-1 from brain endothelial cells is inhibited by N-acetylcysteine through a pathway dependent on mitogen- and stress-activated protein kinase [71].

A unique feature of cytokine release relies on the polarity of the brain endothelial cell, the only cell of the neuroimmune system that is simultaneously both in the CNS (the abluminal cell membrane faces brain interstitial fluid) and in the periphery (the luminal cell membrane faces the circulation). As such, the brain endothelial cell can receive input from one membrane surface that modulates the release of a cytokine from the other membrane surface. For example, LPS applied to the abluminal surface greatly increases the release of IL-6 from the luminal surface, whereas adiponectin applied to the luminal surface reduces IL-6 release from the abluminal surface [68, 72]. This polarity likely underlies one mechanism by which immune signaling can be relayed between the CNS and the circulation.

Some cytokines produced by brain endothelial cells are apparently not secreted but have intracellular roles. IL-32, for example, is associated with endoplasmic reticulum and its expression is under the influence of Akt [73].

Diseases Involving the BBB and Neuroimmune Mechanisms

Immune Cell Trafficking

Under pathological conditions involving neuroinflammation, an inflamed BBB presents additional signals that lead to increased levels of immune cell recruitment to the CNS. For example, whereas initial capture of encephalitogenic T cells by a healthy BBB in EAE relies solely on the interaction between vascular cell adhesion molecule-1 and $\alpha 4$ -integrin, interactions with the inflamed BBB persist in spite of $\alpha 4$ -integrin blockade and likely involve a synergistic interaction with selectins [17]. Up-regulation of adhesion molecules also occurs in response to increased levels of cytokines and chemokines in the brain [74, 75]. Initiation of neuroinflammation by injection of cytokines into the brain also recruits immune cells to the parenchyma, but interestingly this process may be blocked if there is concurrent systemic inflammation [76]. Immune cell trafficking to the CNS has also been found to occur in other neurodegenerative conditions such as AD, Parkinson's disease and neuroAIDS and is thought to contribute to varying extents to disease progression. In Parkinson's disease, T lymphocytes are

present in the midbrain, and leukocyte infiltration occurs in brains of mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [77]. Furthermore, mice deficient in CD4 are resistant to MPTP-induced neurotoxicity in the substantia nigra [77]. In the context of AD, evidence suggests that circulating immune cells of monocyte lineage enter the CNS and can effectively clear amyloid- β (A β) from the brain [78]. Although it has been disputed that monocyte entry into the CNS is an artifact from BBB disruption that occurs following irradiation after adoptive transfer [79, 80], it is noteworthy that BBB disruption does occur in later stages of AD [81]. Therefore, additional studies are necessary to elucidate whether leukocyte trafficking occurs in earlier stages of AD when the BBB remains intact. In neuroAIDS, lentiviral-infected macrophages are recruited to the CNS, acting as Trojan horses that carry HIV across the BBB [82]. Once in the CNS, HIV causes inflammatory reactions in the brain that can result in CD8+ lymphocyte infiltration [83], as found in cases of HIV encephalitis [84]. Together, these findings suggest that immune cell trafficking across the BBB is an adaptive physiological process, but that loss of fine-tuned regulation has serious consequences which can manifest as neurodegenerative disease.

The BBB in Traumatic Brain Injury

Traumatic brain injury (TBI) is a serious condition in emergency medicine, and its pathophysiological profile is varied and complicated [85]. Neuroinflammation is an important component of TBI, contributing to many aspects of its CNS pathology. BBB disruption caused by TBI leads to neutrophil influx [86]. Leukocytes release proinflammatory cytokines, cytotoxic proteases and reactive oxygen species, in turn initiating the immune functions of native glia [87, 88]. Activated glial cells, especially classically activated microglia, then propagate many of the same inflammatory processes as invading neutrophils and contribute to neuroinflammatory processes after TBI [89]. Key contributing factors to secondary brain damage are inflammation, metabolic disturbances and cerebrovascular dysfunction that further increase injury-induced tissue ischemia and brain edema resulting from BBB disruption [90]. The control of neutrophil influx following TBI might attenuate secondary brain injury. At sites of inflammation, neutrophils adhere to endothelial cells by binding to adhesion molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule and platelet endothelial cell adhesion molecule-1 [91]. The central role of matrix metalloproteinase-mediated pathological processes has been demonstrated in

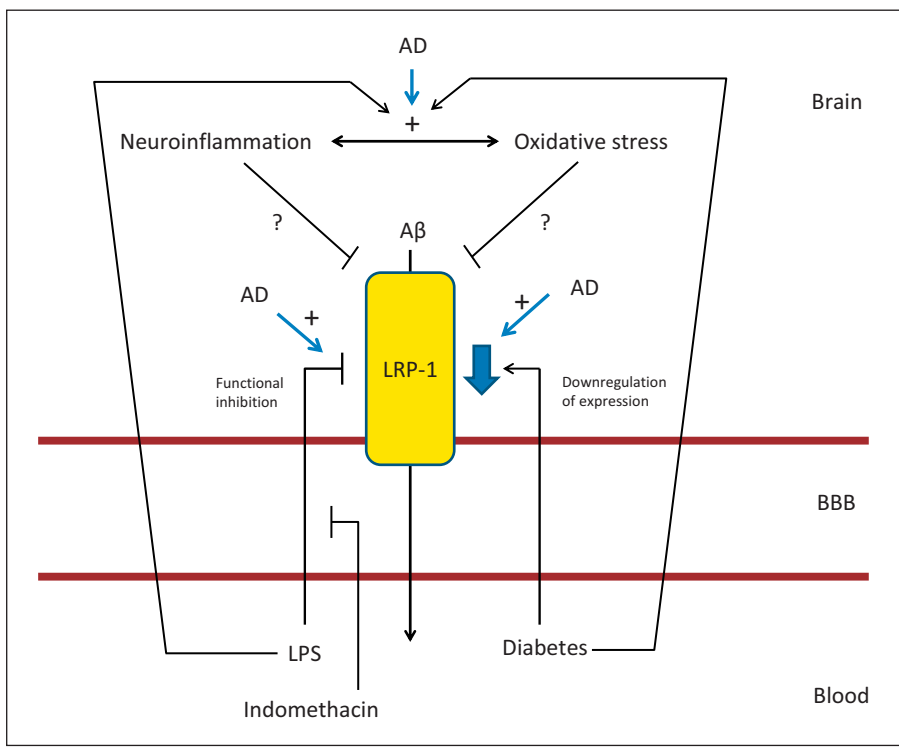


Fig. 2. Inflammatory regulation of LRP-1. Aβ is transported across the BBB in the brain-to-blood direction (efflux) by the transporter LRP-1. In AD, LRP-1 is down-regulated at the BBB and decreased efflux of Aβ occurs, contributing to Aβ accumulation in the CNS. Inflammation induced by peripheral administration of LPS reduces Aβ efflux via LRP-1, and this is inhibited by indomethacin. Diabetes causes downregulation of LRP-1 at the BBB. Both LPS and diabetes cause inflammation and oxidative stress in the CNS, which could potentially contribute to LRP-1 dysfunction.

several models of neuroinflammation [92]. Hypoxia-inducible factor-1α, an upstream transcription factor induced by hypoxia, regulates the subsequent expression of many kinds of proteins responding to the various pathophysiological conditions induced by hypoxia [93]. Expression of matrix metalloproteinase-9 and hypoxia-inducible factor-1α is enhanced after TBI and likely plays an important role in BBB disruption, as inhibition of this expression suppresses BBB disruption and brain edema following TBI [92, 94]. Symptomatic epilepsy and neurodegenerative diseases after TBI are also very serious secondary complications and affect the quality of life in TBI patients. Recently, these complications have also been thought to be closely related to neuroinflammation. A relationship between BBB dysfunction and these diseases has been reported [95]. Thus, BBB disruption and neuroinflammation are important therapeutic targets in every stage of TBI.

BBB Secretions in Disease

Secretion of cytokines from the cells that comprise the BBB may also mediate disease processes. Deane et al. [96] have outlined a pathway by which Aβ protein activates the BBB receptor transporter receptor for advanced glycation end products. In turn, the receptor for

advanced glycation end products induces the release of endothelin-1 from brain endothelial cells, which then mediates vasoconstriction. Endothelin-1 release from brain endothelial cells is also induced by HIV-1 proteins [69]. The endothelin-1 is released from the abluminal side of the brain endothelial cells, thus directly accessing neurons and other cells within the CNS. Endothelin-1 levels in cerebrospinal fluid correlate with the severity of the neuroAIDS syndrome, and endothelin-1 also affects the functioning of BBB transporters, including P-gp, which regulate the retention of antiviral drugs [54, 57, 97, 98].

BBB Transporters

The section above on transporters (“BBB Transporters for Cytokines”) has already outlined how IL transport can mediate the cognitive changes associated with sickness behavior, an adaptive mechanism that likely enhances survival in the short term [99]. That section also briefly considered work showing how transport of TNF-α can mediate toxicity at the substantia nigra and thus contribute to Parkinson’s disease.

One mechanism by which neuroinflammation could contribute to AD is by altering the ability of the BBB to remove Aβ from the CNS. Low-density lipoprotein re-

ceptor-related protein-1 (LRP-1) is a multifunctional protein expressed in a variety of cell types throughout the body [100]. At the BBB, it is best characterized as an efflux transporter for A β [102–104] located at the abluminal surface [101] (fig. 2), whose accumulation in the brain is linked to AD pathogenesis [105]. Additionally, studies using animal models as well as human tissue support a role for an LRP-1 defect at the BBB in the onset and progression of AD [102, 103, 106]. The neurovascular hypothesis as stated by Zlokovic [107] posits that this defect in the brain-to-blood efflux of A β contributes to the progression of AD.

In addition to its dysfunction in AD, impairment of LRP-1 at the BBB occurs with systemic inflammation (fig. 2). Peripheral administration of LPS decreases the efflux of A β from the brain [108]. Furthermore, that study demonstrated that LRP-1 impairment was reversible when mice were treated with indomethacin prior to LPS administration. Interestingly, of 22 cytokines measured in serum in that study, none were found to correlate with the effects of indomethacin on A β transport following LPS administration [108]. This suggests that BBB LRP-1 dysfunction in response to LPS results from cytokines that are produced locally in the CNS and/or from autocrine/paracrine actions of other inflammatory mediators on brain endothelial cells.

AD is associated with increased neuroinflammation as well as increased oxidative stress in the CNS. Given that systemic inflammation also causes increased CNS inflammation and oxidative stress, it is possible that these processes may contribute to LRP-1 dysfunction at the BBB (fig. 2). Elevated levels of 4-hydroxy-2-nonenal (HNE)-bound LRP-1 have been found in the hippocampus of individuals with AD compared to age-matched controls [109], indicating that oxidative damage in AD contributes to LRP-1 dysfunction. Whether these changes occur at the BBB or in other cell types in the CNS has

yet to be determined. Multiple cell types in the brain express LRP-1 [100], and in addition to A β transport, LRP-1 has other defined roles in neurons such as lipid homeostasis [110] and neuronal survival [111]. Therefore, determining which cell types contribute to observed changes in LRP-1 oxidative modifications will provide additional insight into the role of LRP-1 dysfunction in AD.

Other disease models associated with neuroinflammation, such as streptozotocin-induced diabetes [112], also cause decreases in LRP-1 expression at the BBB [113]. Together, these findings suggest that neuroinflammation as a result of multiple pathological conditions causes LRP-1 dysfunction at the BBB and therefore could contribute to the onset and progression of AD through this mechanism.

Penetration of HIV-1 and its proteins across the BBB is enhanced by treatment with LPS [114, 115] and is consistent with the many interactions among HIV-1, the BBB and the neuroimmune system. As noted above, these other interactions include release of endothelin-1, a cytokine whose levels in the CNS correlate with the severity of neuroAIDS and enhanced interactions of immune cells with the BBB.

In summary, the BBB interacts in a variety of ways that connect the immune system and CNS. In some cases, the BBB separates the immune system and CNS, in other cases it acts as a mediator of neuroimmune interactions and in still other cases the BBB itself can be a target of neuroimmune interactions. These diverse interactions are not only important in normal or physiologic interactions but also in mediation of disease processes.

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