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The Blood-brain Barrier in Neuroimmunology: Tales of Separation and Assimilation

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Abstract

Neuroimmunology is concerned with the relations between the central nervous and immune systems and with the mechanisms that drive those relations. The blood-brain barrier (BBB) employs mechanisms that both separate and connect these two systems. In fact, the relative immune privilege of the central nervous system (CNS) is largely attributable to the BBB's ability to prevent the unregulated exchange of immune cells and their secretions between the CNS and blood. Having separated the two systems, the BBB then participates in mechanisms that allow them to influence, communicate, and interact with one another. Likewise, the BBB itself is influenced by immune events that are occurring in the periphery and in the CNS so that these three components (the BBB, the immune system, and the CNS) form neuroimmune axes that adapt to physiological and pathological conditions. To date, four major themes have emerged by which the BBB participates in these neuroimmune axes. The first of these four, the formation of the barrier, acts to separate the immune and central nervous systems. The other three themes provide mechanisms for re-establishing communication: response of the BBB to immunomodulatory molecules (e.g., prostaglandins, cytokines, chemokines, nitric oxide) secreted by immune and CNS cells; the controlled, regulated exchange of chemokines, cytokines, and immune cells between the CNS and the blood (i.e., transport across the BBB); the secretion of immunomodulatory molecules by the BBB, often in a polarized fashion. Taken together, these mechanisms reveal the BBB to be a dynamic, interactive, and adaptable interface between the immune system and the CNS, separating them on the one hand and fostering their interaction on the other hand, adjusting to physiological changes, while being a target for disease processes. This review examines specific examples by which the BBB plays an interactive, defining role in neuroimmunology.

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Introduction

The concept of a blood-brain barrier (BBB) arose from experiments done in Germany in the late half of the 19th and early part of the 20th century. This included behavioral experiments, such as those of Biedl and Kraus (Biedl and Kraus, 1898) who found that bile acids had effects after central but not after peripheral administration, and anatomical experiments, most notably those of Paul Ehrlich who found that most dyes injected peripherally were unable to stain the brain. Ehrlich maintained that this was because brain tissue was unable to bind these dyes (Ehrlich, 1906), but later workers found that the dyes did strain brain when injected centrally (Goldmann, 1913). One hypothesis to explain these phenomena was that a physical barrier existed between the brain and the blood and the major contender for this site in adult mammals was the cerebrovasculature. However, both grossly and by light microscopy, the capillaries of the brain look no different than other capillary beds. It was not until the late 1960's that the ultrastructural studies of Reese and colleagues (Brightman and Reese, 1969; Reese and Karnovsky, 1967) showed that the endothelial cells of the brain differed from peripheral endothelial cells in three fundamental ways: i) the presence of tight junctions fusing together the membranes of endothelial cells in apposition; ii) a greatly reduced number of macropinocytotic vesicles; iii) a greatly reduced number of cannaliculi and fenestrae. Thus, both the intercellular and transcellular routes of leakage are greatly reduced at the capillary bed of the brain.

The lack of unregulated leakage at the BBB means that there is no free passage of immunoactive substances from blood to brain, including immunoglobulins. The lack of production of an ultrafiltrate by the brain's capillary bed means that the CNS does not have a well-developed lymphatic system, a system that has critical roles in immune functioning elsewhere in the body. The presence of a BBB also restricts the trafficking of immune cells into the CNS. For example, immediately after the intravenous injection of lymphocytes, about 100 times more lymphocytes are taken up by the axillary lymph nodes and about 800 times more by the spleen than by the brain (Banks et al., 2012). These and other findings led to the concept of the brain as an immune-privileged region, with this concept being applied early on in rather absolute terms. Exceptions seemed to prove the rule as illustrated, for example, by multiple sclerosis, where enhanced immune cell trafficking was associated with dire consequences for the CNS.

The BBB is best thought of as several barriers in parallel, including the choroid plexus, which form the blood-cerebrospinal fluid barrier and the tanycytes, which form a barrier around the circumventricular organs. All these barriers, as well as the blood-spinal cord barrier and the blood-retinal barrier, share common themes of restricting to varying degrees the unregulated leakage of substances between the blood and their tissue beds. Some of the mechanisms discussed below for the vascular BBB are known to be operational at the

choroid plexus as well, so that it is likely that much of what is reviewed here for the vascular BBB reflects activities at the other barriers as well. However, each of these barriers has unique adaptations that serve the special needs of their tissues and these adaptations likely extend to their neuroimmune functions as well. Discovering how these barriers integrate with each other and with the other great neuroimmune axis, the afferent and efferent limbs of the nervous system, is a major challenge for the field of neuroimmunology.

Barrier Functions

Given that the BBB is key to the separation of the central nervous and immune systems, it may not be surprising that early studies of their interactions involved BBB disruption (Figure 1). For over 80 years, BBB disruption in immune phenomena has been a question of great interest, but the reasons for that interest, and even how the question was posed, has shifted through the generations. Some of the major questions have been: Does the ability of bacterial pyrogen to induce fever depend on BBB disruption? What role does BBB disruption play in the entry into the CNS of bacteria, drugs, or immune cells (conversely, how does the trafficking into brain of bacteria, viruses, or immune cells affect measures of BBB integrity)? Does the vasogenic edema associated with meningitis depend on BBB disruption and is that disruption caused by bacterial pyrogen, endogenous pyrogen, cytokines, or other immunoactive substances? What role(s) do neuroimmune processes play in the disruption of the BBB seen in conditions associated with immune/neuroimmune activation, such as stroke, vascular dementia, and diabetes mellitus? Do physiological neuroimmune processes modulate a normative variance in BBB integrity?

Many early studies investigated the appearance of pathogens in the CNS and later studies were concerned with the effect that pathogens had on the appearance in the CSF of antibodies, drugs, or other circulating substances that were otherwise largely excluded from the CNS. Sepsis, infections, encephalitis, meningitis, and the experimental injection of bacteria or their toxins had all been associated with alterations in the BBB or changes in CSF composition by the early half of the 20th century. For example, Skoog reported in 1937 that allergic reactions could alter the BBB (Skoog, 1937) and that the pontobulbar region of the guinea pig was more susceptible in his model than other brain regions. Eckman, in 1958, showed that 3-8 hours after receiving an injection into the carotid artery of 50 microg of E. coli endotoxin, rabbits had increased brain staining of various substances (trypan blue, Evans blue, fluorescein, and colloidal iron) that are normally excluded by the BBB (Eckman et al., 1958). Allen showed that intravenous doses of bacterial pyrogen produced the onset of fever just as rapidly as intracarotid doses and that whereas low doses of bacterial pyrogen produced fever without disrupting the BBB, high doses did disrupt the BBB and were associated with increased hypothalamic damage (Allen, 1965). Allen also reviewed a series of studies from the 1950's that failed to show any radioactively tagged pyrogen entering the brain. Based on these findings, she concluded that induction of fever by low doses of bacterial pyrogen did not require BBB disruption, but acted indirectly on the brain through release of an endogenous substance, whereas high doses of bacterial endotoxin could disrupt the BBB and damage brain tissues.

These early studies largely depended on the use of dyes, such as Evans blue. These dyes in their free state readily cross the BBB, but in the blood tightly bind to albumin and so do not cross the intact BBB. Various problems with use of dyes have been recognized for decades (Broman, 1950) and some of these problems, such as reduced serum albumin levels or intravascular coagulation, can be especially common when studying immune phenomena. Tibbling in 1977 (Tibbling et al., 1977) formalized the use of the CSF/serum ratio for albumin and for IgG, using them to identify BBB disruption and excess immune activity in the CNS, respectively. Unfortunately for both the BBB and neuroimmune fields, the interpretation of the IgG CSF/serum ratio has often been muddled, sometimes used as an indicator of BBB disruption and sometimes as a measure of intracranial antibody production. The use of CSF to evaluate CNS events, a highly favored approach for decades, has become increasingly rare since the 1980's as the use of radioactively labeled substances and imaging modalities have increasing allowed investigators to focus on brain tissue. This means that there has been a subtle shift from the study of phenomena that relate more to the vascular BBB and perhaps less so to the blood-CSF barrier. This is an important bias to recognize as the BBB and blood-CSF barriers likely play differing, but integrated, roles in neuroimmunology.

As a shift from the study of CSF to the study of brain tissue occurred in the BBB field, a shift from the study of exogenous and endogenous pyrogens to the study of lipopolysaccharide (LPS) and cytokines occurred in the neuroimmunology field. Many of these cytokines, including tumor necrosis factor-alpha (TNF), were quickly proposed as having the potential to disrupt the BBB (Deli et al., 1995; Rosenberg et al., 1995; Sharief et al., 1993). LPS-induced BBB disruption can be blocked by pretreatment with indomethacin and nitric oxide inhibitors, suggesting a dependence on prostaglandins and nitric oxide (Candelario-Jalil et al., 2007; De Vries et al., 1996; Minami et al., 1998a).

Immune-mediated disruption of the BBB is no longer simply a concern for sepsis and CNS infections. An increasing number of diseases are associated with BBB disruption; inflammatory or neuroinflammatory events likely underlie those disruptions. Classic examples of BBB disruption include multiple sclerosis, neurotrauma, vascular dementias, and stroke and all these now are believed to involve neuroinflammatory events. More recent additions to the list of proinflammatory conditions with BBB disruption or inflammation-induced BBB disruption include diabetes mellitus (Huber, 2008; Starr et al., 2003), chronic pain (Huber et al., 2002; Willis and Davis, 2008), and some neurodegenerative diseases (Erickson and Banks, 2013). Likewise, LPS-induced disruption of the BBB can no longer be considered simply a model for disease, as many conditions other than sepsis are associated with the presence of LPS in the circulation, including AIDS gastroenteropathy, periodontal disease, peritoneal dialysis, depression, working in the “bioprotein” industry, sporadic amyotrphic lateral sclerosis, long-distance running, and the ingestion of a high fat meal (Amar et al., 2008; Ancuta et al., 2008; Brenchley et al., 2006; Ghoshal et al., 2009; Maes et al., 2008; Ng et al., 2008; Sikkeland et al., 2008; Szeto et al., 2008; Zhang et al., 2009). Taken together, these suggest that immune-induced BBB disruption is more widespread than recently appreciated and that such disruption can be induced or mediated by LPS, cytokines, progstaglandins, and nitric oxide.

BBB Responses to Immunoactive Molecules

The BBB is able to respond to LPS because of the presence of TLR4 and other toll-like receptors on the membranes of the cells that constitute the BBB (Nagyoszi et al., 2010). Likewise, these cells have receptors for cytokines, chemokines, and other immune-related molecules (Cunningham and De Souza, 1993; Pan et al., 2009; Pan et al., 2008; Takao et al., 1992). As a result, the immune system is able to affect the functions of the BBB beyond that of disruption.

Perhaps the most widely studied effect of LPS on the BBB after disruption is that of alterations in BBB transport systems (Figure 1). Many substances with alterations in their brain/blood or CSF/blood ratios that had been assumed to be caused by BBB disruption are more likely explained by alterations in the transporters for those substances. Immune-related alterations in BBB permeability not caused by BBB disruption occurs for cisplatin, TNF, insulin, HIV-1 and its viral coat protein gp120, insulin, leukemia inhibitory factor, amyloid beta peptide, leptin, pituitary adenylate cyclase activating polypeptide, and immune cells (Banks et al., 2008; Banks et al., 1999; Banks et al., 2012; Dohgu and Banks, 2008; Erickson et al., 2012; Minami et al., 1998b; Nonaka et al., 2004; Nonaka et al., 2005; Pan et al., 1996; Pan et al., 2008; Persidsky et al., 1997; Xaio et al., 2001). The mechanisms for these alterations vary, but basically fall into two broad categories. One category is that of a modulation of a transporter that is responsible for the rate at which the substance crosses. Another category is that of induction of a pathological response, such as adsorptive transcytosis.

The effect of immune modulation of BBB transporters can take several forms. In the cases of insulin, leukemia inhibitory factor, and TNF, uptake is dramatically enhanced because blood-to-brain transporters specific or selective for these substances have increased activity. The enhanced transport is independent of any disruption that occurs. In the cases of amyloid beta peptide, verapamil, most anti-seizures drugs, and many anti-virals, uptake is enhanced because brain-to-blood transporters for these substances have decreased activity (Deane et al., 2004; Ronaldson et al., 2008). One transporter whose response to TNF and LPS has been well worked out is that of P-gp. LPS acts directly on the brain endothelial cell (BEC) and all the components of the reaction are mediated through pathways contained within the BEC (Hartz et al., 2006; Yu et al., 2008; Yu et al., 2007a; Yu et al., 2007b).

This ability of neuroimmune activation to alter BBB transporters has many clinical consequences. For example, seizure activity tends to enhance P-gp activity; thus, the retention by brain of P-gp substrates is reduced (Rizzi et al., 2002). Because most anti-seizure medications are P-gp substrates, this means that seizures themselves act through P-gp to induce resistance to medication. This may explain in part why status epilepticus is especially resistant to treatment with anti-seizure medications.

Pathological reactions also likely have a diverse nature. HIV-1 can enter the CNS as infected immune cells cross the BBB or can cross the BBB as free viruses. Inflammatory events, including exposure to LPS, enhance entry of HIV-1 into the nervous system by both of these processes (Dohgu and Banks, 2008; Persidsky et al., 1997). The cellular mechanisms that these two processes use are different, with immune cell trafficking being dependent on JNK

and STAT1 signaling (Chaudhiri et al., 2008; Ramirez et al., 2010). In comparison, LPS enhances free virus transport through a process dependent on MAPK (Dohgu and Banks, 2008).

An important characteristic of the response of BECs to immune stimuli is their polarized response. In other words, a substance may produce an effect when acting on the blood side of the BBB but not on its brain side. For example, GM-CSF and IL-6 enhance HIV-1 transport across monolayers of BECs when applied to the luminal side (AKA apical, blood side) but not when applied to the abluminal side (AKA basolateral, brain side) of the cells (Dohgu et al., 2011). This can add a type of directionality to BBB-mediated neuroimmune responses.

The effects of LPS on free HIV-1 transport and on P-gp function are mediated at the endothelial cell. As discussed below, many effects of LPS on the BBB require crosstalk between the BEC and other cell types in the periphery or the CNS.

BBB Transport of Immunoactive Molecules

Blood to Brain Transport—A major function of the BBB is to prevent the leakage of substances from the blood into the CNS, thus protecting the brain from a myriad of endogenous circulating substances that can have neurotoxic effects. Cytokines and chemokines are among the substances whose unregulated access to the CNS is prevented by the BBB. However, many cytokines and chemokines are transported across the BBB in the blood-to-brain direction (Figure 1), including the IL-1's, IL-6, IL-15, TNF, CCL2, CCL11, cytokine-induced neutrophil chemoattractant-1, leukemia inhibitory factor-1, epidermal growth factor, and various fibroblast growth factors (Banks et al., 1989; Banks et al., 1994; Banks et al., 1991; Cuevas et al., 1996; Erickson et al., 2014; Ge et al., 2008; Gutierrez et al., 1993; Hsuchou et al., 2013; Pan and Kastin, 1999, 2001; Pan et al., 2000; Pan et al., 2009; Wagner et al., 1999). The difference between entry into the CNS of a neuro-active substance via unregulated leakage vs a regulated transporter is key to the general theme that runs throughout the study of the BBB: the former is associated with BBB dysfunction and can result in neurotoxicity; the latter is controlled ultimately by the CNS, adjusting the properties of the BBB transporter to the needs of the brain.

In the case of TNF, the transporter protein is believed to be the TNF receptors because receptor knockout mice do not transport TNF (Pan and Kastin, 2002). In the case of epidermal growth factor (Pan and Kastin, 1999) and IL-1 (Banks et al., 1991), the evidence suggests that the receptors are not part of the transport process, but as yet to be indentified proteins are acting as the transporters.

Blood-derived cytokines crossing the BBB can act directly on their CNS receptors to alter function. For example, human IL-1 alpha injected intravenously into the mouse caused a cognitive impairment that could be blocked if small amounts of antibody specific to human IL-1 alpha was injected into the posterior division of the septum, an area that avidly transports IL-1 alpha into the brain (Banks et al., 2001). As the only source of human IL-1 alpha in the mouse was the blood, this illustrates that blood-borne IL-1 alpha crossed the BBB and did so in amounts sufficient to affect cognition. Blood-derived cytokines crossing

the BBB can also act indirectly by inducing release of more cytokine from brain stores. This mechanism has been demonstrated by Qin et al (Qin et al., 2007), in which TNF injected into the blood stream crosses the BBB, inducing further release of TNF from brain stores, with this centrally-derived TNF producing most of the CNS effect. Another example of a cytokine crossing the BBB to induce a CNS effect is that of basic fibroblast growth factor which crosses the BBB and accumulates in the hippocampus in amounts sufficient to protect against ischemia-reperfusion injury (Cuevas et al., 1998).

Brain-to-blood Transport—Brain-to-blood passage of several cytokines has been noted. In a series of papers, Reichlin showed that amounts of IL-1 beta, IL-6, and TNF entering the blood from the brain were sufficient to increase their blood levels (Chen et al., 1997; Chen et al., 2000; Chen and Reichlin, 1998; Reichlin et al., 2000; Romero et al., 1996). In these cases, this passage was not saturable, but occurred with the reabsorption of CSF, termed bulk flow. Such passage occurs for any substance that is present in the CSF, but the small volume of total body distribution typical of many cytokines favors the ability of this mechanism to produce elevated levels in the blood.

Only one cytokine has so far been shown to have a saturable component to its brain-to-blood efflux and that is IL-2 (Banks et al., 2004). The combination of lack of a saturable blood-to-brain transporter, robust enzymatic degradation, and the saturable efflux system means that the free (unbound) component of blood-borne IL-2 enters the brain less well than even albumin. Besides helping to exclude their substrates from the brain, efflux systems have been shown to play other roles as well. Efflux, along with the rates of synthesis and degradation, can be a major factor in determining the CNS level of a substance, as illustrated by amyloid beta peptide (Zlokovic, 2005). Impairment of its efflux, both its saturable and bulk flow components, has been shown to occur and likely contributes to the amyloid burden of brain seen in Alzheimer's disease. Impaired efflux of amyloid beta peptide can be induced by inflammation, including treatment with LPS (Erickson et al., 2012; Jaeger et al., 2009). This suggests that neuroinflammation could play a major role in the initiating events of Alzheimer's disease.

Efflux is also a mechanism by which the brain can make substantial contributions to the blood levels of a substance. Efflux of corticotrophin, for example, elevates levels of this peptide to sufficient levels that they affect the release of beta-endorphin from the spleen (Martins et al., 1997).

BBB Secretion of Immunoactive Molecules

The BECs that comprise the vascular BBB and the epithelial cells that comprise the blood-CSF barrier are capable of secreting immunoactive substances, including cytokines, chemokines, nitric oxide and prostaglandins (Figure 1). These secretion of these substances can be either constitutive or inducible. The most compelling studies showing that barrier cells are secreting these substances are those of in vitro cultures that contain the barrier cell and only the barrier cell. The presence of mRNA for the proteins or of the required enzymes for the synthesis of nitric oxide and the prostaglandins are important supporting evidence. Such studies have been conducted with isolated microvessels (which usually also contain

pericytes), immortalized BECs, and primary cultures of BECs. Culture of BBB cells has many difficulties including slow growth of primary BECs and dedifferentiation of immortalized cell lines. Not surprisingly, then, experiments often differ in the details of results, such as which cytokines are specifically secreted and to what degree. Nevertheless, most studies agree that IL-6 is reliably and robustly secreted, both constitutively and in response to immune stimuli. The IL-1's, IL8, IL-10, G-CSF, GM-CSF, interferon inducible protein-10, keratinocyte chemoattractant, TNF, MCP-1, RANTES, and endothelin have also been shown to be secreted (Didier et al., 2002; Fabry et al., 1993; Macvilay and Fabry, 1997; Mandi et al., 1998; McGuire et al., 2003; Simpson et al., 1998; Spranger et al., 2006; Vadeboncoeur et al., 2003; Verma et al., 2006). These studies show that cytokine secretion can be modulated by LPS, HIV-1 and its surface glycoprotein, and adiponectin.

The LPS-enhanced transport of HIV-1 as free virus depends on the ability of BECs to secrete cytokines. LPS stimulates the BECs to increase their release of GMCSF and IL-6 (Dohgu et al., 2011). These cytokines then act at their luminal receptors on the BEC, stimulating transcytosis mediated by the mannose-6-phosphate receptor through a MAPK-dependent pathway (Dohgu et al., 2012).

Many cells are capable of secreting substances into their environment. But BECs are unique in that they face into two environments and do so simultaneously: the periphery and the CNS. BECs, for example, can secrete cytokines from their luminal side into the blood stream or from their abluminal side into the interstitial fluid of the brain. More interestingly, BECs can respond to an immune stimulus at one of its sides by secreting an immunoactive substance from the other. For example, LPS applied to the abluminal surface of monolayers of BECs greatly stimulates the release of IL-6 from the luminal side (Verma et al., 2006). The directionality can go the other way as well as illustrated by the ability of luminal adiponectin to decrease the abluminal release of IL-6 (Spranger et al., 2006) or by the ability of gp120 at the luminal surface to increase endothelin secretion from the abluminal surface (Didier et al., 2002). This endows the BBB with the ability to translate an immune event in the CNS into a peripheral one or, conversely, to translate a peripheral event into a CNS one. The ability to translate neuroimmune input from one side to the other likely forms a fundamentally important neuroimmune axis.

Integration of the BBB with Other Components of the Neurovascular Unit, the Neuroimmune Axes, and the Peripheral Tissues

The BBB is dynamic, changing throughout the life cycle and with disease. Under physiologic conditions, it is slave to the brain, adapting to the changing needs of the brain during development, aging, and other life events. Under pathologic conditions, it may be the target of disease and it may give rise to or promote disease when its adjustments do not match the needs of the brain or adequately adapt to events in the periphery. This responsive dynamism has long been appreciated, and it has been increasingly understood that its roots lie in the crosstalk with the cells that constitute the physical BBB (e.g., the endothelial cells of the vascular BBB and the epithelial cells of the blood-CSF barrier), the other cells of the brain (e.g., neurons, microglia, astrocytes, pericytes, immune cells within the CNS), and the cells in the periphery (e.g., circulating immune cells, peripheral tissues and organs via their

hormonal secretions) (Abbott et al., 2006; Greenwood et al., 2011; Neuwelt et al., 2008; Willis and Davis, 2008). Although the responsive dynamism has been long appreciated conceptually, the mechanisms that underlie it have been less clear.

The previous sections go a long way towards outlining mechanisms for this crosstalk (Figure 2). To recapitulate: The ability of the BEC to respond to and release immunoactive substances provides a mechanism for intercellular crosstalk. The barrier function of these cells means that they are polarized, permitting interactions with the cells of the CNS and simultaneous, independent interactions with the peripheral tissues while preventing the cells of the CNS and peripheral cells from directly interacting with one another. The barrier function coupled with BBB transporters means that substances such as cytokines either do not enter the CNS or do so under regulated conditions that are ultimately under the control of the CNS. Communication between the CNS cells and the periphery is controlled by neuroimmune axes, two of which have been elucidated so far: an indirect relay in which the BBB cell receives input from one cell surface and secretes immunoactive substances from the other and a direct transport of cytokines and chemokines across the BBB. A third axis involving the BBB, the trafficking of immune cells into the CNS, is also a highly regulated process that depends on crosstalk between the immune cells and the cells constituting the BBB (Engelhardt, 2008; Greenwood et al., 2011). A study using simple mathematical modeling has shown that immune cell distribution between the peripheral tissues and the CNS is variably dependent on which cell type dominates in this cross talk and that those relations can be readily altered by immune events and genetics (Banks et al., 2012).

The above sections have discussed some of the direct actions of LPS and immunoactive substances on the BBB. The cases reviewed in depth, such as the effect of LPS on free HIV-1 transport across the BBB, largely involved only the barrier cells. But the concept of the neurovascular unit with its cross talk among the barrier cells, other CNS cells, and other peripheral tissues (with blood as its proxy) implies that many neuroimmune functions will involve interactions of the barrier cells with other cells. Many of these cell-cell interactions are likely to be exceedingly complex and tedious to work out, but there are some interesting examples already in the literature.

A few of these examples have already been discussed. Qin et al have shown that the BBB transports TNF that then acts on microglia to release more TNF that is then toxic to dopaminergic cells in the substantial nigra (Qin et al., 2007). The LPS-enhanced transport of free HIV across BBB monolayers does not require other cells to participate, but it is further enhanced in the presence of pericytes (Dohgu and Banks, 2013). Since LPS does not cross the BBB and pericytes are on the abluminal side of the BBB, this action of pericytes likely involves an LPS-induced release of factors from endothelial cells with those factors then inducing a release of substances from the pericyte, and these pericyte-derived substances then interacting with the BEC to enhance HIV-1 transport. Consistent with this, we found that pericytes that were exposed to the abluminal fluids of monolayers of BEC that had LPS added to their luminal chambers secreted a unique pattern of cytokines, a pattern that differed from that of the added abluminal fluid and from that secreted by LPS-exposed pericytes (Dohgu and Banks, 2013).

One approach to elucidating complex immune interactions is to determine whether monocultures of BECs recapitulate the in vivo BBB response or whether recapitulation requires co-culture with other cells. For example, functional expression of the blood-to-brain insulin transporter does not occur in monocultures of BECs, but requires co-culture with pericytes (Nakaoke et al., 2007). Effects of LPS and nitric oxide on insulin transport are a further illustration of the requirement for crosstalk between BECs and other cells. In vivo studies show that LPS enhances insulin transport across the BBB (Xaio et al., 2001). However, LPS has no effect on the rate of insulin transport across monolayer monocultures of BECs (Banks et al., 2008). This suggests that LPS, although it acts directly on BECs to induce cytokine release and to affect free HIV transport, is in this case not acting directly on the BEC to affect insulin transport. Instead, LPS must be acting on some other cell type to induce a substance that then acts on the BEC to alter insulin transport. To test this, serum from LPS-treated mice was incubated with the BECs, but this did not alter insulin transport. This suggests either that the substance is not circulating but of central origin or that it is a blood-borne substance that is not stable, such as nitric oxide. When cervical lymphocytes were placed in the luminal chamber of the BEC monolayer culture and LPS added to it, the saturable transport of insulin across the monolayers was enhanced. Thus, the findings show that LPS acts through another cell type to enhance insulin transport across the BBB and that immune cells are one cell type that can fulfill that role.

Nitric oxide effects on insulin transport also demonstrate complex cellular interactions (Banks et al., 2008). Treatment of mice with a general inhibitor of nitric oxide synthase (NOS) or an inhibitor specific for neuronal NOS (nNOS) further enhances the LPS effect on insulin transport. This suggests that nitric oxide has an inhibitory effect on insulin transport. However, inhibition of endothelial NOS (eNOS) and inducible NOS (iNOS) inhibits insulin transport and treating animals with L-arginine, the precursor of nitric oxide, stimulates insulin transport. These findings show that nitric oxide can also stimulate insulin transport. Since nitric oxide synthesized by any enzyme is the same molecule, it is unlikely that both the inhibitory and stimulatory effects of nitric oxide are both mediated directly at the BEC. Rather, it is likely that either the inhibitory or stimulatory effect occurs indirectly by acting on another cell type that then secretes a substance to act on the BBB. To determine whether nitric oxide could act directly on BBB cells, in vitro monocultures of BECs were incubated with SNAP, a substance that releases nitric oxide. These studies showed SNAP applied to the luminal side of the monolayers inhibited insulin transport. SNAP applied to the abluminal side also inhibited insulin transport, showing that the paradoxic effect of nitric oxide was not because it had different effects on the polarized BEC. Thus, nitric oxide generated from nNOS could be acting directly on the BEC to inhibit insulin transport, whereas eNOS and iNOS are likely acting on other cells to induce them to release a substance that stimulates insulin transport across the BBB.

The most parsimonious summary of these findings is that LPS does not act directly on the BBB to alter transport of insulin, but indirectly on cells such as lymphocytes to enhance BBB transport. LPS-induced release of nitric oxide from non-BBB cells has complex effects on insulin transport, with nitric oxide generated from nNOS from non-BECs acting directly on BECs to inhibit insulin transport and iNOS- and eNOS-generated nitric oxide acting on non-BECs to release substances that enhance BBB transport of insulin.

Summary

The BBB plays various roles in neuroimmunology. By virtue of its barrier functions, it separates the CNS from the peripheral components of the immune system, making the brain an immunoprivileged organ. It then is involved in a reestablishment of CNS-immune communications by various mechanisms. Its ability to respond to and to secrete immunoactive substances provides a mechanism by which it can be influenced by events in both the CNS and peripheral tissues; this ability also provides a mechanism by which it can influence the CNS and peripheral tissues. The combination of barrier function with ability to respond to and secrete immunoactive substances allows the BBB to form a unique neuroimmune axis, translating the signals it receives on one of its sides by secreting from its other side. The transport of cytokines across the BBB creates another type of neuroimmune axis, providing a mechanism by which peripheral events can directly influence brain. These functions, events, mechanisms, and axes are not static, but are modulated by the environment in which the BBB is embedded. In some cases, these modulations are mediated entirely at the BBB, but other modulations require crosstalk between the cells that form the BBB and the other cells found in the CNS and periphery. Thus, the BBB is a dynamic, interactive, regulatory tissue that is involved both in making the CNS an immunoprivileged organ and in fostering immune-CNS communications by participating in the formation of neuroimmune axes.

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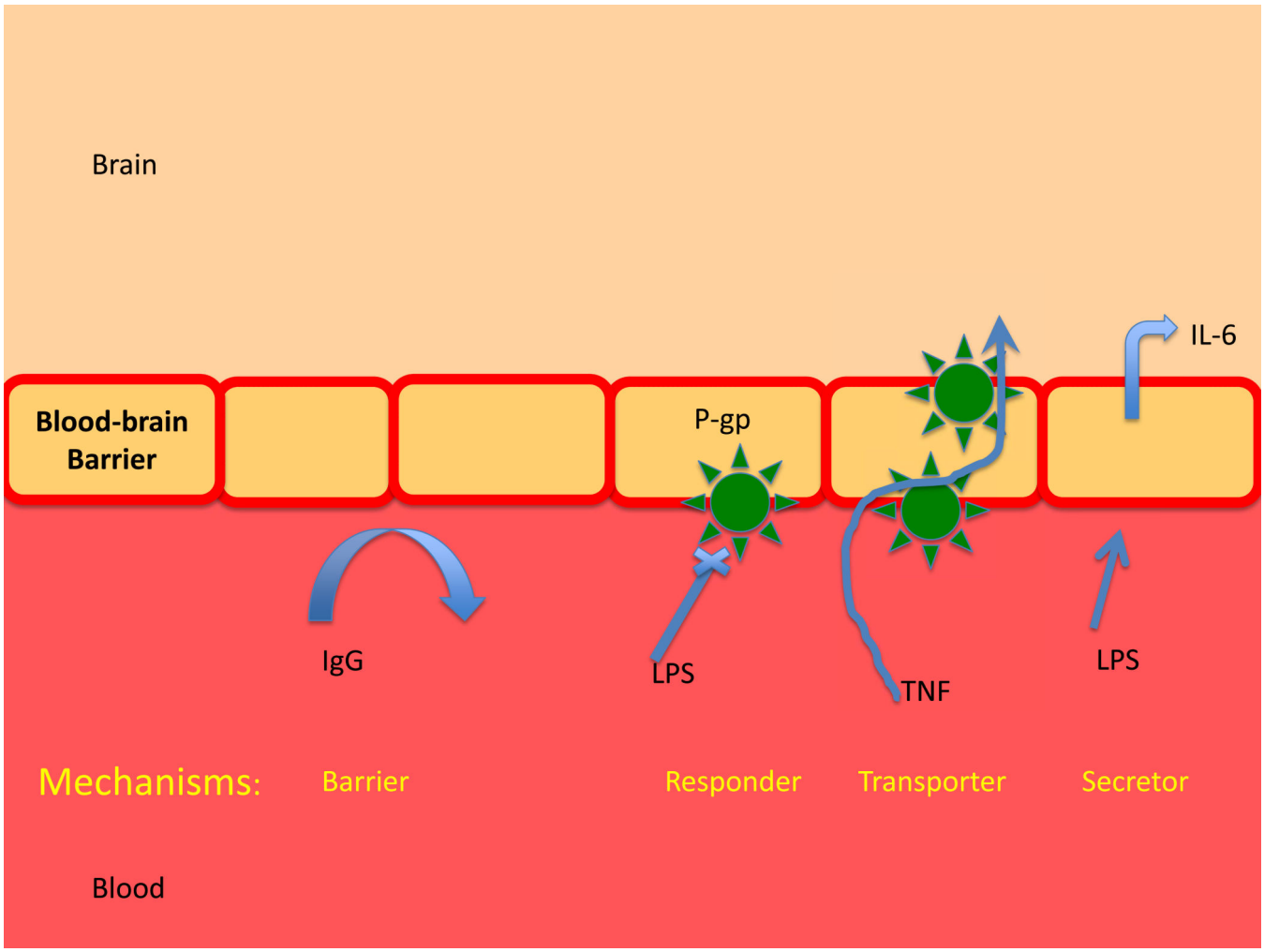

Figure 1.

Illustrates with examples four mechanisms by which the BBB is central to neuroimmune phenomena. The barrier mechanism prevents the unregulated exchange of substances between the brain and the blood; IgG is given as an example. The responder mechanism means that BBB functions are altered by neuroimmune events; the downregulation of the brain-to-blood transporter p-glycoprotein is illustrated. The transporter mechanism allows certain molecules, most notably some cytokines/chemokines, to cross the BBB because of the presence of specific saturable transporter; the transport of TNF is given as an example. The secretor mechanism endows barrier cells with the ability to release immunoactive and immunomodulatory substances in response to neuroimmune events. The release of IL-6 in response to LPS is illustrated.

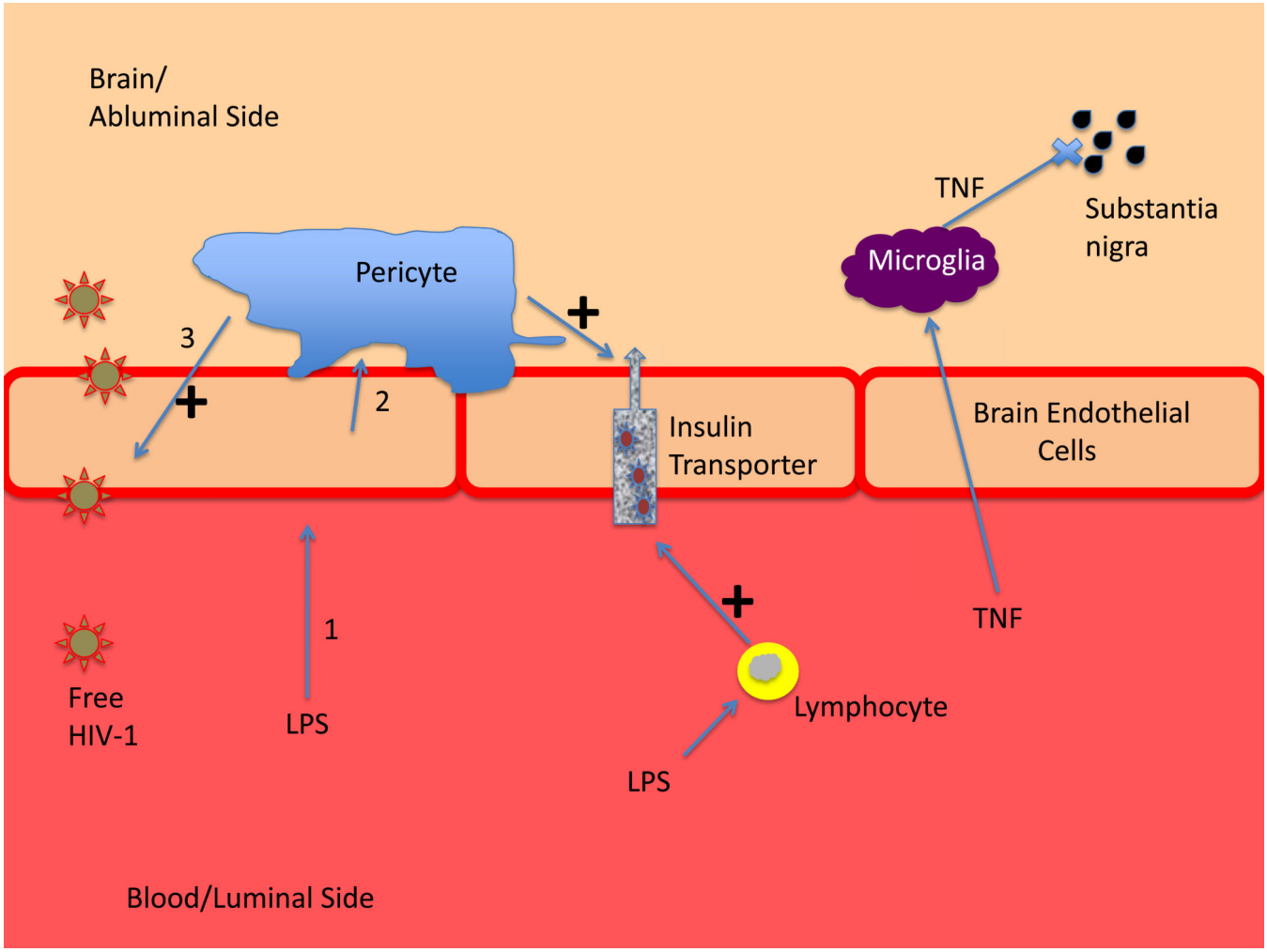

Figure 2.

Integration of the four mechanisms of barrier, responder, transporter, and secretor allows intercellular crosstalk that is important to the adaption of the BBB to the needs of the CNS, adaption to neuroimmune events, and response to disease. The far right panel shows that transport of TNF across the BBB allows blood-borne TNF to interact with microglia, inducing the microglia to release more TNF, which can induce apopotosis in dopaminergic cells at the substantia nigra. The middle panel shows that LPS enhances insulin transport across the BBB by acting indirectly on other cell types, including circulating lymphocytes, to induce them to release substances that then act at the brain endothelial cell. The final panel shows that pericytes induce the insulin transporter in monolayers of brain endothelial cells. It also illustrates that a complex, three step cross-talk between brain endothelial cells pericytes can further induce the LPS-enhanced passage of HIV-1 across the BBB: 1) LPS acts on the luminal side of the brain endothelial cell to 2) induce it to release factors from its abluminal side that act on the pericyte, 3) inducing the pericyte to release substances that then act on the brain endothelial cell to accelerate HIV-1 passage across the BBB.