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Invited Review

# The blood–brain barrier in neuroimmunology: Tales of separation and assimilation

W.A. Banks *

*Geriatrics Research Education and Clinical Center, Veterans Affairs Puget Sound Health Care Center, Seattle, WA, United States*
*Division of Gerontology and Geriatric Medicine, University of Washington School of Medicine, Seattle, WA, United States*

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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.



## 1. 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 (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 1960s 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 canaliculi 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

* Address: VAPSHCS, 1660 S Columbian Way, Seattle, WA 98108, United States. Tel.: +1 206 764 2701; fax: +1 206 764 2569.
*E-mail address:* wabanks1@uw.edu

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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.

## 2. 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 (Fig. 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 h 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



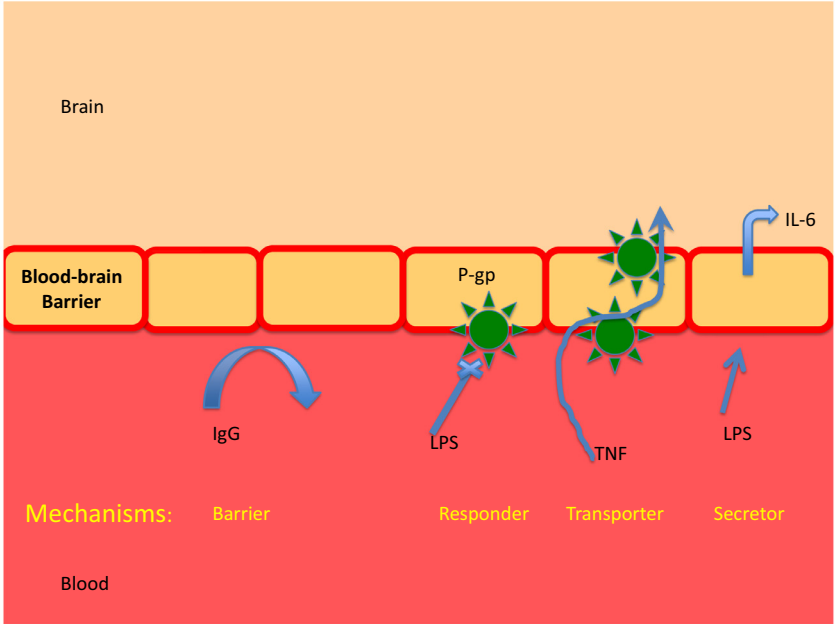


**Fig. 1.** Illustrates with examples four mechanisms by which the BBB is central to neuroimmune phenomena. The barrier mechanism prevents the unregulated exchange of substances between the brain and the blood; IgG is given as an example. The responder mechanism means that BBB functions are altered by 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.

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