Review

Acquired immunodeficiency syndrome and the blood-brain barrier

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The blood-brain barrier (BBB) plays a critical role in normal physiology of the central nervous system by regulating what reaches the brain from the periphery. The BBB also plays a major role in neurologic disease including neuropathologic sequelae associated with infection by human immunodeficiency virus (HIV) in humans and the closely related simian immunodeficiency virus (SIV) in macaques. In this review, we provide an overview of the function, structure, and components of the BBB, followed by a more detailed discussion of the subcellular structures and regulation of the tight junction. We then discuss the ways in which HIV/SIV affects the BBB, largely through infection of monocytes/macrophages, and how infected macrophages crossing the BBB ultimately results in breakdown of the barrier. Journal of NeuroVirology (2009) 15, 111–122.

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Introduction

Since Paul Ehrlich recognized the compartmentalized and restrictive qualities of the central nervous system (Ehrlich, 1885), many researchers have sought to understand the mechanisms that govern passage of substances across the barrier from the blood into the brain. Understanding how the blood-brain barrier (BBB) functions as a selective barrier is an ongoing pursuit that should result in enhanced treatment of central nervous system (CNS) disease, targeted drug therapy, and improved surgical prognosis (Strbian et al., 2008).

The BBB is composed of closely packed unfenestrated brain microvascular endothelial cells (BMECs) situated between the bloodstream and the basement membrane (Figure 1). The basement membrane, composed largely of collagen IV and laminin, is an extracellular matrix that anchors BMECs to the underlying tissues. Surrounding the BMECs of the BBB and in contact with the basement membrane are perivascular macrophages and the foot processes of microglia and astrocytes (Graeber et al., 1992; Hickey and Kimura, 1988; Lassmann et al., 1991; Streit and Graeber, 1993). Astrocytes and microglia support the BBB biochemically to fulfill its purpose as a diffusion barrier and also play an immunoregulatory role (Williams et al., 2001a). Given the intimate juxtaposition among BMECs, astrocytes, perivascular macrophages, and parenchymal microglia, all are likely to encounter agents entering the CNS via the circulation.

Structural components of the BBB and BBB function

Brain microvascular endothelial cells

Brain microvascular endothelial cells are highly dynamic cells that form and regulate tight junctions (TJs), the critical structure responsible for the complex task of barrier regulation. TJs are composed of fibril networks of transmembrane homo- and heterodimeric proteins that can be modified and regulated to allow physiologic processes, such as replacement of perivascular macrophages by circulating monocytes. TJ regulation occurs by way of complex, rapid phosphorylation events that may be initiated in a polarized fashion, functioning differently based on whether the stimulus originates from the luminal or abluminal side of BMECs. The presence of adhesion molecules on the luminal surface of BMECs is very important for leukocyte extravasation into the CNS.
Astrocytes

Astrocytes play a critical role in the formation and coordination of the BBB. It is known that the dense network of foot processes surrounding BMECs develops after birth in the rat (LeVine and Goldman, 1988). Although the BBB can form and function prior to gliogenesis in early prenatal development (Weidenfeller et al., 2007), the contributions of astrocytes to maintenance and signaling to BMECs in health and disease are well studied. While astrocyte foot processes cover over 90% of the surface of brain microvessels (Willis et al., 2004), the gap between astrocytic foot processes and BMECs is known to be at least 20 nm, a sufficiently large space to allow passage of many solutes normally restricted by the intact BBB. However, in coculture of astrocytes and BMECs, transendothelial electrical resistance is increased over the culture of BMECs alone (Rubin et al., 1991). Furthermore, damage or removal of astrocytes in vivo results in a transient increase in BBB permeability (Hamm et al., 2004; Krum et al., 1997). The prominent role of astrocytes in supporting a healthy BBB may be the result of trophic factors secreted by astrocytes that nourish and regulate BMECs (Igarashi et al., 1999).

Perivascular macrophages and parenchymal microglia

Perivascular macrophages and parenchymal microglia are both bone marrow–derived cells that are continuously replaced by monocytes. Bone marrow chimera studies in rodents and transplantation studies in humans show a fairly rapid turnover of perivascular macrophages (30% in 90 days) and much slower turnover of parenchymal microglia (less than 1% in 90 days) (Hickey and Kimura, 1988; Hickey et al., 1992; Lassmann et al., 1986; Matsumoto and Fujiwara, 1987; Unger et al., 1993). The normal turnover of perivascular macrophages may be exploited by pathogens such as human immunodeficiency virus (HIV) as discussed below.

In addition to differences in location, morphology, and turnover between perivascular macrophages and parenchymal microglia, the two cell types can be distinguished by the expression of various myeloid markers (Becher and Antel, 1996; Borda et al., 2008; Sedgwick et al., 1991; Ulvestad et al., 1994a,b; Williams et al., 1992). The differential expression of myeloid markers as well as other markers associated with antigen-presenting function and limited functional studies indicate that perivascular macrophages are the antigen-presenting cells of the CNS and sensors of brain injury (Williams et al., 2001a). Perivascular macrophages and parenchymal microglia can both be activated by inflammation of diverse causes that can modify the rate of cell turnover as well as the morphology and immunophenotype of the cells (Borda et al., 2008).

Permeability properties of the tight junction

Tight junctions (TJs) between individual BMECs are the focal adhesion units responsible for the barrier properties of the BBB. The TJ is an intricate complex containing over 40 transmembrane proteins, anchorage proteins, and TJ-associated proteins in the membrane and cytosol of adjoining BMECs. The normal TJ is characterized as having high transendothelial electrical resistance values between 1000 and 1500 Ω/cm² (Butt et al., 1990). TJs and the BBB in general impose restrictions upon what can pass from the blood into the CNS down to the level of small molecules. The TJ restricts solutes by size, charge, and lipophilicity; there is a direct correlation between lipophilicity and ease of diffusion through the BBB. It is widely accepted that lipophilic alcohols or gases like O₂ and CO₂ can pass