**THE ROLE OF THE BLOOD–BRAIN BARRIER IN INFLAMMATION**

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The cellular basis of the BBB is at the level of the CNS microvasculature and consists morphologically of nonfenestrated endothelial cells with interendothelial tight junctions. In addition, the maintenance of the BBB function is dependent on normal functioning of pericytes, perivascular microglia, astrocytes, and the basal lamina, which are annexed to the capillary and postcapillary venules in the CNS. In some areas in the CNS, the BBB is incomplete or absent, such as the circumventricular organs and the choroid plexus. A blood–cerebrospinal fluid (CSF) barrier is found at the level of apical tight junctions in the choroid plexus epithelial cells.

For more detailed information about the anatomic and physiologic characteristics of the BBB and blood–CSF barriers, see the comprehensive review articles ([11,12](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b11)).

Under normal physiologic conditions, **the BBB provides protection of the CNS by strictly regulating the entry of plasma-born substances and immune cells into the nervous tissue.** A variety of **CNS injuries [including seizures (**[**13**](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b13)**), infections, traumatic and ischemic events] cause transient changes in the physiologic and structural features of the BBB.** In particular, an impairment of BBB integrity and an inflammatory state are common features of several neurologic conditions ([14](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b14)) associated with the late onset of epilepsy.

During inflammation, the enhanced production of cytokines by the endothelial cells of the BBB, the circulating immune cells, and brain parenchymal microglia and astrocytes results in the upregulation of adhesion molecules, activation of metalloproteinases, and catabolism of arachidonic acid at the level of the brain microvasculature ([12,15,16](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b12)). These events contribute to increase the permeability of the BBB through mechanisms that are not yet fully elucidated ([16](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b16)).

Inflammatory events at the BBB and blood–CSF barrier are pivotal for promoting the entry of leukocytes into the CNS, thus determining intrathecal immune reactivity (see later; [Fig. 1](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#f1)). Although immune cells are found to patrol the CSF in the subarachnoid space, the perivascular Virchow–Robin space, and the choroid plexus, relatively few leukocytes are present in the CNS unless inflammation occurs ([3](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b3)). One of the mechanisms by which cytokines contribute to the inflammatory response at the level of the BBB and blood–CSF barrier is by increasing the expression of selectins and adhesion molecules [e.g., intercellular adhesion molecule (ICAM)-1, vascular CAM (VCAM)-1, and platelet endothelial CAM (PECAM-1)], chemokines, and their receptors on endothelial and epithelial cells. These molecules, by interacting with integrin molecules on leukocyte membrane surface, are responsible for leukocyte recruitment from the bloodstream, promoting their adhesion and eventual entry into the perivascular space, CSF, and CNS parenchyma ([3](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b3)).

Figure 1. Schematic representation of the cerebral vasculature and CSF circulation and their relation to inflammatory mediators and antigen transport. Antigenic products (Ag) can be drained from the brain parenchyma to the CSF. From this compartment, Ag may circulate along the ventricular system into the subarachnoid space; from here Ag can enter the venous sinuses through the arachnoid villi and reach the systemic circulation. Alternatively, they can drain into the cervical lymph nodes, traveling along the subarachnoid and perivascular space. Trafficking of leukocytes into the CNS may occur through at least three routes: (a) Leukocytes can migrate into the brain following the formation route of CSF. They can extravasate through the fenestrated endothelium of the chroid plexus, migrate across the stroma core, interact with the epithelial cells, and enter the CSF. This route may be one by which immune cells enter the brain in physiologic conditions (the CSF of healthy individuals contains ∼3,000 leukocytes/ml); (b) Leukocytes can have access to the brain via the arterial blood supply by extravasating at the pial surface of the brain into the subarachnoid space and across the Virchow–Robin perivascular spaces, which are in direct contact with the CSF compartment. In rodent, the cervical lymph nodes are connected by nasal lymphatics to subarachnoid space and perivascular space at the olfactory bulbs; (c) Leukocytes can enter the brain parenchyma by extravasation across the blood–brain barrier nonfenestrated endothelium and basal lamina. Antigen-presenting cells such as dendritic cells and macrophages are found in the subarachnoid space, in the perivascular space, and in the choroid plexus, whereas microglia are located in brain parenchyma; at these locations, these cells may encounter circulating CNS-borne antigens. (Adapted from Aloisi F, Ria F, Adorini L. Regulation of T-cell responses by CNS antigen-presenting cells: different roles for microglia and astrocytes. *Immunol Today* 2000;21:141–7, with permission.)



During inflammatory/immune reactions, activated T cells can enter the CNS by at least three different routes:

* 1

The first pathway follows the formation of CSF; leukocytes extravasate across the fenestrated endothelium in the choroid plexus stroma, cross the epithelium of the choroid plexus, and enter the CSF.

* 2

Leukocytes can extravasate across postcapillary venules at the pial surface of the brain into the subarachnoid space and the Virchow–Robin perivascular space, which is in direct communication with the CSF.

* 3

Leukocytes cross the BBB and the endothelial basal lamina of the postcapillary venules [([3](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b3)); see [Fig. 1](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#f1)].

Leukocytes can be restimulated in the CNS by APCs circulating in the subarachnoid or perivascular space or by APCs located in the brain parenchyma. Antigenic proteins in the CNS, which are mostly inacessible to T cells because of the restrictive nature of the BBB and the lack of a conventional lymphatic system, may become available to recognition by the action of APCs. Thus during inflammatory conditions, microglia and macrophages, endothelial cells of the BBB, and epithelial cells of the choroid plexus are all capable of presenting antigens to T cells ([1,17–19](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b1)). These APCs can express major histocompatibility complex (MHC) class I and II and costimulatory molecules during inflammation, which are essentials for T lymphocytes to recognize and respond to an antigenic peptide. Endothelial cells, unlike perivascular microglia, do not constitutively express MHC class II molecules; however, they can be induced to express these molecules by a variety of cytokines. The role of MHC class II on astroglia remains elusive, and a prevailing view is that these cells exert a negative immunoregulatory function by favoring the induction of a nonresponsive state by the T cells ([17](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b17)).

In addition to be expressed on the surface of APCs, antigenic proteins may drain from the CNS into the cervical lymph nodes along the CSF-draining pathways or enter the venous sinuses through arachnoid villi and reach the spleen ([3,17](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b3)) (see [Fig. 1](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#f1)). CNS antigens also may be presented to naive T cells by dendritic cells, which are localized in the choroid plexus and the meninges. Evidence exists that inflammatory mediators produced in the CNS can stimulate dendritic cells to migrate into the brain parenchyma, where they can phagocytize antigens and subsequently migrate to cervical lymph nodes for antigen presentation to immunocompetent cells ([20](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b20)) (see [Fig. 1](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#f1)).

**STRESS AND IMMUNE/INFLAMMATORY RESPONSES**

Stress and the immune system appear to be strictly interconnected, and activation of the stress axis is demonstrated to occur during seizures ([21–23](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b21)). The stress–induced release of hypothalamic corticotropin-releasing hormone (CRH) leads ultimately to the systemic secretion of glucocorticoids (GCs), epinephrine, and norepinephrine, which in turn strongly influence immune and inflammatory reactions. Conversely, immune molecules, in particular IL-1, IL-6, and tumor necrosis factor (TNF)-α stimulate CRH secretion, thus activating the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system during inflammatory responses. CRH modulates immune/inflammatory reactions through receptor-mediated actions of GCs on target immune tissues and by directly acting on its own receptors on immune cells. However, the actions of CRH as a modulator of stress are not confined to the HPA system but appear to involve also CRH receptors in the limbic areas, such as the amygdala and the hippocampus ([22](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b22)).

GCs have immunosuppressant effects by preventing the migration of leukocytes from the circulation into extravascular spaces, reducing the accumulation of monocytes and granulocytes at inflammatory sites, and suppressing the production and actions of many cytokines and inflammatory mediators. Although stress has been in general regarded as immunosuppressive, evidence indicates that stress hormones differentially regulate the differention of CD4+ T cells into two distinct phenotypes: T helper (Th)1 and Th2 patterns and their consequent type 1 and type 2 cytokine secretion ([24](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b24)). Th1 cells regulate cellular immunity (CD8+ T-cytotoxic cells, natural killer cells, and activated macrophages) by primarily secreting type 1 cytokines: interferon (IFN)-γ, IL-2, and TNF-β, whereas Th2 cells secrete primarily type 2 cytokines, such as IL-4, IL-10, and IL-13, which promote humoral immunity (mast cells, eosinophils, B cells). Strong evidence suggests that stress hormones amplify the Th2 response while suppressing the Th1 response.

When entering the brain, Th cells can interact with microglia, which in turn can efficiently restimulate both Th1 and Th2 cells and release inflammatory mediators ([Fig. 2](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#f2)). Astrocytes appear to have a limited APC capacity restricted to recognition by Th2 cells ([17](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#b17)).

Figure 2. Intracerebral T-cell responses, mediated by intrapenchymal antigen-presenting cells (APCs), APCs decide the differentiation of T-helper cells (Th) into Th1 and Th2 cells, which secrete type 1 and type 2 cytokines, rspectively. These cells are pivotal in the regulation of cellular and humoral immunity, respectively. T cells primed in peripheral lymphoid tissues, or in the perivascular space and CSF by circulating APC*s* (see also [Fig. 1](http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00298.x/full#f1)), when entering the CNS parenchyma can interact with microglia and astrocytes. Microglia can efficiently express major histocompatibility complex (MHC) class II and adhesion/costimulatory molecules [e.g., intercellular adhesion molecule (ICAM)-1, B7] when activated by inflammatory stimuli and can restimulate both Th1 and Th2 cells and release mediators [including chemokines, interleukins, tumor growth factor β (TGF-β) and prostaglandin E2 (PGE2)] that regulate the phenotype, recruitment, activation, and eventually apoptosis of Th cells. Astrocytes appear to have a poor ability to express MCH class II and adhesion/costimulatory molecules, and their APC capacity may be limited to Th2-cell restimulation and inhibition of the Th1 response. CD28, costimulatory signal; TCR, T-cell receptor. (Adapted from Aloisi F, Ria F, Adorini L. Regulation of T-cell responses by CNS antigen-presenting cells: different roles for microglia and astrocytes. *Immunol Today* 2000;21:141–7, with permission.)



In summary, an excessive immune/inflammatory response by activation of the stress system may inhibit cellular immunity while favoring humoral immunity. This mechanism may serve to protect the organism from excessive production of proinflammatory cytokines with tissue-damaging potential. As a consequence, excessive HPA activity may increase susceptibility to infectious agents but enhance resistance to autoimmune/inflammatory diseases dominated by cellular immune responses.