

THE BLOOD BRAIN BARRIER IN HIV INFECTION

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1. ABSTRACT

The blood brain barrier (BBB) serves as a protective mechanism for the brain. It prevents entry of pernicious substances, whether chemical or cellular, from free access to the CNS. In essence, it is a defense mechanism preserving the internal milieu of the brain. The BBB may be disrupted by a number of pathological processes. CNS infection is a well recognized cause of BBB disruption. Among the CNS infections demonstrated to affect the BBB is human immunodeficiency virus (HIV). HIV infects the brain shortly after its acquisition. Studies of cerebrospinal fluid (CSF) as well as dynamic studies of contrast enhanced magnetic resonance imaging have confirmed abnormalities of the BBB in HIV-infected persons. Pathological studies of the CNS have confirmed the *in vivo* studies, and *in vitro* studies have identified a range of pathogenic mechanisms of HIV-associated BBB compromise. This disruption of the BBB may not only contribute to accelerating brain infection by HIV, but may also alter CNS function. Additionally, BBB disruption has implications with respect to antiretroviral therapy. This review will address these issues.

2. OVERVIEW OF THE BBB

After demonstrating that trypan blue injected intravenously stained most organs but the brain, Paul Ehrlich developed the concept of the blood brain barrier (BBB) (1). The BBB protects the CNS from various chemical constituents of the blood. The barrier is an operational definition. An intact BBB may preclude certain substances from entering the brain, such as, large protein molecules and highly charged molecules. Others may be only relatively excluded from the brain and molecules with high lipid solubility, such as, alcohol and anesthetics pass readily from the blood into the brain (2). It is the consequence of not only a physical barrier to the entry of substances from the blood, but also a transport system from the brain and CSF to the blood and vice versa. The physical barrier has been largely attributed to tight capillary

endothelial junctions in the CNS that differ from those of systemic capillaries. These high-resistance tight junctions, demonstrated electron microscopically, provide a continuous cellular layer that separates blood from the brain interstitial space (1). This tight junction exists for both endothelial cells and the arachnoid cells of the meningeal surface. It precludes entry into the brain of molecules such as the tracers, horseradish peroxidase and microperoxidase (molecular weights above 1900 and diameters exceeding 20 ?) (3). The blood brain barrier also serves to restrict the entry of cellular elements of the immune system. It is this relative exclusion from immune surveillance that has led to the expression that the brain is an immunologically privileged site.

Among the characteristics of the CNS endothelial cells are an absence of fenestrations and the presence of few plasmalemmal pinocytotic vesicles which are a factor in transendothelial transport outside the CNS. Glial foot processes of astrocytes that invest the brain capillaries also contribute to the BBB, but not in a structural sense as they do not exhibit tight junctions (3). The high metabolic demands for the maintenance of the BBB are attested to by the high concentrations of mitochondria in the endothelial cells of the brain capillaries that exceed the numbers of those in the endothelia of other organs.

In addition to the physical barrier presented by the capillary endothelia, the chemical composition of the brain extracellular fluid and the cerebrospinal fluid (CSF) is maintained by the buffering capacity of the blood, by regulatory mechanisms at the blood-brain interface, by glial and neuronal uptake of ions, and by stimulation of central chemoreceptors (2). These mechanisms permit the brain to be bathed by extracellular fluid with a constant chemical composition with the exceptions of certain telencephalic areas of the CNS, such as, the pineal gland, the area postrema of the medulla, the median eminence of the hypothalamus, the preoptic region, the subfornical organ,

and the organ vasculosum of the lamina terminals, the BBB is impermeable. . Additionally, the choroid plexus is a region of the brain in which fenestrated capillary beds are found. The blood brain barrier does express specific transporter molecules that facilitate the entry of substances that would otherwise gain entry through this lipophilic barrier only with difficulty. These include transporters for such nutrients as glucose(4) and amino acids(5).

3. BLOOD BRAIN BARRIER AND HIV ENTRY INTO CNS

Neuropathology and CSF studies indicate that HIV enters the brain within days to weeks of infection, well before the development of HIV-associated neurological abnormalities. Thus HIV can be cultured from CSF (6, 7), HIV nucleic acid can be amplified by polymerase chain reaction (8, 9), viral proteins are present (10), and HIV specific IgG synthesis may be detected (11) (12) (13). Furthermore, HIV viral particles have been demonstrated in the brain of an individual dying from iatrogenic illness within weeks of HIV infection (14) and HIV DNA can be found by in situ polymerase chain reaction in the brains of asymptomatic HIV infected individuals (15).

Studies of the simian immunodeficiency virus (SIV) model in the rhesus macaque monkey have been helpful in understanding of the course of CNS infection and neuropathology in HIV. SIV is a lentivirus that is closely related genomically to HIV. Infected macrophages are found in the brain parenchyma shortly after intravenous inoculation of the rhesus macaque with SIV (16). Not only is SIV demonstrable in the brain early in the course of infection(16), but as in man, SIV-specific intrathecal IgG synthesis can be detected(17) accompanied by low CSF viral loads. While no gross disruption of the BBB is apparent during this early infection with SIV, abnormalities are detectable. For instance, an upregulation of the glucose transporter 1 (GLUT1), a regulator of glucose transporter across endothelial cells, is observed (18).

Given its presence in the CNS in the earliest phases of infection, the initial entry of HIV into CNS is probably by subversion of one or more normal mechanisms of trans-BBB transport and/or trafficking, rather than acute BBB compromise. The present consensus is that initial entry of HIV into the CNS occurs via a "Trojan horse" mechanism in which the usual adhesion molecule mediated trafficking of immune cells across a normal BBB leads to entry of productively infected monocytes or lymphocytes (19). Alternate mechanisms, in which initial CNS infection occurs as a result of seeding by HIV-infected brain vascular endothelial cells and/or choroid plexus have also been suggested (20) (21) (22). Finally, entry of HIV across the breached BBB may accelerate, in a positive feedback manner, an accelerating decline in BBB integrity, an also represent an additional burden on CNS mechanisms of viral control and clearance.

Whatever the initial mechanism, it appears likely that the early entry occurs against a setting of normal BBB structure and function, and is generally neurologically

silent. Later HIV-associated compromise of BBB may, however, lead to an acceleration of HIV entry in viremic patients, and impact significantly on neurologic progression.

4. MICROVASCULAR AND BBB COMPROMISE IN HIV INFECTION

Microvascular and BBB changes are a hallmark of HIV infection. Vasculopathy is evident during all phases of HIV infection from early to late disease(23, 24), and neuropathologic series in HIV patients reveal evidence of perivascular serum exudates such as albumin and haptoglobin in brain parenchymal extracellular spaces in the absence of other disorders (25, 26). These abnormalities can be observed in the absence of symptomatically apparent neurological disease. Power et al have attributed the changes in the white matter observed on magnetic resonance imaging (MRI) in the HIV-infected brain to these changes(27). Such an interpretation is supported by more recent studies, which have demonstrated increased CSF/serum albumen ratios in ~15% of HIV infected patients (28), and increased delayed post-contrast enhancement in T1-weighted MRI in subcortical grey matter at 1.5T (29), and frontal white matter at 4T (Chang and Ernst, personal communication). Dynamic contrast enhanced MRI has also demonstrated an increased rCBV in subcortical gray matter in HIV dementia patients, which correlated with the severity of neurologic compromise, and was reversible in some cases following initiation of highly active antiretroviral therapy, HAART (30).

5. MECHANISMS OF HIV-ASSOCIATED BBB COMPROMISE

HIV infects microglia, astrocytes, and brain microvascular endothelial cells (BMEC), as well as perivascular macrophages (20, 21, 31-33) (34), leading to the elaboration of a constellation of proinflammatory cytokines and chemokines, as well as increased expression of matrix metalloproteinases (MMPs) and decreased expression of MMP inhibitor proteins (35). Furthermore, HIV proteins such as Tat and gp120 have been shown to stimulate release of these same pro-inflammatory molecules (36) (37) (38) (39) (40), and to stimulate the upregulation of adhesion molecules in astrocytes (41) and endothelial cells (42) (35). Cytokines such as TNF α also upregulate adhesion molecules including ICAM, VCAM and E-selectin in brain microvascular endothelial cells (BMEC) and astrocytes (43), and stimulate production of MMPs in brain derived tissue cultures (44). Support for a proinflammatory mechanism of BBB compromise in HIV infection can be found in the presence of perivascular inflammatory infiltrates containing HIV-infected macrophages, multinucleated giant cells and microglial nodules, a neuropathological hallmark of HIV infection, and a correlation between the severity of BBB compromise and the degree of glial activation (45, 46). The finding that Tat also induces apoptotic changes in BMEC via a NOS/iNOS-dependent pathway, leading to increased permeability of BMEC monolayers (47), suggests that HIV proteins may directly increase BBB permeability. The

recent observation that BBB breakdown is less severe for a given degree of glial activation in HAART-responsive than in HAART naïve patients (48) lends credence to this idea, suggesting that HAART naïve patients suffer BBB compromise through both HAART-sensitive (virus and/or viral protein dependent) and HAART-insensitive (inflammatory but virus/viral protein independent) pathways.

Clearly, HIV directly or indirectly targets many of the cellular and structural constituents of the BBB, including the endothelial cell layer, perivascular microglia, astrocytes, and basal lamina. These observations suggest that BBB compromise in HIV infection is a result of both sequential and parallel pathogenic pathways: infection of BMEC and astrocytes leads to upregulation of adhesion molecules, and a consequent increase in adhesion of infected and activated monocytes. Increased MMP production by these monocytes, as well as by infected astrocytes and BMEC, lead to breakdown of the extracellular matrix components of the basal lamina, and increased trafficking of infected cells into the CNS, and entry of free HIV and HIV proteins, as well as humoral factors, into the CNS compartment via paracellular routes (49). Increased production of HIV proteins and proinflammatory cytokines by these perivascular infiltrates further upregulate adhesion molecule expression, MMP production, and BBB breakdown in a positive feedback loop.

Finally, disruption of the BBB may be amplified by the presence of co-morbidities. For instance, the presence of CNS opportunistic infections resulting from HIV-associated immunodeficiency, such as cytomegalovirus, toxoplasmosis, etc., may result in BBB breakdown. Similarly, certain drugs of abuse may also be contributory (50). Cocaine has been demonstrated to alter the BBB in a human brain microvascular endothelial cell model and to increase the invasion of macrophage tropic HIV (51). The effects of cocaine may be mediated by an upregulation of pro-inflammatory cytokines and chemokines (51).

6. ROLE OF BBB COMPROMISE IN HIV-ASSOCIATED NEUROLOGIC IMPAIRMENT

Primary HIV-associated neurologic impairments are not uncommon, and while effective antiretroviral therapy has blunted their severity (52), it has been less effective in reducing their incidence (53). Although it is difficult to unambiguously ascribe neurologic impairments directly to BBB compromise, several lines of evidence suggest that BBB breakdown contributes to neurologic decline. Neurologic impairment measured by either the Memorial Sloan-Kettering (MSK) or HIV Dementia Rating Scale (HDS) is correlated with the degree of microvascular abnormality in the basal ganglia measured by contrast enhanced MRI (29, 30). These microvascular abnormalities are reversed by highly active antiretroviral therapy (HAART), and their reversal is accompanied by an improvement in neurological status (30). BBB compromise is a hallmark of CNS inflammation, suggesting that these

correlations may reflect a correlation with the degree of underlying inflammation. Indeed the degree of both neurologic compromise (HDS) and BBB breakdown are correlated with levels of the glial proliferative marker myo-inositol (mI) in the basal ganglia of HIV patients (45, 46). However there is a significant difference in the dependence of BBB permeability on mI levels in HAART-naïve and HAART responsive HIV patients: HAART responsive patients have less BBB compromise, and less neurologic impairment for a given mI elevation than do HAART naïve patients (48), suggesting that BBB compromise per se underlies, at least in part, the neurologic deficits seen in HIV patients. Neurologic impairment is correlated with increased CSF viral load (54), suggesting that one way in which increased BBB permeability may contribute to neurologic impairment is by increasing access of circulating plasma virus to the CNS via paracellular routes. Support for such a view comes from the recent observation that for a given plasma viral load, HIV patients with compromised BBB have significantly poorer neurologic status than patients with intact BBB (55).

7. ANTIRETROVIRAL THERAPY AND THE BBB

The integrity of the BBB has significant implications for antiretroviral therapy. As was noted earlier, HIV infection of the brain can be demonstrated shortly after the initial infection. The brain has been designated as a sanctuary for viral propagation (56, 57). In the absence of effective antiretroviral therapies that cross the BBB, the brain may serve as a site for constant systemic re-seeding by HIV. Alternatively, low level penetration of antiretrovirals into the CNS may lead to the development of antiretroviral resistant strains that could also serve as sources of systemic HIV infection. As importantly, the absence of effective antiretroviral treatment of HIV in the brain would logically predispose to the genesis of HIV dementia. Studies that have addressed the incidence of HIV dementia with respect to the BBB penetration of antiretroviral therapies remain a subject of debate. One Australian study noted an increase in HIV dementia following the introduction of HAART relative to other AIDS defining illnesses and suggested that the newly introduced poorly CNS penetrant antiretroviral agents may be responsible (58).

The BBB penetration capability of the currently available antiretroviral agents is quite variable. Of the nucleoside reverse transcriptase inhibitors (RTIs), zidovudine crosses the blood/CSF barrier best and of the non-nucleoside RTIs, nevirapine does so. Protease inhibitors, in general, have poor ability to cross the BBB as reflected by CSF/blood levels. Nevirapine appears to cross most readily of the protease inhibitors, however, even it does not cross the blood/CSF barrier very effectively (59). Data regarding BBB penetration should be interpreted cautiously, however, as it does not include the levels of the drug that are effective in suppressing viral replication, nor does it consider the way in which penetration may vary with varying BBB compromise. The former must be included in any analysis of the likely effectiveness of a therapeutic regimen, while the latter may vary depending

on the stage of disease, and the degree to which HAART repairs and/or maintains BBB integrity.

8. SUMMARY

HIV infection of the CNS occurs shortly after the systemic introduction of the virus. The BBB is disrupted in association with HIV infection. The alteration of BBB integrity may facilitate the penetration of HIV into the CNS amplifying the local infection. Conversely, the BBB serves as an effective barrier to the ability of many antiretroviral agents to reach sufficient and sustainable levels in the CNS to inhibit viral replication. Paradoxically, the disruption of the BBB may be beneficial in the treatment of HIV dementia, allowing antiretroviral therapies to enter the brain. Its restoration under treatment may have the opposite effect.

There are many questions regarding the BBB in the setting of HIV infection that remain to be answered. These may contribute very significantly to our understanding of HIV neuropathogenesis and treatment.

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