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EDITORIAL

BLOOD-BRAIN BARRIER

BY

M. Adel Shalaby

The blood–brain barrier (BBB) is a highly selective permeability barrier that separates the circulating blood from the brain extracellular fluid in the central nervous system (CNS). The blood–brain barrier is formed by brain endothelial cells, which are connected by tight junctions with an extremely high electrical resistivity of at least 0.1 Ω·m. The blood–brain barrier is composed of high-density cells restricting passage of substances from the bloodstream much more than do the endothelial cells in capillaries elsewhere in the body. The BBB is distinct from the quite similar blood–cerebrospinal fluid barrier, which is a function of the choroidal cells of the choroid plexus, and from the blood–retinal barrier, which can be considered a part of the whole realm of such barriers.

The blood–brain barrier allows the passage of water, some gases, and lipid-soluble molecules by passive diffusion, as well as the selective transport of molecules such as glucose and amino acids that are crucial to neural function. On the other hand, the blood–brain barrier may prevent the entry of lipophilic potential neurotoxins by way of an active transport mechanism mediated by P-glycoprotein. Astrocytes are necessary to create the blood–brain barrier. Astrocyte cell projections called **astrocytic feet** (also known as **"glia limitans"**) surround the endothelial cells of the BBB, providing biochemical support to those cells. A small number of regions in the brain, including the circumventricular organs (CVOs), do not have a blood–brain barrier. The circumventricular organs include:

- Pineal body: Secretes melatonin and neuroactive peptides. It is associated with circadian rhythms. The pineal gland secretes the hormone melatonin "directly into the systemic circulation", thus melatonin is not affected by the blood–brain barrier.
- Neurohypophysis (posterior pituitary): Releases neurohormones-like oxytocin and anti-diuretic hormone into the blood.
- Area postrema "Vomiting center": When a toxic substance enters the bloodstream, it will get to the area postrema and may cause the subject to throw up.
- Subfornical organ: Important for the regulation of body fluids.
- Vascular organ of the lamina terminalis: A chemosensory area that detects peptides and other molecules.
- Median eminence: Regulates anterior pituitary through release of neurohormones.

At the interface between blood and the brain, endothelial cells are stitched together by these tight junctions, which are composed of smaller subunits, frequently biochemical dimers, that are transmembrane proteins such as **occludin, claudins, junctional adhesion molecule (JAM), or ESAM**. Each of these transmembrane proteins is anchored into the endothelial cells by another protein complex

BBB has several important functions:

1. **Protects the brain from "foreign substances"** in the blood that may injure the brain.
2. **Protects the brain from hormones and neurotransmitters** in the rest of the body.
3. **Maintains a constant environment** for the brain.

BBB can be broken down by:

1. **Hypertension**: High blood pressure opens the BBB.
2. **Development**: The BBB is present, but may be not fully formed at birth.
3. **Hyper-osmolarity**: A high concentration of a substance in the blood can open the BBB.
4. **Microwaves**: Exposure to microwaves can open the BBB.
5. **Radiation**: Exposure to radiation can open the BBB.
6. **Infection**: Exposure to infectious agents can open the BBB.
7. **Trauma, Ischemia, Inflammation, Pressure**: Injury to the brain can open the BBB.
8. **Oxidative stress** plays an important role into the breakdown of the barrier. Anti-oxidants such as lipoic acid may be able to stabilize a weakening blood–brain barrier.

BBB as a drug target

The blood–brain barrier (BBB) excludes from the brain ~100% of large-molecule neuro-therapeutics, and more than 98% of all small-molecule drugs. Overcoming the difficulty of delivering therapeutic agents to specific regions of the brain presents a major challenge to treatment of most brain disorders. In its neuroprotective role, the blood–brain barrier functions to hinder the delivery of many potentially important diagnostic and therapeutic agents to the brain.

Mechanisms for drug targeting in the brain involve going either "through" or "behind" the BBB. Modalities for drug delivery/dosage form through the BBB entail its disruption by osmotic means, biochemically by the use of vasoactive substances such as bradykinin, or even by localized exposure to high-intensity focused ultrasound (HIFU). Other methods used to get through the BBB may entail the use of endogenous transport systems, including carrier-mediated transporters such as glucose and amino acid carriers, receptor-mediated transcytosis for insulin or transferrin, and the blocking of active efflux transporters such as p-glycoprotein. However, vectors targeting BBB transporters, such as the transferrin receptor, have been found to remain entrapped in brain endothelial cells of

capillaries, instead of being ferried across the BBB into the cerebral parenchyma. Methods for drug delivery behind the BBB include intracerebral implantation (such as with needles) and convection-enhanced distribution. Mannitol can be used in bypassing the BBB.

Nanoparticles

Nanotechnology may also help in the transfer of drugs across the BBB. Delivering drugs across the blood–brain barrier is one of the most promising applications of nanotechnology in clinical neuroscience. Nanoparticles could potentially carry out multiple tasks in a predefined sequence, which is very important in the delivery of drugs across the blood–brain barrier.

Peptides

Peptides are able to cross the blood–brain barrier (BBB) through various mechanisms, opening new diagnostic and therapeutic avenues

BBB and Diseases

Meningitis

When the meninges are inflamed, the blood–brain barrier may be disrupted. This disruption may increase the penetration of various substances (including either toxins or antibiotics) into the brain. Antibiotics used to treat meningitis may aggravate the inflammatory response of the central nervous system by releasing neurotoxins from the cell walls of bacteria - like lipopolysaccharide (LPS). Depending on the causative pathogen, whether it is bacterial, fungal, or protozoan, treatment with third-generation or fourth-generation cephalosporin or amphotericin B is usually prescribed. .

Epilepsy

Several clinical and experimental data have implicated the failure of blood–brain barrier function in triggering chronic or acute seizures. Acute seizures are a predictable consequence of disruption of the BBB by either artificial or inflammatory mechanisms. In addition, expression of drug resistance molecules and transporters at the BBB are a significant mechanism of resistance to commonly used anti-epileptic drugs.

Multiple sclerosis

Multiple sclerosis (MS) is considered to be an auto-immune and neurodegenerative disorder in which the immune system attacks the myelin that protects and electrically insulates the neurons of the central and peripheral nervous systems. Normally, a person's nervous system would be inaccessible to the white blood cells due to the blood–brain barrier. When a person is undergoing an MS "attack," the blood–brain barrier has broken down in a section of the brain or spinal cord, allowing T lymphocytes to cross over and attack the myelin. The weakening of the blood–brain barrier may be a result of a disturbance in the endothelial cells on the inside of the blood vessel, due to which the production of the protein P-glycoprotein is not working well.

Late-stage neurological trypanosomiasis (sleeping sickness)

Late-stage neurological trypanosomiasis, or sleeping sickness, is a condition in which trypanosoma protozoa are found in brain tissue. It is suspected that the parasites cross through the choroid plexus, a circumventricular organ.

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system that is caused by reactivation of a latent papovavirus (the JC polyomavirus) infection that can cross the BBB. It affects immune-compromised patients and it is usually seen with patients suffering from AIDS.

De Vivo disease

De Vivo disease (also known as **GLUT1 deficiency syndrome**) is a rare condition caused by inadequate transportation of the sugar glucose across the blood–brain barrier, resulting in developmental delays and other neurological problems. Genetic defects in glucose transporter type 1 (GLUT1) appears to be the primary cause of De Vivo disease.

Alzheimer's disease

Some evidence indicates that disruption of the blood–brain barrier in Alzheimer's disease patients allows blood plasma containing amyloid beta (Aβ) to enter the brain where the Aβ adheres preferentially to the surface of astrocytes. These findings have led to the hypotheses that (1) breakdown of the blood–brain barrier allows access of neuron-binding autoantibodies and soluble exogenous Aβ42 to brain neurons, and (2) binding of these auto-antibodies to neurons triggers and/or facilitates the internalization and accumulation of cell surface-bound Aβ42 in vulnerable neurons through their natural tendency to clear surface-bound autoantibodies via endocytosis. Eventually, the astrocyte is overwhelmed, dies, ruptures, and disintegrates, leaving behind the insoluble Aβ42 plaque. Thus, in some patients, Alzheimer's disease may be caused (or more likely, aggravated) by a breakdown in the blood–brain barrier.

Cerebral edema

Cerebral edema is the accumulation of excess water in the extracellular space of the brain, which can result when hypoxia causes the blood–brain barrier to open.

Prion and prion-like diseases

Many neurodegenerative diseases including alpha-synucleinopathies (Parkinson's, PSP, DLBP) and tauopathies (Alzheimer's) are thought to result from seeded misfolding from pathological extracellular protein variants. This prion-like hypothesis is gaining support in numerous studies in vitro and involving in vivo intracerebral injection of brain lysates, extracted protein (tau, alpha-synuclein) and synthetically generated fibers (PFFs in alpha-synucleinopathies). These proteins are also detectable in increasing amounts in the plasma of patients suffering from these conditions (particularly total alpha-synuclein in Parkinson's disease patients). The extent to which and the mechanisms by which these prion-like proteins can penetrate the blood–brain barrier is currently unknown.

HIV encephalitis

Latent HIV can cross the blood–brain barrier inside circulating monocytes in the bloodstream "Trojan horse theory" within the first 14 days of infection. Once inside, these monocytes become activated and are transformed into macrophages. Activated macrophages release **virions** into the brain tissue proximate to brain microvessels. These viral particles likely attract the attention of sentinel brain microglia and perivascular macrophages initiating an inflammatory cascade that may cause a series of intracellular signaling in brain microvascular endothelial cells and damage the functional and structural integrity of the BBB. This inflammation is HIV encephalitis (HIVE). Instances of HIVE probably occur throughout the course of AIDS and are a precursor for HIV-associated dementia (HAD).

Systemic inflammation

During systemic inflammation, whether in the form of infection or sterile inflammation, the BBB may undergo changes which may be disruptive or non-disruptive. These BBB changes likely play a role in the generation of sickness behavior during systemic infection. These changes may also induce or accelerate disease within the brain. Also, in patients with neurological disease. the BBB may be abnormally sensitive to the effects of systemic inflammation.

Brain tumors

It should be noted that vascular endothelial cells and associated pericytes are often abnormal in tumors and that the blood–brain barrier may not always be intact in brain tumors. Also, the basement membrane is sometimes incomplete. Other factors, such as astrocytes, may contribute to the resistance of brain tumors to therapy.

BBB and STRESS

Stressors increase ROS, inflammatory mediators, mitochondrial dysfunction and extracellular glutamate. These mechanisms contribute to Meth-induced BBB disruption in response to a variety of insults. Thus, it is likely that stress could exacerbate Meth-induced BBB disruption by potentiating Meth-induced increases in ROS, inflammatory mediators, mitochondrial dysfunction, and extracellular glutamate.

Most stress episodes provoke a controlled response of the organism, which is essential for survival and may enhance performance. Intense or prolonged exposure to stress, in contrast, may lead to a variety of neuropsychiatric disorders. Stressful stimuli are reported to impair synaptic plasticity in the hippocampus and to inhibit hippocampal neurogenesis. Furthermore, retrospective epidemiological studies indicate that stress is associated with increased risk of dementia and development of neurological or psychiatric disorders, such as Alzheimer's disease or major depressive disorder. The effect of stress is influenced by a number of factors, including individual sensitivity, the brain region affected and the type of stress.

Stress stimuli, among other challenges emerging from the external and internal environment, alter circulating plasma composition. The central nervous system (CNS) is

protected from these fluctuations by barriers, among which the blood-brain barrier (BBB) plays a key role in maintaining homeostasis.

BBB endothelial cells *in vivo* are continuously exposed to **laminar shear stress** to which they respond by structural (cell orientation with flow direction; redistribution of cell fibers and flattening) and functional remodeling showing significant evidences of differentiation.

Shear stress plays a key role in modulating endothelial structure and function. It is a stress resulting from the application of opposing forces parallel to a cross sectional area of a body. As blood flows, the vascular wall is constantly subjected to physical forces, which regulate important physiological blood vessel responses, as well as being implicated in the development of arterial wall pathologies. Changes in blood flow, thus generating altered hemodynamic forces, are responsible for acute vessel tone regulation, the development of blood vessel structure during embryogenesis and early growth, as well as chronic remodeling and generation of adult blood vessels.

Shear stress enhances the RNA levels of ion channel genes and other relevant transporters. It facilitates endothelial-leukocyte cross-talk to respond to pro-inflammatory stimuli.

Shear stress modulates the bio-energetic behavior on the BBB endothelial cells. Laminar shear stress inhibits endothelial cell proliferation. It increases cytoskeleton protein expression while decreasing that of cytosol, nucleus and membrane.

Blood-Brain Barrier Damage (BBBD) induces release of **α_2-Macroglobulin (α_2M)**. α_2M is a broad spectrum protease inhibitor naturally present in serum and interstitial fluids. α_2M production can be stimulated by interleukin 6. Glucocorticoids may stimulate α_2M release and inhibit up-regulation of MM metalloproteinases gelatinase A (MMP-2) and gelatinase B (MMP-9). α_2M has a peptide stretch, called the “bait region,” that contains specific cleavage sites for different proteinases. This protein also binds to a number of different growth factors and cytokines suggesting that α_2M may play an additional role in cellular growth regulation. α_2M is primarily synthesized by liver cells. It has been suggested that α_2M can also be synthesized by astrocytes. In addition to liver cells and astroglia, blood cells may also produce α_2M. So, a rapid increase of α_2M in serum occurs in patients after BBBD.

Associate Editor
Prof. Dr. Mohamed Adel Shalaby