Blood brain barrier

Blood-brain barrier (BBB)

- Brain is surrounded by protective fluid cerebrospinal of the brain and spine and a protective membrane called the meninges .Both provide further defence against physical injury.
- Another protective element is the blood–brain barrier .
- This is a barrier between the brain’s blood vessels) capillaries)and the cells and other components that make up brain tissue .
- Whereas the skull ,meninges and cerebrospinal fluid protect against physical damage ,the blood–brain barrier provides a defence against disease-causing pathogens and toxins that may be present in our blood.

Blood-brain barrier (BBB)

- The blood-brain barrier (BBB) is a component of the neurovascular unit (NVU)
- BBB acts as the blood-brain interface, mediating communication between the central nervous system (CNS) and the periphery.
- The BBB separates the circulation from the brain which brain from and transport regulation of serum factors and neurotoxins.
- The BBB is a physical barrier according to involve specialized tight junctions and other structure that prevent unregulated leakage
- Also acts more selectively permeable as a transport interface a secretory body, and a metabolic barrier (containing and releasing certain enzymes locally)

Blood-Brain Barrier structure

Blood-Brain Barrier (BBB) is a selectively permeable membrane that regulates the passage of a multitude of large and small molecules into the neurons by cellular transport channels that facilitate the transport of essential molecules into the brain.

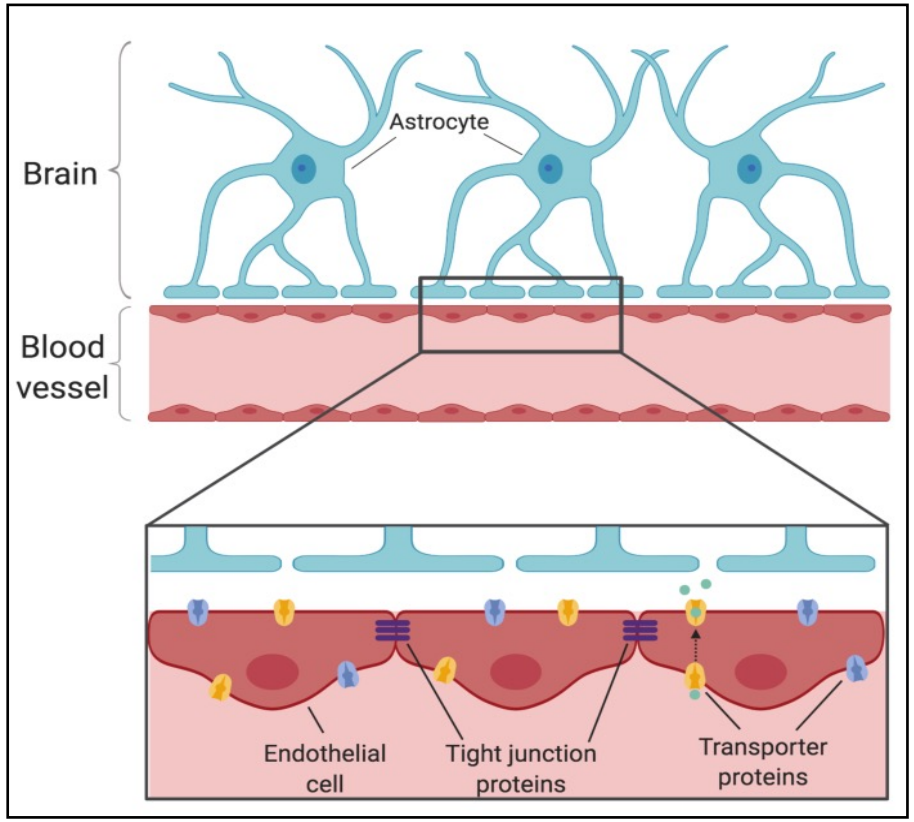
cellular transport channels include:

- Amino acid transporters
- Glucose transporter 1 (GLUT1)
- Nucleouside & nucleotide transporters
- Monocarboxylate transporters (MCT1 and MCT2)
- Ion transporters (Na+/K+-ATPase pumps)

- the BBB is not the same in all regions throughout the brain. Therefore, observations in one brain region or subregion might not persist in another.
- The diameter of blood vessels and composition of the BBB can change depending on the requirements of the region and the type of blood vessel (i.e., arterioles to capillaries to venules).

1. Brain Endothelial Cells

- **Endothelial Cells are t**he first line of defense against circulating factors in the brain
- Is a monolayer of brain endothelial cells which are connected by tight junctions and adherens junctions
- These endothelial cells are different from peripheral endothelial cells in that they express tight junction proteins, creating a stronger barrier, and have decreased pinocytosis, restricting vesicle-mediated transcellular transport and transporters
- The highly organized **Endothelial Cells,** tight junctions, and adherens junctions former provide structural support to the endothelial wall, while the latter physically connect adjacent cells. Additionally, the tight junctions circumscribe the cells and provide a seal with all adjacent cells. Therefore, the endothelium functions as an impermeable barrier between the capillary lumen and brain tissue.



- They make up the largest surface area at the blood-CNS interface.
- With this large surface area, they can readily transport proteins and molecules into and out of the brain most efficiently.
- Endothelial cells are polarized, exhibiting a luminal and abluminal side, with different transporters and cellular machinery expressed at each side.
- There are other cell types present that are a part of the NVU or that affect BBB functions, including neurons, astrocytes, and pericytes.

The BBB endothelial cell in the mature mammalian brain is characterized by different features, which make them phenotypically different from other ECs located at different parts of the body.

BBB endothelial cells characteristic:

1. Flattened appearance
2. The expression of inter-endothelial tight junctions
3. The presence of very few caveolae at the luminal surface
4. Contain a high number of mitochondria when compared to ECs from other vascular districts

BBB endothelial cells permeability:

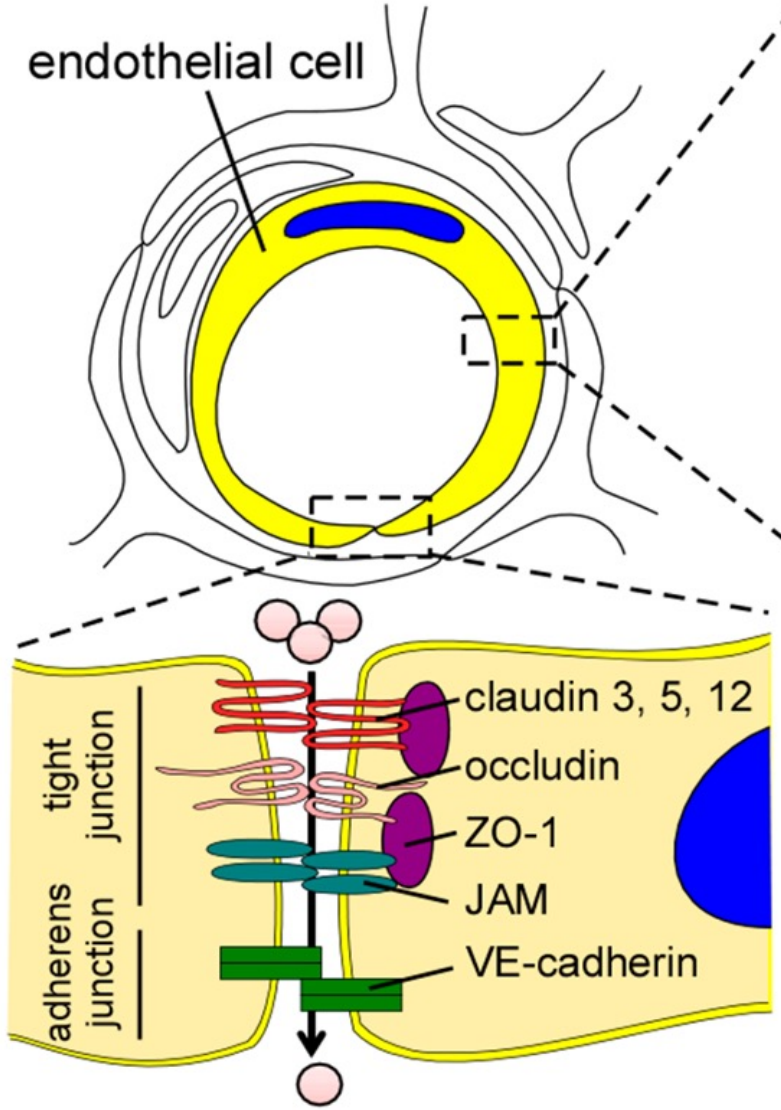
The paracellular flux of hydrophilic molecules across the BBB endothelium is hindered by the tight junctions sealing the paracellular pathways between adjacent endothelial cells.

The TJs also provide a fence around the cell, separating its luminal portion from the basolateral region.

Across the endothelium, there is rapid free diffusion of oxygen from the blood to the brain and carbon dioxide diffusion in the opposite direction, which is essential for normal brain metabolism and regulation of pH in the brain ISF, neurons, and other NVU cells.

Besides, small lipophilic molecules, with a molecular weight (MW) < 400 Da forming < 8 hydrogen bonds, can cross the BBB. Glucose, amino acids, and other nutrients enter the brain via carrier-mediated transporters.

In contrast, the uptake of larger molecules such as insulin, leptin, and iron transferrin are facilitated via receptor-mediated endocytosis



Tight junction and adherens junction complexes

Molecular barrier properties mediated by specific transporters

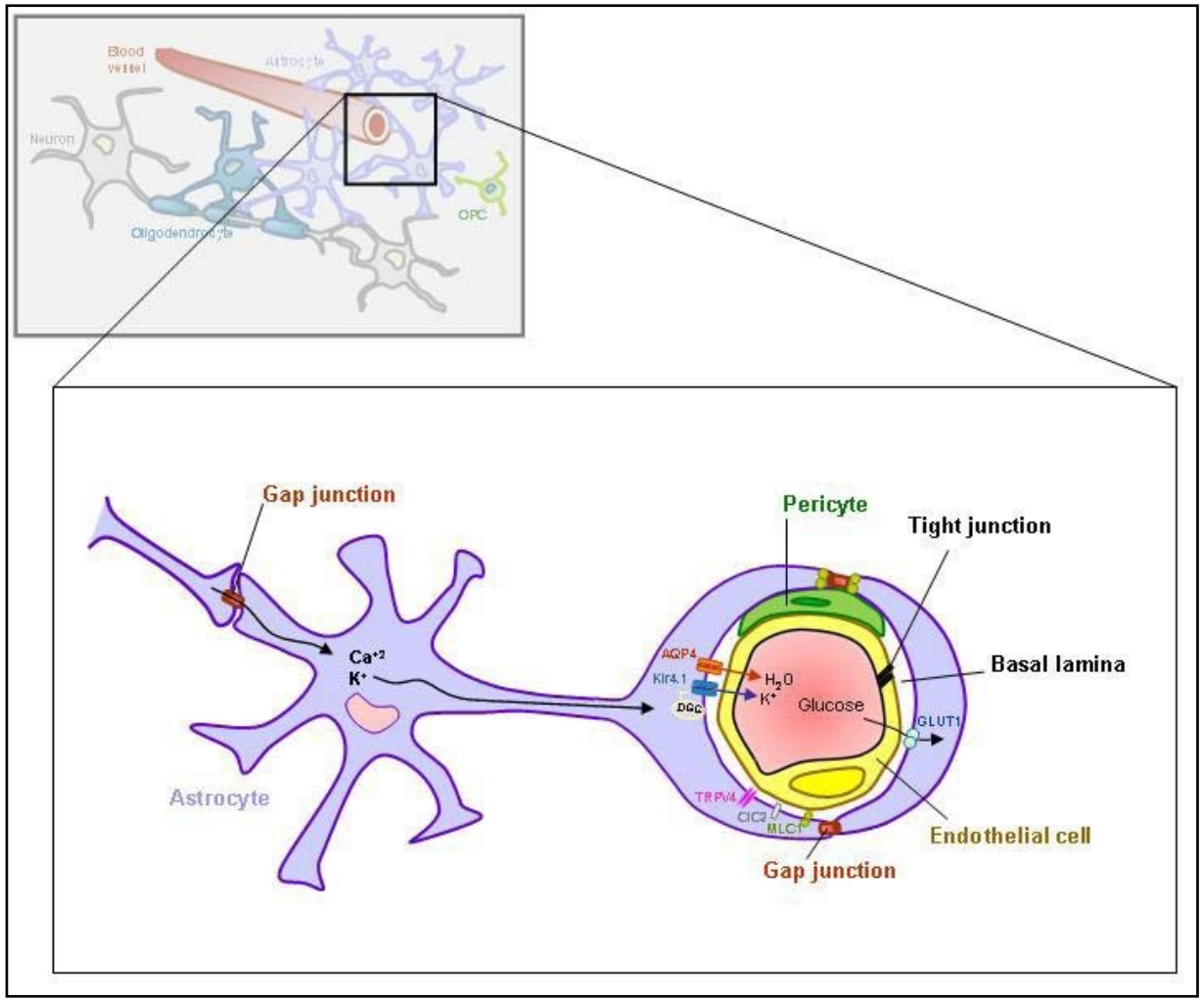
blood	BBB	brain
transport system		**substrate**
active efflux transporters		small lipophilic molecules O_2, CO_2
transcellular lipophilic pathway		ethanol nicotine
carrier protein-mediated pathway		glucose amino acid nucleotide
receptor-mediated endocytosis		insulin transferrin IgG
adsorptive endocytosis		albumin histone

2. Neurons

- Neurons are close to the capillaries and connect with astrocytic end feet near the BBB.
- It is estimated that nearly every neuron has its capillary (Neurons are rarely more than 8–20 µm from a brain capillary)
- The proximity to the endothelial cells, allows neurons to respond to the ever-changing local milieu, especially regarding ion balance.
- Neurons play a role in regulating blood flow, and microvascular permeability, interact with the extracellular matrix, and can release factors to stimulate angiogenesis.
- Following a vascular insult, signals from neurons and astrocytes can recruit microglia which secrete proinflammatory cytokines
- Neurons help tighten brain endothelial cells in culture by aiding in tight junction protein synthesis and localization
- These data support a synergistic role in the regulation of other cell types by neurons and highlight how these cells communicate with one another.
- Indeed, the neuronal circuitry is linked to the blood vessels by water channels present in astrocytes.

3. Astrocytes

- Astrocytes are the most abundant cells in the brain, providing an environment to help regulate all aspects of neuronal function (survival, development, metabolism, neurotransmission). They act as metabolic sensors in the brain responding to changes
- At the BBB astrocytes help provide maintenance and repair support through the release of several effector molecules
- The astrocytic end feet ensheath the vascular tube and help to regulate ion and water regulation
- Aquaporin-4 is an astroglial water channel that regulates perivascular fluid and solute movement through the glymphatic system, a unique exchange between perivascular cerebrospinal fluid (CSF) and interstitial fluid present in the CNS



- Using this system, the brain can regulate fluid flow throughout the CNS and aid in the clearance of toxins. In addition, the connection between neurons and blood vessels allows astrocytes to relay signals regarding blood flow as well as control brain water content
- Astrocytes and endothelial cells have a symbiotic relationship. Astrocytes secrete a range of chemical factors, including various growth factors that induce aspects of the BBB phenotype in endothelial cells in vitro and likely in vivo while endothelial cells aid in astrocytic differentiation. Astrocytic endfeet are polarized and guided to cerebral vessel walls by pericytes.
- Astrocytes are highly branched cells with small bodies found both in white matter (fibrous astrocytes) as well as in grey matter (protoplasmic astrocytes). The podocytes of both fibrous and protoplasmic astrocytes not only encircle nerve fibres and neuronal somas (respectively), but they also surround the abluminal surface of the capillaries. At this point, the processes are referred to as perivascular endfeet.

The physiological and biochemical function of Astrocytes

1. Compartmentalization of the neural parenchyma
2. Maintenance of the ionic homeostasis of the extracellular space
3. pH regulation
4. Neurotransmitter uptake and processing by providing energy-rich substrates to the neurons
5. Mediation of signals from neurons to the vasculature

4. Pericytes

- Pericytes sit on the abluminal surface of the endothelial cell and are embedded in the vascular basement membrane and are physically connected to brain endothelial cells by way of gap junctions and peg and socket arrangements.
- Pericytes help to maintain and stabilize the monolayer of brain endothelial cells by regulating angiogenesis and depositing extracellular matrix.
- Pericytes are essential for the development of tight junctions, including in the development of barrier functions in utero
- In addition, there is cross-talk from the brain endothelial cell to the pericyte on pericyte proliferation and migration.
- Pericytes can regulate blood flow in response to neural activity suggesting an important role in mediating vascular tone and highlighting the neural communication necessary for this particular function.

- Studies conducted on other mammals have implicated pericytes as integral components in the formation of the blood-brain barrier. These cells encircle endothelial cells of capillaries and are able to contract in order to regulate capillary blood flow. Consequently, the contractility also regulates the amount of blood flowing through the capillaries, thus enhancing the blood-brain barrier. Furthermore, some theories suggest that pericytes not only promote the formation of tight junctions, but they also inhibit the production of chemicals that promote vascular permeability.

- Their close association with ECs allows the exchange of ions, metabolites, second messengers, and ribonucleic acids between the two cell types
- Pericytes also play essential roles in maintaining BBB integrity, aiding in angiogenesis, and microvascular stability
- Pericytes, which also feature contractile characteristics similar to smooth muscle cells, can regulate (to some extent) the capillary diameter and the cerebral blood flow (CBF)
- Furthermore, pericytes may display phagocyting functions helping with the removal of toxic metabolites.
- They have also been reported to have multipotent stem cell capabilities.
- Studies have shown that PCs express receptors for vascular mediators, such as catecholamines, angiotensin, vasoactive intestinal peptides, endothelin-1, and vasopressin. These data strongly suggest that PCs play an essential role in cerebral autoregulation.

5. Microglia

Derived from hematopoietic precursors that migrate from the yolk sac into the CNS parenchyma, microglia act as the brain's main line of defense past the BBB and play a vital role in innate immune responses in the CNS. Although located in close proximity to endothelial cells of brain microvessels, little is known about potential microglial–endothelial communication in forming and regulating the homeostatic BBB.

One study has demonstrated that microglia associate with endothelial tip cells along nascent vessels in the developing brain and promote the fusion of tip cells in the stages following vascular endothelial growth factor-mediated tip cell induction

Microglia can exist in one of two active states:

1. **M1 pathway:** microglia primarily release proinflammatory cytokines like interleukin-1b antitumor necrosis factor-a
2. **M2 pathway:** microglia are involved in tissue repair, phagocytosing damaged neurons and foreign material, releasing chemokines and vascular endothelial growth factors, and activating neurotrophic pathways

In the case of multiple sclerosis, the release of proinflammatory cytokines and reactive oxygen species by activated microglia can exacerbate myelin damage and increase BBB permeability potentially via downregulation of adherens junction [AJ, such as vascular endothelial (VE)-cadherin] and TJ (occludin and claudin-5) proteins

Physiological functions of the BBB at the blood–brain interface

1. Maintain ionic homeostasis and brain nutrition:

The BBB provides a controlled microenvironment via a combination of specific ion channels and transporters, which keep the ionic composition optimal for neural and synaptic signaling functions. For example:

the levels of potassium in CSF and ISF are maintained at ~ 2.5–2.9 mM. In comparison, plasma concentration is approximately 4.5 mM, despite fluctuations that can occur in potassium plasma levels following exercise or a meal, imposed experimentally, or resulting from pathology

Other ions such as calcium and magnesium and pH are also actively regulated at the BBB and BCSFB. Calcium and potassium homeostasis controls neuronal excitability but is also essential for the transmigration of macrophages across the BBB. Furthermore, Ca^{2+} is involved in the modulation of BBB integrity and endothelial morphology

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For essential water-soluble nutrients and metabolites required by nervous tissue, the BBB allows for low passive permeability. In contrast, for other nutrients that cannot pass, there are specific transport systems expressed in the BBB to ensure an adequate supply of these substances. The selective and region-specific (luminal and abluminal surfaces of the ECs) expression of these transporters confers the normal polarity of the BBB endothelium.

The differentiation of the endothelium into a barrier layer begins during embryonic angiogenesis and in the adult is primarily maintained by a close inductive association with several cell types, especially the endfeet of astrocytic glial cells.

2. Regulate levels of neurotransmitters

- The central and peripheral nervous systems share many of the same neurotransmitters, so the BBB helps to keep the central and peripheral transmitter pools separate, minimizing ‘crosstalk’ and protecting the brain from unexpected changes in their plasma levels.
- For example, blood plasma contains high levels of the neuroexcitatory amino acid glutamate, which fluctuate significantly after the ingestion of food. High levels of glutamate in the brain ISF will have harmful effects on neuronal tissues. An example is a case of glutamate secretion from hypoxic neurons during ischemic stroke, which results in considerable and permanent neurotoxic/neuroexcitatory damage to neural tissue
- The transfer of neurotransmitters from the brain to blood is primarily dependent on Na+-coupled and Na+-independent amino acid transporters. The BBB limits the influx of some amino acids including the neurotransmitters glutamate and glycine, while it effluxes many other essential amino acids.

3. Limit plasma macromolecules leak into the brain

The production of CSF from plasma, under normal conditions, passed through an efficient filtration process in the choroid plexus to remove unneeded plasma proteins.

This process helps in controlling the protein content of CSF and results in minimal quantities of proteins in CSF compared to the plasma protein levels

Under physiologic conditions, the BBB prevents many macromolecules from entering the brain through normal paracellular or diffusion routes. The leakage of these large molecular weight serum proteins into the brain across a damaged BBB can have severe pathological consequences. For example, the leakage of plasma proteins such as albumin, prothrombin, and plasminogen has a detrimental effect on nervous tissue, causing cellular activation, which can lead to apoptosis

There is a wide distribution of different activators for these proteins within the CNS. These include factor Xa, which converts prothrombin to thrombin, or tissue plasminogen activator, which converts plasminogen to plasmin. The resulting proteins, thrombin or plasmin, can bind to their receptors in brain tissue and initiate cascades resulting in seizures, glial activation, glial cell division and scarring, and cell death. Thus, the BBB works as a “gatekeeper,” allowing the entry of only the beneficial materials.

4. Protect the brain against neurotoxins

- Many potential neurotoxins are circulating in our blood, including those from endogenous sources such as metabolites or proteins, or exogenous ones such as xenobiotics ingested in the diet or otherwise acquired from the environment.
- The BBB function is to regulate the entry of different circulating substances based on CNS needs.
- The transport barrier represented by multiple ABC energy-dependent efflux transporters (ATP-binding cassette transporters) occupies the BBB luminal surface.
- It actively pumps many of these agents out of the brain.
- The adult CNS has a limited regenerative capacity if damaged, and fully differentiated neurons have a minimal ability to divide and replace themselves under normal circumstances.
- There is a continuous steady rate of neuronal cell death from birth throughout life in the healthy human brain, with relatively low levels of neurogenesis.
- That is why any factor promoting an acceleration of the natural rate of cell death (e.g., increased access of neurotoxins into the brain) would become prematurely debilitating.

Homework

1. **Could you please explain the different ways of transport across the BBB that includes Passive diffusion, Active efflux, Carrier-mediated transport (CMT), and Receptor-mediated transport (RMT)?**

2. **In details, give an example of Neurological diseases in relation to the blood–brain barrier and descripe the pathological condition?**