Blood-brain barrier

Despite the availability of numerous therapeutic substances that could potentially target CNS disorders, an inability of these agents to cross the restrictive blood-brain barrier (BBB) limits their clinical utility. Novel strategies to overcome the BBB are therefore needed to improve drug delivery.

General information

The passage of water-soluble substances from the blood to the CNS is limited by tight junctions (zonulae occludentes) which are found between brain capillary endothelial cells, limiting penetration of the cerebral parenchyma (blood-brain barrier, BBB), as well as between choroid plexus epithelial cells (blood-CSF barrier) [1].

A number of specialized mediated transport systems allow transmission of, among other things, glucose and certain amino acids (especially precursors to neurotransmitters).

The efficacy of the Blood-brain barrier is compromised in certain pathological states (e.g. tumor, infection, trauma, stroke, hepatic encephalopathy…), and can also be manipulated pharmacologically (e.g. hypertonic mannitol increases the permeability, whereas steroids reduce the penetration of small hydrophilic molecules).

The BBB is absent in the following areas: choroid plexus, hypophysis, tuber cinereum, area postrema, pineal and preoptic recess.

Means of assessing the integrity of the BBB:

- visible dyes: Evan’s blue, fluorescein
- radioopaque dyes (imaged with CT scan [2]): iodine (protein-bound contrast agent)
- paramagnetic (imaged on MRI): gadolinium (protein-bound contrast agent)
- microscopic: horseradish peroxidase
- radiolabeled: albumin, sucrose

Traditionally, the BBB has been considered to be a major hindrance to the use of chemotherapy for brain tumors. In theory, the BBB selectively excludes many chemotherapeutic agents from the CNS, thereby creating a “safe haven” for some tumors, e.g. metastases.

This concept has been challenged [3]. Regardless of the etiology, the response of most brain tumors to systemic chemotherapy is usually very modest, with a notable exception being a favorable response of oligodendrogliomas and gliomas lacking MGMT activity.

The blood brain barrier (BBB) is a highly selective permeability barrier that separates the circulating blood from the brain extracellular fluid (BECF) in the central nervous system (CNS).

The blood-brain barrier is formed by capillary endothelial cells, which are connected by tight junctions with an extremely high electrical resistance of at least 1000Ωcm-2.

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. A small number of regions in the brain, including the circumventricular organs (CVOs), do not have a blood-brain barrier.

The blood-brain barrier occurs along all capillaries and consists of tight junctions around the capillaries that do not exist in normal circulation.

Endothelial cells restrict the diffusion of microscopic objects (e.g., bacteria) and large or hydrophilic molecules into the cerebrospinal fluid (CSF), while allowing the diffusion of small hydrophobic molecules (O2, CO2, hormones).

Cells of the barrier actively transport metabolic products such as glucose across the barrier with specific proteins.

This barrier also includes a thick basement membrane and astrocytic end feet.

Drug delivery to the central nervous system (CNS) is complicated by the blood-brain barrier. As a result, many agents that are found to be potentially effective at their site of action cannot be sufficiently or effectively delivered to the CNS and therefore have been discarded and not developed further for clinical use, leaving many CNS diseases untreated. One way to overcome this obstacle is intracerebroventricular (ICV) delivery of the therapeutics directly to cerebrospinal fluid (CSF). Recent experimental and clinical findings reveal that CSF flows from the ventricles throughout the parenchyma towards the subarachnoid space also named minor CSF pathway, while earlier, it was suggested that only in pathological conditions such as hydrocephalus this form of CSF flow occurs. This transependymal flow of CSF provides a route to distribute ICV-infused drugs throughout the brain. More insight on transependymal CSF flow will direct more rational to ICV drug delivery and broaden its clinical indications in managing CNS diseases [4)].

Blood-brain barrier disruption

Blood-brain barrier disruption

Blood-brain barrier and chemotherapy agents

Blood-brain barrier and chemotherapy agents.

Blood-brain barrier opening

Blood-brain barrier opening

1)
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4)
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