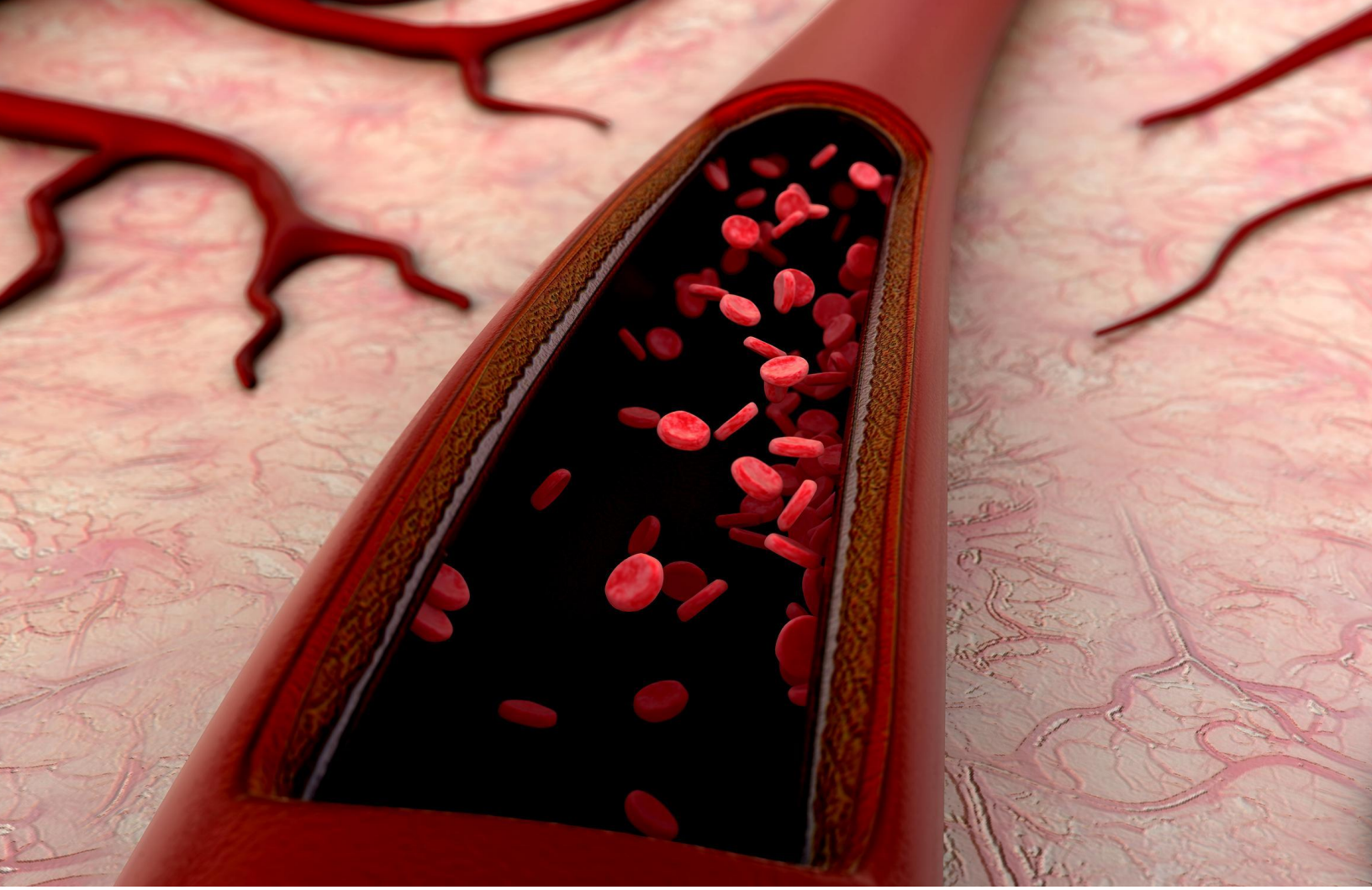
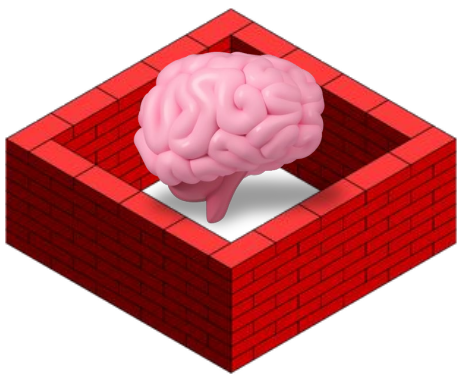


BLOOD-BRAIN-BARRIER

The Blood-Brain Barrier (BBB) is a highly selective, semi-permeable membrane between the blood and the interstitium of the brain, allowing cerebral blood vessels to regulate molecule and ion movement between the blood and the brain

- Blood-Brain-Barrier (BBB)
- Structure of BBB
- Transport through BBB
- BBB Dysfunction
- Neurotherapeutics



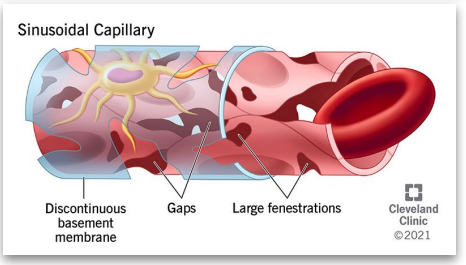
Blood-Brain-Barrier (BBB)

Although the brain accounts for only about 2% of total human body weight, it receives 15% to 20% of the body's blood supply. Because brain cells will die if the supply of oxygen-carrying blood is interrupted, the brain has top priority for blood flow

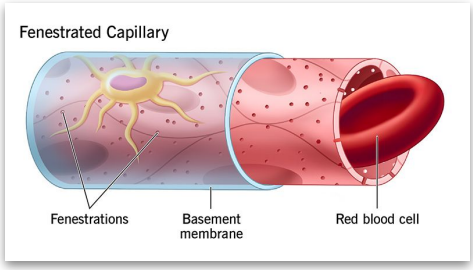
The BBB exists to maintain a homeostatic environment for CNS



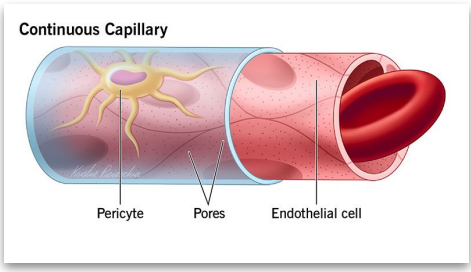
The capillaries of the brain are the most likely location of the BBB



Liver, Spleen & Bone marrow



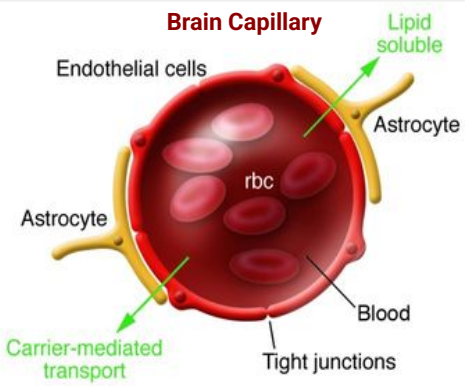
Kidneys, Endocrine glands & Choroid plexus

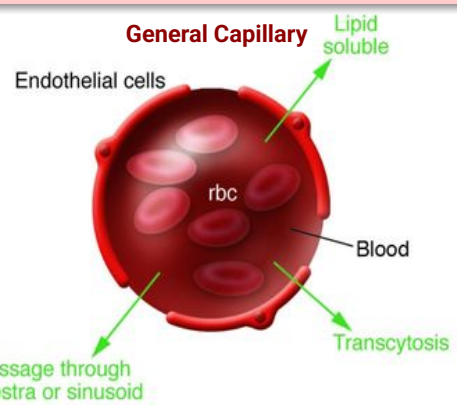


Brain- BBB, Skin & Muscles, Lungs

The Brain's essential gatekeeper

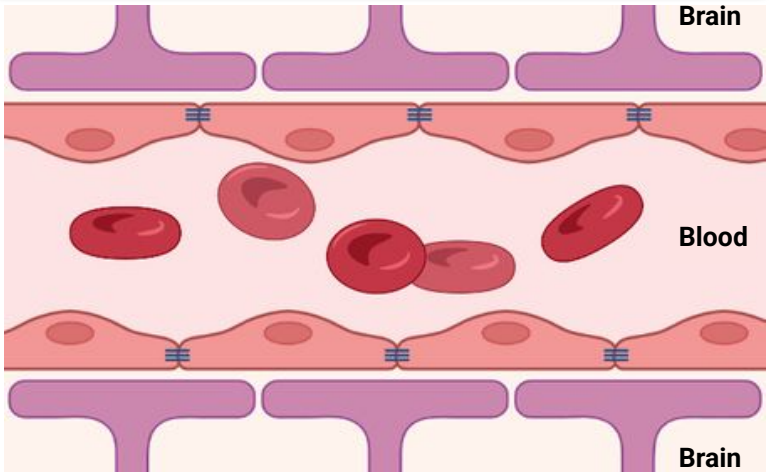
The Blood–Brain Barrier (BBB) serves as the brain's highly selective security system, maintaining a stable and protected environment for neural function. Much like vigilant guards controlling entry, the endothelial cells and their tight junctions allow only essential nutrients, glucose, and molecules to pass through while blocking toxins, pathogens, and unwanted substances from entering the brain





Neurovascular unit

The BBB functions as part of the neurovascular unit, which includes neurons, astrocytes, pericytes, endothelial cells, and smooth muscle, this integration ensures tight regulation of nutrient delivery, waste removal, and protection from toxins



Features of BBB

- Tightly sealed Endothelial cells (ECs) with no pores
- Thicker with multiple membrane
- Very low and specific permeability
- Highly selective transport pathways
- Supported by Pericytes + Astrocyte end feet
- Very low rate of pinocytosis
- Immune cells are highly restricted unless any disease/ injury
- Lipid barrier is strong- only small lipid soluble can diffuse

Physical barriers

- Endothelial Cells (EC)
- Tight Junctions (TJ)
- Transport pathways
- Pericytes
- Low pinocytosis

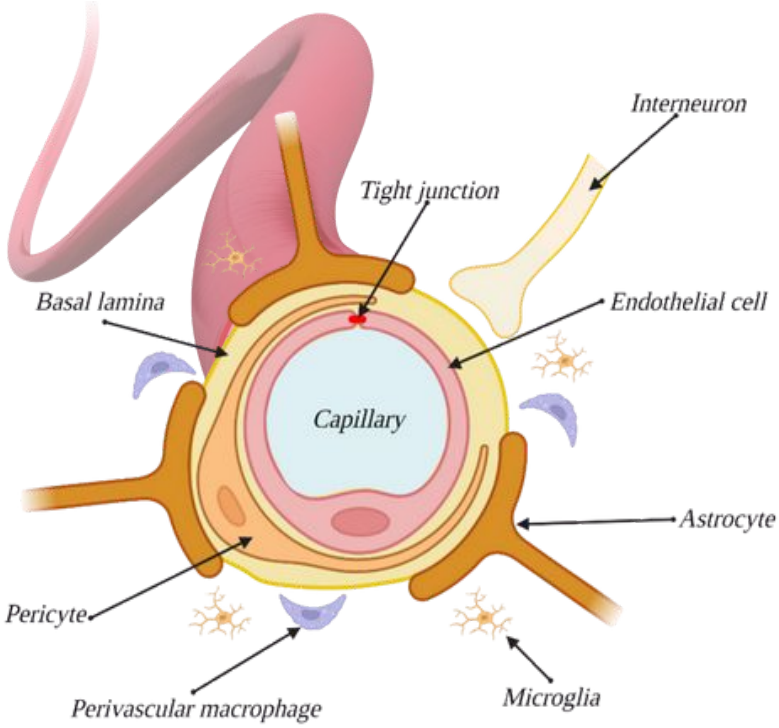
Metabolic barriers

- Enzymes
  - Monoamine oxidase
  - CYP450s
  - Peptidases
- Efflux transporters

Note: This report is generated based on publicly available data

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Structure of BBB



The BBB is a highly specialized interface that separates the brain from circulating blood. Its structure provides a tightly regulated environment that restricts harmful substances while allowing the passage of essential nutrients. This selective barrier is crucial for maintaining the stability of the central nervous system and ensuring proper neuronal function

Tight Junction (TJ)

- Tight junctions are specialized junctions between endothelial cells (ECs) in brain capillaries
- They form the seal between ECs, blocking paracellular diffusion
- The complex TJ protein network consists of transmembrane proteins: Claudins, Occludins, JAMs, Cytoskeleton protein, Scaffolding proteins (Zonula occludentes- ZO-1, 2, & 3)

Endothelial Cell (EC)

- Brain endothelial cells (BECs) constitute the core component of the BBB, regulating substance exchange between blood and the brain
- They lack fenestration and are interconnected by tight junctions, restricts paracellular diffusion
- EC have a higher mitochondrial content necessary to maintain integrity and the high metabolic output of the BBB

Pericytes

- Pericytes are mural cells that line capillary networks and regulate basal capillary diameter, among many roles in microvascular homeostasis
- Regulating blood flow in capillaries.
- These cells have different shapes depending on where they are located in the blood vessel network

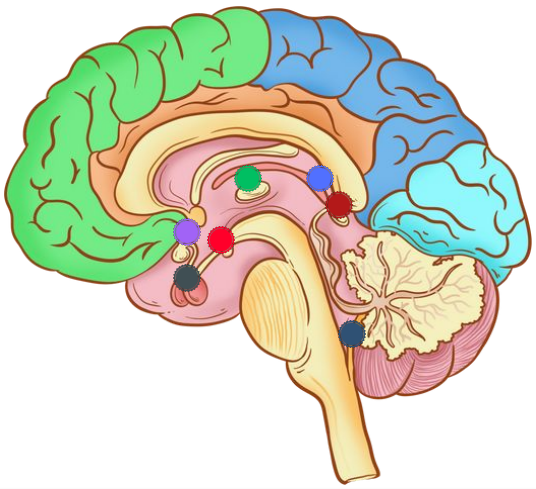
Astrocytes

- Astrocytic end-feet, together with pericytes, extensively cover >99% of the cerebrovascular surface
- Astrocytes express gap junction proteins
- Participate in the regulation of blood flow and supporting aspects of the barrier's selective permeability

Basal Lamina

- The Basal lamina (BL) is a unique form of the extracellular matrix found underneath endothelial and epithelial cells.
- It provides structural support, cell anchoring and signalling transduction
- In the brain, two types of BL are found: an endothelial BL and a parenchymal BL which are separated by pericytes

Circumventricular Organs : Windows of the Brain



Circumventricular organs (CVOs) serve as specialized brain regions where the blood–brain barrier is naturally absent or reduced, allowing direct communication between the brain and peripheral circulation

Their unique structure enables vital functions such as hormone secretion, osmotic regulation, and immune signaling, making them critical interfaces for maintaining homeostasis despite their BBB permeability.

- The Tight junctions between endothelial cells are discontinuous
- These areas participate in hormonal control
- Blood vessels have fenestrations (pores) that permit the diffusion of blood-borne molecules
- They regulate the autonomic nervous system and endocrine glands

The absence of the BBB makes CVOs susceptible to infections by blood-borne pathogens as shown by infections with the parasites (*Trypanosoma brucei)*

Areas of brain without a BBB

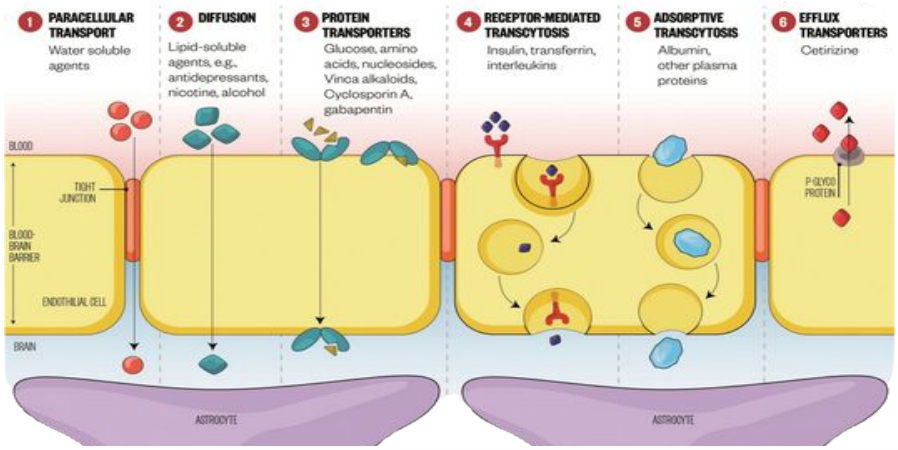
- Pineal Gland
- Median eminence
- Posterior pituitary
- Subcommissural organ
- Organum vasculosum of the lamina terminalis (OVLT)
- Subfornical organ
- Area postrema

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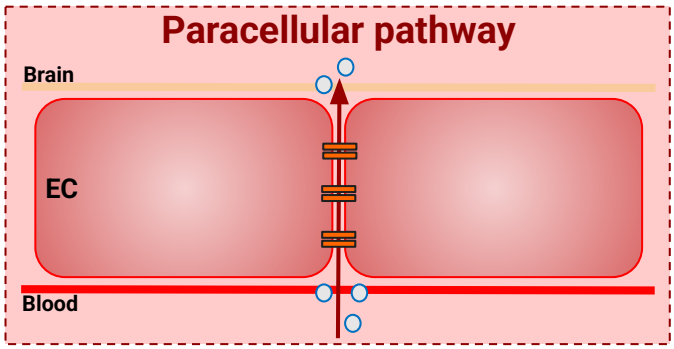
Transport through BBB

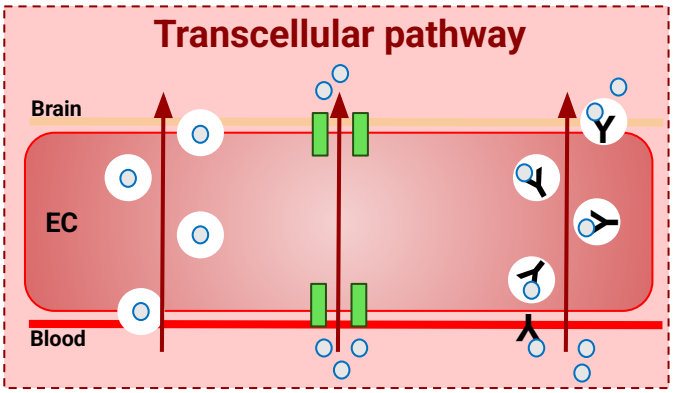
Transport across the BBB is a tightly regulated process that maintains the brain's delicate microenvironment. It ensures that essential nutrients and signaling molecules reach the central nervous system while preventing the entry of toxins and pathogens

This regulation is critical for normal neuronal function, energy metabolism, and overall brain homeostasis. Disruption of these transport processes can lead to accumulation of toxic substances, nutrient deficiencies, and impaired neuronal signaling



Proper BBB function also plays a key role in protecting the brain from inflammation and oxidative stress. Maintaining the integrity of BBB transport is therefore essential for cognitive health and resilience against neurological disorders.





Paracellular Pathway – The paracellular pathway allows water-soluble molecules to pass between endothelial cells, normally restricted by tight and adherens junctions. Disruption of these junctions increases BBB permeability, letting plasma proteins, toxins, and immune cells enter the brain, contributing to neuroinflammation and neuronal stress

Transcellular Pathway – The transcellular pathway transports molecules through endothelial cells, ensuring selective entry of essential nutrients and removal of waste. Dysfunction in this pathway, due to altered transporter or receptor activity, can impair nutrient delivery and clearance of toxic metabolites, affecting neuronal function and brain homeostasis.

Efficient and selective transport across the BBB is essential for maintaining brain homeostasis and ensuring therapeutic agents reach their targets. Understanding and modulating these pathways is critical for developing effective brain-targeted treatments.

Paracellular Transport

- Movement of substances across an epithelium by passing through the spaces between cells
- The paracellular pathway is the principal route blocked by the tight junctions of cell gaps
- The tight junctions are not perfect, small and soluble substances could sufficiently cross through

Passive Diffusion

- Movement of fat soluble (lipophilic) molecules passively diffuse across BBB
- Lipophilic drugs can dissolve in the lipid membranes of the endothelial cells and enter the brain.
- Log P (lipophilicity) is a key predictor of its ability to cross the BBB by this method.

Protein Transporters

- Movement of specific molecules in and out of the brain facilitated by the transporters
- Carrier-mediated transporters can transport essential nutrients and drug molecules that resemble these nutrients across the BBB
- When the molecule binds, the transporter undergoes a change in its shape, or conformation

Receptor-mediated transcytosis

- Movement of substances across an epithelium by passing through the spaces between cells
- The paracellular pathway is the principal route blocked by the tight junctions of cell gaps
- The tight junctions are not perfect, small and soluble substances could sufficiently cross through

Adaptive transcytosis

- Movement of +vely charged upon binding to the -vely charged surface of EC and transported across the BBB
- Positively charged large molecules interact with specific cell surface binding sites that induce endocytosis and subsequent transcytosis

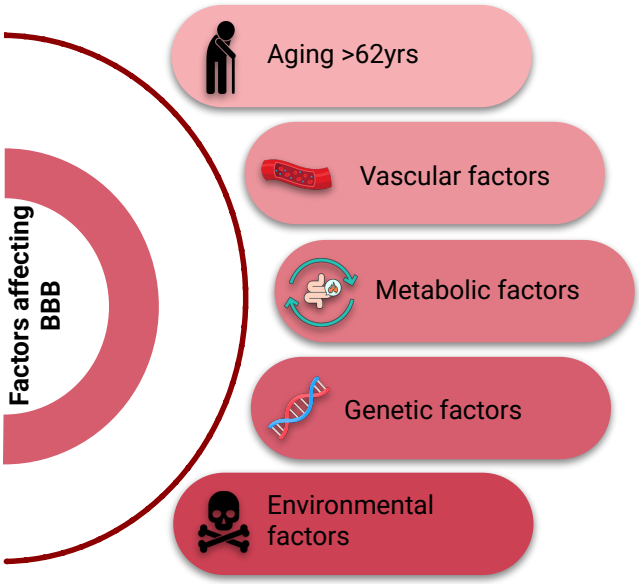
Efflux transporters

- Multiple efflux transporters are involved in drug transport at the BBB
- Efflux pumps play a crucial role in protecting the brain by actively transporting substances, including drugs and toxins, from the brain back into the bloodstream

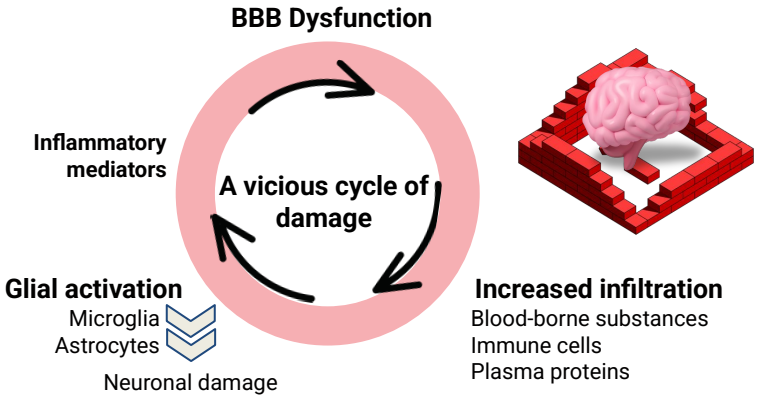
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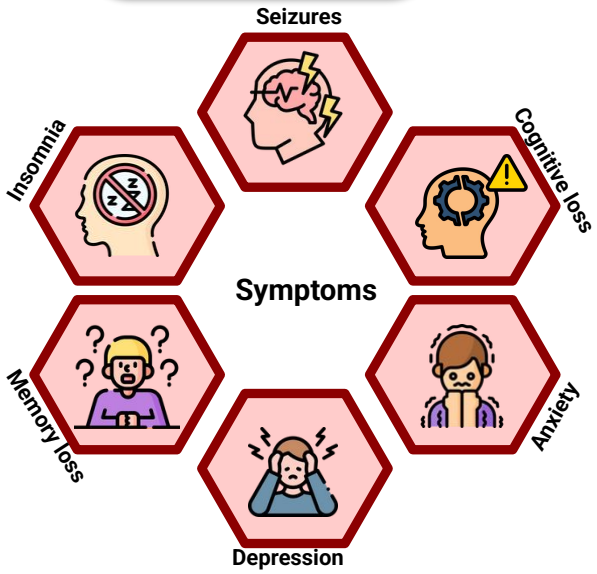
BBB Dysfunction

Disruption of the BBB alters the brain's tightly regulated microenvironment, compromising nutrient transport and defense mechanisms. When barrier integrity is weakened, toxic molecules, immune cells, and inflammatory mediators infiltrate the brain, triggering oxidative stress and neurovascular instability. This cascade affects neuronal communication, energy metabolism, and glial function, ultimately disturbing cognitive and behavioral processes. Persistent BBB impairment can further amplify inflammation and vascular damage, creating a self-perpetuating cycle that accelerates neurological decline and increases susceptibility to CNS disorders



- The functional alterations of structural and cellular components in the BBB are responsible for BBB dysfunctions
- BBB function naturally weakens with age, a "second hit" such as inflammation or ischemia can worsen this decline
- This combined effect may lead to neuronal damage and contribute to various neurological disorders

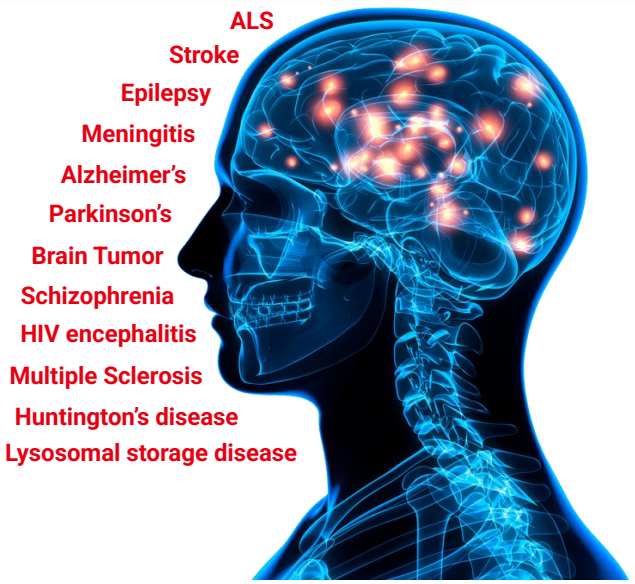




BBB dysfunction lead to neuroinflammation, in turn releases inflammatory molecules -worsens disease
This synergistic breakdown is a major reason why many neurodegenerative diseases are progressive and difficult to treat

Disorders associated with BBB impairment

BBB dysfunction is found in numerous diseases, including neurodegenerative conditions



Diagnostic Markers

- CSF/Serum Ratios
- CSF/plasma-ratio of albumin (QAlb)
- Immunoglobulin G Ratio (Q-IgG)
- Soluble platelet-derived growth factor receptor beta (sPDGFRβ)-Pericyte
- S100β-Astrocyte
- GFAP and Neurofilament light chain
- MMPs and elevated cytokines (IL-6, IL-8, and TNF-α)
- Neuroimaging techniques: DCE-MRI, CT scan

In neurological disorders, the BBB does not break down uniformly, some brain regions become leaky, while others remain intact, reflecting localized vascular and neuronal damage linked to inflammation and metabolic stress. Despite these partial leaks, much of the BBB still functions as a barrier, continuing to limit drug penetration and posing a major challenge for achieving consistent therapeutic delivery across the brain

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Neurotherapeutics

Most drugs for brain diseases are ineffective because they fail to cross the BBB and reach diseased cells and tissues in the brain at sufficient dosages. Under pathologically disrupted conditions, the BBB remains a formidable obstacle for the brain-targeted delivery of therapeutics. Improvement in BBB penetration is an urgent need for the development of brain-targeted therapeutics

Drug delivery to brain

Neurotherapeutics represents a multidisciplinary field in neuroscience that focuses on developing novel treatments for neurological disorders. It comprises various applications such as therapeutic interventions, pharmacological agents, gene therapies, cognitive behavioral therapies, and neuromodulation techniques

Criteria for a drug to cross BBB

- Smaller in structure
- Greater lipid solubility (High LogP)
- MW : less than 400Da
- Polar surface area (PSA) : less than 80 Å²
- H-bonds : 6-8
- Less rotatable bonds
- Less attachment to blood proteins

Temporary BBB disruption

- Osmotic BBB disruption (Time: 2 to 3 hours, Serious side effects)
- Chemical Disruption of the BBB (Time: 3 to 15 mins, Serious side effects)
- Focused Ultrasound (Time: 4 to 6 hours, Less side effects)

Transport Across BBB

- Receptor mediated transcytosis (RMT) (Target : TfR ,IR, LDLR, IGF-1R, FcRn),
- Carrier mediated transcytosis (CMT) (Target: GLUT1, LAT1, P-gp, FcRn)
- Adsorption mediated transcytosis (AMT)
- Cell mediated transport (Immune cells , Platelets)

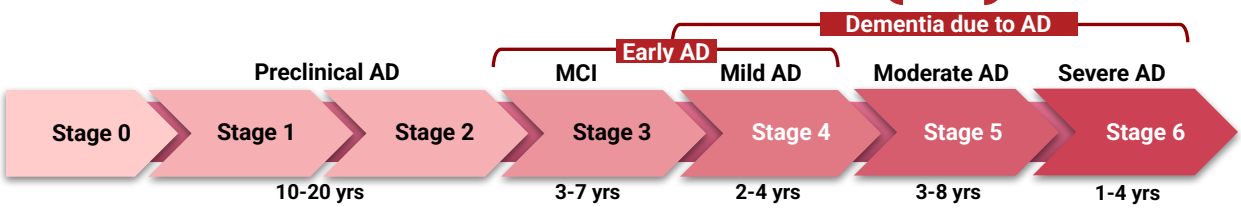
Routes does not bypass the BBB

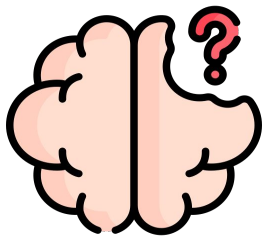
- Oral administration
- Intravenous delivery
- Intramuscular / Subcutaneous delivery

Routes does bypass the BBB

- Intra-nasal delivery
- Intrathecal delivery
- Intracerebroventricular

BBB in Alzheimer's disease (AD)





Alzheimer's disease (AD) is characterized by multiple pathological hallmarks, including Aβ accumulation, abnormal tau protein aggregation, and a chronic neuroinflammatory response

- These processes interact to cause synaptic dysfunction, neuronal loss, and progressive cognitive decline.
- Increasing evidence shows that alterations in the BBB also play a critical role in AD pathogenesis, influencing both Aβ dynamics and neurodegeneration

BBB Dysfunction and Impaired Aβ Transport

The BBB normally regulates bidirectional movement of Aβ between the blood and the brain and in AD, this balance is disrupted

- The RAGE receptor, responsible for Aβ influx (blood-to-brain), becomes upregulated, while the LRP-1 receptor, which mediates Aβ efflux (brain-to-blood), is downregulated
- Additionally, carrier-mediated transport systems such as ABC transporters, GLUT-1, and P-glycoprotein (P-gp) are decreased, impairing both glucose delivery to neurons and Aβ clearance (Aβ40 and Aβ42). This results in Aβ accumulation and further neuronal stress.

Role of Neuroinflammation, Genetics, and Aging in BBB Breakdown

- Neuroinflammation and oxidative stress further aggravate BBB disruption, promoting leakage of toxic molecules into the brain parenchyma.
- Factors such as Aβ and tau pathology, the ApoE ε4 allele, and aging contribute to endothelial dysfunction and tight junction loss
- BBB breakdown has been detected years before the onset of cognitive symptoms such as memory loss, suggesting it may be an early biomarker and therapeutic target in AD progression

Therapeutic innovation in AD increasingly focuses on the BBB to enhance both brain protection and drug delivery

- Current strategies aim to restore BBB integrity through endothelial and pericyte stabilization, anti-inflammatory, and antioxidant mechanisms
- Delivery-focused approaches such as receptor-mediated transcytosis, nanoparticle systems, intranasal routes, and focused ultrasound are being developed to improve the transport of antibodies, peptides, and gene therapies into the brain

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FDA approved therapeutics for AD

Name of the drug	Indication (AD)	Route of Administration	BBB penetration
Donepezil (ARICEPT)	All stages		Passive Diffusion
Rivastigmine (EXELON)	Mild to Moderate		Passive Diffusion
Galantamine (RAZADYNE)	Mild to Moderate		Passive Diffusion
Memantine (NAMENDA)	Mild to Severe		Passive Diffusion
Lecanemab (LEQEMBI)	Early AD		Low Passive Diffusion and Adsorptive transcytosis
Donanemab (KISUNLA)	Early AD		Low Passive Diffusion and Adsorptive transcytosis

BBB Technology

BrainShuttle — Roche

Alector Brain Carrier — alector

J-Brain Cargo — JCR Pharmaceuticals

xB3 — bioasis, Johnson & Johnson

ALPL-NeuroShuttle — voyager therapeutics

MODEL — abbvie

BrainTransporter — BIOARCTIC

Grabody-B — ablbio

G-Technology — 2bbb crossing the barriers

Transport Vehicle — DENALI

G2Brain — GATE2BRAIN Medicines beyond barriers

BBB Shuttle — Lundbeck

STAC-BBB — Lilly, Sangamo Therapeutics

Enhanced Brain Delivery — JCR Pharmaceuticals, ACUMEN

NeuroAccess — Cordance Medical

BBB technology — NEONC

In conclusion, the blood-brain barrier (BBB) remains a formidable obstacle in treating neurological diseases because it restricts the entry of most therapeutic agents into the brain. To overcome this, advanced nanoscale drug delivery technologies are being carefully engineered with specific chemical compositions and surface properties to facilitate the efficient and safe delivery of various therapeutics, including small-molecule drugs, proteins, and genes. By employing both passive and active strategies, these technologies offer a controlled and non-invasive mechanism to cross the BBB, thereby significantly enhancing brain-targeted drug delivery

Advantages of BBB technology

- Delivery of large therapeutic molecules
  - (mAbs, enzymes, oligonucleotides, peptides)
- Targeted Delivery
- Lower systemic dose- Reduced side effects
- Improved Drug Efficacy

Note: This report is generated based on publicly available data

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