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A Review on Blood Brain Barriers Receptor

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Abstract

The blood–brain barrier is playing a critical role in controlling the influx and efflux of biological substances essential for the brain's metabolic activity as well as neuronal function. Thus, the functional and structural integrity of the BBB is pivotal to maintain the homeostasis of the brain microenvironment. The different cells and structures contributing to developing this barrier are summarized along with the different functions that BBB plays at the brain–blood interface. We also explained the role of shear stress in maintaining BBB integrity. Furthermore, we elaborated on the clinical aspects that correlate between BBB disruption and different neurological and pathological conditions. Blood vessels are critical to deliver oxygen and nutrients to all of the tissues and organs throughout the body. The blood vessels that vascularize the central nervous system (CNS) possess unique properties, termed the blood–brain barrier, which allow these vessels to tightly regulate the movement of ions, molecules, and cells between the blood and the brain. This precise control of CNS homeostasis allows for proper neuronal function and also protects the neural tissue from toxins and pathogens, and alterations of these barrier properties are an important component of pathology and progression of different neurological diseases. The physiological barrier is coordinated by a series of physical, transport, and metabolic properties possessed by the endothelial cells (ECs) that form the walls of the blood vessels, and these properties are regulated by interactions with different vascular, immune, and neural cells. Understanding how these different cell populations interact to regulate the barrier properties is essential for understanding how the brain functions during health and disease.

Keyword: Blood–brain barrier, Brain diseases, Neurovascular unit

Introduction:

The blood–brain barrier (BBB) is a highly selective semipermeable border of endothelial cells that prevents solutes inthe circulating blood from *non-selectively* crossing into the extracellular fluid of the central nervous system where neurons reside. The blood–brain barrier is formed by endothelial cells of the capillary wall, astrocyte end-feet ensheathing the capillary, and parricides The blood–brain barrier (BBB) is a highly selective semipermeable border of endothelial cells that prevents solutes in the circulating blood from non-selectively crossing into the extracellular fluid of the central nervous system where neurons reside.he blood–brain barrier is formed by endothelial cells ofthe capillary wall, astrocyte end-feet ensheathing the capillary, and pericytes embedded in the capillary basement membrane. This

system allows the passage of some small molecules by passive diffusion, as well as the selective and active transport of various nutrients, ions, organic anions, and macromolecules such as glucose and amino acids that are crucial to neural function.[3] in the capillary basement membrane This system allows the passage of some small molecules by passive diffusion, as well as the selective and active transport of various nutrients, ions, organic anions, and macromolecules such as glucose and amino acids.

Additionally, the BBB presents significant challenges for drug delivery in treating neurological diseases, making the study of these mechanisms essential for developing effective therapeutic strategies. Overall, the BBB is a focal point of research aimed at improving our understanding of brain health, disease mechanisms, and potential treatments.

The brain is a complex organ that regulates numerous bodily functions, and its communication with the rest of the body is tightly regulated. One of the crucial components of this regulatory mechanism involves blood-brain receptors, which play an essential role in the communication between the central nervous system (CNS) and the circulatory system. These receptors help regulate the passage of molecules between the blood and the brain, contributing to maintaining homeostasis within the brain's environment.

Before diving into blood-brain receptors, it's important to understand the role of the blood-brain barrier (BBB). The BBB is a protective barrier that separates the brain's blood vessels from the brain tissue. Its primary function is to protect the brain from harmful substances and maintain a stable environment by allowing selective entry of necessary molecules, such as glucose and oxygen, while blocking potentially toxic compounds.[1]

Structure of blood brain barrier

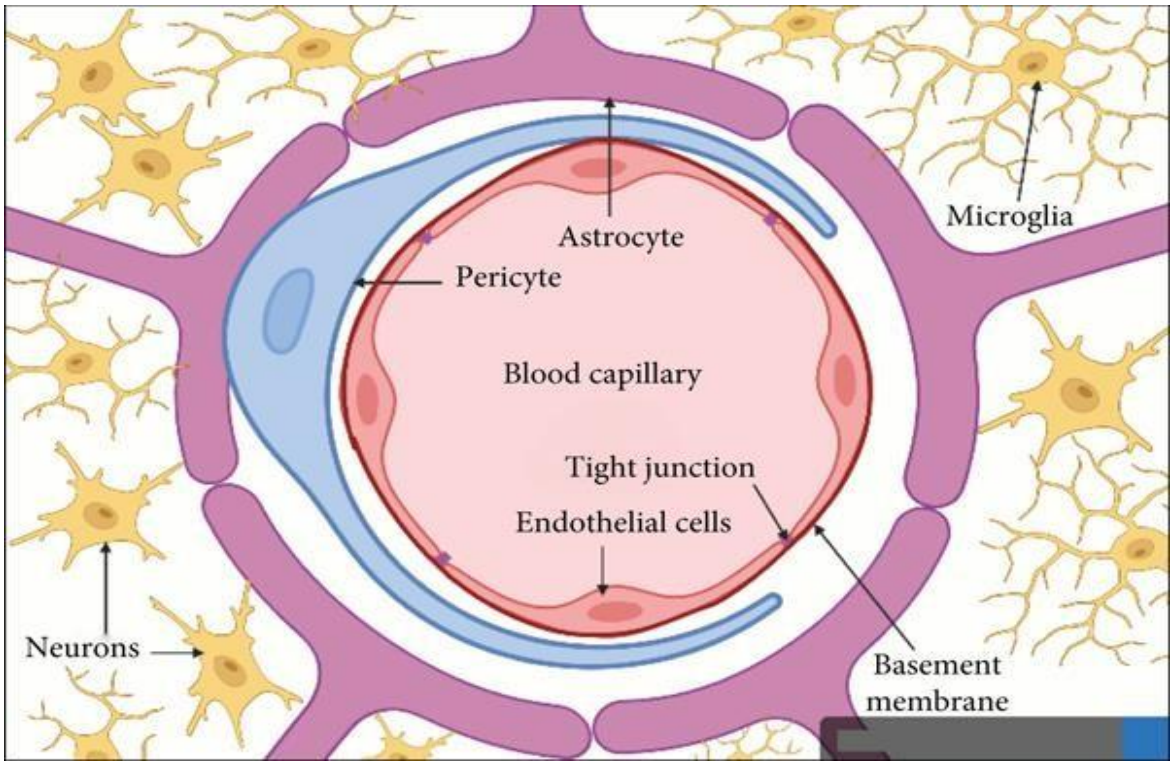

Fig.Transverse section of blood brain barrier

BBB may be present in all vertebrates and some of the extremely intelligent invertebrates with a well-developed CNS such as insects, squid, andoctopus. The BBB's growth is critical to the complex brain's successful evolution. It is mainly made up of capillary endothelial cells, astrocytes, andpericytes, as well as some other elements, such as neurons, basement membrane, and microglia , that contribute to immunological function . These components, which are frequently referred to as a neurovascular unit (NVU),preserve a healthy BBB to guarantee appropriate central nervous system activity.

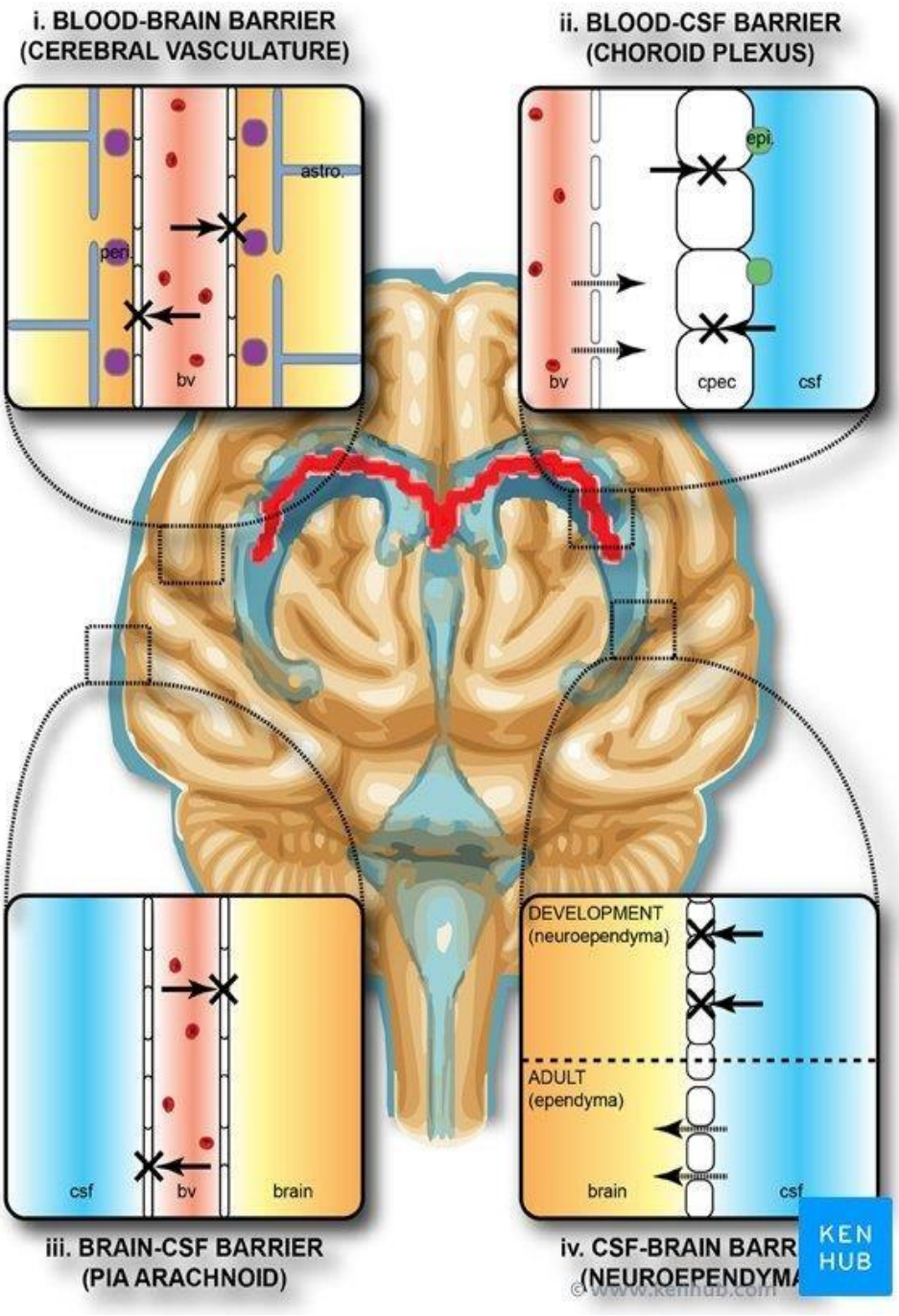

Fig.Blood brain barrier

Location:

The brain has a large network of arterial and venous vessels taking and from brain tissue. However, most of the action occurs at the level of the capillaries. Both the luminal and abluminal outer surface of the vessel sides are lined by key structures that contribute to the integrity of the cells.
Firstly, squamous epithelial cells form the endothelial wall of the capillaries;the luminal surface of these cells comes into contact with circulating blood and its constituents. The abluminal surface is in contact with a circumferentially continuous basement membrane.[2]

Function of blood brain barrier:

The blood-brain barrier prevents toxic substances, large molecules, and neurotransmitters released in the blood from entering the brain. The blood- brain barrier prevents toxic substances, large molecules, neurotransmitters released in the blood from entering the brain.

Mechanism of BBB:

The blood vessels that vascularize the central nervous system CNS possess unique properties, termed the blood brain barrier, which allow these vessels to tightly regulate the movement of ions, molecules, and cells between the blood and the brain. Substances cross the blood-brain barrier (BBB) by a variety of mechanisms. These include transmembrane diffusion, saturable transporters, adsorptive endocytosis, and the extracellular pathways Mechanisms for drug targeting in the brain involve going either "through" or "behind" the BBB. Modalities for drug delivery to the brain in unit doses through the BBB entail its disruption by osmotic means, or biochemically by the use of vasoactive substances, such as bradykinin or even by localized exposure to 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. Some studies have shown that 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 targeted are.[3]

Agonists antagonist properties:

Astrocytes, an important component of the BBB, promote BBB breakdown in subjects with AIS by secreting inflammatory factors. The glucagon-like peptide-1 receptor agonist exendin-4 protects the BBB and reduces brain inflammation from cerebral ischemia, and GLP-1R is expressed on astrocytes.The development of the bradykinin agonist Labradimil as a means to increase the permeability of the blood-brain barrier Labradimilis a 9- amino-acid peptide designed for selectivity for the bradykinin B_2 receptor and a longer plasma half-life than bradykinin. It has been developed to increase the permeability of the blood-brain barrier (BBB) and is the first compound with selective bradykinin B_2 receptor agonist properties to progress from concept design through to tests of efficacy in patient. A cannabinoid type 2 receptor agonist attenuates blood–brain barrier damage and neurodegeneration in a murine model of traumatic brain injury.[4]

Dysfunction of BBB:

BBB dysfunction, which compromises the BBB integrity, has been reported in various disease conditions such as multiple sclerosis, stroke, Alzheimer's disease, Parkinson's disease, ischemia, infections, and brain tumors. The chronic effects of BBB dysfunction include cerebral edema, seizures, epileptogenesis, neuropsychiatric symptoms, behavioral deficits, and decline in cognition. In some conditions such as Parkinson's and epilepsy, a temporary opening ofthe BBB has been reported due to production of inflammatory mediators. In brain tumors, the permeability is increased because of TJ complex disturbance and cumulation of growth factors such as vasogenic factors such as vascular endothelial growth factor , andproinflammatory chemokines such as interleukin-1β (IL-1β); interferon-γ (INF-γ); and tumor necrosis factor-α (TNF-α). In ischemia, formation of reactive oxygen species mediates the effect.

Matrix metalloproteinases (MMPs) have also been correlated with the severity of stroke in patients and lead to BBB leakage bydegradation of the TJs and basal lamina proteins, leukocyte infiltration, edema of the brain, and hemorrhage . The effects of various pathological conditions and their impact on the BBB stroke Astrocytes secrete transforming growth factor-β (TGFβ), which downregulates brain capillary endothelial expression of fibrinolytic enzyme tissue plasminogen activator and anticoagulant thrombomodulin.

Proteolysis of vascular basement membrane/matrix

Induction of aquaporin 4 (AQP4) mRNA and protein at BBB disruption

Treatment with arginine vasopressin V1 receptor antagonist reduced the increase in BBB permeability induced in stroke model

Trauma. Bradykinin, a mediator of inflammation, is produced and stimulates production and release of interleukin-6 (IL-6) from astrocytes, which leads to opening of the BBB

Multiple sclerosis: Breakdown of the BBB Tight junctionabnormalities
Downregulation of laminin in the basement membrane Selective loss of clouding in experimental autoimmune encephalomyelitis.[5]

Different drugs across blood brain barrier:

Liposome:

Liposomes are lipid vesicles consisting either one or more phospholipid bilayers. They consist of an aqueous core and phospholipid bilayer shell. The coreacts as a carrier for encapsulation of hydrophilic drugs, while amphiphilic and lipophilic drugs could be solubilized within the phospholipid bilayers. The liposomes have been used in drug delivery systems for a long time, and it possesses the advantages of simple preparation, low toxicity, and relatively low cost. Both lipophilic and hydrophilic drugs are easy to combine with liposomes . However, high detection and clearance rates of liposomes by the reticuloendothelial system (RES) in the liver could reduce the half-life of drugs.

Reducing the sizes and polyethylene glycol (PEG) modifications are the better way for improving the duration time of liposomes in the body. PEG show a lot of advantages, such as high hydrophilicity, chain flexibility, electrical neutrality and lack of functional groups—these advantages could prevent itself from interacting unnecessarily with the biological components. Moreover, it has been suggested that PEGs with a molecular weight from 2000 to 5000 g/mole are necessary to suppress plasma protein adsorption. In order to penetrate to BBB, after conjugationwith specific antibodies, the targeting property to CNS of these liposomes become more effective

Melphalan, or phenylalanine mustard, crosses the BBB via transport on the BBB large neutral amino-acid carrier.ldopa gabapentin, paraquat, and melphalan are examples of BBB delivery via LAT1 of drugs that have structures that mimic the endogenous substrate, neutral amino acids[6].

Uses:

The blood vessels that vascularize the central nervous system (CNS) possess unique properties, termed the blood–brain barrier, which allow these vessels to tightly regulate the movement of ions, molecules, and cells between the blood and the brain.

Side effects:

Blood–brain barrier dysfunction contributes to pathology in a range of neurological conditions including multiple sclerosis, stroke, and epilepsy, and has also been implicated in neurodegenerative diseases such as Alzheimer's disease. The blood–brain barrier is generally very effective at preventing unwanted substances from accessing the brain, which has a downside. The vast majority of potential drug treatments do not readily cross the barrier, posing a huge impediment to treating mental and neurological disorders.[7]

Drug induced loss of BBB permeability and associated

Neurodegeneration

The neurovascular unit and the BBB are affected by various drugs of abuse, which alter vessel permeability via disruption of tight junction proteins complexes (junction adhesion molecules, endothelial cell-selective adhesion molecules, occludins, and claudins), transport systems, and intracellular signaling. BBB disruption, which affects immune cell transmigration and neuroinflammation and contributes to an imbalanced redox system, affects the brain's microenvironment and homeostasis, leading to neurotoxicity[9].

Cocaine:

Cocaine is a highly addictive stimulant that restricts dopamine and monoamine reuptake through dopamine transporter (DAT) antagonism (Monoamine oxidase inhibition leads to imbalanced free-radical production, which generates oxidative stress and neuroinflammation. Continuous cocaine administration has been shown to contribute to a 50% increase in BBB permeability, with a concomitant decrease in transendothelial electrical resistance (TEER) due to basement membrane and neurovascular capillary disruption, due to up-regulated matrix metalloproteinase (MMP) and tumor necrosis factor (TNF-α) expression . Moreover, TJ protein loss and alteration, specifically decreased JAM-2 and zonula occludens-1 (ZO-1) levels, are characteristic of cocaine transit across the BBB. CCL2 (C-C motif chemokine ligand-2) and CCR2 (C-C motif chemokine receptor-2) expression upregulation has also been reported (. Cocaine

use affects intercellular junctions and causes cell ruffling, which contributes to increased permeability and decreased TEER values across BBB monolayers ; Srinivasan et al., 2015).

An alternate pathway for cocaine-induced BBB permeability alteration involves platelet- derived growth factor (PDGF) intermediates. Cocaine binding to sigma receptors evokes a proteolytic signal cascade that initiates PDGF-B chain assembly, a fundamental intermediate for increased membrane permeability that inhibits store-operated calciumentry[10]

Drugs	Pathways involving in BBB leakiness-gene/proteins of interest	Effect on BBB	
Cocaine	Activated leukocyte cell adhesion molecule (ALCAM)	↑	
	C-C Motif CheniokineLigand-2 (CCL2)	↑	
	C-C Motif Chemokine receptor- 2 (CCR2)	↑	
	CXCL10(eheniokine (C-X-C motif) ligaud-1)	↑	
	Intercellular adhesion molecule-1 (ICAM-1)	↑	
	Junction n 1 adhesion molecule 2 (JAM-2)		↓
	Matrix metalloproteinase (MMP)	↑	
	Pro-inflammatory cytokines (TNF-α, IL-l β, and IL-6)	↑	
	Src-PDGFR-p-NF-KB	↑	
	Tumor Necrosis factor-alpha (TNF-α)	↑	
	Vascular cell adhesion molecule (VCAM),	↑	
	Zonula occludens-1 (ZO-1)		↓
METH	Actin related protein 2/3 (3Arp2/3) complex	↑	
	Claudin-5		↓
	Glial fibrillary acidic protein (GFAP)	↑	
	Glucose transporter (GLUT1)		↓
	Glutathione (GSH)		↓
	Interleukin (IL)-6	↑	
	Interleukin (IL)-8	↑	
	Matrix metalloproteinase- 9 (MMP-9)	↑	
	Matrix metalloproteinase-1 (MMP-1)	↑	
	Nuclear transcription factor- κB (NF-κB)	↑	
	p53 upregulated modulator of apoptosis (PUMA)	↑	
	Reactive oxygen species (ROS)	↑	
	Rho-associated protein kinase (RhoA ROCK)	↑	
	Sigma-1 receptor	↑	
	Tumor Necrosis factor-alpha (TNF- α)	↑	
	Zonula occludens-1 (ZO-1)		↓

Conclusion :

The conclusion on blood-brain barrier (BBB) receptors emphasizes their critical role in regulating the entry of various molecules into the brain, maintaining central nervous system (CNS) homeostasis, and protecting the brain from harmful substances. BBB receptors, such as nutrient transporters, efflux pumps, and receptor-mediated transcytosis pathways, selectively allow essential nutrients, hormones, and other molecules into the brain while preventing the entry of toxins and pathogens.Understanding BBB receptors is vital for drug delivery strategies targeting the CNS. Many potential therapeutics struggle to cross the BBB, making receptor-mediated transport an attractive method for delivering drugs across this protective barrier. By leveraging specific receptors, scientists aim to improve treatment for neurological disorders like Alzheimer's disease, Parkinson's disease, and brain tumors.In summary, BBB receptors are key to both maintaining brain health and offering avenues for the development of CNS-targeting therapies, but more research is required to fully exploit these mechanisms for clinical use.[11]

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