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The blood-brain barrier: an overview: mechanisms, functions, treatment & Clinical implications

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Abstract: -All of the body's tissues and organs depend on blood arteries to carry oxygen and nutrients to them. The blood-brain barrier, a special property of the blood arteries that vascularize the central nervous system (CNS), enables these vessels to tightly control the transit of ions, chemicals, and cells between the blood and the brain. Correct neuronal function is enabled by the careful regulation of CNS homeostasis, which also safeguards neural tissue from toxins and infections. Alterations to these barrier qualities play a significant role in the pathophysiology and development of various neurological illnesses. The endothelial cells (ECs), which make up the blood vessel walls, have a variety of physical, transport, and metabolic characteristics that help to coordinate the physiological barrier. The unique characteristics of the Blood-Brain Barrier must be taken into account in any programme for drug discovery or delivery that seeks to target or avoid the CNS.

***Keywords*: - Treatment, Blood–brain barrier; CNS; Degenerative; Disruption; Integrity; Markers; Neuroinflammation; Permeability; TEER; Tight junctions; Transcytosis.**

Introduction

The blood-brain barrier separates circulating blood from the brain's extracellular fluid in the central nervous system and is a highly selective semipermeable. It is formed by brain endothelial cells connected by tight junctions and astrocyte end-feet surrounding the endothelial cells. The blood-brain barrier allows the passage of gas, water, and some lipid-soluble molecules by passive diffusion, as well as the selective transport of nutrients such as glucose and amino acids crucial to neural function. However, it prevents the entry of many potentially harmful substances into the brain, including toxins, pathogens, and most large molecules. This selective barrier is essential in maintaining a stable environment for optimal neuronal function and protecting the brain from injury and disease*(Abbott et al.,2013)*.
Three biological components comprise the brain microvasculature's blood-brain barrier (BBB): endothelial cells, pericytes (PCs), and astrocyte end-feet. Tight junctions (TJs) between the cerebral endothelial cells constitute the BBB, a barrier that selectively blocks most blood-borne chemicals from entering the brain. The TJ barrier is maintained and induced by astrocytes, even though they do not have a barrier function in the mammalian brain *(Ballabh et al.,2004)*. They achieve this by tightly wrapping the vessel wall with their end feet. The choroid plexus, which secretes a cerebrospinal fluid (CSF), is isolated from the blood by the blood-CSF barrier. The subarachnoid CSF is separated from the blood by the arachnoid epithelium. The endothelial cells and nonfenestrated capillaries produce an entirely poreless basement membrane *(Sharif et al.,2018).*

The blood-brain barrier (BBB) plays a crucial role in permitting the passage of essential substances like water, nutrients, and gases needed for neural function while blocking the entry of harmful substances like toxins, pathogens, and large molecules into the brain. It also facilitates eliminating metabolic or harmful products from the brain to maintain a healthy microenvironment within the CNS fluid. However, traumatic brain injuries, ischemia, chemical or environmental toxins, and other harmful insults to the brain can alter the BBB and allow harmful substances like proteins to enter the CNS fluid, causing imbalanced osmotic pressure and resulting in brain edema*(Sharma et al.,2016).*

Effective delivery of therapeutics to the central nervous system (CNS) is challenging due to the presence of the blood-brain barrier and the blood-cerebrospinal fluid barrier. Despite the efficacy of many potential drugs at their target site, their clinical development has failed due to inadequate delivery to the CNS, leading to the undertreatment of CNS diseases. Recent research has revealed that these barriers act as physical and transport, and metabolic barriers. The complex group of interacting cells that comprise the neurovascular unit, responsible for the formation of the BBB, adds to the complexity. This article discusses various existing and upcoming strategies for improving drug delivery to the CNS *(Begley et al.,2004)*. Many neurologic conditions, like stroke and neuroinflammatory disorders, might worsen by BBB dysfunction, such as TJ seal failure*(Ballabh et al.,2004)*. Additionally, BBB dysfunction occurs in almost all neurodegenerative diseases and traumatic CNS injuries, leading to cell injury and edema formation. Appropriate drug therapies that can cross the BBB to target brain tissues are necessary to effectively treat these brain disorders *(Sharma et al.,2016).*

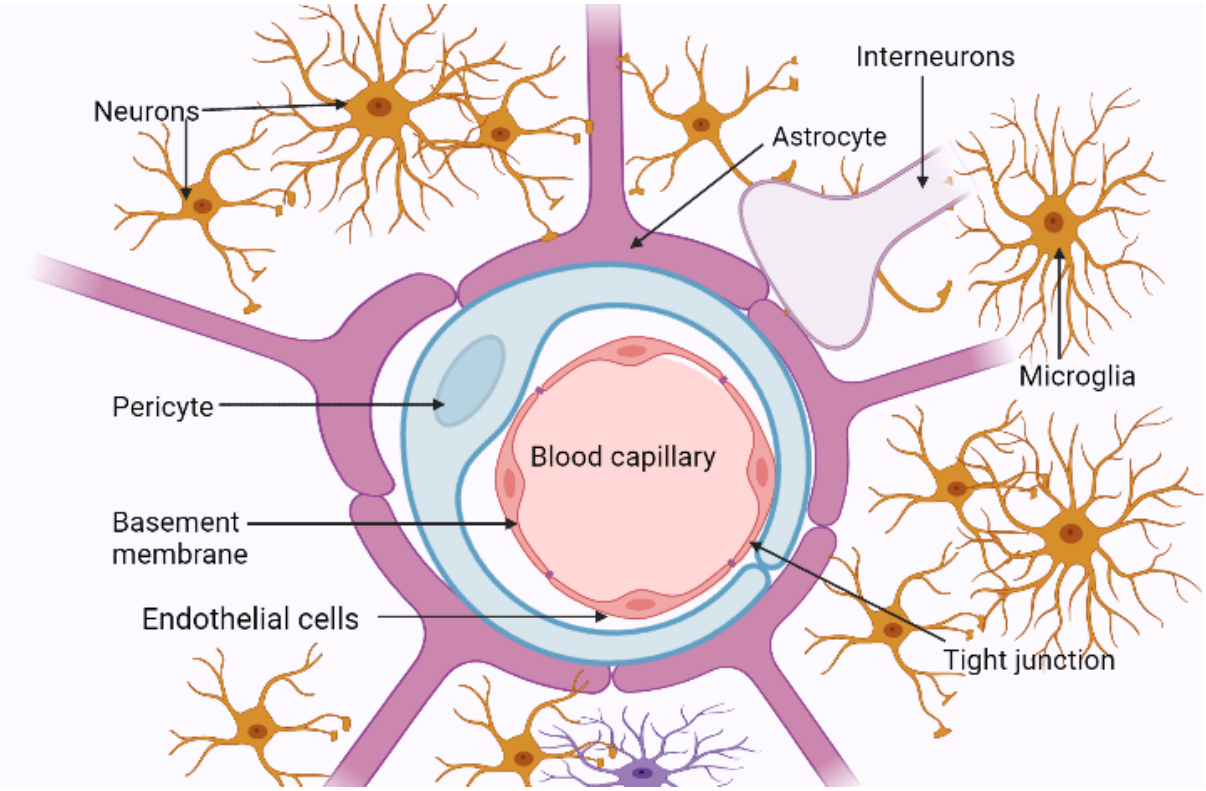

Fig 1. Brain microvascular endothelial cells (BMECs), which make up the majority of the blood-brain barrier, form tight junctions at endothelial cell interfaces with the help of claudins, occludin, and junctional adhesion molecules. Paracellular flux is severely constrained by the establishment of tight junctions, and the high expression of efflux proteins on the luminal surface of endothelial cells makes passive transcellular transport difficult. The blood-brain barrier is made up of BMECs, astrocytes, and pericytes in addition to BMECs. Less structural support is provided by these cells for the development and functioning of the blood-brain barrier.

The function of the Blood-Brain Barrier

Blood-brain barrier controls the molecular traffic and keeps out toxins (minimizes neuronal cell death and preserves neural connectivity). Maintains a low protein environment in CNS, limits the proliferation rate and allows immune surveillance, and represents minimal cell damage and inflammation *(Lorin et al., 2020).*The blood-brain barrier dual function-they have carrier function and barrier function. The paracellular barrier which is formed by endothelial junctions restricts the free movement of H2O solution compounds. The transcellular barrier is made possible by low-level endocytosis and transcytosis which can inhibit the transport of substances to the cytoplasm. Enzymatic barriers are a complex set of enzymes, including acetylcholinesterase, alkaline phosphatase, gamma-glutamyl transpeptidase, and other drug-metabolizing enzymes capable of degrading different compounds. Cerebral endothelium expresses a large number of efflux transporters [ABC, ATP-binding cassette transporters like ABC1 (P-glycoprotein). The carrier's function is to supply nutrients to the brain and remove metabolites. The small lipid-soluble molecules and blood gases like oxygen and carbon dioxide diffuse passively through the blood-brain barrier while the essential nutrients like amino acids require specific transport proteins in order to the brain. The blood-brain barrier is extremely restrictive due to its inherent specialization and "built-in" safeguards, but it is unable to stop the exchange of toxic substances from the blood to the brain when their transport is governed by the same physiologic properties as the exchange of nutrients, therapeutic substances, or hormones. Endothelial cells (ECs) of the cerebral capillary wall make up the BBB, which is held together by tight junctions (TJs). More than any other capillaries in the body, the TJs, which are bordered by pericytes, astrocytes, and the basal lamina, are what help the BBB's extremely selective character by limiting the flow of chemicals from the blood to the brain *(dong et al.,2018)*. The blood-brain barrier serves as a filter, regulatory which molecules can permit from the blood into the brain. Because the endothelial cells are situated so closely together, they keep any damaging toxins or pathogens from reaching your brain. All over the body Endothelial tissue is founded in the inner part of blood vessels. Usually, these endothelial cells are slackly spaced to permit substances to move from your blood to other tissues (*Wolff et al.,2015).* This enzyme forms the basis of a pump that simultaneously

transports Na+ out of the endothelium into the brain, and K + out of the brain into the endothelium However, in the brain's capillaries, the endothelial cells are more tightly connected, generating a barrier that keeps some molecules from crossing from the blood to the brain. Astrocytes and other neural cells also edge the brain's blood vessels to help the endothelial cells preserve this blood-brain barrier *(Shen et al.,2017).*

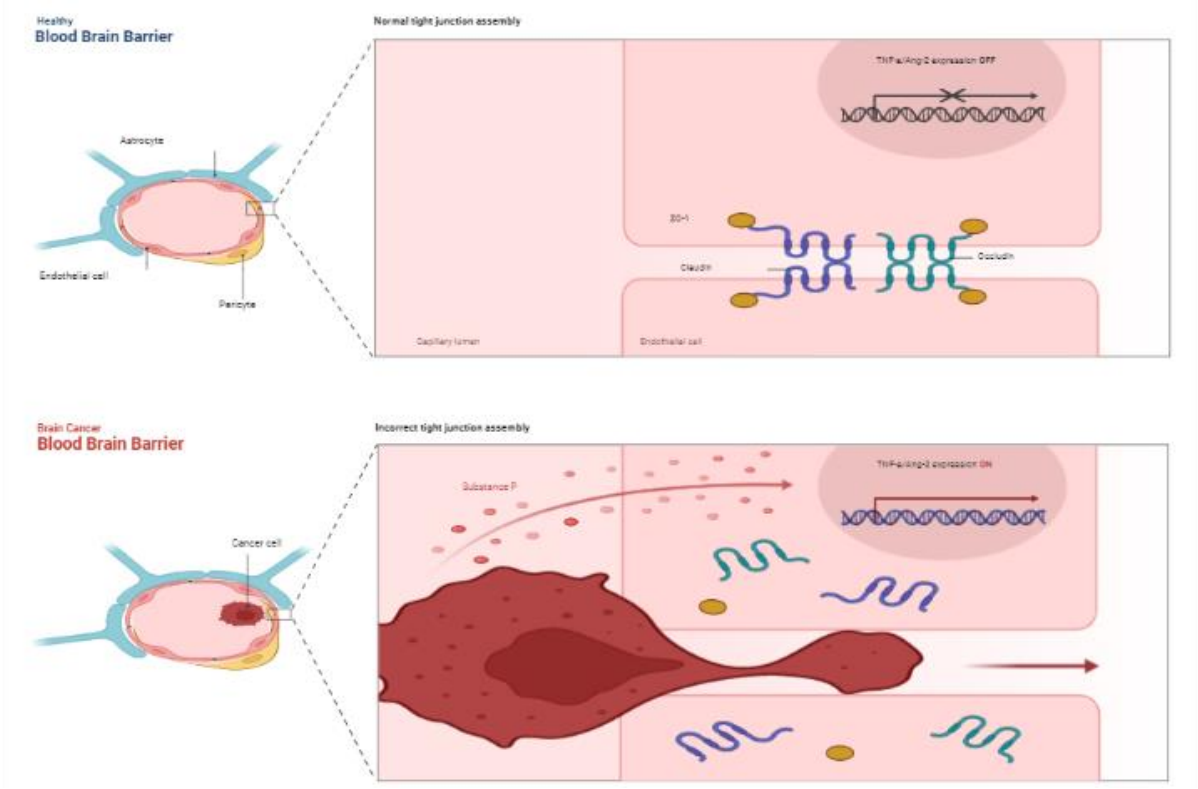

Fig 2. **Healthy blood-brain barrier:** A healthy blood-brain barrier is characterized by tightly packed cells and well-assembled tight junctions, preventing harmful substances from passing into the brain.
Incorrect tight junction assembly: The tight junctions between cells become loose and disorganized, allowing cancer cells to penetrate the blood-brain barrier and invade the brain tissue. This results in the blood-brain barrier breakdown and can lead to various neurological problems.

Although the blood-brain barrier possesses several things out of the central nervous system, it is not impermeable. Some imperative molecules, like oxygen, can get past the blood-brain barrier. Fat-soluble essentials with small particles can also pass through the barrier, with caffeine and alcohol. Other elements, like glucose, can be transported from the blood to the brain by a system of transport proteins. To regulate passage, an intricate system of carrying proteins surface receptors on endothelial cells resolves specific molecules from the bloodstream, such as insulin, and expels them on the opposite end of the endothelium into the brain. At the equivalent time, efflux pumps force endothelial cells for unwanted molecules (including many pharmaceutical products) and eject them into the blood. An increasing body of research proposes that endothelial cells work thoroughly with various cell types, with situated neurons and glial cells in the brain that together controls the absorptivity of the blood-brain barrier *(neuwelt et al.,2011*

The BBB is a physical and metabolic barrier between the brain and systemic circulation, which serves to regulate and protect the microenvironment of the brain *(Pardridge et al.,1999)*. The physical barrier is formed by the endothelial tight junctions, and the transport barrier results from membrane transporters and vesicular mechanisms. The roles of associated cells are outlined especially the end feet of astrocytic glial cells, pericytes, and microglia. The embryonic growth of the Blood-Brain Barrier and changes in pathology are designated. The Blood-Brain Barrier is an issue of rapid and continuing regulation, which may be a concern in pathology. All the database for drug discovery or delivery, to target or evade the CNS, wants to deliberate the different characteristics of the Blood-Brain Barrier. The blood-brain barrier is largely determined by lipid solubility. Certain molecules needed for brain metabolism, however, cross this barrier more readily than their lipid solubility alone would suggest *(Oldendorf et al.,1970*). Such compounds are transported via specific carrier-mediated transport systems or facilitated diffusion. Some of these carders are symmetrically distributed both on the luminal and abluminal membranes of the endothelial cells, while others have an asymmetric distribution *(Goldstein et al., 1986).*

Even though many of the molecular components involved in brain angiogenesis have now been identified, their exact mechanisms of action are still not fully understood. Moreover, as these mechanisms also apply outside the CNS, it seems improbable that they are intricate in the Blood-Brain Barrier difference producing highly specific endothelial cells. However, the biggest remaining obstacle to understanding the roles of these proteins for the development of the vascular bed in the CNS is the consequence that transmutations in their genes consistently lead to toxic phenotypes during early embryogenesis before BBB differentiation starts. The growth of the BBB is a multistep process instigating angiogenesis. Pre-existing vessels sprout into the embryonic

neuroectoderm, giving rise to new vessels which show various Blood-Brain Barrier properties, including the expression of TJs. Barrier elements of the Blood-Brain Barrier developed as rising vessels come into interaction with pericytes and astroglia. This progression holds the elaboration of TJs, reduced transcytosis, downregulation of leukocyte adhesion molecules, and improved efflux transporter expression. Sealing of inter-endothelial Tight Junctions is completed throughout maturation and must be kept throughout life *(Obermeier et al., 2013)*. Several known cellular and molecular mechanisms facilitate brain angiogenesis, with constant research focusing on more CNS-specific pathways (Wnt/Beta-catenin) and molecules (GPR124) as crucial in the differentiation and maturation of the BBB *(Engelhardt et al., 2014)*.The BBB separates the brain from circulating blood components and is formed by endothelial cells associated with tight junction proteins. Brain capillaries are bounded by the basement membrane, pericytes, and the end feet of astrocytes. Mechanism of the blood-cerebrospinal fluid barrier (BCB), an elaborate physical barrier compound of tight junction proteins among the choroid plexus epithelial cells. One of the important characteristics of the choroid plexus epithelial cells is a secretory function producing CSF.

BBB simply allows some molecules to cross but inhibit other large molecules from movement, other parts such as neurohypophysis or posterior pituitary release other essential neurohormones such as oxytocin into the blood. These non-BBB areas are essential in controlling the brain fluids and the anterior pituitary through the relief of neurohormones. Specific enzymes within the non-BBB are important in transporting compound nutrients such as glucose and amino acids that are not allowed by the BBB into the brain *(Friedman et al., 2015)*. However, Blood-Brain Barrier may be the most predominant site for the transportation of oxygen, amino acids, and glucose, the non-blood barrier areas also play a significant role in a variable of the brain's calcium ion homeostasis. Certain hormones are allowed entry into the brain through non-blood barriers such as the choroid plexus that induces insulin into the brain. They support in carrying out activities for the influx of molecules such as thiocyanate and penicillin as well as the neurotransmitter metabolites *(Sharif et al.,2018).*

The important function of the Blood Brain Barrier is the protection of brain homeostasis. This is accomplished via tightly regulated ion and solute transport between the intravascular plasma and the Central Nervous System through molecular exchange pathways that transport molecules from the blood to the brain and brain to blood. Though, not all molecules need transport mechanisms across the Blood-Brain Barrier. Gases such as carbon dioxide and oxygen, as well as lipophilic molecules with a molecular weight under 400 Da, can freely diffuse across the Blood Brain Barrier. Whereas astrocytes play a significant role in stabilizing and keeping BBB integrity, the capillary ECs and pericytes contain the most critical BBB transport mechanisms and pathways *(Zeisel et al.,2015).*

Mechanism Transport across the Blood-Brain Barrier

Cerebral capillary ECs are exclusive from peripheral capillary ECs in that they are completely up of a significant number of tight junctions, have fewer cytoplasmic vesicles, and have a higher concentration of mitochondria. These tight junctions edge paracellular movement and divide the membranes of ECs into two different sides with dissimilar membrane compositions (Zaragozá et al.,2020). To counteract this limitation of solute movement, several transport paths have been recognized to allow for the passing of molecules across the Blood Brain Barrier (Abbott et al., 1996). The mechanism of diffusion of substances into the brain is accomplished via paracellular or transcellular pathways. To a slight amount, small water-soluble molecules can use simple diffusion to be transportable through the tight junctions of the BBB. Correspondingly, small lipid-soluble substances, such as alcohol or steroid hormones, can transcellular penetrate the BBB via the dissolution of their lipid plasma membrane. For all other substances, including glucose and amino acids, specialized transport routes are needed to cross the BBB (Chen et al.,2012).

Transport proteins are important for the mechanism of specific solutes, such as glucose or amino acids, to cross the BBB. These solutes are attached to a protein transporter at one side of the membrane, which then triggers a conformational change in the protein and the consequent transport of the element from high concentration to low concentration. A charged compound needs to be moved against the concentration gradient, and ATP will be consumed to supply the energy for the processing mechanism (Chen et al.,2012).

Efflux Pumps are responsible for the emission of both endogenous and exogenous elements, for example, drugs, from the brain into the blood. Of individual importance, active drug efflux transporters of the ATP-binding cassette (ABC) gene family are seen as significant determinants of drug distribution to and elimination from the CNS. This mechanism is seen as a significant obstacle in that it can limit the spreading of medications that are advantageous to treat CNS diseases *(Löscher et al., 2005).*

Receptor-Mediated Transcytosis (RMT) consents for the discriminating uptake of macromolecules. Cerebral ECs have receptors for the endorsement of specific molecules, including the insulin receptor, transferrin receptor, and lipoprotein transport receptor. Selective individual molecules bind to their receptors in clathrinid-coated pits, specific areas of the plasma membrane or cell membrane. These coated pits then invaginate into the cytoplasm and are fraught-free to form coated vesicles. The ligand can disassociate from the receptor once acidification of the endosome is complete, which formerly allows it to cross to the other side of the membrane *(Puglar et al .,2018).*

Adsorptive-Mediated Transcytosis (AMT) also known as pinocytosis, is caused by the interaction between a positively charged protein and the negatively charged surface of the cell membrane. In ethos, cationic molecules can bind to the luminal surface of endothelial cells and consequently undergo exocytosis at the abluminal surface. The high mitochondrial gratified cerebral endothelial cells undertake the necessary means for the molecules to move through the endothelial cytoplasm *(Puglar et al .,2018).*

Cell-Mediated Transcytosis (CMT) is a well-established mechanism for pathogen entry into the brain which utilizes immune cells, like macrophages and monocytes, to travel across the BBB. Whereas the other previously revealed transport pathways allow only molecules with individual properties to cross the BBB, CMT can be used for any form of the molecule to cross the BBB. For

example, HIV-infected cells utilize CMT via diapedesis to conclude intact endothelial cells of the BBB. This path of transport has more recently been recognized as a possible direction of drug transport for pharmaceutical uses *(Hervé et al., 2008).*

Conditions	Conditions change in Blood-Brain Barrier properties
Alzheimer	Blood-brain barrier leakage ↓Regional CBF ECE2 activation ↓ P-gp expression LRP-1 and RAGE-induced amyloid deposits Up-regulation of ABCG2 Parkinson
Parkinson	↓ TJ proteins ↓ mRNA coding for P-gp ↑MRP2 expression Epilepsy
Epilepsy	↓ TJ proteins, TJ opening Albumin, IgG, and leukocyte extravasation ↓ regional CBF in temporal lobe epilepsy ↑ P-gp, MRP1, MRP2, and BCRP expression Link between ABCC2 polymorphism and pharmacoresistance
Multiple sclerosis	↑CBF and PS ↓ TJ proteins Leakage of the BBB and inflammatory cell infiltration ↓ P-gp, MRP-1, and MRP-2 expression
Schizophrenia	Albumin and IgG extravasation
Depression	Albumin extravasation
Aging	↓regional Albumin extravasation ↓P-gp expression
HIV	Blood-brain barrier tight junction disruption.
Pain	Inflammatory pain alters BBB tight junction protein expression and blood-brain barrier permeability.
Glaucoma	Opening of the BBB, possibly through the diffusion of endothelin-1 and matrix-metalloproteinase-9 into peri-capillary tissue.
Lysosomal storage diseases (LSD)	May show changes in BBB permeability, and/or transport, depending on specific LSD.
Infectious or inflammatory processes	e.g., bacterial infections, meningitis, encephalitis, and sepsis The bacterial protein lipopolysaccharide (LPS) affects the permeability of BBB tight junctions. This is mediated by the production of free radicals, IL-6, and IL-1 β Interferon-β prevents BBB disruption. Alterations in P-glycoprotein expression and activity in the blood-brain barrier. Increased pinocytosis in brain microvessel endothelium and swelling of astrocytes end-feet.

Table 1. Different pathophysiological conditions and Blood-Blood Brain disruption.

Treatment ways in Blood-Brain Barrier

Researchers are developing ways to get medications past the Blood-Brain Barrier. One of the methods involves a transport system, in which the medications are created in such a way that antibodies bind to specific receptors or on the endothelial cells to help the drug pass through the barrier and get to the brain. Another method involves an ultrasound to temporarily open a portion of the blood-brain barrier. In this method, patients are injected with microscopic bubbles that can spread through the circulatory system. An ultrasound is used to vibrate the bubbles in the brain and temporarily open the blood-brain barrier *(Shen., 2017).*

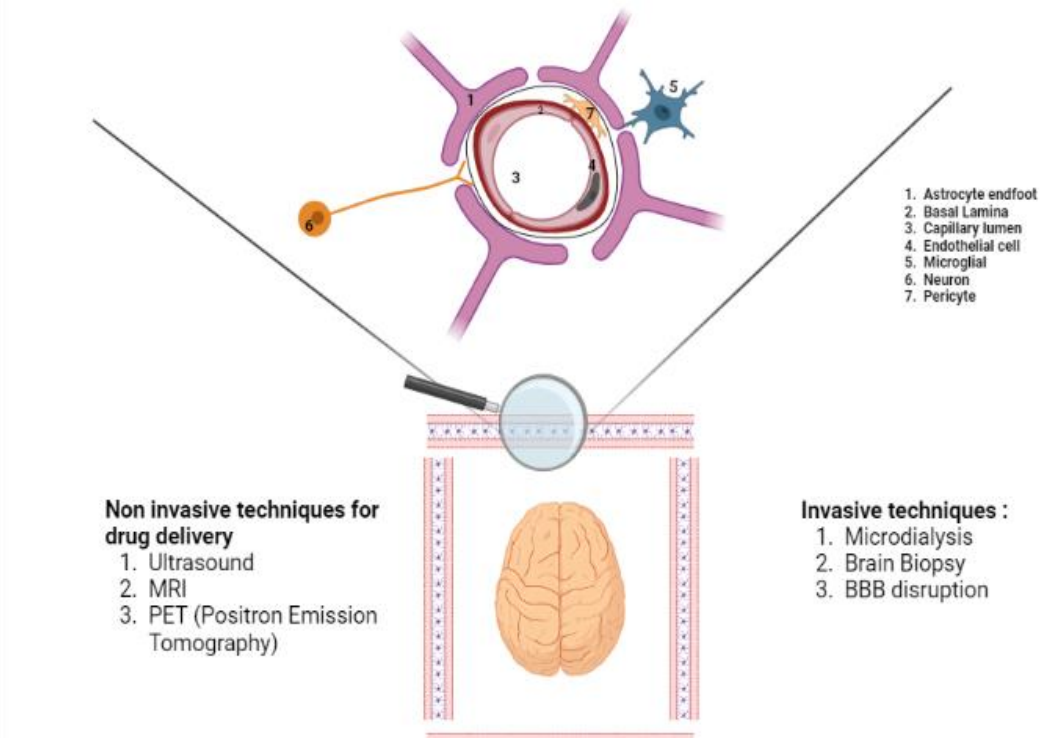

Fig 3. The blood-brain barrier and techniques for brain drug delivery.

Charged compound interaction- Positively charged substance such as cationized albumin and histone interacts with negatively charged components of the EC membrane allowing the adsorptive mediated endocytosis to overcome the Blood-Brain Barrier. This is also being tested in order to be used in diagnostics, neuroimaging, and as a treatment for mental disease *(Ballabh et al.,2004)*.

Surgical approaches- One of the simplest methods of brain drug delivery is direct local drug infusion and is commonly used in an emergency where the drug must reach the brain urgently but there is a limitation in this method due to low diffusion coefficient of the drugs *(Jajes et al., 2014)*. The drug diffusion depends on the location of the drug administration, liposolubility, molecular mass, polarity, and tissue affinity.

Microchips- The method of microchip delivery of the drug is by implanting a solid-state electronic silicon device into the brain is a way to deliver a precise quantity of drugs under specific physiological conditions. There is a study going on for the treatment of brain tumors using microchips by microelectromechanical system technology to deliver the drug with temporal control over the release kinetics *(Santini et al., 1999)*. This device has a liquid crystalline polymer reservoir, which is capped by a MEMS microchip.

Intranasal administration- It is an alternative non-invasive method of delivering drugs to the CNS. The therapeutically active compounds are absorbed through sensorial neurons located in the olfactory bulb and delivered to the CNS through the CSF of the olfactory region. *(Illum et al.,2000).*

Molecular Trojan horses (TH)- they are the vectors that are able to bind to the specific receptor while carrying drugs that do not accept the chemical modification allowing them to cross the Blood-Brain Barrier. The complex is called a chimeric peptide because of its mixed structure and double functionality, targeted transport (TH), and pharmacological activity (drug) *(Jajes et al., 2014).*

Targeted drug delivery- An efficient drug delivery can reduce considerably the dose of the drug needed and in consequence improve the safety of in-vivo. This is the major point in drug commercialization. This method strategy consists of attaching ligands that are specifically recognized by BCECs receptors such as sugar residues, folic acid, or even engineered mAbs *(lockman et al., 2002; Mishra et al.,2006)* Targeting moieties can be attached directly to the surface of the carrier system or on the external end of the PEG if its PEGylated, forming which is known as third generation carriers.

Each nanotechnology-based drug delivery can be subdivided into first, Second, and third generations depending on their surface modification.

AKGs- Recent studies with the anticancer agent have been carried out in rat glioma tumor models after systematic administration of various AKGs. The result was increased delivery of the drug to the site to the level of the drug uptake after hyperosmotic shock and fat greater than upon the biochemical disruption *(Jajes et al., 2014).*

Intra-ventricular and intra-thecal administration- This method consists of the direct delivery of the drug to the CSF bypassing the Blood-Brain Barrier and blood-CSF barrier. The procedures are done by direct injection piercing the skull and into the ventricles or through the lumbar both of them with considerable associated risks *(Blasberg et al., 1975)*. Liposomes, nanoparticles, nano-polymers, and solid lipid nanoparticles are the carrier that can be administrated parentally facilitating the delivery of drugs to the brain *(Jajes et al., 2014).*

Strategy	Pros	Cons	Clinical trial
Nanotechnology	Sustained cargo release. Easy parenchymal uptake.	Fast removal	Phase II
CPPs	Excellent penetrating ability	Fast removal Non-specificity Immunoresponsive	Phase II
Hyperthermia	Low cellular toxicity Easy to perform. Drug compatible	↑intracranial pressure. Necrosis Tissue damage	Phase II
Cell-mediated delivery	Low cytotoxicity Controlled drug release Targeted transport	Require high cell quantity. Cell injury	Phase I
RMT	Site-specific	Low dissociation rate Rapid cargo degradation. Possible toxicity	Phase III

Table 2. Various strategies to cross Blood-Brain Barrier

Advantages and disadvantages of the Blood-Brain

The blood-brain barrier's primary function protection of the brain from circulating toxins or pathogens that might cause brain infections while simultaneously enabling critical nutrients to flow through it. Although it appears that the blood-brain barrier protects our brains by limiting what can enter and leave, this mechanism has some drawbacks.

some of the main advantages and disadvantages of the blood-brain barrier are:-

Protection: The blood-brain barrier acts as a barrier, preventing harmful substances in the blood from reaching the brain. This is important because the brain is sensitive to many toxins that can damage or kill brain cells.

Regulates Brain Environment: The blood-brain barrier regulates the exchange of substances between the bloodstream and the brain. This helps to maintain a stable environment for the brain, which is important for proper brain function.

Protects from Microbial Infection: The blood-brain barrier prevents the entry of many types of pathogens, including bacteria and viruses, into the brain. This helps to prevent infections of the brain, which can be very dangerous.

Disadvantages of the Blood-Brain Barrier:

Drug Delivery: The blood-brain barrier can make it difficult to deliver drugs to the brain. Many drugs cannot cross the BBB, which can make it difficult to treat brain diseases.

Oxygen & Nutrient Availability: The blood-brain barrier can also limit the availability of oxygen and nutrients to the brain. While the BBB protects the brain from harmful substances, it also limits the entry of many important substances that are needed for brain function.

Injury response: The blood-brain barrier can limit the ability of the brain to respond to injury. When the brain is injured, it needs access to a variety of substances to repair damage and regenerate brain cells. The blood-brain barrier can limit the entry of these substances into the brain, which can slow down the recovery process.

Developing and Refining Novel Approaches for Drug Delivery

Since innovation is now on the drug delivery side, it is a matter of fact that proteins and polypeptides can be delivered directly to the brain by many methods. A few to the list are-

- Trojan horse approaches using fusion molecules
- Using macrophages and monocytes to transport therapeutic molecules into the brain
- Using viral vectors to transport genes into the brain
- Disrupting the blood-brain barrier with focused ultrasound to enable therapeutic molecule delivery

- Bypassing the blood-brain barrier by delivering drugs to the brain intranasally via the olfactory or trigeminal nerve pathways

Drug Delivery Approaches that aid to the Current Advances in Brain Tumor Therapy

Because of their limited penetration through the BBB, most brain tumor treatments are unsuccessful. Intra-arterial drug delivery, intrathecal and intraventricular drug, intratumoral delivery, receptor-mediated transport, rupture of BBB, prevention of drug efflux via BBB, and utilization of intranasal drug delivery channel are a few known techniques.

Clinical trials of intra-arterial delivery of brain tumor drugs show minimal improvement in the survival of brain tumor patients. Still, neurosurgeons at New York Presbyterian Hospital/Weill Cornell Medical Center recently demonstrated for the first time the successful intra-arterial delivery of a monoclonal antibody like bevacizumab to the tumor region via transient blood-brain barrier disruption. When medications are administered intravenously, they have a restricted ability to penetrate the extracellular area of the brain from the CSF. The convection-enhanced diffusion (CED) technology is utilized in transcranial brain drug delivery systems to bypass the BBB and boost the effective penetration of medication into tumor regions. Microdialysis has also been used in neurooncology since it was proposed as an efficient way of intratumoral medication delivery. This approach uses passive drug diffusion over the BBB to distribute medications away from the dialysis catheter. On the other hand, receptor-mediated endocytosis and exocytosis help therapeutic chemicals traverse the BBB of brain tumors.

Drugs based on receptor-targeted monoclonal antibodies are transported across the BBB using receptor-mediated transport mechanisms. BBB disruption is another convenient way to solve drug distribution problems in the brain. Several techniques, such as osmotic disruption, bradykinin-analog or alkylglycerol mediated disruption, MRI-guided targeted ultrasound BBB disruption, and so on, are used to break the blood-brain barrier. However, bradykinin analog-mediated drug administration has been abandoned due to its ineffectiveness when combined with carboplatin. Recently, an MRI-guided targeted ultrasound BBB disruption approach has been employed to break the BBB to deliver drugs more effectively *(Pardridge et al.,2012).* Using intranasal medication delivery routes is a promising drug delivery approach that can bypass the BBB. This strategy removes the risk of surgery and the nonspecific medication spillover effect on normal tissue. Intranasal delivery is an effective medication delivery strategy that uses the specific anatomic connections between the olfactory and trigeminal neurons of the nasal mucosa and the central nervous system. Drugs delivered by this route reach the cerebrospinal fluid (CSF), spinal cord, and brain parenchyma exceptionally quickly. This delivery system effectively provides anticancer medicines such as raltitrexed, 5-fluorouracil, GRN163, and methotrexate to the brain. More research into intranasal therapeutic drugs is needed, and it could be a promising candidate for clinical trials in brain tumor patients.

Developing New Models That Better Represent the BBB

Translating basic science to therapeutic applications is a complicated process that will necessitate increased development of both vitro and animal models. In vitro models have played a vital role in discovering and developing novel medications for CNS illnesses. Stem cell technologies have created 2-D and 3-D models for studying BBB permeability and transport. More than 40 animal models have been established to examine BBB collapse in human disease and elucidate mechanisms contributing to it, including pericyte degeneration and fibrinogen deposition. Systems biology techniques that employ mathematical modeling can aid in explaining mechanisms and predicting responses in terms of safety and efficacy *(Caterina eta al., 2017)*.

Developing Biomarkers

The field is progressively moving toward the preclinical use of biomarkers of target engagement and toxicity. Biomarkers can increase the efficiency of clinical trials, cutting their costs. Biomarkers that validate medication transport into the brain and BBB permeability status would allow for clinical trial subject categorization. New imaging and molecular techniques enable researchers to investigate brain vasculature and BBB disruption in living animals and humans and to correlate these findings with cognitive changes.

Building Collaborations to Advance Understanding of the BBB

Because the BBB is complex and genuinely multidisciplinary, collaborative and cooperative research approaches are essential. Collaborations such as public-private partnerships benefit all stakeholders, including academic researchers, industry, and patients. Because the BBB serves as an interface between the blood and the brain, research funding may have a significant impact. Advancing new BBB research will necessitate a greater emphasis on basic and translational science and attracting and supporting more young researchers. Consortia might create training programs and offer incentives to entice scientists to enter and stay in the sector. Attracting the interest and experience of researchers from other domains would promote innovation in BBB science.

Molecular Trojan Horses (MTH)

Recently, Molecular Trojan Horse (MTH) mediated drug delivery has been exploited to ferry drug molecules over the BBB. The primary goal of this sort of delivery system is to send specific compounds to the brain after connecting them to a protein that can cross the BBB. THL (Trojan horse liposome) technology is one of the most recent advances in MTH. This technology's application to transvascular nonviral gene therapy of the brain suggests a viable solution to the transvascular brain gene delivery challenge. THLs are made of PEG-conjugated lipids that enclose plasmid DNA expressing proteins or shRNA/siRNA. THL-mediated RNAi gene therapy resulted in a significant drop in EGFR protein expression in the tumor location *(Bhowmik et al.,2015)*.

Discovery of Blood-Brain Barrier Carrier-Mediated Transport Systems

Physiology of blood-brain barrier carrier-mediated transport Crone44 demonstrated the first evidence of saturable or CMT of a solute across the BBB for D-glucose utilizing the indicator dilution approach, a venous sampling-carotid artery injection method. Then, Oldendorf45's Brain Uptake Index approach, a tissue sampling-carotid artery injection method, was employed to quantify the saturable kinetics of BBB transport of different water-soluble metabolic substrates. The Michelis-Menten kinetics of BBB CMT for the vital metabolic substrates were determined46. This research revealed that the BBB nutritional transporters had a wide range of affinity (Km) and maximal transport activity (Vmax) *(Caterina eta al., 2017)*.

Active Efflux Transporters and Enzymatic Blood–Brain Barrier

Active efflux transporters (AET) facilitate the asymmetric efflux of metabolites and medicines from the brain to the circulation. The basic AET system within the BBB is p-glycoprotein, a product of the MDR (multidrug resistance) gene MDR1, also known as the ABC (ATP-binding cassette) subfamily B member 1. (ABCB1). Terasaki and colleagues quantified the expression of multiple other members of the ABC gene family of transporters at the BBB, in addition to p-glycoprotein*(Ballabh et al.,2004)*. 48 The AET systems may collaborate with BBB-expressed enzymes such as P450 enzymes. 77 Both the AET systems and the enzymatic barriers are modulable. The p-glycoprotein activity of the blood-brain barrier is inhibited by vascular endothelial growth factor,78. The CYP1A1 and CYP1B1 P450 enzymes are increased by environmental toxins that activate the aryl hydrocarbon receptor at the BBB, such as dioxin derivatives. 79 In addition to ecological pollutants or growth hormones, illness states such as aging can change BBB permeability*(Czupalla et al.,2014)*.

Blood–Brain Barrier Penetrating Genetically Engineered IgG Fusion Proteins

Because of the availability of endogenous RMT systems within the BBB, such as the insulin receptor or the TfR, recombinant proteins can be re-engineered as BBB-penetrating medications using molecular Trojan horse (MTH) technology.

An MTH is a peptide or peptidomimetic MAb that crosses the BBB via a particular RMT mechanism. . Insulin as an MTH is not favored because it promotes hypoglycemia. Because the plasma concentration of endogenous Tf, 25 mol/L, is so high, the Tf-binding site on the BBB TfR is wholly saturated by endogenous Tf. RMT-specific MTHs could also be peptidomimetic MAbs that bind exofacial epitopes on the BBB receptor that are spatially far from the endogenous ligand binding site. A genetically designed chimeric MAb against the mouse TfR, known as the cTfRMAb, has been developed for BBB delivery in mice*(Ballabh et al.,2004)*.

IgG fusion proteins can be genetically created as bifunctional molecules that cross the BBB via RMT and exert pharmacological effects in the brain after transport into the brain using the genes encoding the heavy and light chain of either the modified HIRMAb or the cTfRMAb.

Conducting Complex Preclinical Studies

Preclinical evaluation of complex compounds capable of crossing the BBB is difficult. Still, it is vital to identify the characteristics that would allow them to go through the development phase and into clinical translation, according to Stanimirovic. Evaluating the toxicity of complex fusion molecules delivered to the brain presents several challenges, including immunogenicity, targeting of different brain areas, and the potential for cross-linking with surface proteins and evoking a cascade of high-level immune activation, known as a cascade of high-level immune activation known as a "cytokine storm." According to Hunt, species-specific biologies add complexity to toxicity and efficacy because various species may express varying quantities of the desired target receptor. Predictive models, he suggested, would help evaluate doses in preclinical research.

Disadvantages

BBB dysfunction is present in various conditions, such as multiple sclerosis (MS), epilepsy, and stroke, where it plays a significant role in the pathology. In contrast, in other disorders, such as Alzheimer's disease, the occurrence and magnitude of BBB breakdown are a subject of ongoing research and debate. Disruption of the BBB results in ion dysregulation, edema, and neuroinflammation, which can cause neuronal dysfunction, increased intracranial pressure, and neuronal degeneration. The vast majority of possible medication treatments cannot pass the barrier, providing a significant challenge in treating mental and neurological illnesses *(Czupalla et al.,2014).*

Defective blood-brain barriers have been associated with neurological illnesses such as Parkinson's, Huntington's, and amyotrophic lateral sclerosis. This means that the barriers keep biomolecules essential for healthy brain activity, particularly regarding medication delivery and metabolic activities.

The blood-brain barrier (BBB) blocks most medications from entering the brain. The epithelial-like tight junctions inside the brain capillary endothelium are responsible for this feature.

The Aberrant Expression of blood-brain Components in Brain Tumors

Claudins and occludins, BBB components, are either downregulated or not expressed in brain tumors. Claudin-1 loss and downregulation of claudin-3 and claudin-5 expression have previously been documented in high-grade glioma. This difference in claudin expression induces the loosening of BBB tight junctions; however, claudins' role in altering BBB tight junction function is unclear. Claudin-1 proteins affect many signaling pathways, limiting the production and operation of specific cell-cell adhesion molecules *(Bhowmik et al.,2015).*

It has also been revealed that claudin-5 modulates BBB permeability during brain tumor spread. Occludin, another transmembrane protein, is similarly lost in microvessels in astrocytomas and metastatic adenocarcinomas. Their role in endothelial tight junction opening is also quite likely. High-grade astrocytomas secrete vascular endothelial growth factor (VEGF), which inhibits occludin expression and promotes endothelial cell permeability. Aside from VEGF, astrocytoma and other brain tumors release cytokines, scatter elements, and hepatocyte growth factors. These factors seem to be involved in the downregulation of tight junction molecules, which results in leakage. The prognosis and median survival of brain tumor patients are not satisfied. This is due to the molecular heterogeneity of the brain tumors, the presence of CSCs, and the lack of effective drug delivery. Rapid progress is required in brain tumor characterization and BBB research *(Czupalla et al.,2014).*

Biotechnology produces only effective molecule medications that do not cross the BBB. While small compounds are expected to be freely transported through the BBB, 98% of all small molecules are not. The BBB is the main obstacle impeding progress in novel treatments for brain illnesses or radiopharmaceuticals for brain imaging.

Conclusion

The blood-brain barrier is an important biological barrier that tightly regulates the CNS's milieu to support healthy neuronal activity. Because disruption of the blood-brain barrier can result in severe pathology seen in many different diseases and because crossing the blood-brain barrier is a crucial factor in the development of CNS-acting therapeutics, this barrier is very important to take into account when determining treatments for various neurological diseases. Current research has found numerous molecules necessary for blood-brain barrier function as well as numerous cellular and molecular signaling activities that control the BBB's development, adult function, and response to damage and disease (Fig 1.). Although great progress has been made, many questions still remain. Though much has been accomplished, there are still a lot of unanswered questions. Are there distinct or overlapping mechanisms that control each of the blood-brain barrier's various properties? How are various signaling channels coordinated to control various blood-brain barrier functions Which routes influence the blood-brain barrier characteristics during development and which are necessary for barrier maintenance throughout life? Certain blood-brain barrier characteristics, such as tight junctions and transport, are dynamically altered in response to brain activity and can change the blood-brain barrier and impact behavior, brain function, and neuronal activity (Table1.). In addition, a variety of neurological diseases and pathologies, including neoplasia, hypertension, dementia, epilepsy, infection, multiple sclerosis, and trauma, are linked to increased BBB permeability. Any condition that interferes with BBB function will have a knock-on effect on cerebral blood flow and vascular tone, which will further affect BBB transport. In this study, we discussed a number of important BBB-related topics, including the cellular components' roles and functions as well as the involvement of external physical stimuli like shear stress Blood- brain barrier have any specialised regions that control the growth or operation of localised neurons. lack of maintenance signals or neurological illness that causes the loss of blood-brain barrier properties. In order to restore the blood-brain barrier function during neurological disease and to create strategies for BBB bypass drug delivery, it will be necessary to understand.

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Illustrations were created with BioRender (http://Biorender.com, accessed on 28 march 2023)

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The authors declare that they have no competing interests.

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