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{Review Article}

Blood Brain Barrier dynamics & Nano carrier transport mechanism in CNS Disorder

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Abstract

Diseases of the central nervous system (CNS) are a leading cause of death and disability globally. The blood–brain barrier (BBB), however, frequently makes it difficult for medications used to treat CNS disorders to penetrate the brain parenchyma and exert their therapeutic effects. The blood–brain barrier has a high degree of selectivity and is semi-permeable. Transport of chemicals between the blood and the central nervous system is mostly controlled by the blood-brain barrier. Numerous brain-based drug delivery techniques that circumvent the BBB have been developed to improve medication delivery for the treatment of CNS diseases. Among them, nanoparticles (NPs) have been emphasized due to their multiple excellent properties. The article provides an overview of the many types of nanoparticles and delves into how their size, shape, charge, and surface ligands impact their capacity to pass the blood-brain barrier.This ends with a review of the present difficulties in using nanomaterials to deliver drugs to the brain and a discussion of potential remedies. This seeks to suggest novel methods of diagnosis and treatment for CNS disorders. Additionally reviewed and discussed are the most recent research on virus-mimicking nano carriers for drug delivery across the blood-brain barrier. However, there are ways to deliver drug-loaded nanocarriers to the central nervous system. It includes and talks about many approaches and pathways for nano-formulated drug delivery systems to reach the brain through the blood-brain barrier, which will help with more precise diagnosis and treatment of CNS disorders.

Keywords: blood–brain barrier, nanomaterials, brain drug delivery, BBB viral disruption, trans nasal route

INTRODUCTION

In addition to eliminating carbon dioxide and other metabolic wastes from the circulatory system, the human brain's 644 kilometers of blood arteries supply brain cells with oxygen, energy, metabolites, and nutrients.

Despite making up only 2% of the body's overall mass, the brain needs 20% of its glucose and oxygen. It can swiftly enhance blood flow and oxygen transfer to its active regions through a process called neurovascular coupling. Barrier layers at the primary interfaces

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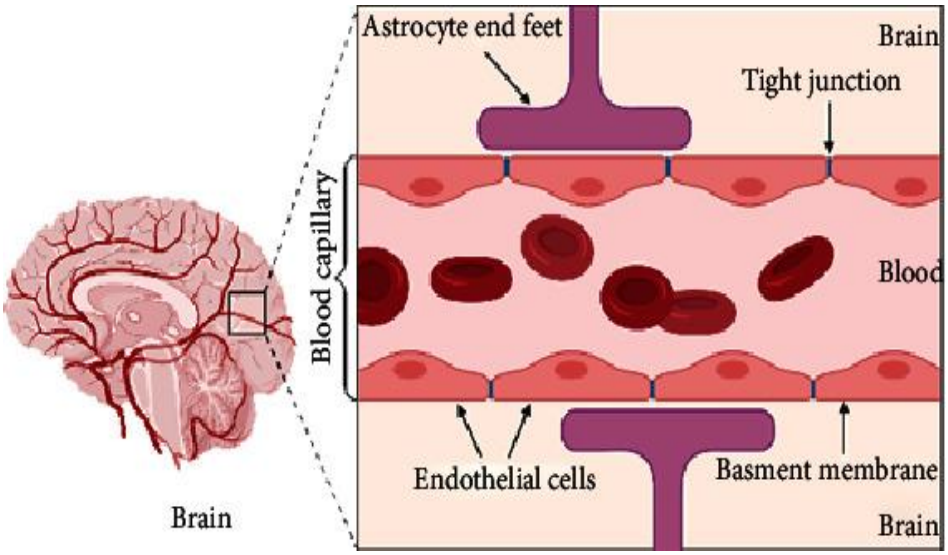
between blood and neural tissue, known as the blood-brain barrier (BBB), help in this control.

(Figure 1).



A schematic diagram of brain and simple longitudinal zoom in blood brain barrier

In the cerebral microvessels of the majority of vertebrates, the blood-brain barrier (BBB) is a dynamic, semipermeable, and highly selective mechanism. It divides the extracellular fluid of the brain from the circulation. It is essential for controlling the movement of chemicals required for brain activity.

The blood-brain barrier (BBB) is a dynamic, semipermeable, and highly selective system found in the cerebral microvessels of most vertebrates. It separates the brain's extracellular fluid from the bloodstream. It is crucial for regulating the flow of chemicals needed for brain function.

Ehrlich, Bield and Kraus, Lewandowsky, and Edwin Goldmann then conducted ground-breaking studies on the permeability of different substances from blood to brain tissues or the other way around, which led to the identification of a special barrier structure in the brain's microvessels.

By shielding the brain from potentially harmful compounds found in the blood, the blood-brain barrier maintains a stable cerebral environment. By controlling the movement of molecules into and out of the central nervous system (CNS), the blood-brain barrier (BBB) maintains homeostasis. It also keeps blood cells, plasma components, and pathogens out of the brain by forming a tightly regulated neurovascular unit (NVU) that is made up of astrocytes, endothelial cells, and pericytes. These cells cooperate to maintain the chemical components of the neural environment, which keeps the brain functioning normally. The brain's blood capillaries are distinct in two ways.

. First, the endothelial cells that border these capillaries' walls are bound together by tight junctions (TJs), a key element of the barrier. Water-soluble substances in the blood are kept from easily entering the fluid environment of cerebral tissues by these junctions, which also stop them from passing through cells. Second, these capillaries are surrounded by end-feet astrocytes, which serve as a partially effective barrier.

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In the cytoplasm of BMECs, the BBB creates an enzymatic barrier and a paracellular barrier made up of different transporters. Enzymes such as alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (-GTP) help break down unnecessary substances in the blood that passes through the brain. The structure and function of the blood-brain barrier, the many channels that carry different molecules between the blood and the brain, and the factors that contribute to BBB are all summarized in this article.

dysfunction, discussing some of the most significant biomarkers that may be utilized to anticipate BBB disruption

The epicenter of a wide range of physiological activity is the brain. To carry out particular tasks, it combines signals from the internal environment with information from the external environment.

The chemical environment in which these cells function must be tightly controlled because of all the unique actions that take place at the neuronal level. This is the blood-brain barrier's main purpose.

The general architecture of the blood-brain, blood-nerve, and blood-cerebrospinal fluid barriers that are present throughout the nervous system will be examined in this article. Furthermore, the brain regions that do not have a blood-brain barrier as well as clinically significant locations in relation to this membrane will receive particular attention.

Defination

The selectively permeable Blood-Brain Barrier (BBB) membrane controls the entry of several large and tiny chemicals into the neuronal milieu. Several cellular transport channels dispersed throughout the membrane help it accomplish this. Among these are amino acid transporters.

GLUT1, or glucose transporter 1 Essential chemicals are transported into the brain by nucleouside and nucleotide transporters, monocarboxylate transporters (MCT1 and MCT2), and ion transporters (Na+/K+-ATPase pumps).

The amino acid transporters may unintentionally introduce unwanted heavy metals into the immediate surroundings of the brain in addition to aiding in the absorption of amino acids. Consequently, this will cause neurotoxicity at high enough doses. The MCT transporters and GLUT1 transfer glucose, lactate, and ketones, respectively.

BLOOD BRAIN BARRIER STRUCTURE

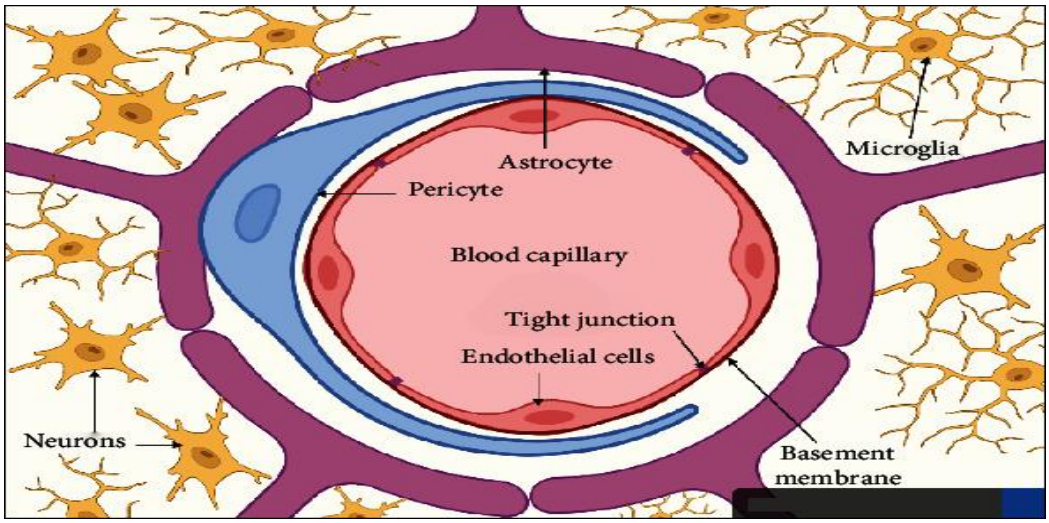

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Figure-1. A schematic diagram of transverse section in blood-brain barrier

All vertebrates and certain highly intelligent invertebrates with a fully developed central nervous system, such insects, squid, and octopuses, may have the BBB. The successful evolution of the complex brain depends on the formation of the BBB. It is mostly composed of pericytes, astrocytes, and capillary endothelial cells, with a few additional components that support immune function, including neurons, the basement membrane, and microglia. These elements, commonly referred to as a neurovascular unit (NVU), maintain a healthy blood-brain barrier to ensure proper activation of the central nervous system.

1. Endothelial Cells and Tight Junctions

The mesoderm is the source of endothelial cells (ECs). They are modified forms of simple squamous epithelial cells that line capillary walls. Compared to cells from other vascular areas, brain endothelial cells have a distinct character. For restricting polar substances, they possess tight junctions, junctional adhesion molecules (JAMs), luminal/abluminal polarization, and particular transport mechanisms.

They are found in large quantities in mitochondria, which are thought to be essential for producing ATP and managing the ion gradients required for transport processes. Furthermore, it is thought that brain ECs have a unique vascular metabolism that alters the physical properties of chemicals, altering their solubility, reactivity, and transport properties, so forming a barrier. The pericytes and astrocytic endfeet, which are located nearby, control the special properties of brain ECs.

Proteins on adjacent cells and their connections with cytoplasmic scaffolding proteins, such as zonula occludens (ZOs), the actin cytoskeleton, heterotrimeric G-proteins, and protein kinases, mediate intercellular communication and signaling. Special tight junctions (TJs), which are 50–100 times closer than those in peripheral capillaries, seal the endothelial cells. This results in a very high transendothelial electrical resistance (TEER) in blood vessels and limits the passive transmission of molecules to the brain.

The TJs are occludin (Ocln) and members of the claudin family (Cldn), which are specialized to endothelium. The ZO family (ZO-1, -2, -3) connects these proteins to the actin cytoskeleton. The increased TEER is believed to be caused by the proteins claudin 3 (Cldn3), claudin 5 (Cldn5), and maybe claudin 12 (Cldn12). TJ formation and BBB function depend on Cldn5, however mice that have their embryonic Cldn5 removed experience early postnatal brain edema and mortality. The 60–65 kDa protein occludin has a carboxy (C)-terminal domain that can attach itself to zonula occludins protein 1 (ZO-1).

TJ regulation appears to be its primary function. When endothelial cell junctional proteins are not properly regulated, the blood-brain barrier becomes compromised, allowing for systemic access into the brain and potentially causing edema or neurotoxicity. The junctional complex and the actin cytoskeleton may be connected by the junctional proteins. Adherens junctions stabilize a cell-cell interaction in the junctional region. Brain endothelial cells include junctional adhesion molecules, such as JAM-A, JAM-B, and JAM-C, which contribute to the formation and maintenance of TJs.

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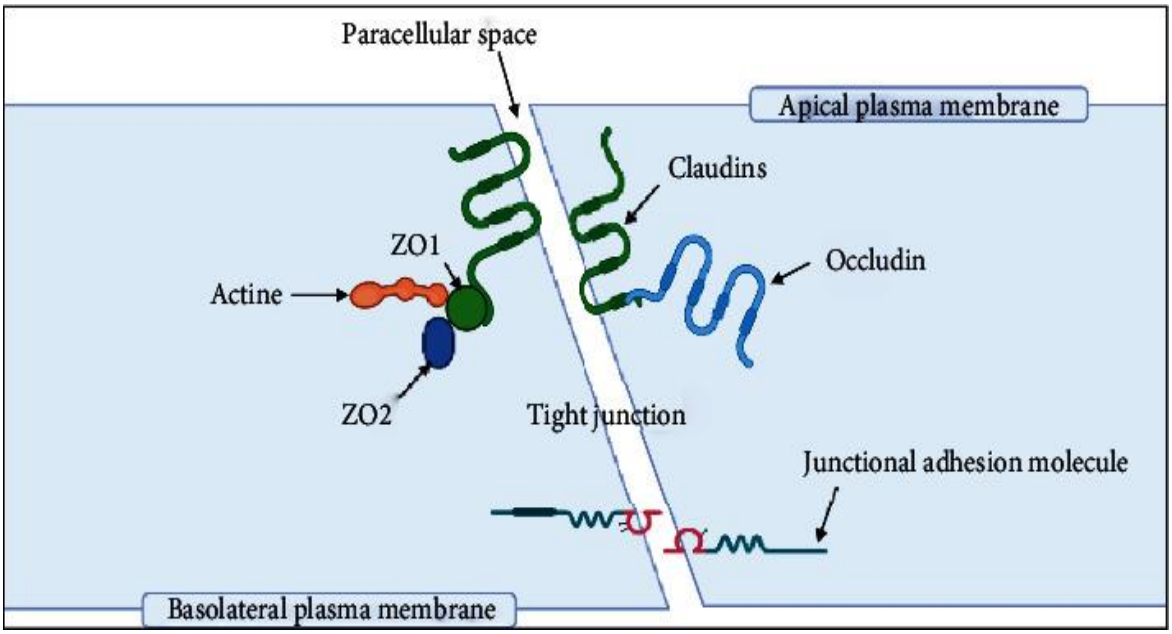

Figure-2. A schematic diagram of transverse section in capillary endothelial cells

2. Astrocytes

Astrocytes are multipurpose, star-shaped cells that serve as K+ and neurotransmitter buffers and direct the migration of growing neurons. They are characterized by the expression of the intermediate filaments vimentin (Vim) and glial fibrillary acidic protein (GFAP), and they assume a stellate shape with many appendages. Astrocytes, the most prevalent cell type in a vertebrate's central nervous system, contain specialized endfeet that cover almost the whole surface of cerebral capillaries.

The formation of astrocytes from radial glia and normal brain precursor cells in late gestation suggests that astrocytes cannot regulate early BBB-inducing mechanisms. The potassium channel in the NVU's endfeet membrane is in charge of preserving ionic concentration, water homeostasis, and a functionally mature blood-brain barrier. According to a number of studies, proper control of astrocyte function is thought to be crucial for improving BBB function and reducing BBB disruption following brain trauma. During inflammation, the pattern of astrocytic cells changes to A1 and A2 active cells. According to gene According to profile, the A2 form enhances healing characteristics, while the A1 phenotype is detrimental and has several complement proteins upregulated. Otherwise, in a preclinical model of multiple sclerosis, Eilam and colleagues found that the absence of astroglial interaction with blood vessels damaged the blood-brain barrier. Furthermore, it has been shown that astrocyte-derived factors are responsible for both BBB breakdown and repair.

3. Pericytes

In the middle, between endothelial cells, astrocytes, and neurons, are brain capillary pericytes. The relationships between pericytes and endothelial cells are essential for the BBB's proper development, growth, stability, and maintenance . Pericytes govern cerebral blood flow and BBB permeability, and they also have a strong phagocytic activity associated with the removal of toxic foreign substances. Therefore, the pathophysiology

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of a number of diseases associated with microvascular instability is significantly influenced by the dysfunction or absence of BBB pericytes.

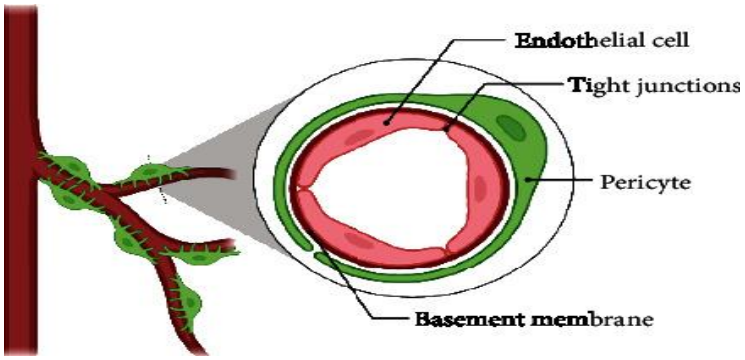

Figure.3. A schematic diagram of blood brain barrier showing pericyte

4. Basement Membrane

The basement membrane (BM), in addition to cells and biomolecules, is essential for regulating BBB permeability. Through interactions with extracellular matrix (ECM) proteins, this membrane maintains the barrier function, links cells, and controls intercellular communication. Collagen, nidogen, laminin, sulfate, proteoglycans, and other glycoproteins are among the components that make up BM. In the capillary basement membrane, endothelial cells interact with extracellular matrix proteins like collagen, perlecan, and laminin through α and β integrin receptors.

In addition to acting as a barrier for substances and cells attempting to enter the brain tissue, BM also acts as an anchor for numerous signaling processes in the vasculature. One of the main causes of BBB deterioration and leukocyte leakage, which is observed in a number of neurological disorders, is matrix metalloproteinases' disruption of BM.

5. Microglia

One type of neuroglia that can be found throughout the brain and spinal cord are called microglia. They comprise around 5–20% of the total glial cell population in the brain tissue. By supplying immunity, absorbing harmful foreign substances, healing damaged brain tissue, and taking part in extracellular signaling, they support nerve cells. Additionally, there is growing evidence that activated microglia can control the expression of tight junctions, enhancing the BBB's efficiency and integrity. Therefore, the dynamic and continuous interactions between the cellular components of the neurovascular unit maintain and regulate the properties of the BBB.

BBB Formation

Animal models may offer a window into human development because chordate BBB formation is evolutionarily conserved. In mammals, the origination and identification of the BBB begin at the early embryonic interval. Mature cells, such as astrocytes and myelinated neurons, do not appear until soon after birth, despite the fact that it begins to function immediately.

According to the data from developmental research, the early development of the central nervous system (CNS), where the vascular and neurological systems interact in concert to facilitate the easy construction of the BBB, shapes the BBB's properties. Like all other

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organs, the brain is vascularized during development by the vascular plexus that surrounds it. The perineural vascular plexus (PNVP), which envelops the neural tube, is the source of the blood-brain barrier. Cellular interactions inside the expanding NVU and intricate connections to the developing CNS drive the multistep procedure that forms its foundation.

This indicates that multiple cells and the developmental substances they release are involved in the intricate process of the BBB's growth. Every cell in the NVU contributes to the BBB's development and creation.

The PNVP is established by vasculogenesis in the head mesenchyme that covers the neural tube, paving the way for the development of the BBB. The formation of BBB capillaries and the invasion of the primitive brain during PNVP formation are caused by a unique mechanism of angiogenesis. Through neuroprogenitor cell migration and reproduction in the neural tube, the nutrition supply from these tiny vessels contributes to brain formation.

The BBB is seen at several locations along the brain's vasculature: (I) the endothelial cells' barrier, (II) the avascular arachnoid epithelium's barrier, and (III) the choroid plexus's creation of the CSF blood barrier.

BBB Function

The blood-brain barrier (BBB) is a physiological process that alters the permeability of cerebral capillaries, allowing certain substances—like certain medications—to freely enter brain tissue while blocking others. The BBB's primary function is to protect the brain from changes in blood ion, amino acid, peptide, and other element concentrations. Because the brain is encased in a hard, bony skull, its volume must be preserved. By preventing the unchecked passage of salts and water from the bloodstream into the cerebral extracellular fluid, the blood-brain barrier plays a crucial part in this process.

The BBB secretes brain extracellular fluid at a controlled rate, which is crucial for preserving the proper brain volume, in contrast to other body tissues where the extracellular fluid is created by capillary leakage. Water and salts seep into the brain tissue when the blood-brain barrier is compromised by an injury or infection, resulting in edema and elevated intracranial pressure that can be lethal. As a result, the BBB is crucial to the brain's proper operation and shields it from issues with fluid production in the body.

BBB Dysfunction

Age and a number of neurological conditions, including multiple sclerosis, Alzheimer's disease, stroke, and epilepsy, can cause BBB failure. Damage or ensuing pathological alterations, such as inflammatory responses, lipid peroxidation, excitotoxicity, calcium-mediated injury, and metabolic abnormalities, might compromise the stability of the blood-brain barrier.

Pathological BBB breakdown causes two outcomes:

(1) increased transcellular entry of inflammatory T lymphocytes across brain endothelial cells as a result of adhesion molecule activation, and

(2) increased paracellular leakage of soluble mediators into the central nervous system as a result of tight junction disruption.

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Some of the molecular mechanisms that cause changes to the blood-brain barrier have been discovered through studies using animal and cell culture models of the disease. A number of BBB characteristics, such as transporters, TJs, transcytosis, and gene expression, may alter as a result of this dysfunction. All of which resulted in altered signaling and immune infiltration, which can ultimately lead to neurodegeneration and neuronal dysregulation.

Furthermore, direct harm to endothelial cells and poor BBB permeability are mechanisms for BBB breakdown, which results in an irreversible disruption of the BBB because of BBB cell death.

Because it permits an unchecked flow of chemicals from the bloodstream into the cerebral tissue, BBB damage causes ion dysregulation, edema, and neuroinflammation, all of which can result in impaired neuronal function, increased intracranial pressure, and nerve cell death. However, little is understood about the mechanisms behind BBB dysfunction and how it contributes to the onset, course, and recovery of disease. However, BBB malfunction results in increased infiltration of various white blood cell types into the cerebral parenchyma and extravasation of intravascular fluid, which in turn promotes inflammation of the brain.

VCAM-1 and ICAM-1 expression on endothelial cells increased during inflammation. Furthermore, the endothelial cells' elevated CAM enhanced white blood cells' capacity to attach to adhesion molecules including VLA-4 and LFA-1. One of the main ways white blood cells cross the blood-brain barrier is through the interaction of the aforementioned adhesion molecules. VCAM-1 plays a crucial role in the adhesion mechanism on ECs that permits T cells to pass through the blood-brain barrier. Several studies have demonstrated that T cells use a4-integrin to bind to the endothelial ligand VCAM-1 on inflammatory cerebral arteries, and that inhibiting VCAM-1-a4-integrin interactions prevents circulating T lymphocytes from migrating into the brain.

PHYSIOLOGICAL TRANSPORT MECHANISMS

One of four transport mechanisms—passive diffusion, carrier-mediated transport, adsorptive-mediated transcytosis, or receptor-mediated transport—allows substances to flow through the blood-brain barrier. Only the previously described lipid-soluble tiny molecules are capable of using the transport process known as passive diffusion. Lipid-mediated diffusion allows these molecules to freely move across the blood-brain barrier. Since the size restriction and the requirement to be lipophilic are unusual properties, there aren't many known compounds that employ this transport mechanism.

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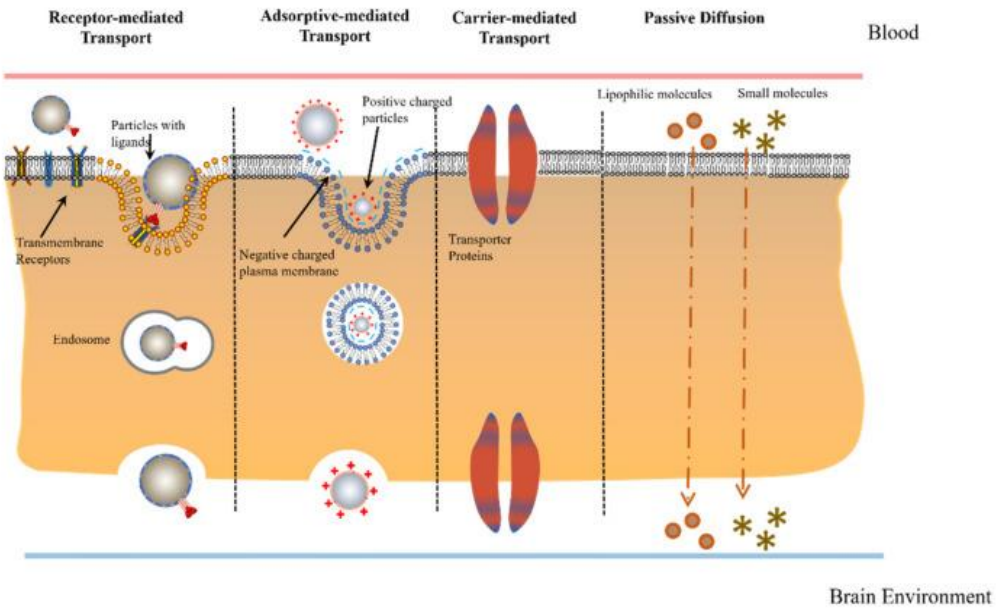

Figure: Physiological transport mechanisms crossing the BBB.

One of the most widely used transport methods is carrier-mediated transfer. Through the appropriate transmembrane proteins on the cell membrane, substances enter the endothelial cells. Glucose transfer by glucose transporter type 1 (GLUT1) is one example. GLUT1 actively transports glucose, mannose, and galactose across the blood-brain barrier after recognizing them. The transfer of phenylalanine via the large neutral amino-acid transporter type 1 (LAT1) is another illustration. Phenylalanine and 10 other major neutral amino acids can be transported across the blood-brain barrier by LAT1. To a lesser degree, it can also carry some neutral amino acids. LAT1 has also been utilized in medicine delivery systems. Parkinson's disease medication L-DOPA can also effectively pass the blood-brain barrier through LAT1.

The electrostatic interaction between the negatively charged cell membrane and the positively charged ligands causes adsorptive-mediated transcytosis (AMT). It is unidirectional from the blood to the brain and is mediated by clathrin-dependent endocytosis. The other most prevalent transport mechanism is receptor-mediated transport (RMT). Transcytosis of the ligands is mediated by peptide receptors on the cell membrane rather than a transmembrane transporter. Without exporting into the brain parenchyma, this system facilitates the movement of blood to the brain, brain to blood, and blood to brain capillary endothelium.

VIRAL DISRUPTION MECHANISM

Many viruses, including the rabies virus, human immunodeficiency virus-1 (HIV-1), and Japanese encephalitis virus (JEV), can infect the central nervous system (CNS) by different pathways in addition to the physiological transport systems. These infections can result in severe neurologic disorders. A brief overview of flavivirus, coronavirus, and other neurotropic viruses is given, along with a review of Table 1 and a discussion of their potential disruption mechanisms. Viral-induced CNS disorders are both caused by and

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impacted by BBB disruption [11]. Research into these virally induced BBB breakdown processes could help create new BBB-breaking techniques.

Table

Viral disruption of the BBB and its effects on BBB transportation.

Virus	Causative agent	Effects on CNS
Flaviviridae	Hepatitis C virus (HCV)	Human brain endothelial cells express functional receptors that support HCV entry and replication; HCV infection promotes endothelial permeability and cellular apoptosis.
	West Nile virus (WNV)	Increase activity and mRNA expression of matrix metalloproteinases (MMP) 9 in mouse brains; a Trojan horse mechanism.
	Japanese encephalitis virus (JEV)	Increase MMP9 expression in a reactive oxygen species (ROS)-dependent manner.
	Dengu Virus	Mediated via the release of histamine by a virus-induced cytokine.
	Zika Virus	Downregulation of occludin and claudin-5 levels. A cell-type-specific paracellular pathway to cross the placenta monolayer.
coronavirus	SARS-CoV-2	Spike protein S1 binding to ACE2 . Much higher affinity.
	HCoV-OC43	Neuronal retrograded (olfactory bulb) and hematogenous pathway May have neuronal degeneration .
	HCoV-229E	Invasion via the circulation of bloodstream . Neuro-invasive under immune-suppressed environment.
	SARS-CoV	ACE2 receptor. Both hematogenous route and olfactory bulb
Other viruses	HSV	Bloodstream and neuronal route. Up-regulate MMP2 and MMP9 and disrupt BBB
	Rabies virus	Rabies virus glycoprotein as brain-targeted ligand andthe nicotinic acetylcholine on neuronal cells as receptor
	MAV-1	Stimulate an innate host response to induce BBB disruption Possible invasion by a Trojan horse mechanism via monocytes
	Theiler's murine encephalomyelitis virus	Induce acute encephalitis with alterations in tight junction protein expression .

Some flaviviruses, including the Zika virus, Dengu virus, Japanese encephalitis virus, and West Nile virus (WNV), are thought to infiltrate the central nervous system (CNS) by a variety of methods. Flaviviruses are important emerging human infections. The

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experimental models have demonstrated the breakdown of the blood-brain barrier during flavivirus infection. Investigations are underway to determine the invasion processes, which are thought to be diverse. Brain microvascular endothelia and brain endothelial cells have been found to have Hepatitis C virus (HCV) entry receptors, which facilitate the virus's entry and reproduction. By upregulating the expression of matrix metalloproteinases 9 (MMP9), JEV and WNV infiltrate the central nervous system.
This protein contributes to BBB failure by cleaving the tight junction proteins occludin and claudin-5 and degrading the basement membrane.
Furthermore, two wild-spread coronaviruses that have been shown to be neuro-invasive and neurotropic are HCoV-OC43 and HCoV-229E. Under immune-suppressed conditions, HCoV-229E can primarily infect the central nervous system (CNS). This neuro-invasion of the virus is mostly dependent on bloodstream circulation, which facilitates the movement of infected monocytes and macrophages to the CNS. However, in addition to the hematogenous pathway, HCoV-OC43 penetration may also be neural retrograded.
Glutamate excitotoxicity and neuronal degeneration may result from the virus's enhanced cytokine production, which may begin in the olfactory bulb and spread to the cortex and hippocampus. Additionally, a preliminary investigation revealed that HCoV-OC43 RNA could be found in infected mice's central nervous systems and would remain there for a year.
With 29,903 bp, SARS-CoV-2 is a SARS-like single-stranded RNA coronavirus that shares a high degree of genetic similarity with both bat coronavirus RaTG13 (97%) and SARS-CoV (79.5%). Spike glycoproteins (S-proteins) on the viral surface can attach to the cell membrane and cause infection of host cells, just like other coronaviruses like SARS-CoV. Human angiotensin-converting enzyme 2 (hACE2), which is expressed in the lungs, heart, kidneys, intestines, and brain cells, is highly favored by the S-proteins of SARS-CoV and SARS-CoV-2, according to recent research. However, SARS-CoV-2 has a roughly 10- to 20-fold higher affinity and shares distinct binding sites when it interacts with the ACE2 receptor.
A common zinc metallopeptidase that has been shown to be expressed in both the cardiovascular and non-cardiovascular regions of brain nuclei, ACE2 may be able to control blood pressure. Because of its strong affinity for ACE2, this virus may be able to penetrate and infect CNS cells through hematogenous or neuronal retrograde dissemination. In addition to the symptoms like fever, dry cough, and exhaustion, this virus can also induce headaches, anosmia, dysgeusia, seizures, acute myelitis, and even disturbances of consciousness. Random
Additionally, SARS-CoV-2 was found in brain tissue in certain instances, suggesting that the virus may be involved in the central nervous system. Panciani et al. also explained SARS-CoV-2's CNS invasion using the three-phases paradigm.
The model comprised
(i) neuro-invasion through the olfactory nerve or circulation,
(ii) immune-mediated CNS injury;
(iii) reduced viral load by CNS clearance.

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The coronavirus that caused the SARS outbreak, SARS-CoV, is another that can cause neuro-invasive illness. It is known that SARS-CoV can infect monocytes, macrophages, and dendritic cells after entering the central nervous system (CNS) through the hematogenous pathway.

In both human and animal models, SARS-CoV has been shown to spread to the central nervous system. The virus has been detected in the sera and CSF fluids of two individuals, and intranasal infection in transgenic mouse models expressing hACE2 demonstrated the virus's presence in the central nervous system and its dissemination through the olfactory bulb.

Other viruses that are thought to be neurotropic and have a significant impact on the central nervous system include the rabies virus and the herpes simplex type 1 virus (HSV-1). The glycoprotein of the rabies virus, a highly neurotropic RNA virus, may have a high specific affinity for the neuronal cell adhesion molecule, the low-affinity nerve growth factor receptor, and the nicotinic acetylcholine receptor (nAchR) on neuronal cells. The presence of these receptors or co-receptors has complicated cell infection.

Numerous processes, including retrograde axonal transport, nAchR-mediated transcytosis, and clathrin- and caveolae-mediated endocytosis, were hypothesized to be involved in the viral entry into neuronal cells. HSV-1 is a double-stranded DNA virus that is neurotropic. Like other neurotropic viruses, it can induce neurodegeneration by invading the central nervous system (CNS) through both the circulation and neurons. Furthermore, there would be an increase in MMP in the extracellular matrix, particularly MMP2 and MMP9, which might cause the BBB to be disrupted and result in edema and bleeding.

These viruses' modes of infection can be divided into the following categories: cell-associated virus transport (viruses infect or are carried by blood circulating cells, which undergo blood-to-tissue transmission); passive diffusion (viruses passively diffuse between endothelial cells); endothelial cell infection (viral tropism is compatible with endothelial cell infection and virus replication in endothelial cells allows for virus release on the basolateral membrane of the endothelium, thus releasing infectious viral particles toward the adjacent tissue); and virus transcytosis (endothelial cells are not infected but nevertheless take up circulating viral particles into non-degradative endosomal vesicles). cross-migration between endothelial cells. These CNS entrance points are not exclusive of one another and can change based on the infection or immunological environment. In the actual model, certain viruses might employ many pathways, if it is possible.

BLOOD BRAIN BARRIERS AND CNS DISEASES

The prevalence of CNS disorders has been rising globally, yet the BBB has significantly hampered the development of targeted therapies for prevention. For the treatment of CNS disorders, numerous nanomaterial-based approaches have been developed to get beyond the BBB. The BBB is also discussed, as is the potential for the nanomaterials to target CNS disorders such as Alzheimer's, stroke, Parkinson's, brain tumors, autism, and schizophrenia. demonstrating the central nervous system disorders linked to blood-brain barrier disruption. Because tailored drug delivery is necessary to reach the precise

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location of action in the brain, nanotechnology has been discovered to play a crucial role in treating the following CNS illnesses.

. After the drug molecule is trapped with the nanomaterials, it will effectively reach the site by attaching to the blood, which should follow the penetration from the brain barriers according to the illness pathophysiology and the medication's mechanism of action.

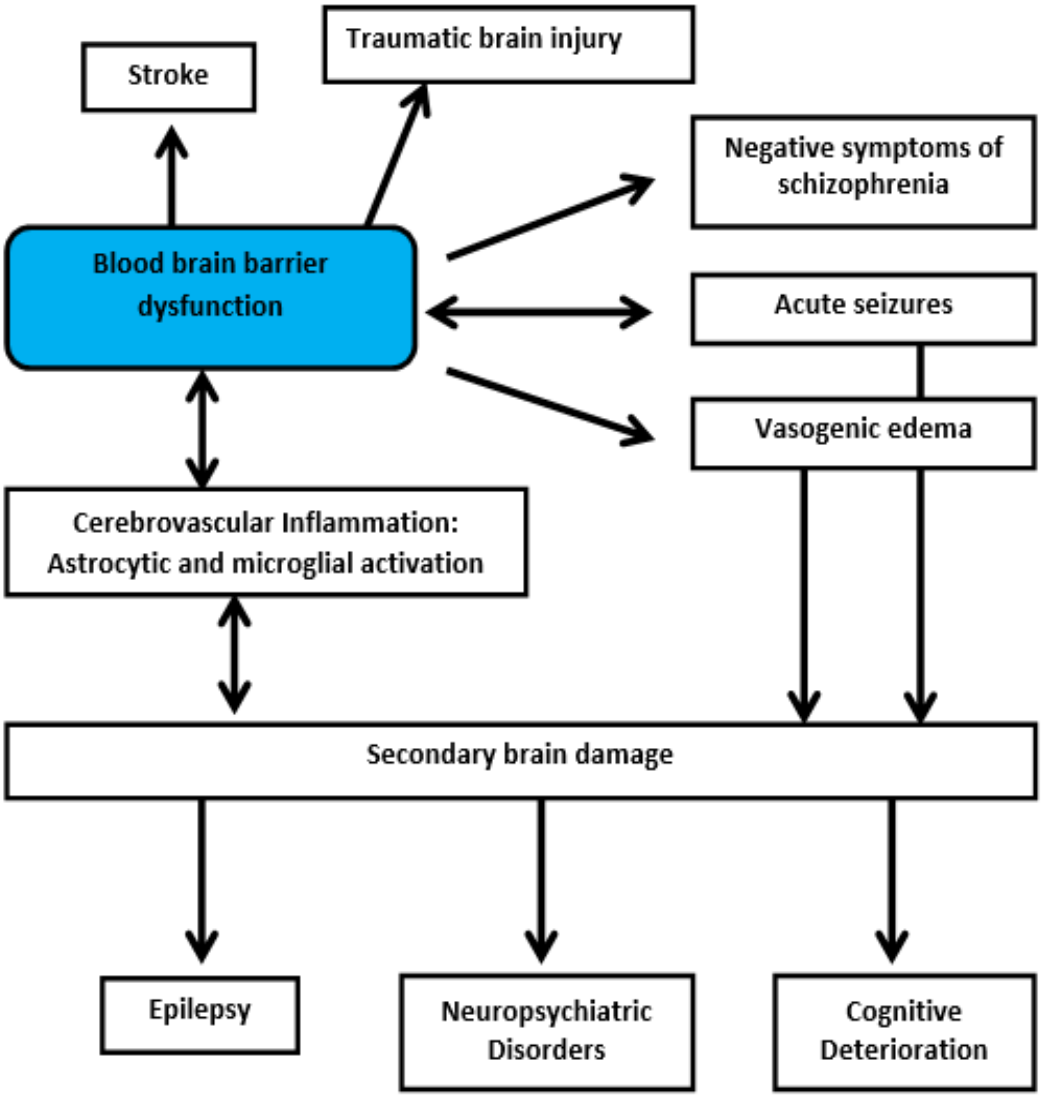

Figure : Overview of Blood brain barrier associated with CNS disorders Role of Blood Brain Barriers in Various CNS Disorders

1. **ALZHEIMER'S DISEASE**

Alzheimer's disease (AD) is characterized by progressive loss of synaptic and neuronal function, atypical angiogenesis, brain hypo-perfusion, neurovascular inflammation, and altered blood-brain barrier transport of Alzheimer's neurotoxin amyloid peptide (A) between blood and brain, all of which may start or contribute to a circularity of the disease process. Alzheimer's disease is largely influenced by the BBB. According to the neurovascular theory, one of the primary causes of an elevated amyloid load in the brain and the sign of Alzheimer's disease is a decline in the BBB's ability to remove Aβ.

Regarding pericytes, astrocytes, and microglia, the blood-brain barrier (BBB) keeps circulating blood components apart from neurons and preserves the chemical makeup of

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the neuronal "milieu," or the appropriate and consistent environment that neurons maintain in the brain. This is also necessary for the proper operation of neuronal circuits, synaptic transmission, synaptic modifications, angiogenesis, and neurogenesis in the adult brain.

2. PARKINSON DISEASE

The comorbidities linked to the disruption of the blood-brain barrier that causes parkinsonism include physiological conditions such as astrocyte inflammation, T-leukocyte infiltration, and microgliosis in the affected person's brain. These conditions are related to the permeability of the blood-brain barrier and the loss of dopaminergic neurons. Additionally, the release of numerous pro-inflammatory cytokines, such as TNF-α, IL-1β, and interferon-γ, as well as the high production of ROS and NO in the microglia and astrocytes of these PD patients, which are believed to be linked to BBB impairment. Lewy bodies, which are made of α-synuclein and protein inclusions, are seen in neurons that have selectively degenerated dopaminergic neurons in substantianigra, which results in dopamine depletion in the striatum.

The difference in albumin ratios in the parkinsonian brain has shown a correlation between the pathology course and progressive BBB damage. Additionally, there are some correlations between vascular modifications, cerebral blood flow deficiencies, and the loss of BBB integrity in the striatum and substantia nigra of PD patients.

3. STROKES

The most prevalent kind of stroke, known as an ischemic stroke, is characterized by a blockage of blood flow to a portion of the brain because of a thrombus or blood clot, cerebral edema (swelling of the brain), which can cause the blood-brain barrier to break down and endothelial cell tight junctions to reassembly. This leads to a 60% one-year patient survival rate because the brain is deprived of blood flow during the stroke episodes because of a hemorrhagic stroke caused by a bleeding vessel, or ischemic stroke caused by a blood clot.

The pathophysiology of this condition shows that both hemorrhagic and ischemic strokes result in oxygen and nutrient deprivation, which causes brain cell death, neuronal dysfunction, and ultimately patient death. In addition, during an ischemic stroke episode, the blood-brain barrier has a brief opening period that can last anywhere from minutes to hours, followed by a refractory interval, after which the BBB may reopen over a period of hours to days. Therefore, edema development, endothelium activation, leukocyte recruitment, cytokine and ROS production, and a reduction in cerebral damage through blood resupply are all directly linked to the reopening of the blood-brain barrier.

Drug delivery in this stroke condition should take into account the compromised tight junctions, the early and late BBB opening while utilizing the BBB-opening time window, and the receptors expressed on the endothelial cells' luminal side that may be useful for nanoparticle BBB-crossing.

4. BRAIN TUMOUR

As the most common primary brain tumor, glioblastoma (GB) is a diverse group of primary and metastatic neoplasms in the central nervous system (CNS) with a very bad prognosis and a very low patient survival rate. The study of brain tumor therapy has

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advanced because of the difficult characteristics of the complex and diverse molecular biology, which causes patients exposed to the same treatment methods to have varying prognoses.

The term "primary brain tumors" (PBT) describes cancers that start and spread inside the brain. The development of a metastatic brain tumor begins when a primary cancer that initially affects other parts of the body invades the central nervous system (CNS) by causing inflammation or by interacting with any carcinogen that is spread by primary cancer, such as lung cancer, breast cancer, colorectal cancer, renal cell cancer, or melanomas outside the CNS. Therefore, because of the blood brain barrier's intricate and vital structural makeup, anticancer agent-loaded nanomaterials can be transported across the BBB.

is still a major obstacle in the treatment of brain tumors, and the characteristics and design approaches of nanoparticles (NPs) mostly depend on the kind of disease, stage of development, and location of infected tissue.

5. PSYCHOSIS

The pathogenesis of numerous CNS illnesses is largely influenced by altered blood–brain barrier function, with psychosis being the most common disorder linked to a number of comorbidities. The endothelium of brain microvessels impacted by nearby cells forms the blood–brain barrier, which serves a number of vital purposes that are related to the illness state in psychosis. In addition to providing the brain with oxygen and nutrients like glucose, amino acids, and other precursors of neurotransmitters, the endothelium also eliminates waste materials and significantly limits the permeability of infections and extremely poisonous and neuroactive substances. Tight connections between neighboring cells limit the diffusion of polar solutes through the intercellular gap, which is regarded as a paracellular channel, at both the blood–brain barrier and the choroid plexus.

The pathophysiology of psychosis associated with the blood–brain barrier or the neurovascular unit can include changes in the expression of drug transporters and ion channels on endothelial cells and glia, increased extravasation of plasma proteins and leakiness of tight junctions, increased adhesion and transmigration of leucocytes, and up-regulation of luminal adhesion molecules. The following new approaches are proposed to investigate the role of the blood-brain barrier in psychosis:

Using dynamic contrast-enhanced MRI to quantify blood-brain barrier permeability in vivo

PET ligands (such as 2-amino-[3-^{11}C] iso-butyric acid) for measuring blood–brain barrier permeability in vivo Models of the blood-brain barrier created in vitro using patient-induced pluripotent stem cells assessment of peripheral antibodies to CNS-restricted antigens (such as anti-S100B antibodies) as a sign of persistent disruption of the blood–brain barrier Evaluation of how altering genetic loci linked to psychosis affects the formation and function of the blood-brain barrier in animal models extensive multicenter research with sizable sample sizes and analysis of correlations between risk factors for psychosis and indicators of rupture of the blood-brain barrier

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Combining serum levels of S100B with magnetic resonance spectroscopy measurements of potential cerebral metabolites is one example of how to integrate and identify blood–brain barrier integrity markers across many modalities.

DRUG LOADED NANOCARRIES ACROSS THE BBB

Numerous research examining the effectiveness and capacity of nanomaterials as medication carriers to traverse the blood-brain barrier have been published in recent decades. To get around the BBB, inorganic nanomaterials including CdSe/ZnS quantum dots, gold NPs, and silica NPs have been created. Both silica and gold nanoparticles are thought to be biocompatible and have demonstrated size-dependent transport efficiency when passing across the blood-brain barrier, with the efficiency significantly declining with increasing size.

In the meantime, when employing quantum dots as cargo across the blood-brain barrier, their cytotoxicity should be taken into account. To increase their biocompatibility, surface modification techniques like PEGylation should be used. Because of their high degree of physical and chemical plasticity and adjustability in degradation, both synthetic and natural polymeric-based nanomaterials, including hydroxyl polyamidoamine (PAMAM), poly(D, L-lactide-co-glycolide) (PLGA), and chitosan, demonstrate their promise as drug carriers. Furthermore, lipid-based NPs, like liposomes, have demonstrated a high drug-loading capacity and comparatively low toxicity due to their amphiphilic phospholipid bilayer structure.

Transferrin, lactoferrin, glucose, and glutathione polyethylene (PEG)-modified liposome NPs have been shown to be successful methods for enhancing BBB permeability. Therefore, working with these materials to improve BBB transportation is quite promising. This section reviews and discusses the various physiological transcytosis mechanisms that underlie the utilization of nanoparticles as medication delivery vehicles.

CARRIER-MEDIATED TRANSCYTOSIS

Brain capillary endothelial cells constitute the blood–brain barrier, a dynamic contact that regulates the flow of various chemicals between the blood and the brain. This barrier has multiple transporter systems that actively and selectively permit the passage of desired molecules, including endogenous substances and nutrients like peptide, amino acid, and glucose, which are essential for brain function and metabolism, in addition to being able to block the majority of drug molecules. Numerous carrier-mediated systems, including the glutathione transporter, the monocarboxylic acid transport system (MCT), the large neutral amino acid transporter (LAT), and the glucose transporter (GLUT), can carry these molecules.

Clearly designing and synthesizing novel compounds to imitate the nutritional analogues with high affinity to the transporters is the first step in a strategy to manipulate carrier-mediated transcytosis and penetrate the blood-brain barrier. In order to cross the blood-brain barrier, these molecules are then made to conjugate as ligands on the surface of drug carriers. However, this approach is heavily reliant on the medication's well-designed structure because it is difficult to use carrier-mediated transcytosis to pass the blood-brain barrier by merely attaching the drug to another nutritional analogue molecule. The movement of a medication across the blood-brain barrier using hexose-

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related transporters has garnered interest recently. outlines the carrier-mediated transcytosis-based drug delivery method that was built.

Nanomaterial Based BBB Crossing Mechanism

Although the BBB is necessary to preserve the distinct neuro-parenchymal milieu, it also acts as an impenetrable barrier for a variety of therapeutically significant medications due to the penetration factor of these active drug ingredients. Drugs designed to work in the central nervous system (CNS) can be injected directly into the CNS using invasive procedures if avoidance is limited, or they can be administered systemically if they can cross the blood–brain barrier (BBB). There is a distinct permeation process of blood brain barriers with regard to their crossing pathways, as illustrated in the picture, despite the fact that this barrier is made up of several cell types, including endothelial cells, pericytes, astrocytes, and microglial cells.

There are two types of BBB crossing mechanisms based on nanomaterials:
1) invasive mechanism;
2) non-invasive mechanism,

where the invasive mechanism requires physical opening of the blood-brain barrier and transports the nanomaterials across the BBB via a paracellular pathway. The invasive mechanism, also known as the paracellular mechanism, includes the local delivery strategy and the temporary BBB disruption strategy. Similar to the non-invasive method, the transcellular pathway—also referred to as the transcellular mechanism—is used to transfer the nanomaterials over the blood-brain barrier while the BBB remains intact.

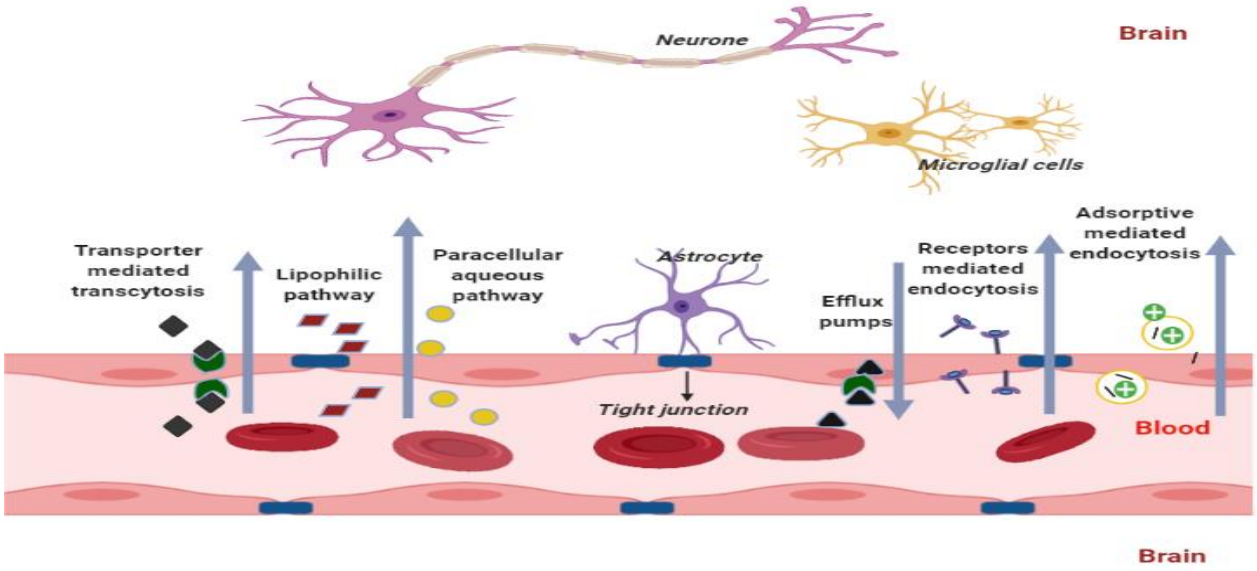

Figure: Permeation mechanism of blood brain barrier

FACTORS AFFECTING NANOPARTICLE PERMEABILITY

With the growing use of nanomaterials for disease treatment, particularly as drug delivery vehicles, the field of nanomedicine has advanced quickly in recent years. There are four primary steps in the design of nanodrug carriers. The primary physical characteristics of nanocarriers are their size and shape, surface charge, surface modification, and chemical makeup (pH, lipophilicity, and biodegradability). Both their

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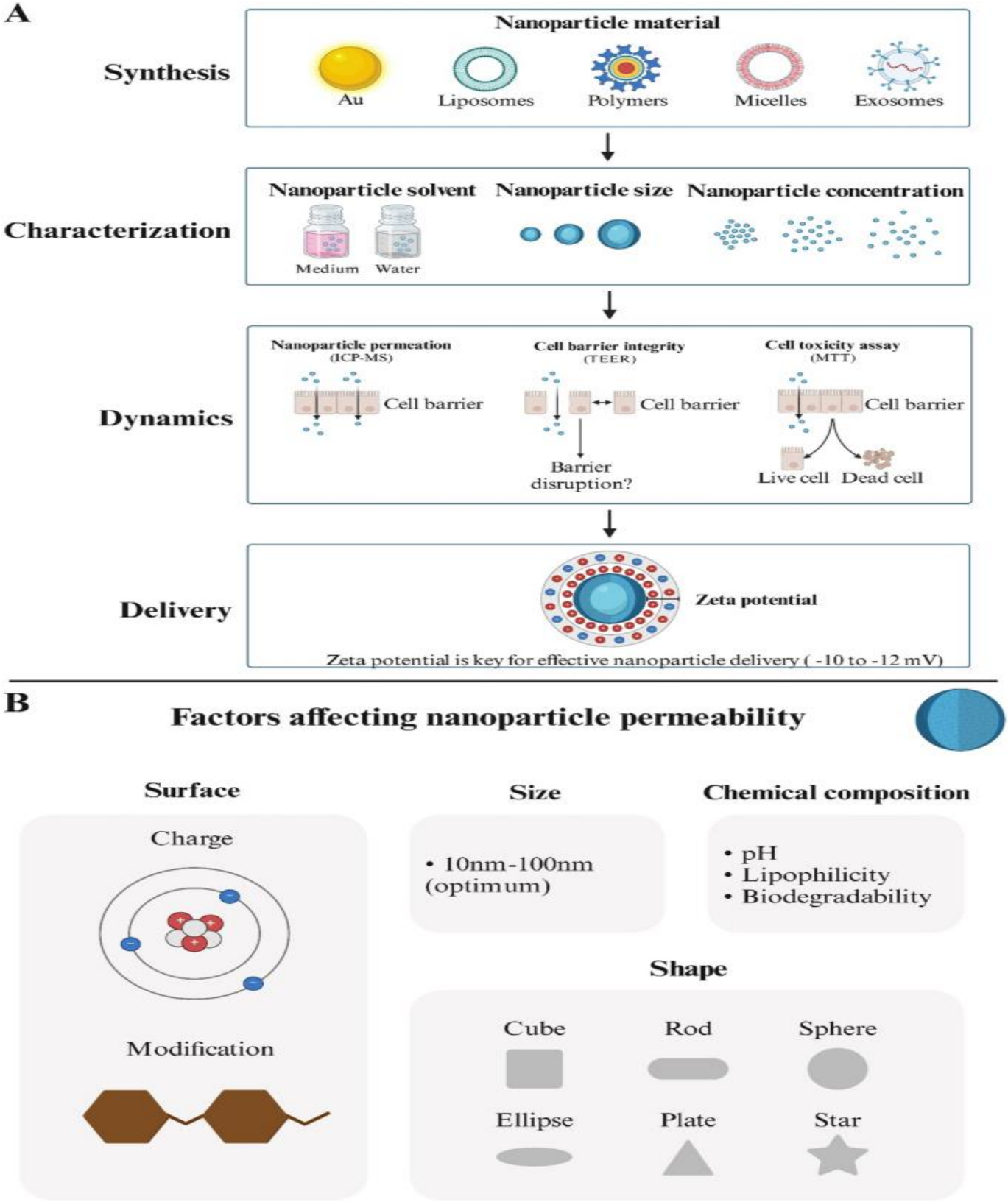
pharmacokinetic characteristics and the variety of biomedical applications depend heavily on these attributes.



The subject of nanomedicine has rapidly developed in recent years due to the increasing usage of nanomaterials for disease treatment, especially as drug delivery vehicles. The design of nanodrug carriers involves four main processes. Size and form, surface charge,

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surface modification, and chemical composition (pH, lipophilicity, and biodegradability) are the main physical attributes of nanocarriers. These qualities are crucial for their pharmacokinetic properties as well as the range of biological uses they have.

Size and shape

One important aspect affecting a nanoparticle's capacity to cross the blood-brain barrier is its size. According to studies, they are more permeable to the BBB the smaller they are. Liver filtration, on the other hand, is more effective in removing nanoparticles smaller than 5 nm. The BBB effectively prevents nanoparticles bigger than 200 nm from passing through. Therefore, research aiming at medication transport across the BBB frequently uses nanoparticles with a diameter of 10–100 nm. It is not removed by renal filtration, but it also increases permeability to the blood-brain barrier.

Furthermore, after passing through the blood-brain barrier (BBB), which makes up around 20% of the brain's volume and is typically about 20 nm wide, nanoparticles have to make their way into the extracellular area of the brain. Larger nanoparticles would therefore be constrained by the brain's extracellular space. However, using an in vitro blood–brain barrier model based on μHuB, Nowak et al. tested the permeability of various sizes of carboxylated polystyrene nanoparticles to the BBB and discovered that 200 nm NPs were 10 times more permeable than 100 nm. This demonstrates that although smaller nanoparticles are generally more likely to breach the blood-brain barrier, this is not always the case. Since the size characteristics of various nanoparticles are influenced by their structure, distinct nanomedicine carriers should be the focus of size design.

Likewise, the form of the nanoparticles has a critical role in the BBB penetration. Nanoparticles are typically spherical, but they can also be shaped as rods, cubes, ellipses, and plates. Rod-shaped nanoparticles collect more in the brain than spherical ones because they stick to the brain endothelium more easily. The nanoparticles' biodistribution, capacity to pass through endothelial cells, and clearance rate are all influenced by their form. Fu and others.

thoroughly assessed how up-conversion nanocrystals' physical aspect ratio affected their cellular uptake characteristics and discovered that those with an aspect ratio of two had the best cellular internalization efficiency and were significantly less harmful to cells. This implies that the application and design of nanodrug carriers depend on NPs of various forms.

Chemical composition

The BBB is composed of extremely lipophilic endothelial cells. Lipophilic nanoparticles can therefore more effectively traverse the blood-brain barrier and effectively transport medication molecules into the brain parenchyma. Lipid nanoparticles have recently been used by researchers to develop a variety of medicine delivery methods for the brain. For instance, liposomes, noisomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). In order to regulate pharmacokinetics and affect the drug release rate of nanoparticles, their biodegradability is essential. This improves the nanoparticles' biocompatibility, avoids pharmacological side effects, and lessens needless intracerebral drug accumulation.

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The pH of the nanoparticles is also determined by their chemical makeup, which affects the BBB's permeability. Weakly basic medicines primarily exist in a non-dissociative state at a plasma pH of 7.4, and they are more readily transported across the blood–brain barrier by nanocarriers. Consequently, the permeability of certain nanoparticles to the blood-brain barrier, as well as their level of biocompatibility and long-term effectiveness, will be directly influenced by their chemical makeup.

Surface charge

The surface charge is another important component that controls the permeability of nanoparticles to the BBB. Surface charge influences how nanoparticles interact with endothelial cells and are absorbed by peripheral brain regions in the bloodstream. Positively charged nanoparticles have been demonstrated to be more readily absorbed by cells than neutral or negatively charged ones. Compared to positively charged nanoparticles, neutral nanoparticles are roughly 100 times less permeable. Positively charged nanoparticles can pass through the blood-brain barrier more easily because endothelial cells have a higher concentration of negatively charged proteoglycans. Neutrally charged nanoparticles, on the other hand, can quickly deliver medications to sick locations and diffuse more quickly throughout the brain.

Reactive oxygen species, which can damage cells and cause necrosis or apoptosis, can be produced by positively charged nanoparticles. Positively charged nanoparticles were also more readily absorbed and cleared by macrophages. Therefore, it is conceivable to balance reduced biotoxicity with improved BBB permeability by carefully altering the surface charge of the nanoparticles. Chen et al. modified the surface of mesoporous silica nanoparticles (MSNs) to create a range of MSNs with varying charges. According to experiments, negatively charged MSNs may be able to transport medications across the blood-brain barrier (BBB) without the need for ligand/receptor protein interactions or outside stimulation. Poly amidoamine and poly ethylenimine (PEI)
(PAMAM), both positively charged polymers, increase the permeability of the blood-brain barrier but are harmful to cells such as neurons and red blood cells. In conclusion, altering the surface charge of nanoparticles can enhance their capacity to transport medications into the central nervous system through the BBB's natural transport mechanism.

Surface modification

When improving the nanoparticles' inherent physicochemical qualities is insufficient to provide the desired effect, another method to control their permeability to the BBB is surface modification or conjugation of active functional groups to the nanoparticles. To improve their targeting capabilities, nanoparticles can be functionalized with ligands or active functional groups because of their enormous specific surface area. Yin et al. created a drug-carrying nanoparticle based on black phosphorus (BP) and pterostilbene (Pte). It was modified by using polydopamine (PDA), which led to the creation of the BP-Pte@PDA delivery system.

By selectively breaking down and releasing the medication in ischemic brain areas, this delivery method considerably lowers infarction, enhances neurological function, and prevents apoptosis. Using lactoferrin and musk, Qi et al. produced a dual-modified liposome that efficiently penetrated the blood-brain barrier and improved docetaxel's

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brain-targeting effectiveness, leading to a more successful treatment for gliomas. In order to reduce their toxicity, Wiwatchaitawee et al. combined polyethylene glycol (PEG) with PEI or PAMAM. They then assessed biodistribution in a healthy mouse model, which was found to be extremely safe and active. These illustrations demonstrate how surface-modified functionalized nanoparticles can effectively treat a range of illnesses and have improved biocompatibility and drug-carrying capabilities.

NEW STRATEGIES TARGETED FOR NANOPARTICLES TO ENHANCE BRAIN DRUG DELIVERY

The presence of blood-brain barriers, which restrict entry into the brain and shield it from infections or dangerous substances, may make it impossible for pharmaceutical compounds to reach the brain while in circulation. These barriers permit the diffusion of only a small percentage of substances and stop even tiny molecules from diffusing into the brain. Because of their unique characteristics, medicinal chemicals are often excluded from this barrier, even though many necessary molecules can permeate past it. Furthermore, these nanoparticles get beyond this barrier, travel via several pathways to neurons, and provide the necessary theranostic effects on the damaged brain. Because they can pass through the narrow connections between the vessel's endothelial cells and allow the medicine to cross the blood-brain barrier, a variety of nanoparticles have been utilized to accomplish so. Drug transfer through the endothelial cell layer can also be facilitated by NP endocytosis and transcytosis. By conjugating or coating ligands, NPs can target particular cells. Then, using these ligands, they can move from the circulation across the blood-brain barrier by receptor-mediated transcytosis. Lipid nanoparticles' lipophilic characteristics allow them to penetrate the blood-brain barrier and enter the brain via a variety of transport pathways, including receptor-mediated endocytosis, transcellular and paracellular pathways, and transcytosis.

The image illustrates the most recent nanotechnology methods that improve drug delivery in the brain. It is recognized to be both transcellular and paracellular. Depending on the size and lipophilicity of the substances, solutes are transported through the cell membrane by passive diffusion. Drugs are transported unidirectionally from the blood to the brain by carrier mediated transport (CMT), also known as carrier-mediated inflow. Diffusion can be either passive or active, depending on the situation. With the aid of carrier systems or transporters, it primarily plays a key role in the movement of numerous vital polar molecules into the brain, including glucose, amino acids, and nucleosides.

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Figure: Development of new strategies based on NP's technology for drug delivery to the brain

By conjugating the material with ligands like lactoferrin, transferrin, and insulin, receptor-mediated transport primarily facilitates the passage of macromolecules like proteins and peptides across the blood-brain barrier. Despite this, it is a significant transport pathway that is primarily of relevance for the delivery of drugs to the central nervous system. Similarly, conjugating the particle to cationized ligands or peptides like albumin causes adsorptive mediated transport, a form of endocytosis. Electrostatic interaction between a positively charged material (cationized peptide-albumin) and negatively charged spots on the surface of brain endothelial cells (BECs) (such as glycoprotein) is the general principle of AME, which is dependent on transport.

Given the current state of drug delivery system development, which aims to prevent disorders of the central nervous system and blood-brain barrier, newer approaches are being developed to target these brain-associated disorders. To achieve this, nanocarriers must be good candidates for drug delivery across the blood-brain barrier (BBB) and have a number of distinctive features that can be summed up as follows. particle with a diameter of less than 100 nm; biocompatible, biodegradable, and non-toxic; stable in blood, meaning that proteins don't opsonize it; BBB-targeted (i.e., endocytosis mediated by receptors, ligands, and cell surfaces); non-inflammatory and without neutrophil activation; no aggregation of platelets; avoiding the endothelium and reticulo-reticular systems; extended period of circulation; economical and scalable in terms of the production process; Adaptable to proteins, peptides, nucleic acids, or tiny molecules; controlled drug release or the ability to modify drug release profiles.

CONCLUSION

The effectiveness of many modern technologies is still poorly understood or has not been subjected to clinical examinations, despite the fact that a better understanding of the structure and function of the blood-brain barrier and how its malfunction is subsequently linked to neurological diseases may aid in the development of contemporary diagnostic and therapeutic techniques that target the BBB for serious diseases.

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More research and challenges are therefore required to concentrate on creating targeted drug delivery systems as a future strategy that supports combinatorial or nanotherapy to eliminate or alter this barrier in pathological conditions like brain tumors and brain stem cell carcinomas.

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