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Blood-Brain Barrier: A Comprehensive Review of Its Structure, Function and Role in CNS Diseases

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ABSTRACTS

The blood-brain barrier (BBB) is a highly specialized and dynamic structure that plays a crucial role in maintaining the homeostasis of the central nervous system (CNS). Composed of endothelial cells, pericytes, and astrocytic end-feet, the BBB regulates the exchange of molecules between the bloodstream and the CNS, thereby protecting the brain from harmful substances and maintaining its internal environment. Despite its importance, the BBB is often compromised in various neurological disorders, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis, leading to increased permeability and the infiltration of toxic substances into the brain. This review aims to provide a comprehensive overview of the structure, function, and regulation of the BBB, as well as its role in CNS diseases.

KEYWORDS: Blood-brain barrier, Neurovascular unit, Central nervous system, Endothelial cells, CNS Diseases.

1. INTRODUCTION

The most important organ in humans for regulating body functions is the brain [1]. The interface between the blood and the brain is known as the blood–brain barrier (BBB). It shields the brain from chemicals and cells that may otherwise infiltrate it. The brain's capillary endothelial cells are where the BBB is found [2]. The microvascular endothelium, astrocytes, basement membrane, pericytes, and neurons that are physically close to the endothelium make up the blood–brain barrier (BBB). The functional neurovascular unit includes all of these components [3]. Vascular endothelial cells (ECs) comprise the inner layer of blood vessels [4]. The blood-brain barrier (BBB), an active permeability barrier and transport system formed by endothelial cells (ECs) of brain capillaries, plays a crucial role in regulating the brain fluid milieu. The blood–brain barrier (BBB) preserves brain homeostasis and shields the brain environment

from circulating viruses and poisons [5]. The paracellular route is sealed off by intricate tight junctions (TJs) between brain ECs made up of occludin (Ocln) and claudin (CLDN) family proteins [6]. Additionally, brain endothelial cells express large numbers of active efflux transport proteins such as P-glycoprotein (P-gp), Multidrug Resistance Protein-1 (MRP-1), and Breast Cancer Resistance Protein (BCRP), and they have limited alternative transport pathways (such as fenestra, trans endothelial channels, and pinocytotic vesicles). Other enzymatic components of the BBB also contribute to brain protection [6]. Actin, the principal cytoskeleton protein responsible for preserving the endothelium's structural and functional integrity, is connected to membrane proteins by cytoplasmic proteins [7]. The central nervous system (CNS) and circulation are actively interfaced by the blood-brain barrier (BBB), which limits the free flow of various chemicals between the two compartments and is essential for maintaining the CNS's homeostasis [8]. The BBB's primary physiological function is to keep the brain tissue's microenvironment steady [9].

Paul Ehrlich and Edwin Goldmann published the first reports of evidence supporting the existence of a barrier between the central nervous system (CNS) and the systemic circulation in 1885 and 1913, respectively. Stern and Gaultier first used the term "blood-brain barrier" (BBB) in 1922 [10]. The CNS compartment's nutrition delivery and metabolite removal are managed by the blood-brain barrier. In CNS diseases, where barrier permeability typically rises dramatically, the BBB is also crucial [11]. Most compounds' octanol/water partition coefficients can be used to predict their BBB permeability [12]. All areas of the brain have the blood-brain barrier (BBB), apart from those that control the autonomic nervous system and the body's endocrine glands, where blood arteries allow blood-borne chemicals to diffuse across the blood vessels [13].

The lack of a fully non-invasive, temporary, and regionally selective brain drug delivery mechanism limits the current treatments for neurological and neurodegenerative illnesses. The blood-brain barrier makes it very challenging to provide medications to the brain [14]. Nearly all macromolecular medications and most small-molecule medications are unable to pass through the blood-brain barrier. Therefore, it is crucial to design drug delivery systems that can efficiently transfer therapeutic drugs into the central nervous system (CNS) to treat CNS disorders. Since CNS disorders, such as Parkinson's and Alzheimer's diseases, strokes, and brain malignancies, are the primary causes of disability worldwide, they have been receiving increasing attention [15].

2. HISTORY

Humphrey Ridley was the first to show that small cerebral arteries had lower permeability than peripheral microvessels near the end of the 17th century, which is when the blood-brain barrier (BBB) originally emerged. The revelation that the brain is separate from the bloodstream was rediscovered by Paul Ehrlich in 1885. Max Lewandowski verified Ehrlich's findings and called this novel idea bluthirnschranke, which is the German term for the blood-brain barrier [16]. Ehrlich contended that the poor affinity of the CNS for the dye was the reason for these phenomena. However, Goldmann challenged this claim, because the brain was colored but not the surrounding tissues when the same dyes were injected into the subarachnoid space. Expanding on these investigations, Lina Stern and others conducted tests in which they injected blood and various vehicles into the brain parenchyma. The outcomes of these dye experiments led Stern to coin the phrase "blood brain barrier" and propose that it serves a physiological purpose in maintaining brain homeostasis [17]. Lewandowsky coined the term "bluthirnschranke," or "blood brain barrier," while researching the restricted brain penetration of potassium ferro cyanate [13]. The groups of Raff and

Brightman independently presented the first convincing evidence of astrocytes' role in the development and upkeep of the blood-brain barrier in 1987 [18].

3. STRUCTURE COMPONENTS OF BLOOD BRAIN BARRIER

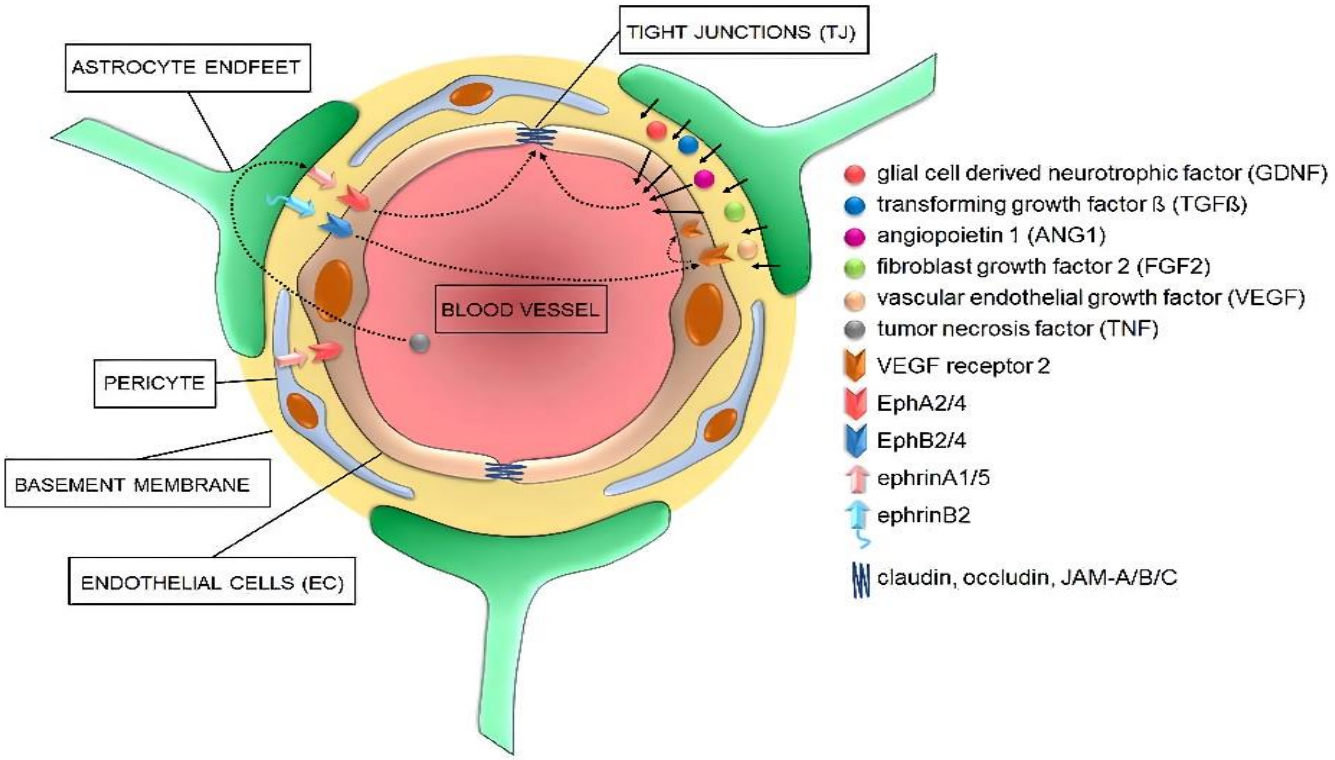

Figure 1: Blood Brain Barrier Structure [19]

Tight connections hold endothelial cells together to form the BBB, a specialized substructure of the circulatory system. The vessel's inner wall is lined with luminal and abluminal membranes, which serve as a permeability barrier. The BBB's limited permeability to big and ionic compounds is characterized by the combination of these two membranes and tight junctions [14]. Endothelial cells (ECs) which make up the blood vessel walls, and mural cells, which reside on the EC layer abluminal surface, are the two primary cell types that make up blood vessels [20]. Endothelial cells, mural cells (i.e., vascular smooth muscle cells and pericytes), the basement membrane, glia cells (astrocytes and microglia cells), and neurons typically make up the neurovascular unit (NVU), which together support the integrity of the blood-brain barrier [4].

3.1. ENDOTHELIAL CELLS

The BBB's central anatomical unit is made up of CNS endothelial cells [16]. The brain's blood arteries are lined with a continuous monolayer of specialized endothelial cells [21]. Because of its unique characteristics, the brain microvascular endothelium can tightly regulate the flow of ions, chemicals, and cells between the blood and the brain. Tight junctions (TJs), which connect the ECs of the CNS microcapillaries, limit the paracellular movement of polar solutes [22]. Increased mitochondrial content, low pinocytotic activity, and the absence of fenestrations are characteristics of BBB ECs [23]. BMVECs, or brain microvascular endothelial cells, are found where the blood and brain meet [3]. The following structural elements of BMVEC are in charge of these special qualities: (i) Adherent junctions (AJ) made up of cadherins, catenins, vinculin, and actinin; (ii) Tight Junctions (TJ) made up of TJ proteins [occludin,

claudins, zonula occludens (ZO)-1, ZO-2, ZO-3, cingulin, AF6, 7H6; and (iii) Junctional adhesion molecules [3]. The transporters that CNS ECs express fall into two major types.

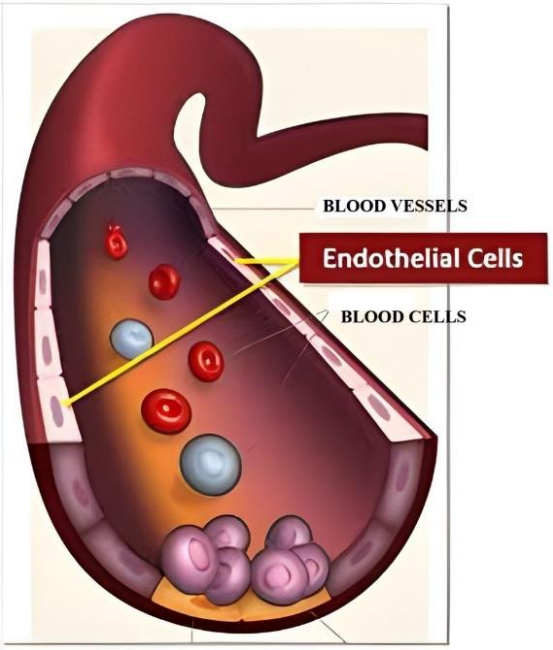

Figure 2: Endothelial Cells [24]

Efflux transporters are the first; they are polarized to the luminal surface and carry a wide range of lipophilic substances toward the bloodstream that would otherwise diffuse over the cell membrane. The second are extremely specific nutrient transporters that help move particular nutrients into the central nervous system (CNS) and remove particular waste products from the CNS into the bloodstream [20]. In addition, the BBB endothelium contains more mitochondria than other vascular ECs. This is essential for the production of ATP, which supports the BBB's metabolic work capability and provides the ion gradient needed for certain transport processes [22]. Percent of Coverage -100% [25].

3.2. ASTROCYTES

Astrocytes are essential for preserving the integrity of the BBB and controlling its activity. They produce pro- or anti-inflammatory mediators that influence BBB permeability and peripheral immune cell infiltration [4]. Glial cells called astrocytes wrap more than 99% of the BBB endothelium. The configuration of endothelial cells and astrocytes is influenced by one another; their interactions cause and alter the BBB's formation as well as the distinct BMVEC phenotype [3]. TGF-b, GDNF, and BFGF are among the inducing factors produced by astrocytes that have been found to be involved in the induction and modulation of the BBB phenotype [23]. Astrocytes are essential for the CNS's defence, homeostasis, and regeneration. Both neurodegenerative disorders and brain aging are influenced by the loss of astroglia function and reactivity [23]. The vascular tube is nearly entirely encased in the end feet of the basal process, which also contain a distinct array of proteins such as aquaporin4, dystrophin, and dystroclycan [20]. On the other hand, pro-inflammatory cytokines that function as neurotoxins and inflammatory modulators can be secreted by activated astrocytes, which can harm neurons [22]. In the past, astrocytes were divided into two categories: i) Fibrous astrocytes, which are located in the less vascularized white matter, and ii) Protoplasmic astrocytes, which are found in the well-vascularized grey matter. Astrocytes coat the vasculature, make contact with neurons, and physically divide synapses or nodes of Ranvier in both grey and white matter regions [21].

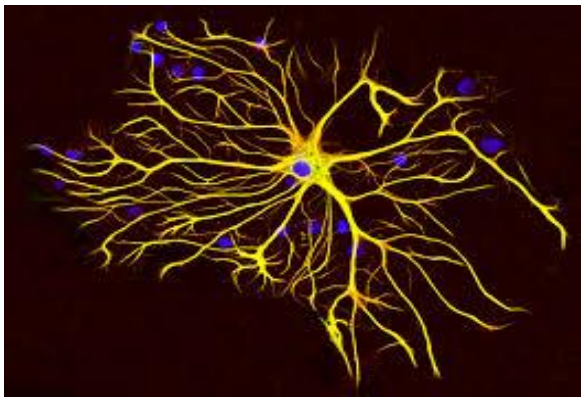

Figure 3: Astrocytes [26]

In addition to feeding neurons, astrocytes also manage the BBB, remove and recycle neurotransmitters, govern immunological responses, and maintain the extracellular potassium balance [27].

3.3. PERICYTES

Between endothelial cells and astrocyte end feet are pericytes, which are a part of the neurovascular unit [1]. Mural cells called pericytes are found abluminal to the ECs and encase blood vessels. They are embedded in the basement membrane [16]. Around capillary walls, flat, undifferentiated, contractile connective tissue cells called pericytes form [3]. They regulate the establishment of tight junctions between cerebral endothelial cells, brain angiogenesis, BBB differentiation, and microvascular structural stability [9]. Pericytes exhibit wide variations in morphology, gene expression, and function. They have distinct structures and vessel coverage at the capillary, pre-capillary, and post-capillary vascular zones, demonstrating their morphological variability along the vascular tree [21]. The hypothesis of pericytes involvement in junctional permeability is supported by the disruption of the blood-brain barrier brought on by their separation [13]. CNS pericytes to ECs ratio: 1:3-1:1 is the percentage of coverage - 22 32% [25].

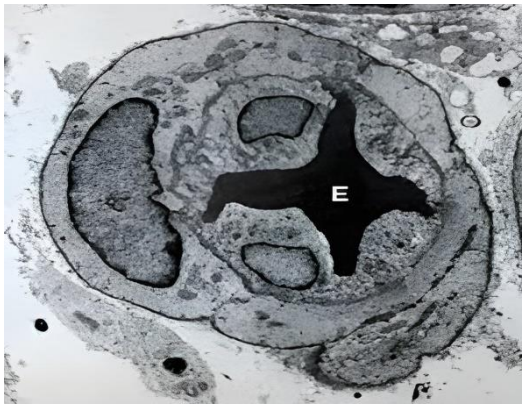

Figure 4: Pericytes [28]

3.4. NEURONS

The developmental impact of neurons on the BBB phenotype is poorly understood. On the other hand, there is some evidence that neurons can control blood vessel activity in response to metabolic demands by triggering the expression of BMVEC-specific enzymes [13]. Tight control of the microcirculation and the tissue it supplies is necessary due to the high degree of neuronal activity and the dynamic nature of their metabolic requirements. Although functional neuroimaging showed a strong correlation between blood flow and regional brain activity, the precise mechanism is still unclear. Pathological diseases that reduce cerebral blood flow or perfusion pressure can cause breakdown of the blood-brain barrier [3].

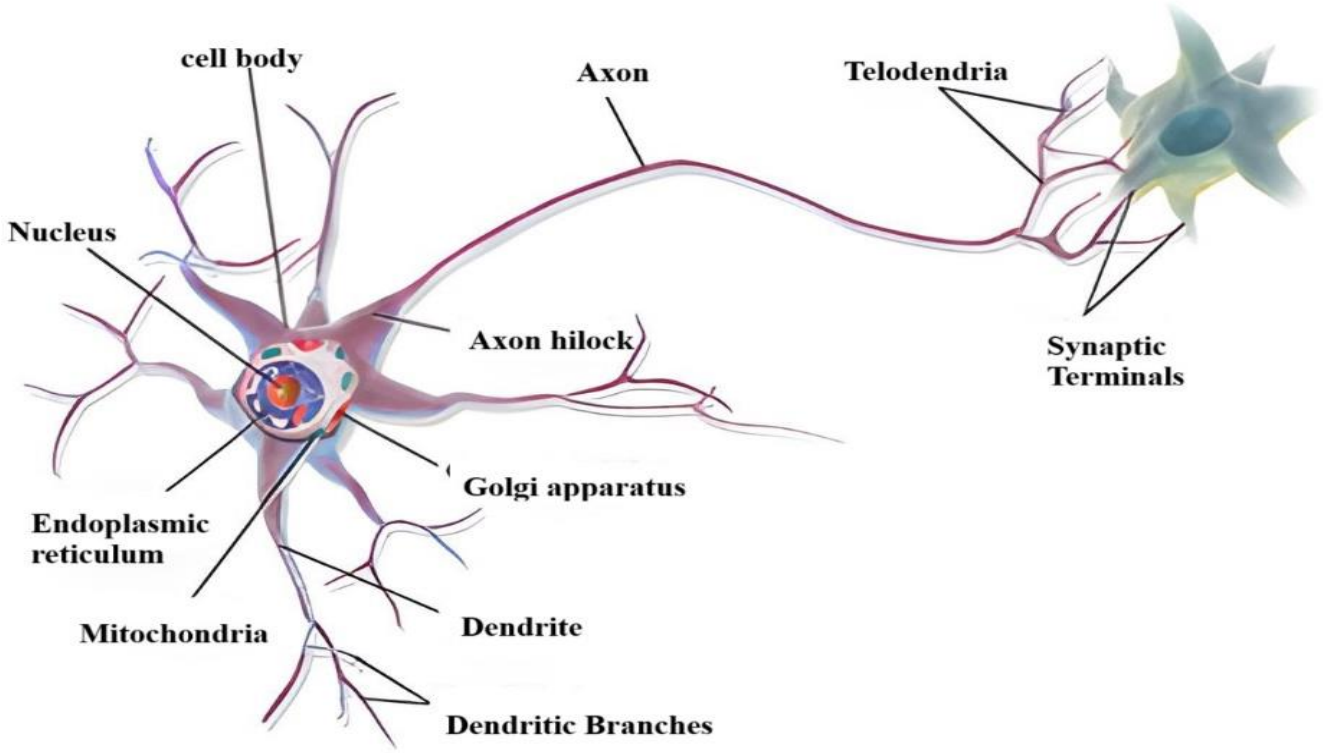

Figure 5: Neurons [29]

More recently, there has been evidence in the literature suggesting neurons, through a process called neurovascular coupling, modified substrate supply across the BBB and controlled cerebral blood flow. This process is crucial for the establishment and maintenance of the BBB. According to other research, neuronal activity influences the production and function of the BBB efflux transporter, and neurons interact with ACs to affect BBB function [16]. When a neuron is near a brain capillary, its soma, axon, or dendrite may contact with pericytes and endothelial cells through the basement membrane [1].

Percent of Coverage – NA [25].

3.5. MICROGLIA

Long-lived resident immune cells of the central nervous system, microglia make about 12–16% of the brain's total cell population. They are the principal cell type that helps to maintain neuronal homeostasis by protecting the brain from immunologic insults [1]. Because they monitor the immediate surroundings and alter their phenotype in response to homeostatic disruptions of the central nervous system, microglia are crucial to immunological responses of the central nervous system. These cells can be classified as either resting or active microglia. While cells have long, thin processes and small bodies when they are at rest, active microglia change from long to short processes to take on a phagocytic shape [13]. Since postnatal ablation of microglia cannot result in BBB damage, further research is necessary to understand the physiological effects of microglia at the BBB [16]. Microglia, which are derived from hematopoietic progenitors that migrate from the yolk sac into the CNS parenchyma, serve as the brain's primary Défense mechanism outside of the blood-brain barrier and are essential for innate immune responses in the central nervous system [30]. Percent of Coverage - 12-16% of the total brain population [25].

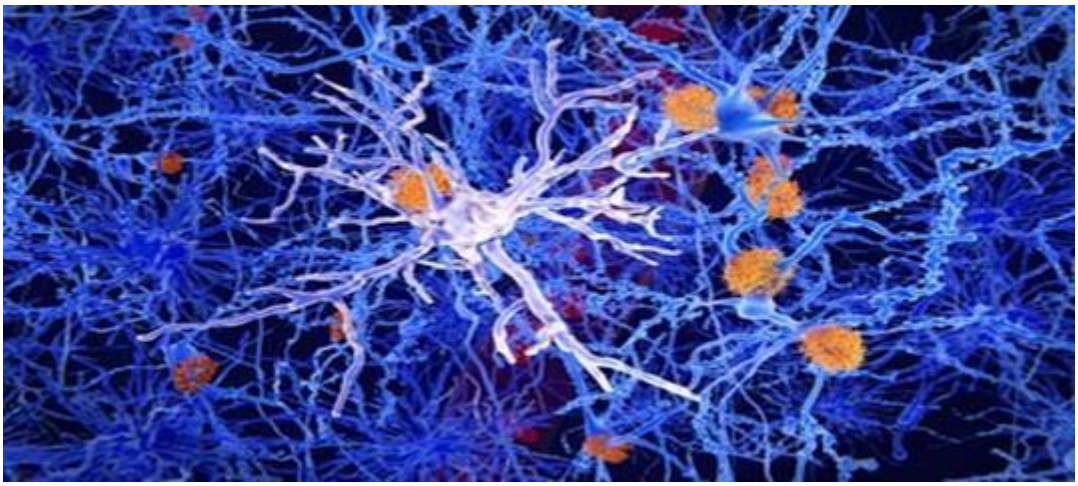

Figure 6: Microglia [31]

3.6. BASEMENT MEMBRANE

Different cell types, including ECs, ACs, and PCs, synthesis and deposit the basement membranes (BM), which surround the vessels and are a distinctive acellular component of the NVU and a highly dynamic constituent of the BBB [16]. One crucial component of the BBB is the basement membrane. By engulfing pericytes and encircling BMVEC, it secures the cells and creates a link with the neighbouring brain resident cells [13]. The inner vascular basement membrane and the outer parenchymal basement membrane are the two types of basement membranes (BM) that encircle the endothelial vascular tube [32]. A noncellular basement membrane that is composed of important proteins, including collagens, laminins, nidogens, perlecan, and agrin, as well as type IV isoforms, fibrillins, vitronectin, fibronectin, elastin, and heparan sulphate, is what envelops the cerebrovascular endothelial tube [21,1]. Integrins are involved in cell attachment to the basal lamina [9]. When this brain basement membrane protein is disrupted, pericytes change from a resting to a contractile phenotype. This turns into decrease levels of aquaporin 4 in astrocytic end-feet and the expression of TJ in endothelium [30].

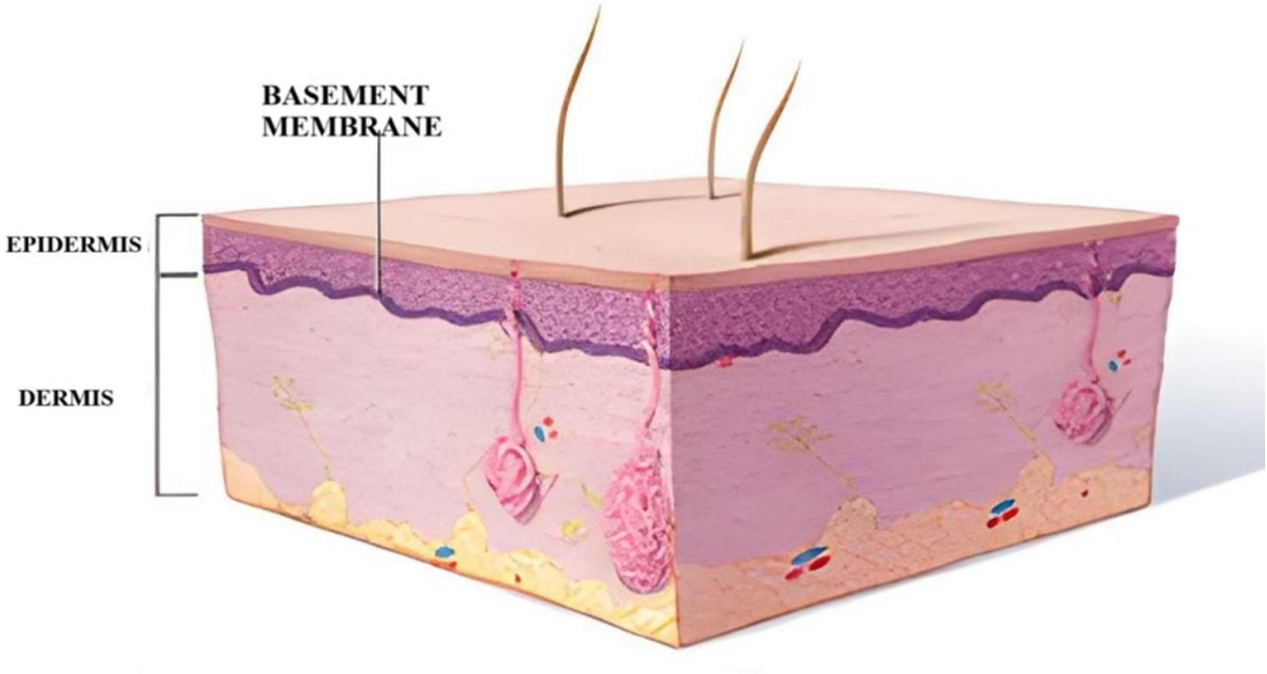

Figure 7: Membrane Basement [33]

3.7. TIGHT JUNCTION

The primary structures in charge of the barrier qualities are TJ [13]. The cerebral endothelial capillaries, which have tight cell connections, are where the blood-brain barrier (BBB) functions. The belt-like areas of adhesion between neighbouring cells are called tight junctions. Because of these connections, there is very little room between cells, which severely restricts paracellular transport. Transmembrane proteins such occludin, claudins, junctional adhesion molecule (JAM), or ESAM make up tight junctions [9]. TJs are cell adhesions made up of many transmembrane proteins that connect two cells' membranes via direct interaction through their extracellular components. The BBB's paracellular permeability is determined by the particular combination of TJ proteins, and CNS TJs are specialized in their molecular and structural P-face composition to form a high resistance electrical barrier [13].

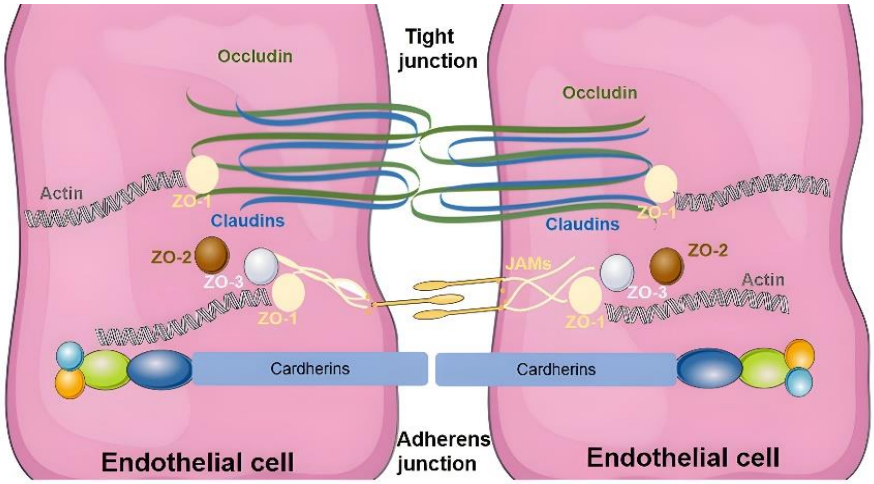

Figure 8: Tight Junction [34]

Sensitive markers of both normal and disrupted BBB functional states include occludin, claudin-5, and ZO-1 [35]. At the BBB, claudin-5 is by far the most common claudin. However, both claudin-1 and claudin-12 expression can be increased, and there are constitutive low levels of claudin-3. Certain claudins, like claudin-2, create ion or water-permeable holes, however the BBB does not seem to have them [36].

4. FORMATION AND REGULATIONS

Despite the fact that the ECs exhibit major BBB characteristics, significant transplantation research has demonstrated that these characteristics are controlled by interactions with the CNS microenvironment [20]. The gut endothelium can develop BBB-like characteristics in vivo with only transplanted CNS tissue, indicating that the neural microenvironment plays a part in BBB creation. When astrocytes are transplanted into adult rats' brain tissues, local ECs acquire barrier characteristics. A number of proteins released by astrocytes are enough to produce EC barrier characteristics both in vitro and in vivo. According to these findings, astrocytes may offer dynamic BBB regulation in response to particular stimuli, but they are not required for BBB development. Reactive astrocytes, for example, have been demonstrated to be essential for neurological illness BBB repair [37]. The time-period of BBB creation is determined by the cellular and molecular regulation of BBB development [38]. Apoptosis, branching morphogenesis, cellular proliferation and polarity, and the preservation of stem cells in an undifferentiated, proliferative state are all regulated by Wnt signalling [13].

5. MODES OF TRANSPORT ACROSS THE BBB

The active transport of particular solutes and metabolites into the brain is facilitated by a number of influx and efflux transporters that are expressed on the surface of CNS endothelial cells. Carrier-mediated transport via solute carrier transporters (SLCs), selective transport via ATP-binding cassette transporters (ABCs), vesicular trafficking by transcytosis categories into which transport across the BBB can be divided [39]. Lipid solubility is important because passive diffusion is the basic process by which lipid molecules are delivered across the blood-brain barrier. The method of lipidization is used to chemically change medicinal substances into a lipophilic state in order to get beyond this barrier. Lipid-soluble drugs that can cross the blood-brain barrier can be altered by adding lipid or functional groups [40].

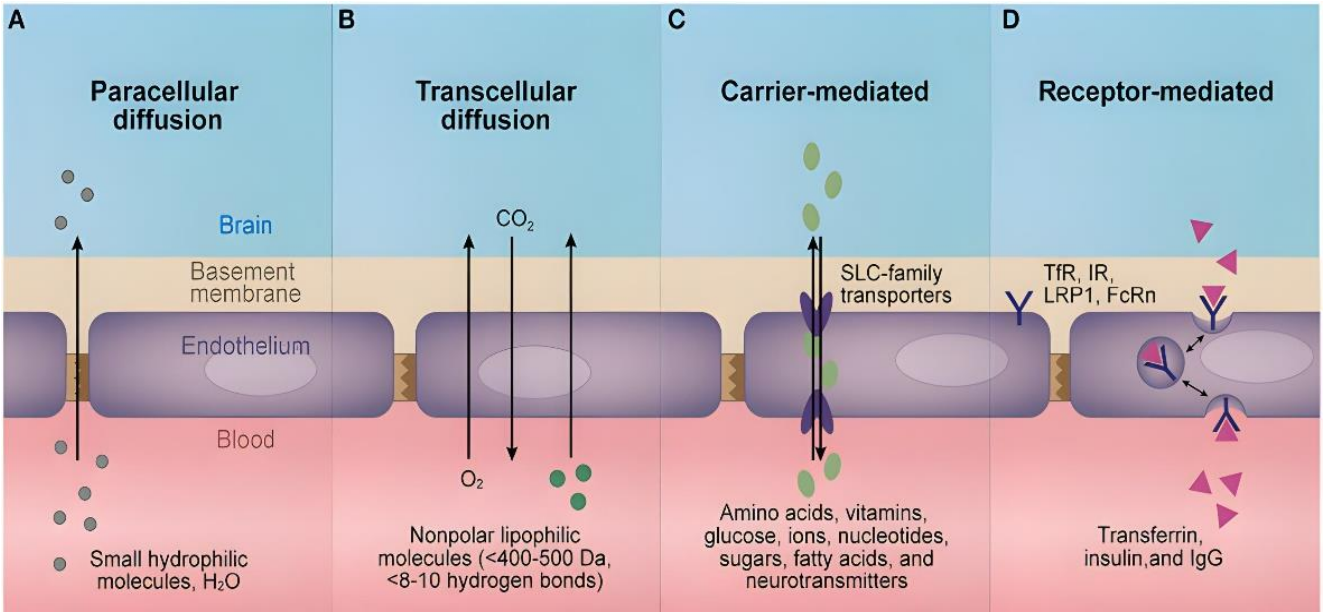

Figure 9: Representation of modes of transport across the BBB [41]

6.1. PASSIVE DIFFUSION

6.1.1. Paracellular Transport

Paracellular diffusion is the term used to describe movement between cells. Because of the presence of tiny tight junctions, the paracellular transport of substances across an intact blood-brain barrier is severely restricted. If they don't have the ability to be actively transported, hydrophilic compounds rely heavily on this mode of transportation. The diffusing molecule's concentration difference determines the rate of diffusion. Both sides of the membrane have the same concentration of diffusing molecules at equilibrium. This transport method has a permeability limit and is size-dependent [9]. Specialized TJ proteins effectively block the bulk flow of water and plasma-sourced solutes via the paracellular route, as well as the passive diffusion of lipophilic or low molecular weight substances and immune cell passage through the spaces between brain capillary endothelial cells [1].

6.1.2. Transcellular Transport

Simple diffusion, assisted diffusion, adsorptive mediated endocytosis (pinocytosis), receptor mediated endocytosis, and/or influx (and efflux) transporters at the blood-brain barrier are the several ways that transcellular transport takes place. The size and lipophilicity of the molecule are important for simple diffusion. The concentration differential on either side of the BBB determines the rate of diffusion, and at equilibrium, the concentrations on both sides of the membrane are equal. The rate of diffusion may become

blood-flow limited for substances that readily penetrate the blood-brain barrier [9]. Using receptor and carrier proteins found on the luminal and abluminal membranes of barrier type endothelial cells, the transcellular route transports chemicals in both directions by either energy-dependent or independent mechanisms. Additionally, macromolecules including albumin, immunoglobulins, and other proteins, as well as some non-lipid-soluble compounds with tiny molecular weights, are transported by fluid-phase and adsorptive endocytosis [1].

6.2. CARRIER MEDIATED TRANSPORT

Carriers and receptors found in the plasma membrane of the BBB's endothelial cells make up transporters. Carriers are membrane-restricted systems that are often used to move molecules with molecular masses under 500–600 Da and a fairly defined size. Since ATP drives the majority of these systems, they all have at least one intracellular ATP-binding domain. Others don't need ATP because they are equilibrating systems. These transporters' activity is sensitive to temperature, and increasing ligand concentrations can cause them to become saturated. Both competitive and noncompetitive inhibitors, as well as blocking their phosphorylation by protein kinases, can affect their function [42]. Carriers and receptors found in the plasma membrane of the BBB's endothelial cells can cause carrier-mediated transport to occur in the opposite direction of the concentration gradient [9]. Molecular biology of transport mediated by carriers across the blood-brain barrier [32].

6.3. RECEPTOR MEDIATED TRANSPORT

The transport of circulatory substances such as transferrin, low-density lipoproteins, leptin, insulin, and insulin-like growth factor into the brain is mediated by receptor-mediated transcytosis, the primary pathway for trafficking molecules across the blood-brain barrier. However, aging is associated with a shift to ligand-nonspecific caveolar transcytosis [1]. Through receptor-mediated endocytosis/transcytosis (RME/RMT), chemicals can either enter the endothelium or cross it to enter the brain without the barrier's characteristics being compromised. The following steps make up the process: At the luminal (blood) side of the blood-brain barrier, the compound undergoes first endocytosis when a vesicle forms from the plasma membrane. It then moves through the cytoplasm of the endothelial cell, and in the event of transcytosis, it is exocytosed at the abluminal (brain) side of the brain capillary endothelium [22]. The neutral amino acid transporter facilitates carrier-mediated transport of L-DOPA, the traditional pseudo-nutrient, across the blood-brain barrier [43].

6.4. FACILLATED DIFFUSION

The availability of the assistance molecules limits the pace of diffusion in the case of facilitated diffusion. The increased concentration of diffusing molecules will not boost the rate of transport after all the helper molecules are saturated; rather, it will just lengthen the waiting line for the helper. Passive, or energy-independent, facilitated diffusion helps move materials including monocarboxylates, hexoses, amines, amino acids, nucleosides, glutathione, short peptides, across the blood-brain barrier [9].

6.5. ATP-BINDIMG CASSETTE TRANSPORTERS

Many medications may be less likely to enter the brain and more likely to exit the brain when ABC transporters, such as P-gp and multidrug resistance related proteins, are present. As a result, extensive study on drug transport to the brain is concentrated on them. Since it keeps blood-borne drugs from

entering the brain and makes it easier for them to leave the brain parenchyma, P-gp is a transporter for the development of the multidrug resistance phenotype [13].

7. NANOPARTICLES FOR DRUG DELIVERY ACROSS THE BBB

To increase NPs' BBB penetration proficiency, many tactics have been used. For cargo administration with high BBB penetration capability, one popular method is to control the Wnt/β catenin signaling generated by glial cells and decrease their binding to multiprotein receptor complexes on brain ECs [44]. Both invasive and non-invasive methods can be used to deliver medications to the brain. The employment of nanomaterials as a drug delivery system offers a varied way to providing medications, as the methodology may be modified to match the individual requirements of the drug delivery process. A variety of nanomaterials can trap, encapsulate, absorb, or adhere to drug moieties. Compared to other microparticles, nanoparticles or nanomaterials have the notable benefit of being able to be used for intravenous distribution [45]. Numerous nanoparticles, including poly (ethylene glycol), poly (lactic-co-glycolic acid), and others, have unique physicochemical characteristics and multifunctional modification, making them essential delivery systems for therapeutic medicines across the blood-brain barrier [44].

7.1. Applications of nanomaterials in delivering drugs across BBB

Nanomaterials that offer many benefits for the transport of chemotherapeutic drugs, including liposomes and micelles, have become viable weapons in cancer therapy. Because these nanocarriers have a hydrophilic shell and a hydrophobic core, they can dissolve insoluble medications [45]. Also, Numerous strategies have been developed to overcome the BBB, similar as medicine delivery systems, polymeric and solid lipid NPs (SLNs), solid lipid carriers, liquid chargers (LCs), microemulsions (MEs), and hydrogels [46].

Nanocarriers can passively target tumors and inflammatory regions by altering their surface, such as via PEGylation, which takes advantage of fenestrated vasculature and raises medication concentrations at the tumor location [45].

8. FUNCTION

The BBB can metabolize drugs and nutrients since it is an enzymatic barrier [47]. Through a variety of processes, the BBB is essential for maintaining brain nourishment. For water-soluble nutrients and metabolites that are vital to the nervous system, the blood-brain barrier has a low passive permeability [22]. Similar to their peripheral counterparts, brain capillaries primarily supply parenchymal cells, including neurons, with oxygen and nutrition while also eliminating waste products [1]. BBB disruption can result from dysfunction in any one of the intricate cellular and non-cellular components that work together to sustain BBB function. In vascular biology, ECs are crucial for preserving vessel wall integrity, permeability, and homeostasis as well as preventing thrombosis. Pericytes aid in maintaining ECs' TJs [4]. Through gene profiling of isolated CNS endothelial cells, genes that specifically control BBB integrity and function independently of CNS angiogenesis have been found [17]. Additionally, the BBB acts as a barrier to keep certain poisons in the blood from harming the central nervous system [22]. Taurine (2-aminoethanesulfonic acid) is believed to be involved in osmoregulation, neuromodulation, and central nervous system development. Dietary taurine is crucial for preserving its appropriate level due to its restricted biosynthesis [11]. Drugs and minerals can be metabolized by the BBB, an enzymatic barrier [48].

9. DYSFUNCTION

An imbalance of ions, transmitters, and metabolic products in the interstitial fluid brought on by BBB malfunction can lead to aberrant neuronal activity [27]. Multiple sclerosis, epilepsy, and stroke are among the conditions that cause BBB failure. While the incidence and degree of BBB breakdown are more debatable and the subject of emerging research in some disorders, such as Alzheimer's disease (AD), BBB dysfunction is a key component of the pathophysiology in many others. Ion dysregulation, edema, and neuroinflammation brought on by BBB disruption can result in neuronal malfunction, elevated intracranial pressure, and neuronal degeneration. But little is known about the mechanisms behind BBB malfunction and how it affects the development and course of illness or recovery [37]. BBB disruptions are caused by functional changes in the structural and cellular elements of the BBB. Tight junction expression, distribution, and the local microenvironment that may facilitate TJ opening, transport systems, enzymes, and basement membrane disruption are some examples of these changes. These changes may ultimately result in serum components and immune cell infiltration into the brain parenchyma, disturb CNS homeostasis, and harm the surrounding brain tissues [22].

10. REPAIR

Enhancing BBB integrity with glucocorticosteroid (GC) therapy is now the sole effective and most popular therapeutic strategy. The majority of knowledge on GCs' methods of action emerged in the setting of autoimmune illnesses, and they are typically used to regulate undesirable inflammatory responses. GCs have been demonstrated to help MS patients regain the integrity of their blood-brain barrier [27]. Vascular endothelial growth factors (VEGFs), which include VEGF-A, B, C, and D, are a well-known class of angiogenic factors. With the help of VEGF-specific receptors (VEGFR-1, VEGFR-2) VEGFs increase the permeability of newly created BBB and stimulate the migration and proliferation of endothelial cells [22]. The body's normal healing process may include the rebuilding of the blood-brain barrier, although this recovery is frequently insufficient or incomplete, particularly following severe insults such as ischemic stroke. The cells that make up the BBB itself, including astrocytes, pericytes, and endothelial cells, are the main players in the endogenous repair processes [48].

11. DISRUPTION

Many pathological situations and disorders, including stroke, diabetes, seizures, hypertensive encephalopathy, acquired immunodeficiency syndrome, multiple sclerosis, traumatic brain traumas, Parkinson's disease (PD), and Alzheimer's disease (AD), cause disruptions in the blood-brain barrier (BBB) [49]. Because albumin is toxic to astrocytes, its admission into the brain's interstitial space may be the source of the neuropathology that follows BBB rupture [43].

Pathophysiology of BBB Disruption	**Associated Diseases**	**Therapeutic Targets**
Upregulation of VEGF and Activation of VEGFR2	AD, PD, epilepsy, ischemic stroke	anti-VEGF antibody and VEGFR 2 inhibitor (e.g., SU5416)
Activation of endothelin receptors, ETA, ETB (Endothelial receptor A and B)	Stroke and epilepsy	Inhibition of ETA and ETB (e.g., S-0139, BQ788)

Downregulation of VE-Cadherine	MS, Stroke	Inhibition of miR-27a/VE by CD5-2; antibody against ICAM (Enlimomab)
Disorganization of adherens junctions	MS, Stroke	Stabilize the adherens junctions using sphingosine-1-phosphate (S1P)
Reduced expression of TJ proteins	Depression, Stroke, Stress	Induction of TJs protein expression. (e.g., antisense oligonucleotide for miR-501-3p, HDAC1inhibitor, MS-275-Entinostat)
Imbalance of AMP-activated protein kinase pathway	Stroke	Activation of AMP-activated protein kinase pathway by melatonin
Activation or upregulation of inflammatory cytokines e.g., Tumor necrosis factor (TNF-), IL-1, TNF-, IL-6	Stroke, TBI, Cognitive impairments, Seizures, MS	Inhibition of inflammatory cytokines (e.g., etanercept, anti-IL-6 antibody, and natalizumab)

Table 1. Neuropathology Of BBB [22].

12. CNS DISEASES

The number of people with CNS disorders has been rising globally, but the BBB has significantly hampered the development of treatments [15]. Diseases and pathophysiology have long been known to affect BBB permeability and/or function. Multiple sclerosis, Alzheimer's disease, AIDS, AIDS-related dementia, inflammation-like encephalitis and meningitis, hypertension, seizures, and psychiatric disorders are among the diseases that alter BBB permeability [42].

12.1. Alzheimer's Disease (AD):

The pathophysiology of AD has been linked to BBB damage, where the barrier integrity is adversely affected by high levels of Amyloid β deposition and accumulation [22]. An important area of ongoing research is the degree of BBB disruption in AD and its role in pathogenesis. BBB function in AD patients has been investigated using a number of methods, such as measuring blood/CSF albumin concentrations, staining postmortem brain tissue for serum components, and using several imaging modalities [37]. The rupture of the blood-brain barrier, impaired glucose transport, reduced cerebral blood flow, and increased capillary tortuosity with altered rheology are some of the potential processes linked to the cerebrovascular dysfunctions of Alzheimer's disease that have been documented [15].

12.2. Epilepsy

Epilepsy is a chronic disease, patients that undergo experimental BBB disruption with osmotic shock experience seizures, and seizures and epilepsy can result from conditions where the BBB is impaired, including infection, inflammation, stroke, and traumatic brain injury [37]. Investigations have documented the link between epilepsy and disturbance of the blood-brain barrier. One cause of epilepsy or one of its effects is disturbance of the blood-brain barrier. Research has indicated that seizures may result in a disruption of the blood-brain barrier. On the other hand, a wealth of evidence indicates that disturbance of the blood-brain barrier may cause epilepsy or worsen the illness [22].

12.3. Multiple sclerosis

Multiple sclerosis (MS) is a neuroinflammatory disease characterized by demyelination and immune cell infiltration of the central nervous system (CNS) by lymphocytes and macrophages [15]. The most frequent neuro-inflammatory demyelinating illness affecting the central nervous system (CNS) is multiple sclerosis (MS), which impacts both the white and gray matter. While cortical lesions are characterized by

demyelination and mild neuronal loss, white matter lesions are characterized by inflammatory infiltration, demyelination, gliosis, and axonal loss [50]. The activation of astrocytes that separate from the arteries is another factor contributing to neurovascular unit dysfunction in multiple sclerosis [39].

12.4. Stroke

In an ischemic stroke, the brain is not receiving blood during the stroke episode because of a bleeding vessel in a haemorrhagic stroke or a blood clot-induced vascular obstruction. Both haemorrhagic and ischemic strokes result in brain cell death, neuronal malfunction, and patient death due to oxygen and nutrient deprivation [15]. The time course of BBB failure during a stroke is biphasic [37].

12.5. Meningitis

The rupture of the BBB may improve the movement of different substances inside the brain by changing permeability and result in inflammation of the meninges. E. Coli can produce PDGF-B and ICAM-1 for both in vitro and in vivo models of meningitis, according to a recent study. Increases in PDGF-B and ICAM-1 may help break down the blood-brain barrier and cause neuroinflammation by attracting neutrophils or monocytes, respectively, and downregulating TJ proteins [22].

12.6. Parkinson’s disease

The pathogenesis of Parkinson's disease (PD) is primarily characterized by alpha-synuclein (α-syn) overexpression and neuron degradation, which impairs cognitive and motor function. As a result, a lot of PD treatments concentrate on giving molecules to fix these dysregulations [51]. It has been demonstrated that reactive gliosis is a typical astrocyte characteristic during BBB disruption, which may have consequences for astrocyte roles in both the development of Parkinson's disease and BBB protection [23]. Since Parkinson's disease (PD) also typically produces an excess of aggregated α-syn, comparable effects on astrocytes and, thus, on the function of the Brain capillary endothelial cells (BCEC) barrier may be anticipated in PD, where BBB integrity loss is also noticeable [52].

13. CONCLUSION

It can be concluded the blood–brain barrier is a functional system that may be considered as an organ where a variety of mechanisms and procedures operate both locally and across time. The BBB is an essential biological and cellular barrier that regulates the flow of chemicals into and out of the brain parenchyma, preserving the homeostasis of the CNS microenvironment. Several pathways that are triggered by different signals must be regulated for the BBB to develop. A complex structure in the central nervous system, the blood-brain barrier (BBB) carefully controls the flow of ions, chemicals, and cells between the central nervous system and the periphery. It preserves the healthy biochemical microenvironment and guards against harm to the brain. Nanoparticles for drug delivery of across the BBB is play an abundant role in treatment of CNS Diseases. The functions and dysfunctions of the BBB, neurological conditions that are either directly or indirectly linked to BBB disruption, and repairing the damaged BBB have all been discussed. Lastly, CNS diseases states may be induced or increased by NVU dysfunction.

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