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Blood Brain Barrier Dysfunction in Neurodegenerative Diseases: Molecular Mechanisms, Transport Systems, and Disease-Specific Alterations

Arzoo Rehman[1], Mubeen Riaz[1], Maham Zaheer[2], Anis Murtaza[3], Fariha Javaid[4], Najia Shabbir[5], Muhammad Saad Naeem[6], Mahzaib Jamil[3], Jaweria Noor[3], Hafiz Aamir Ali Kharl[7]

[1]College of Pharmacy, University of the Punjab, Lahore, Punjab, Pakistan.
[2]Department of Pharmacy, Lahore College for Women University, Lahore, Punjab, Pakistan.
[3]Faculty of Pharmacy, Capital University of Science & Technology, Islamabad, Pakistan.
[4]School of Biochemistry and Biotechnology, University of the Punjab, Lahore, Punjab, Pakistan.
[5]Department of Pharmacy, Iqra University H9 Campus, Islamabad, Pakistan.
[6]Department of Pharmacy, Faculty of Health & Pharmaceutical Sciences, University of Agriculture, Faisalabad, Punjab, Pakistan.
[7]Narcotics Forensic Laboratory, Ministry of Interior & Narcotics Control, Islamabad, Pakistan.

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Correspondence to: Hafiz Aamir Ali Kharl, Narcotics Forensic Laboratory, Ministry of Interior & Narcotics Control, Islamabad, Pakistan.
Email: aamirkharl43@gmail.com

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ABSTRACT

The blood-brain barrier (BBB) is a very specialized dynamic interface which maintains homeostasis in the central nervous system through tightly controlled molecular and cellular interchange between the blood and the brain. It is growingly recognized that BBB dysfunction is a rather acute and primary pathogenic factor of neurodegenerative diseases but not the result of neuronal death. This review summarizes existing information about the molecular pathways involved in the disruption of BBB in several of the most common neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. We pay attention to changes of endothelial tight junctions, pericyte degeneration, astrocyte malfunction, neuroinflammation, oxidative stress, and remodeling of the extracellular matrix that all undermine the integrity of barriers. Besides that, we also discuss disease-specific modifications in BBB transport systems including glucose transporters, ATP-binding cascade efflux pumps, receptor-mediated transcytosis routes, and the ion transport and clearance of toxins, which play a pivotal role in nutrient delivery, toxin clearance, and drug permeability. A clear comprehension of these molecular and transport changes in various conditions of neurodegeneration offers insight to the disease progressions and heterogeneity. Lastly, we comment on the early therapeutic interventions and drugs that are now being developed to repair BBB functionality or selectively regulate its transport characteristics with the BBB serving as a source of biomarker and as a potential therapeutic target in neurodegenerative disease.

1. INTRODUCTION

Different progressive disorder of nervous system, have destructive effects on motor functions that are very challenging, and these diseases include Huntington's Disease, Amylotrophic Lateral Sclerosis, Parkinson's Disease, and Alzheimer's Disease. These illnesses show similar fundamental molecular pathways including protein misfolding and oxidative stress (Ciurea et al., 2023). Parkinson's disease is defined by rigidity and rhythmic movements due to loss of dopaminergic neurons in the pigmented midbrain region. Alpha Synuclein, a protein that can fold incorrectly and accumulate inside neurons to create clusters known as Lewy bodies, is at the center of this decline (Jellinger, 2014). According to studies, alpha synuclein has "prion-like" feature that is defined as the innate structural plasticity, forming beta pleated sheet containing aggregates able to produce assemblage in neighboring compartments (Hijaz & Volpicelli-Daley, 2020). This clarifies the process underlying the Parkinson's disease spread through interconnected brain regions. Mitochondrial dysfunction is also included in the pathology of disease. PINK1 and Parkin genes become impaired that are involved in the control of the quality of mitochondria and this impairment diminishes the capability of cell to remove the battered mitochondria (Ge et al., 2020). This dysfunction also increases the oxidative stress that compromises the existence of dopamine producing neurons.

The amyloid beta (Aβ) peptide, plays central role in Alzheimer disease. Beta and Gamma Secretase enzymes

are used to break the APP to produce Aβ fragments. These fragments make aggregates together outside the cell that are considered markers of AD. TDP-43 is a protein that is assembled in motor neurons in almost all ALS cases. TDP-43 is often located in the nucleus, where it is essential for RNA processing (Sehar et al., 2022). But in ALS, it undergoes unusual changes and produces poisonous clumps in the cytoplasm. These changes result in loss of function of motor neurons. A gene called SODI gene undergoes mutation that results in mitochondrial pathology (Toader et al., 2024).

2. Physiology and Barriers of the BBB

2.1 Function and Protective role of the BBB

Neurovascular barrier properties changes due to factors like location and state of diseases. It is essential to comprehend these differences in order to create tailored delivery strategies (Furtado et al., 2018).

2.1.1 Blood–Brain Barrier (BBB)

Brain barrier cell-cell junctions combine with pericytes and astrocytic end feet to produce the BBB, an especially designed basement membrane. Because of this intricate structure, paracellular transport is restricted, necessitating specialized delivery strategies for CNS medications. In order to prevent xenobiotic entry, the BBB exhibits high level of efflux proteins while maintaining low intercellular flux (Grant et al., 2025). Through receptor mediated transcytosis, the three receptors- transferrin receptor (TfR), insulin receptor (IR) and low-density lipoprotein receptor related protein 1 (LRP1) support limited large molecule trafficking (Aragón-González et al., 2022). Receptor counts differ in separate cerebral regions and act as targets of controlled targeted delivery of medications.

2.1.2 CSF-Blood Barrier and Brain Clearance Pathways

Although the choroid plexus cell layer has strong epithelial connections that form another barrier to the cerebrospinal fluid (CSF), it also contains porous fenestrated capillaries. Because medication administered by means of brain spinal fluid can reach tissues surrounding the brain ventricles by mass flow pathways that completely avoid the protective brain barrier, this anatomical variation is therapeutically significant. Delivery techniques must adjust to these changes in pathways that impact medication stay and distribution because neurodegeneration impairs glymphatic clearance (Solár et al., 2020).

2.1.3 Disease-Specific Barrier Modulation

Neurodegenerative disorders inherently change barrier properties in the manner that can be targeted therapeutically, according to a novel theory in CNS delivery of drugs. High amyloid aggregation causes leaky zones in BBB in AD that enhanced the permeability of drugs. Similarly, by promoting the release of inflammatory messenger molecules, neuro inflammatory processes in MS and PD increase the accessibility of the BBB (Barchet & Amiji, 2009).

2.1.4 Physicochemical Constraints

For tiny compounds to have a therapeutic brain interaction, they must have molecular weight below 400 Da, a computed partition coefficient of 2-4, a PSA of below 70 Å2, no net charge. These limits are exceeded by macromolecules made up of proteins and RNAs, which demand distribution via carrier mediated mechanisms. These CNS focused modifications of Lipinski's "Rule of Five" explain why complicated neurotherapeutics have not been as successful in conventional medicinal chemistry (Yang, 2025).

3 Transport across the BBB

3.1 Passive diffusion

Usually, BBB can easily allow passive diffusion of many lipid-soluble molecules and entrance inside the brain. LogD (octanol/water) which is a partition coefficient used in calculating lipid solubility of a drug molecule at pH 7.4. The speed of drug entrance into the brain is generally dependent on its lipid solubility. LogD value helps in understanding of how unionized and ionized drug molecules behave in solution, unlike logP value which is concerned only to unionized drug species (Fong, 2015). Passive movement drug of small molecules inside the brain is also dependent on weight of drug molecules. The permeation of drug across CNS will not actively increase in accordance to the profile of drug's solubility in lipophilic phase as the molecular weight of drug is more than 400 Da. The drug's diffusion across the BBB actively reduces when the drug's molecular surface area goes from 52 A2 (of a drug molecule having molecular weight 200 Da) to the 105 A2 (of a drug molecule having molecular weight 450 Da) (Sweeney et al., 2018).

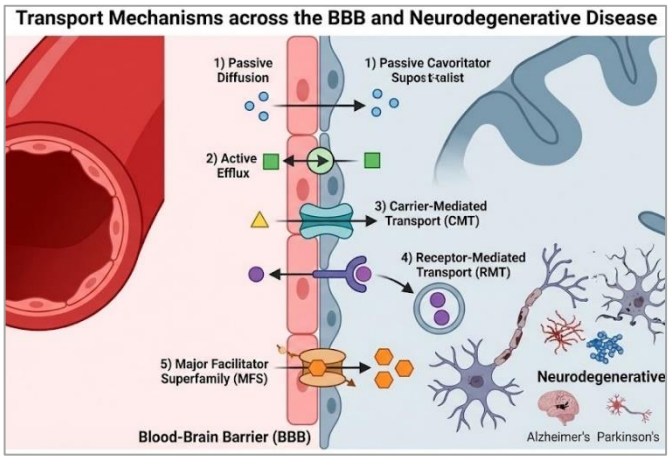
There are certain restricting factors which inhibit the entry of drug compounds into the brain like the ability of formation of > 6 hydrogen bonds of compound and polar surface area (PSA) >80. Every H-bond pair present in drug substance forming a functional group of polar nature usually reduces the drug's penetration in log order of one. Other considerations which greatly decreases permeation across CNS includes the great tendency of drug plasma protein binding with an insignificant off-rate and the molecule's rotatable bonds. The drugs diffusion across CNS is not solely dependent on factors discussed above as there are certain efflux transporters which control its penetration (Hitchcock & Pennington, 2006).

3.2 Active efflux

A variety of ATP-binding cassette (ABC) proteins are exposed on the luminal, endothelial membrane of the BBB. The penetration of various toxins, like therapeutic agents is hindered across CNS due to presence of such ATP-powered efflux pumps. The high exposure of such efflux pumps is associated to the pharmaco-resistant characteristics of CNS. Various pathological conditions for instance AD and PD have been discussed for low expression of ABC BBB transporters (Al Rihani et al., 2023). In a study of AD in an animal model, there is seen the rise in level of amyloid β-peptide (Aβ) inside the CNS which is due to the decrease functional activity of ABC transporters (Wang et al., 2016).

Figure 1

Transport mechanisms across the BBB & Neurodegenerative Diseases



3.3 Carrier-mediated transport (CMT)

Various vital nutrients polar in nature, like amino acids and glucose, that are necessary for body activity are halted for permeation inside brain due the presence of BBB. That's why, other ways are considered for the transport of essential nutrients into the brain. There are genes from the Solute Carrier (SLC) Transporter Gene Family that encodes CMTs. The diffusion of large number of substances across biological phospholipid membranes is assisted with membrane-bound proteins encoded by greater than 300 transporter genes. The transcellular diffusion of various substances is assisted by the SLC transporters such substances include fatty acids, hormones, nucleotides, organic anions, amines, amino acids, carbohydrates, monocarboxylic acids, choline, and vitamins (Segal & Zlokovic, 2012).

3.4 Receptor-mediated transport (RMT)

The amino acid CMT systems cannot utilize for permeation across the BBB of larger peptides and proteins due the presence of peptide bonds in them. For such substances, like neuroactive peptides, regulatory proteins, hormones, and growth factors RMT systems play a role for their penetration inside the brain. Transcytosis is process involving endocytic mechanisms which utilizes in transferring large molecular mass substances across BBB. Transcytosis facilitates the permeation of variety of molecules and complex substances inside the brain instead of the presence of tight junction and various physical barriers in brain. Receptor-mediated transcytosis (RMT) and the adsorptive-mediated transcytosis (AMT) are two divisions of vesicular transport system (Li et al., 2023). In RMT, an endocytic process initiated through ligation of macromolecules to receptors having specificity to ligands which are present on surface of cell. A vesicle is formed as a result of pinching of caveola which is a cluster of receptors and its attached ligand. Internalization of receptor and its bound ligand into the ECs and exocytosis across the cytoplasm on the contrary side of the cell take place. As a result of such the exocytotic event, the ligand and receptor split apart. On contrary in AMT, transcytosis takes place with the induction of endocytosis via interaction between cationic macromolecular drug substances with particular ligating sites on cell surface (Parton & Richards, 2003).

3.5 Major facilitator superfamily

Endothelial facilitator superfamily domain-containing protein 2a (MFSD2a) facilitated the movement of vital omega-3 fatty acids for instance, docosahexaenoic acid (DHA). Recent studies demonstrated importance of the above discussed family of transporters as its role in preserving BBB integrity in animal model study of mice having damaged BBB and DHA deficient due to absence of MFSD2a (Parnova, 2022).

3.6 Immune cell movement across the BBB

Because of low neutrophil count and greatest potential of immune cell-BBB interaction, CNS's immune privilege arises. Mononuclear cells gain entry into the brain and settle there permanently as immunologically capable microglia during development of embryo under normal conditions. Their transcellularly diapedesis takes place via endothelial cytoplasm, despite of paracellularly which occurs via tight junction opening. While the TJs between endothelial cells become irregular in inflammatory conditions because of release of pro-inflammatory agents like cytokines (Kadry et al., 2020). Mononuclear leukocytes, monocytes, and macrophages are equally competent to the resident microglia and take transcellular and paracellular ways for entry into CNS. In few scenarios, these immune system cells can convert into a microglial subtype.

4. BBB Dysfunction in Neurodegenerative-disorders

4.1 Alzheimer's disease

It is evident that the both disruption and dysfunction take place inside the BBB in the initial stages of AD. A buildup of Aβ and the formation of neurofibrillary tangles occur as a result of BBB disruption involving plasma leakage due to damaged integrity of BBB and BBB dysfunction which includes low cerebral blood flow, reduced transport capability and rise in vascular inflammation. Recent studies shows that the CBF reduced and developed AD biomarkers like Aβ, amyloid, and tau proteins preceded by vascular impairment (Wang et al., 2025).

4.1.1 Impaired BBB integrity

Cells infiltration of RBCs and WBCs and the leakage of blood components like fibrinogen, thrombin, albumin and hemosiderin have been shown in the research studies involving patients of AD and animal models. The result of such research studies demonstrates the damaged BBB integrity (McLarnon, 2021).

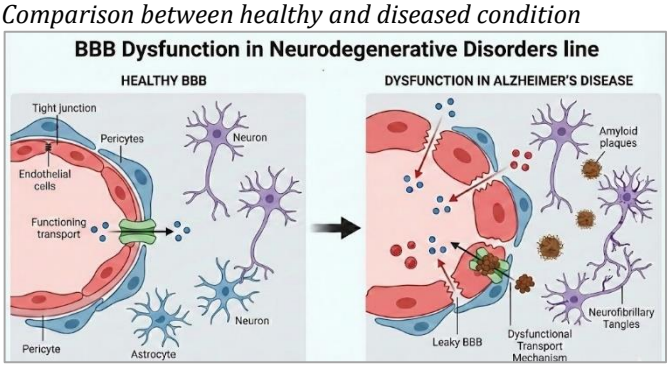
4.1.2 Dysfunctional transport mechanism

Glucose regulation and utilization impairment is a specific disruption seen in AD. A decline in Glut in the ECs of AD patients spotlight the dysfunctionality of the BBB. There is decrease absorption of glucose in mild cognitive impairment (MCI) patients. The early stages of AD under Fluorodeoxyglucose-PET imaging exhibits reduced metabolic activity in the posterior cingulate cortex and temporoparietal hypo-metabolism which occurs prior to structural modifications. In various areas of brain like cingulate cortex, parietal cortex and temporal cortex, the glucose absorption reduced apparently in late stages of AD (González et al., 2022). There is connection between CBF,

glucose metabolism disturbances and Aβ clearance as in various studies it is shown the reduction in CBF and demonstration of low-density LRP1 dampens due to Glut1 deficiency .On the other hand, reduction in D-glucose transport in mice model occurs due to phosphorylated tau (p-tau) that has no immediate influence on Glut but promotes neuronal death. Extracellular proprotein convertase subtilisin/kexin type 9 (PCSK9) which influences LRP1 on ECs and viable demonstration of β-site amyloid precursor protein cleaving enzyme 1 (BACE1) are the factors the halted the Aβ clearance (Ramanathan et al., 2015).

Figure 2

Comparison between healthy and diseased condition



4.1.3 CBF reductions

Arterial spin labeling magnetic resonance imaging have demonstrated the reduce CBF and cerebrovascular reactivity dysfunction in various regions of brain in AD patients and animal models. CBF can be used as a vital diagnostic tool in preclinical AD as reduce CBF precedes both brain impairment and noticeable alteration in Aβ and tau biomarkers (Zhang et al., 2017).

Excessive Aβ promotes the generation of ROS in cerebral cortex regions of AD patients, which results in rise in intracellular ET1 concentration. Pericyte contraction and capillary constriction arises because of this elevation which stimulates the endothelin-A receptor on pericytes, that eventually reduces CBF (Korte et al., 2020).

4.1.4 Vascular inflammation

Disruption of BBB causes inflammation that results in response of BBB impairment that shows a dual nature. This impairment provides protection of microglial cells in acute inflammation responses, on contrary it turns harmful in chronic phases. In initial phases of AD, the accumulation of Aβ flushed out due to elevated immune response (Huang et al., 2021).

4.2 Parkinson's Disease

It is characterized by selective degeneration of dopaminergic neurons in the substantia nigra pars compacta region of the brain, together with the accumulation of α-synuclein–containing Lewy bodies and neurites (Gan et al., 2024) Beyond neuronal pathology, significant vascular alterations are evident, as endothelial cells (ECs) within the basal ganglia display functional deterioration marked by reduced expression of the tight junction components occludin and ZO-1. Concurrently, diminished levels of the efflux transporter P-glycoprotein (P-gp), which is essential for neurotoxin clearance, have been documented in PD and are closely associated with dysregulation of 1 (LRP1) protein.

PD model systems demonstrate cellular deposition of LRP1-ICD generated via γ-secretase and matrix metalloproteinase mediated cleavage. This process facilitates the infiltration and accumulation of α-synuclein preformed fibrils (αSyn PFFs), causing occluding depletion and suppression of P-gp activity. In the presence of αSyn PFFs, LRP1-ICD interacts with (PARP1), increasing PAR production and promoting ECs secretions into dopaminergic neurons. This interaction amplifies the αSyn PFFs damage to both ECs and neurons (Huang et al., 2023). As a central contributor of Parkinson's disease–related neurodegeneration, the LRP1-ICD/PARP1 represents a promising vascular-based therapeutic target. Stimulation of pericytes by αSyn induces secretion of inflammatory cytokine and MMP-9, contributing to BBB breakdown. α-Syn-induced astrocytic stimulation leads to VEGF-A and NO production, contributing to vascular disruption and tight junctions' impairment. Autopsy analyses of PD brains reveal elevated collagen IV deposition in the basement membrane. Aberrant angiogenic regulation has been observed in early PD and experimental 6-OHDA models. This has been associated with the significant capillary network damage seen in the substantia nigra (Schapira & Gegg, 2011).

4.3 Amyotrophic Lateral Sclerosis

It is marked by decline of motor neurons in CNS, spinal cord and brain stem, gradually damaging voluntary muscle movement and resulting motor dysfunction. Impairment of the blood brain barrier and the blood–cerebrospinal fluid barrier is apparent in both sporadic and inherited amyotrophic lateral sclerosis, arising before motor neuron degeneration (Zayia & Tadi, 2020). Study of ALS patients and experimental mouse models has revealed endothelial cell degeneration, marked by cellular injury, edema, and vacuole formation in cytoplasm , in addition to reduced levels of tight junctions such as occludin protein, ZO-1,and claudin-V. Its patients exhibit increased expression of BM components like collagen IV, whereas model mice show a decrease in collagen IV. Microbleeds in the deeper regions of the motor cortex have been observed in MRI examination in ALS patients, while the exact mechanisms driving this BBB impairment remain unclear. Iron (Fe2+), originating from hemoglobin breakdown, is involved in early ALS disease development through oxidative injury, leading to damage to motor neurons, intensifying changes in permeability of blood brain barrier (Garbuzova-Davis & Sanberg, 2014).

Astroglia adjacent to degenerating motor neurons show elevated production of inflammatory mediators, particularly cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). The cytoplasmic buildup of TDP-43 in neuronal and glial populations correlates with activation of immune and neuroinflammatory processes.In cultured astrocytes, TDP-43 elevate IL-1β, IL-6, and TNF-α levels and promoting microglial proliferation via NF-κB activation. TDP-43 overexpression in ALS promotes infiltration of immune cells such as CD3+ T cells, CD4+ T cells, and monocytes, along with IgG permeability, activation of endothelial cells and pericytes.(Che et al., 2024) Consequently, BBB disruption is marked by

decreased tight junction integrity(TJs), structural deterioration of pericytes and endothelial cells, increased infiltration of immune cells, and accumulation of circulating neurotoxic plasma proteins (Drachman et al., 2002).

4.4 Multiple Sclerosis

Multiple sclerosis is an immune related chronic inflammatory disorder within CNS. Due to impaired BBB, permitting infiltration of immune cells into the brain neural tissues, leading to myelin loss and inflammation. Gd-MRI has revealed that BBB breakdown is a fundamental step in MS development. BBB associates markers, including raised Qalb levels, enhanced MMP-9 activity in in cerebrospinal fluid and serum, and elevated CSF leukocytes, are detected at various diseases stage. Throughout all disease stages inflammation is persistent, with heightened immune-mediated activity in the initial stages (Haase & Linker, 2021). Leukocyte transmigration across the BBB involves complex molecular interactions with endothelial cells. T and B immune lymphocytes, along with monocytes, are stimulated in the peripheral compartment before entering the CNS. Recent studies utilizing radiotracers, MMP PET, have shown that increased MMP activity is present around active lesions. The movement of immune cells across the BBB involves interactions with ECs, alterations in endothelial transcellular and paracellular transport, and structural changes of the immune cells (Chen et al., 2024). MRI observation indicates widespread brain hypoperfusion at all MS phases, implying a connection to oxygen deficient state. The underlying mechanism to decrease perfusion may include astrocyte energy metabolism compromise due to a lack of β2-adrenergic receptors, secondary to β2-adrenergic receptor deficiency, and enhanced vasoconstriction from increased ET-1. Elevated nitric oxide levels and associated cellular hypo responsiveness, in conjunction with vasculitis, are additional drivers of the complex cerebrovascular pathology of MS (Dong et al., 2012).

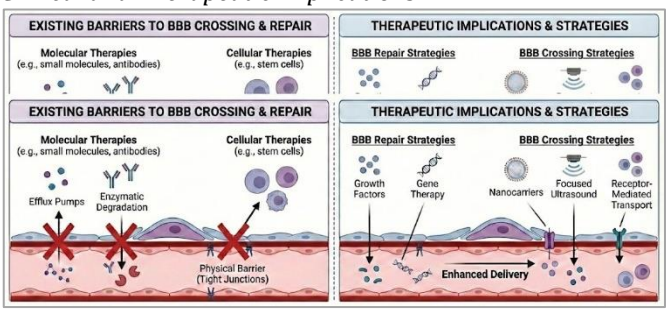
5. Clinical and Therapeutic Implications

5.1 Existing barriers of molecular and cellular therapies of BBB repairing and cross.

Multiple obstacles in the therapeutic implementation, including molecular and cellular approaches for barrier restoration. For instance, large-scale production and quality assurance, especially for genetically engineered cell lines, are technically challenging, lengthy, and expensive. Viral gene therapy strategies experience analogous limitation (Ting et al., 2022).

Figure 3

Clinical and Therapeutic Implications



Additionally, require tightly regulated administration to reduce unwanted outcomes. The FDA approved AAV-mediated therapies such as Zolgensma and Luxturna support promising applicability of AAV vectors within the CNS. Upcoming research may aim at refining these strategies, creating uniformed procedures, and expanding their clinical applicability. In contrast, these challenges could be addressed by the production of novel DDS (Rust et al., 2025).

6. CONCLUSION

Accumulating evidence strongly indicates that blood–brain barrier (BBB) impairment is the key initiator of disease progression rather than just a subsequent outcome of neuronal degeneration. As seen in neurodegenerative disease, morphological damage to TJs, endothelial damage, pericyte depletion, and transporter dysfunction often occur before severe neuronal loss. Early vascular changes result in the aggregation of harmful proteins, decreased nutritional transport (such as glucose via GLUT1), changed cerebral blood flow, and uncontrolled entrance of peripheral immune cells and plasma-borne substances into brain. Collectively, these alterations promote inflammation, neuronal dysfunction, and neuronal loss

Recognizing BBB disruption as the main causative factor modifies therapeutic techniques for neuronal disorders. Upcoming therapy trends should emphasize on the preservation, recovery, or regulation of BBB structure and function instead of neuro-centric approaches. Because endothelial cells, transport mechanisms, inflammatory signals, and vascular–neural interactions are targeted, neuron-centric approaches alone may be considered less effective in delaying disease onset and progression. Consequently, the BBB should be recognized as a key therapeutic target whose maintenance and repair are required for effective management of neuron degenerative conditions, beyond its function as a pharmacological drug delivery barrier.

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