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Review

The Crucial Role of the Blood–Brain Barrier in Neurodegenerative Diseases: Mechanisms of Disruption and Therapeutic Implications

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Abstract: The blood–brain barrier (BBB) is a crucial structure that maintains brain homeostasis by regulating the entry of molecules and cells from the bloodstream into the central nervous system (CNS). Neurodegenerative diseases such as Alzheimer's and Parkinson's disease, as well as ischemic stroke, compromise the integrity of the BBB. This leads to increased permeability and the infiltration of harmful substances, thereby accelerating neurodegeneration. In this review, we explore the mechanisms underlying BBB disruption, including oxidative stress, neuroinflammation, vascular dysfunction, and the loss of tight junction integrity, in patients with neurodegenerative diseases. We discuss how BBB breakdown contributes to neuroinflammation, neurotoxicity, and the abnormal accumulation of pathological proteins, all of which exacerbate neuronal damage and facilitate disease progression. Furthermore, we discuss potential therapeutic strategies aimed at preserving or restoring BBB function, such as anti-inflammatory treatments, antioxidant therapies, and approaches to enhance tight junction integrity. Given the central role of the BBB in neurodegeneration, maintaining its integrity represents a promising therapeutic approach to slow or prevent the progression of neurodegenerative diseases.

Keywords: blood–brain barrier; neurodegenerative diseases; oxidative stress; neuroinflammation; neurotoxicity

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1. Introduction

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), as well as ischemic stroke, represent a growing public health concern because of their association with progressive neuronal loss, cognitive decline, and motor dysfunction [1–3]. While the underlying causes of these diseases are complex and multifactorial, the breakdown of the blood–brain barrier (BBB) is a crucial and increasingly recognized element involved in their pathogenesis [4–6]. The BBB is a highly specialized and selectively permeable structure that is essential for maintaining the brain's microenvironment by regulating the transport of molecules between the bloodstream and the brain [7–9]. It not only supports brain homeostasis but also protects neural tissue from potentially harmful agents, toxins, and inflammatory cells [9–11].

However, in neurodegenerative diseases, the integrity of the BBB is frequently compromised. This allows molecules from the blood, including inflammatory cells, cytokines, and

toxins, to infiltrate the brain parenchyma [6,12–14]. This infiltration exacerbates neuroinflammation, oxidative stress, and neuronal dysfunction, thereby accelerating the disease process [6,12–14]. Studies have shown that BBB disruption is both a consequence and cause of neurodegeneration, as increased permeability creates a pathological feedback loop in which neuronal injury exacerbates further BBB impairment [6,12–14]. Protection and restoration of the BBB can therefore serve as a crucial therapeutic target for neurodegenerative diseases [6,15,16]. Stabilizing the integrity of the BBB may help reduce the influx of harmful agents, mitigate neuroinflammation, and preserve neural function [6,11,12].

In this review, we aim to provide a detailed understanding of the mechanisms involved in BBB disruption in neurodegenerative diseases, explore the pathological impacts of this disruption, and discuss potential therapeutic strategies to protect and restore BBB integrity. By emphasizing the importance of maintaining a healthy BBB, we aim to highlight its role in mitigating the progression of neurodegenerative diseases.

2. Structure and Function of the BBB

The BBB is a highly specialized, selectively permeable interface that separates the brain from the systemic circulation [9,11,17]. It primarily maintains a tightly regulated environment within the central nervous system (CNS) that is conducive to optimal neuronal function while shielding the brain from potential harm [9,11,17]. The BBB consists of a network of endothelial cells, pericytes, astrocytic endfeet, and a supporting basement membrane, each contributing uniquely to its integrity and selective permeability [18–20] (Figure 1).

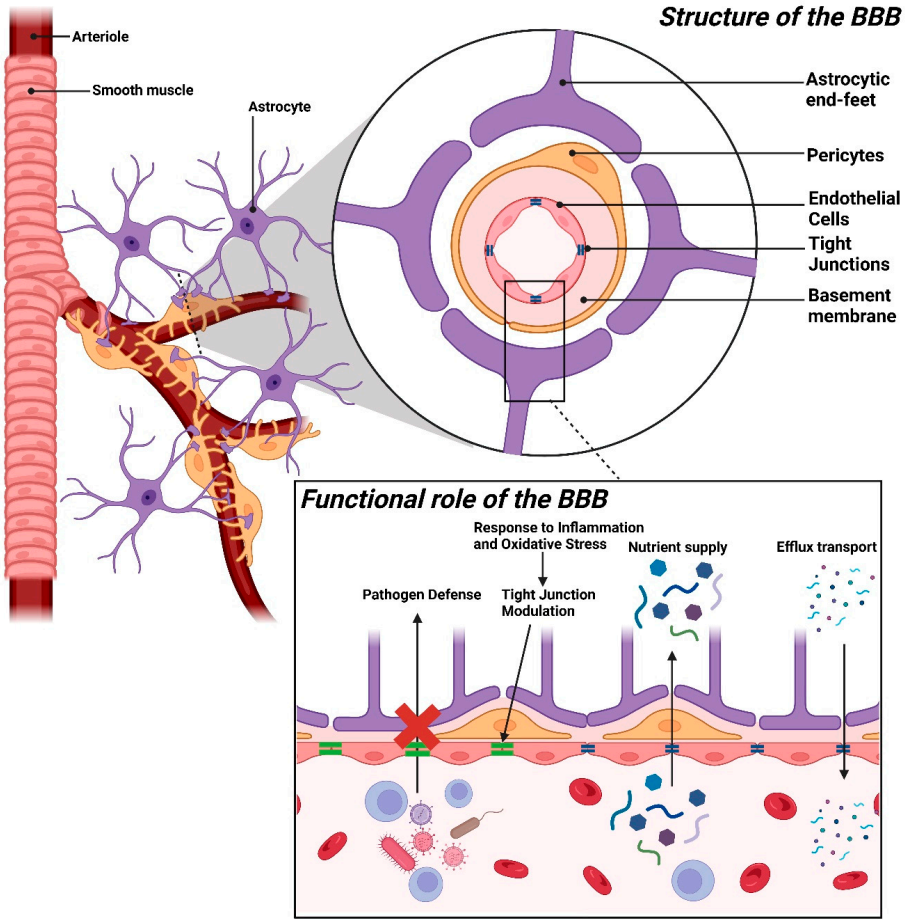

Figure 1. Structure and function of the BBB. The BBB is a specialized, selectively permeable interface that separates the brain from the systemic circulation. It plays a crucial role in maintaining the stability

of the CNS by tightly regulating the exchange of substances and protecting neurons from toxins and inflammation. It consists of endothelial cells connected by tight junctions, pericytes embedded in the basement membrane, astrocytic endfeet, and an extracellular basement membrane, each uniquely contributing to its integrity and selective permeability. Endothelial cells form the core of the BBB, with unique tight junctions restricting paracellular movement and regulating substance passage. Pericytes support structural integrity, influence blood flow, and enhance tight junction stability. Astrocytic endfeet provide biochemical support, regulate ion and water homeostasis, and maintain neurotransmitter balance, while the basement membrane anchors BBB components and restricts immune cell infiltration, thereby protecting against inflammation. The BBB also supplies the brain with essential nutrients and removes metabolic waste, dynamically adapting to neural activity, oxidative stress, and hypoxia to support CNS homeostasis. These functions emphasize the importance of the BBB in maintaining CNS health and underscore the therapeutic potential of approaches that preserve or restore BBB integrity in neurodegenerative diseases. The figure was created using Biorender.com (Agreement number: CE27KUKTJR).

2.1. Endothelial Cells and Tight Junctions

Endothelial cells serve as the primary structural and functional component of the BBB. They form a continuous monolayer along the cerebral microvasculature [17,18]. They are uniquely adapted to maintain BBB selectivity, which regulates the movement of substances between the bloodstream and the brain and is crucial for maintaining neural function [9,21]. Unlike peripheral endothelial cells, BBB endothelial cells exhibit specialized structural features, including unique tight junctions, low rates of transcytosis, and selective transport systems, which create a highly restrictive environment and ensure that only specific molecules necessary for brain health enter the CNS [21,22].

2.1.1. Structure and Composition of Tight Junctions in BBB Endothelial Cells

BBB endothelial cells are joined by specialized tight junctions. This feature distinguishes them from peripheral endothelial cells [11,21]. These tight junctions are composed of a complex network of proteins, including claudins (particularly claudin-5), occludins, and junctional adhesion molecules (JAMs) [21,23]. These proteins form a highly resilient, nearly impermeable barrier that restricts the paracellular movement of ions, macromolecules, and other potentially harmful agents. This allows the BBB to tightly regulate the internal environment of the brain [21,24]. Claudin-5, one of the most abundant tight junction proteins in the BBB, is crucial for preventing the diffusion of small ions and solutes, thereby contributing to the high-resistance barrier unique to brain endothelial cells [23,25].

Tight junction proteins are further anchored to the endothelial cell cytoskeleton via zonula occludens (ZO) adaptor proteins, including ZO-1, ZO-2, and ZO-3. This connection provides structural stability to tight junctions and enables dynamic adjustments in response to physiological cues, such as neural activity or blood flow changes [21,23,24]. For example, ZO proteins can reorganize tight junctions in response to signaling molecules, such as cytokines, growth factors, and hormones, enabling the BBB to rapidly adapt to environmental or metabolic changes [26,27]. Consequently, the BBB is a highly organized and resilient barrier capable of withstanding fluctuations under both normal and pathological conditions [6,11,19].

2.1.2. Communication with Other Cells and Response to the Neural Environment

BBB endothelial cells are not isolated in their function; they closely interact with pericytes, astrocytes, and microglia to form the neurovascular unit (NVU) [18,26,28]. This unit is a highly integrated system in which signaling molecules are continuously exchanged between these cells to maintain and regulate BBB integrity [18,29,30]. For instance, astrocytes release glial cell-derived neurotrophic factor (GDNF) and other signaling molecules that promote the expression and stability of tight junction proteins in endothelial cells [31–33].

Moreover, pericytes, which envelop endothelial cells on the abluminal side, release factors like transforming growth factor-beta (TGF-β) and platelet-derived growth factor-B (PDGF-B), further enhancing tight junction integrity and improving BBB stability [34–36].

The ability of endothelial cells to dynamically respond to the neural environment is vital for BBB homeostasis [18,21,37]. For example, in response to increased neural activity, endothelial cells can transiently alter tight junction permeability to enable a controlled increase in blood flow and nutrient supply to active brain regions; this process is closely linked to neurovascular coupling [38,39]. Additionally, endothelial cells can respond to inflammatory signals, oxidative stress, or hypoxia by modulating their tight junctions or activating efflux transporters, thereby protecting the brain from potential damage [40–42].

2.2. Pericytes

Pericytes are a vital cellular component of the BBB. They are embedded within the basement membrane that envelops the walls of brain capillaries [20,43,44]. These mural cells are situated closely along the abluminal side of endothelial cells and play a crucial role in maintaining BBB integrity, neurovascular regulation, and CNS homeostasis [44–46]. They can form physical contacts and communicate with endothelial cells via direct cell-to-cell interactions and paracrine signaling, thereby influencing the structural and functional properties of the BBB. Thus, they are crucial for maintaining brain health [44,47,48].

2.2.1. Structural and Functional Support to the BBB

Pericytes maintain the structural integrity of the BBB by modulating the extracellular matrix (ECM) composition and supporting endothelial cell adhesion and alignment within the basement membrane [49–51]. Moreover, they secrete various ECM proteins, such as collagen, laminin, and fibronectin, which reinforce the physical barrier properties of the basement membrane and provide a stable scaffold for endothelial cells [34,52]. Through this interaction, pericytes help maintain vessel wall stability, thereby reducing the likelihood of BBB disruption under physiological stress or injury [34,52]. They are also essential for regulating cerebral blood flow (CBF) within the microvasculature [44,53,54]. They possess contractile properties mediated by contractile proteins, such as smooth muscle actin. Consequently, they can constrict or dilate capillaries, thereby modulating blood flow to specific brain regions in response to neuronal activity [44,46,55]. Through this process, known as neurovascular coupling, active brain regions can receive an adequate supply of oxygen and nutrients to support cognitive functions and overall brain health [56–58]. Pericyte dysfunction or loss can impair this regulation, leading to hypoperfusion and facilitating the progression of neurodegenerative diseases [34,52].

2.2.2. Influence on Tight Junction Formation and Maintenance

In the BBB, pericytes play crucial roles in the formation, maturation, and maintenance of endothelial cell tight junctions [34,52]. Through signaling pathways, such as the TGF-β and Notch signaling pathways, pericytes promote the expression of tight junction proteins, including claudin-5, occludin, and JAMs, which are essential for forming a high-resistance barrier [24,29,59]. Moreover, pericytes secrete angiopoietin-1 and PDGF-B, which help stabilize tight junctions and strengthen BBB integrity [34,52]. In the absence of pericytes, endothelial cells exhibit increased permeability, enabling unregulated paracellular transport and compromising BBB function [34,60].

2.2.3. Role in Response to Injury and Inflammation

In addition to their structural and regulatory functions, pericytes play crucial roles in CNS injury response and inflammation management, acting as the first responders to damage within the NVU [48,61,62]. They can detect injury or inflammatory signals

and react by adjusting their phenotype to facilitate BBB repair and inflammation resolution [29,48,63]. Upon injury, pericytes release signaling molecules, such as cytokines and chemokines, which modulate endothelial and immune cell behaviors [48,64,65]. They can also differentiate into fibroblast-like cells to promote scar formation and wound repair around damaged blood vessels, thereby reinforcing BBB integrity in response to any stress or insult [66,67].

Pericytes can contribute to immune surveillance by regulating leukocyte transmigration across the BBB [68–70]. In neuroinflammatory conditions, pericytes can alter the expression of adhesion molecules to limit or facilitate the movement of immune cells into the CNS, providing an additional layer of immune control within the BBB [65,69,71]. However, in chronic inflammatory states associated with neurodegenerative diseases, prolonged activation of pericytes can lead to the excessive production of inflammatory mediators; this may exacerbate BBB breakdown and worsen disease pathology [35,62,68].

2.3. Astrocytic Endfeet

Astrocytes, a type of glial cell in the brain, extend their processes, known as astrocytic endfeet, to cover more than 90% of the capillary surface in the brain [32,72]. These endfeet play a crucial role in maintaining the structural and functional integrity of the BBB by providing biochemical support to endothelial cells [32,73,74]. By secreting growth factors, cytokines, and other signaling molecules, astrocytes regulate endothelial cell behavior and strengthen tight junctions [75–77]. Astrocytic endfeet also contribute to ion and water homeostasis, which is essential for maintaining the unique extracellular environment required for neuronal function [78].

2.3.1. Support to Endothelial Cells and Maintenance of Tight Junctions

Astrocytes are vital for maintaining the structural stability of the BBB. Moreover, they closely interact with endothelial cells to modulate their function [31,74]. They release various growth factors, including GDNF, epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF), which promote the survival, growth, and differentiation of endothelial cells [31,33,79]. These growth factors help endothelial cells stably express tight junction proteins (such as claudin-5, occludin, and JAMs), thereby enhancing cell adhesion and promoting BBB integrity [31,32,80].

Astrocytes also regulate the inflammatory response within the brain by releasing cytokines and chemokines that help endothelial cells respond to inflammatory conditions [75,81,82]. For instance, interleukin-6 (IL-6) modulates the reactivity of endothelial cells to inflammation, thereby minimizing BBB damage caused by immune responses [75–77]. Moreover, astrocytes secrete anti-inflammatory factors, such as TGF-β, which help protect endothelial cells from inflammatory damage and promote BBB stability [75–77].

2.3.2. Regulation of Ion and Water Homeostasis

Astrocytic endfeet are essential for maintaining ion and water homeostasis in the brain [83–85]. They are particularly rich in aquaporin-4 (AQP4) water channels, which regulate water balance in the extracellular space [75–77]. AQP4 enables rapid water movement in response to brain swelling or inflammatory conditions, thereby alleviating edema and promoting BBB stability [77,84,86].

Astrocytes also play a crucial role in controlling potassium ion (K^+) concentrations to maintain electrical stability within the brain [87,88]. When neuronal activity increases, local K^+ concentrations increase. Astrocytes quickly absorb these excess ions to prevent excessive neuronal excitation [89,90]. This regulation helps maintain normal synaptic function and creates a stable extracellular environment for neurons [88,90].

2.3.3. Metabolic Support and Energy Transfer

Astrocytes provide essential metabolic support to neurons by storing glucose as glycogen and breaking it down to lactate, which is then supplied to neurons as an energy source [91–93]. Lactate is a particularly important energy source for neurons during high activity periods [94–96]. This metabolic support helps sustain neuronal energy metabolism and promotes optimal neuronal function [92,93,95]. Astrocytes also participate in the glutamine–glutamate cycle to maintain neurotransmitter balance [97,98]. They absorb excess glutamate from the synaptic cleft and convert it to glutamine, which is then supplied to neurons [99–101]. This process prevents excitotoxicity from excessive excitatory neurotransmitters and ensures stable neurotransmission [100,102,103].

2.4. Basement Membrane

The basement membrane is a dense, specialized ECM that underlies the BBB. It plays a crucial role in maintaining the structural and functional integrity of the BBB [20,104]. The basement membrane is primarily composed of collagen (types IV and XVIII), laminin, fibronectin, heparan sulfate proteoglycans, and other glycoproteins. It provides essential support to BBB cells, anchoring endothelial cells and pericytes to form a cohesive, stable barrier [20,104,105].

2.4.1. Structural Support and Stability

The basement membrane is not merely a passive support structure. Instead, it is an active component that contributes to the structural resilience and stability of the BBB [9,11,20]. It serves as a physical scaffold for endothelial cells and pericytes, allowing them to maintain their positions and form a tightly regulated barrier essential for CNS protection [9,19,20]. Laminin and collagen are key components of the basement membrane. They provide elasticity and tensile strength, enabling the BBB to withstand pressure fluctuations associated with blood flow while preserving its integrity [106–108]. This structural support is vital for maintaining tight junctions between endothelial cells, which are crucial for the selective permeability of the BBB [7,8,11].

2.4.2. Biochemical Signaling and Cellular Interactions

The basement membrane also plays a crucial role in biochemical signaling [109–111]. It serves as a reservoir for growth factors, cytokines, and other signaling molecules that are released in response to physiological or pathological stimuli [112,113]. These signals influence the behavior of endothelial cells and pericytes, thereby regulating cell proliferation, migration, and survival [59,68,114]. For instance, the basement membrane releases VEGF and fibroblast growth factor (FGF), which promote endothelial cell survival and integrity, particularly in response to injury or stress [50,115,116]. Moreover, laminin and collagen in the basement membrane interact with integrins and other receptors on endothelial cells and pericytes, mediating cell adhesion and stabilizing the BBB [117,118]. This interaction is crucial for maintaining tight junction integrity. It provides a signaling pathway that reinforces tight junction proteins, such as claudin-5 and occludin, thereby enhancing the ability of the BBB to resist harmful substances [10,24,119].

2.4.3. Barrier to Cellular Infiltration

The basement membrane mainly serves as a barrier to cellular infiltration [120–122]. In a healthy state, it restricts the migration of peripheral immune cells, such as leukocytes, preventing them from entering the CNS [123,124]. This selective restriction is crucial for protecting the CNS from potential inflammatory damage, as uncontrolled immune cell infiltration could cause neuroinflammation and compromise the BBB [6,125]. However, un-

der pathological conditions, e.g., in neuroinflammatory or neurodegenerative diseases, the basement membrane becomes degraded. This degradation can lead to increased immune cell migration into the CNS, exacerbating tissue damage [126–128]. Matrix metalloproteinases (MMPs), which are upregulated in conditions like multiple sclerosis and AD, can degrade components of the basement membrane, such as collagen and laminin [129–131]. This degradation disrupts the structural integrity of the BBB and enables peripheral immune cells and inflammatory mediators to infiltrate brain tissue, contributing to further neurodegeneration and breakdown of the BBB [130,132].

2.4.4. Role in Communication Within the NVU

The basement membrane also facilitates communication within the NVU, which includes endothelial cells, pericytes, astrocytes, and neurons [18,28,30]. It acts as a biochemical interface between these cell types, supporting their coordinated functions [18,28,30]. For example, astrocytic endfeet are anchored to the basement membrane. Here, they release signaling molecules, such as GDNF and TGF-β, which modulate the activity of endothelial cells and pericytes [32,133,134]. This signaling network within the NVU helps maintain BBB integrity and responds adaptively to neural activity, injury, or metabolic changes [38,135,136].

2.5. Functional Role of the BBB

Under normal physiological conditions, the BBB serves as a crucial defense mechanism that tightly regulates CNS homeostasis [8,11,137]. By acting as a highly selective barrier, it prevents harmful agents, such as pathogens, toxins, and peripheral immune cells, from entering the brain, thereby protecting neuronal tissue from damage and inflammation [8,126]. This selective permeability creates a stable environment that supports optimal neuronal function and overall brain health [138,139] (Table 1).

2.5.1. Protection of the CNS and Selective Permeability

The BBB primarily shields the CNS from potentially harmful substances, maintaining an environment conducive to neural health [6,9,11]. Tight junctions between endothelial cells, combined with specialized transport systems, restrict the passage of pathogens, toxins, and other molecules, thereby minimizing the risk of infection and inflammation in the brain [9,24,140]. The BBB serves as a crucial protective mechanism for the CNS by acting as a selective barrier against circulating pathogens, such as bacteria and viruses [141,142]. Even during bloodstream infections, the BBB significantly reduces the likelihood of pathogens entering the brain, thereby lowering the risk of various infections, such as meningitis and encephalitis [143,144]. Pathogens typically manage to penetrate this barrier only in cases of severe infection or BBB disruption, highlighting the vital role of the BBB in disease prevention [141,142]. Moreover, the BBB restricts the access of peripheral immune cells, including T cells and macrophages, to prevent excessive immune responses that could otherwise lead to inflammation and neuronal damage [6,145]. This immune regulation is essential, as the brain's neural tissue is highly sensitive to inflammation, which could disrupt neural circuits, impair synaptic signaling, and ultimately result in neuronal cell death if left unchecked [146,147].

2.5.2. Nutrient Supply and Waste Removal

In addition to protecting the CNS from external threats, the BBB maintains the metabolic requirements of the brain [148]. It selectively allows the passage of necessary nutrients and ions. Moreover, it systematically removes metabolic waste products, thereby sustaining a stable environment for neuronal function [8,137,149].

The BBB plays an essential role in nutrient transport and waste removal, both of which are crucial for brain function [8,137,148]. Neurons and glial cells have high metabolic demands and rely on a steady supply of nutrients [150,151]. The BBB facilitates the transport of glucose, amino acids, and ions through specialized carriers and transport systems [152–154]. For example, glucose transporter-1 (GLUT1) selectively transports glucose, the primary energy source of the brain, across the BBB to provide a constant energy supply for ATP production and neurotransmitter synthesis [155–157]. Amino acids are essential for protein synthesis and neurotransmitter production. They cross the BBB via specific transporters, such as large neutral amino acid transporter 1 (LAT1), which can handle large neutral amino acids, including dopamine and serotonin precursors [154,158,159]. The BBB also tightly regulates ions, such as K^+ and calcium ions, to maintain ionic stability and support synaptic transmission [6,160]. In addition to being involved in nutrient delivery, the BBB contains efflux transporters, such as ATP-binding cassette (ABC) transporters (e.g., P-glycoprotein [P-gp] and breast cancer resistance protein) that actively remove metabolic waste products, xenobiotics, and other potentially harmful substances [161–163]. This efflux system prevents toxin accumulation, thereby preserving a clean environment that supports neuronal health and reduces oxidative stress in the brain [164–166].

2.5.3. Adaptive Regulation in Response to Neural Activity

The BBB is not a static barrier; it dynamically adjusts its permeability in response to the brain's metabolic needs, neural activity, and environmental conditions [6,138,167]. This adaptability is essential for maintaining CNS homeostasis and enabling the brain to quickly respond to changes in activity and demand [8,138,168].

The BBB dynamically adapts to meet the brain's demands during various conditions, such as increased neural activity, inflammation, oxidative stress, and hypoxia [165,169]. During heightened neural activity, such as intense cognitive processing or physical exertion, neurons require more oxygen and glucose [170–172]. Hence, the BBB increases blood flow to active brain regions through vasodilation and neurovascular coupling, thereby ensuring an adequate supply of these essential nutrients [57,173,174]. During inflammation or oxidative stress, the BBB can modulate tight junctions and enhance transporter activity to protect the CNS [6,24,175]. For example, it may strengthen tight junctions to prevent immune cells and inflammatory molecules from entering the brain, thereby reducing the risk of neuronal damage [57,173,174]. Moreover, during oxidative stress, the BBB may boost the activity of efflux transporters, such as P-gp, to expel toxic substances and lower oxidative load, thereby preserving neural integrity [176–178]. Under hypoxic conditions, the BBB can upregulate glucose and metabolite transporters to sustain neuronal energy levels. Additionally, it can enhance antioxidant defenses in endothelial cells to counteract the oxidative damage often associated with low oxygen levels [172,179,180]. These adaptive mechanisms collectively help maintain the internal environment of the brain and protect neural tissue from potential damage [6,138].

The BBB plays a fundamental role in CNS protection, nutrient supply, waste removal, and adaptive regulation in response to neural activity [6,138]. Its selective permeability is crucial for preventing the entry of harmful substances and immune cells, thereby maintaining a stable environment for neuronal health [6,138]. The BBB regulates the supply of nutrients and removal of metabolic waste, ensuring that neurons and glial cells receive the resources required for optimal function [8,181,182]. Its dynamic responses to changes in neural activity, inflammation, and hypoxia further highlight its importance as an active regulator of brain homeostasis [6,138]. The functional roles of the BBB underscore its importance for maintaining CNS health and highlight the need for therapeutic strategies that can protect and support BBB integrity in neurodegenerative diseases [6,138].

2.6. BBB Dysfunction in Neurodegenerative Diseases

In neurodegenerative diseases, such as AD, PD, and multiple sclerosis, the BBB becomes increasingly compromised, disturbing the balance essential for brain health [12,183,184]. As tight junctions between endothelial cells weaken and transport mechanisms break down, blood-derived toxins, inflammatory molecules, and immune cells can infiltrate the brain [12,183,184] (Table 1). Such BBB disruption exacerbates neuroinflammation, accelerates neuronal damage, and promotes degeneration, establishing a self-perpetuating cycle that drives disease progression and facilitates cognitive and functional decline [12,183,184] (Table 1).

The integrity of the BBB is crucial for maintaining a stable internal environment in the CNS [11,19,185]. Its selective permeability ensures that only essential nutrients and ions reach the brain and waste products are efficiently removed [19,138]. However, in neurodegenerative diseases, this precise regulation is disrupted, allowing harmful substances to penetrate the BBB and disrupt neuronal function [12,183,184]. The breakdown of the BBB structure compromises the brain's defense against external stressors and internal imbalances, resulting in increased vulnerability to inflammation and toxin accumulation [8,20,186].

The BBB is an intricately designed barrier that plays essential roles in CNS protection, brain homeostasis, and neuronal health [19,138,185]. Each component of the BBB functions together to regulate selective permeability, providing the brain with a controlled environment crucial for optimal neuronal function [167,187]. In neurodegenerative diseases, this balance is disrupted because of BBB dysfunction. Consequently, harmful agents can infiltrate and accelerate disease progression [12,183,184]. The preservation of BBB integrity is therefore vital for maintaining the protective environment of the brain and supporting overall neural health [8,11,186].

Table 1. Critical functions of the BBB and its disruption in neurodegenerative diseases.

	Functions	Contents	References
Function of the BBB	Protection of the CNS and selective permeability	The BBB protects the CNS by preventing harmful substances from entering it, ensuring neural health.	[6,9,11]
		Tight junctions and specialized transport systems block pathogens, toxins, and other molecules, reducing infection and inflammation risks.	[9,24,140]
		The BBB acts as a selective barrier against circulating pathogens such as bacteria and viruses, minimizing infections like meningitis and encephalitis.	[141,142]
		The BBB limits peripheral immune cell access, preventing excessive immune responses that could cause inflammation and neuronal damage.	[6,145]
		This immune regulation is vital to protect sensitive neural tissue from inflammation, preserving synaptic signaling and preventing neuronal death.	[146,147]

Table 1. *Cont.*

	Functions	Contents	References
Function of the BBB	Nutrient supply and waste removal	The BBB supports brain metabolism by transporting essential nutrients and removing metabolic waste.	[8,137,149]
		GLUT1 transports glucose for energy production and neurotransmitter synthesis, while LAT1 facilitates the uptake of amino acids for protein and neurotransmitter production.	[154–159]
		The BBB regulates ions such as K^+ and Ca^{2+} to maintain ionic stability and support synaptic transmission.	[6,160]
		Efflux transporters, including P-gp, remove waste, xenobiotics, and toxins, preventing accumulation and oxidative stress.	[161–163]
	Adaptive regulation in response to neural activity	The BBB dynamically adjusts its permeability to meet the brain's metabolic needs, neural activity, and environmental conditions.	[6,138,167]
		During heightened neural activity, the BBB increases blood flow and nutrient delivery to active brain regions through vasodilation and neurovascular coupling.	[170–172]
		In response to inflammation and oxidative stress, the BBB strengthens tight junctions and enhances efflux transporter activity to protect the CNS.	[57,173,174]
		Under hypoxia, the BBB upregulates glucose and metabolite transporters and boosts endothelial antioxidant defenses to counteract oxidative damage.	[172,179,180]
BBB disruption in neurodegenerative diseases	Weakened tight junctions and transport breakdown allow harmful substances to enter the brain	In neurodegenerative diseases, BBB disruption allows harmful substances to impair neuronal function.	[12,183,184]
	BBB disruption fuels neuroinflammation, neuronal damage, and degeneration in a vicious cycle	BBB disruption worsens neuroinflammation, accelerates damage, and drives cognitive decline in a self-perpetuating cycle.	[12,183,184]
		BBB disruption weakens brain defense, causing toxin buildup and increased vulnerability.	[8,20,186]

3. Mechanisms of BBB Disruption in Neurodegenerative Diseases

BBB disruption is a significant hallmark in several neurodegenerative diseases, including AD, PD, and multiple sclerosis, as well as acute disorders such as ischemic stroke [3,6,184,188]. Although each disease involves unique pathological changes, several shared mechanisms contribute to BBB breakdown [6,184,188] (Figure 2, Table 2). These include oxidative stress, chronic inflammation, protein accumulation, and vascular dysfunction, which collectively weaken the structural and functional integrity of the BBB [6,184,188] (Table 2).

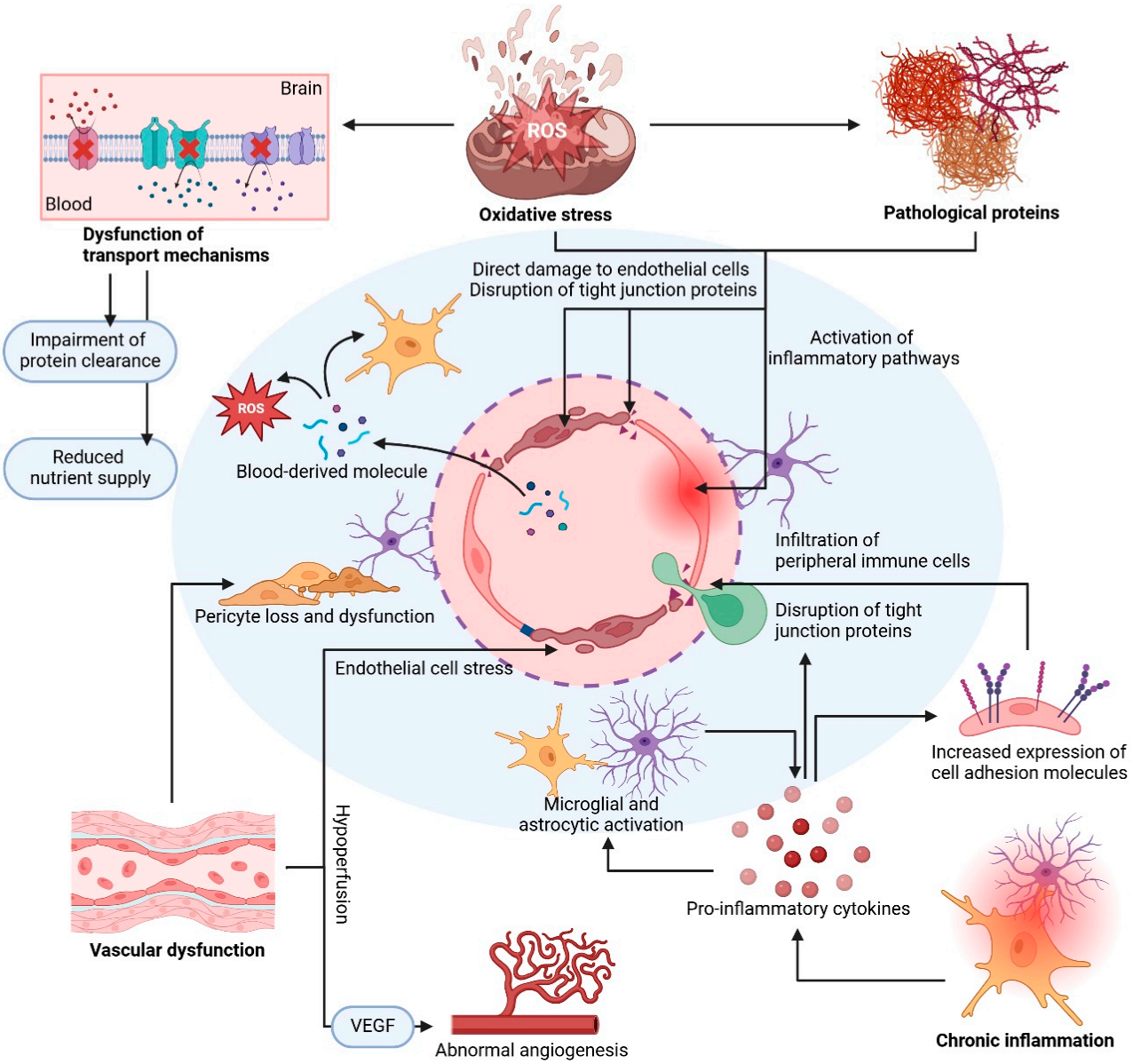

Figure 2. Mechanism of BBB disruption in the brain. Disruption of the BBB is a hallmark of several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Oxidative stress, chronic inflammation, pathological protein accumulation, and vascular dysfunction collectively weaken BBB integrity. Oxidative stress leads to increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which damage endothelial cells and tight junction proteins, thereby compromising the BBB and increasing its permeability. Chronic inflammation involves the release of proinflammatory cytokines by activated microglia and astrocytes, which weaken tight junctions and increase cell adhesion molecules. This facilitates immune cell infiltration into the CNS. Pathological proteins, such as Aβ, alpha-synuclein, and tau, accumulate and directly damage endothelial cells and tight junctions. They also activate inflammatory pathways that further destabilize the BBB. Vascular dysfunction, including hypoperfusion, vessel remodeling, and pericyte loss, limits oxygen and nutrient supply to the brain and weakens BBB stability. Lastly, impaired transport mechanisms disrupt nutrient supply and waste clearance, exacerbating neuronal damage. These factors collectively form a vicious cycle of BBB disruption and neurodegenerative disease progression. The figure was created using Biorender.com (Agreement number: ME27KUPC8L).

3.1. Mechanisms of Oxidative Stress-Induced BBB Damage

Oxidative stress is a primary contributor to BBB breakdown in neurodegenerative diseases [189–191]. It involves an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the ability of the brain to detoxify these reactive molecules or repair the resulting cellular damage [192–194]. In neurodegenerative diseases, oxidative stress is significantly elevated. This results in cumulative damage to BBB components, particularly endothelial cells and tight junction proteins, which are crucial for maintaining BBB integrity [24,195,196]. ROS, including superoxide anions, hydroxyl radicals, and hydrogen peroxide, are byproducts of normal cellular metabolism [197,198]. However, in neurodegenerative diseases, ROS production is often significantly elevated because of mitochondrial dysfunction, NADPH oxidase activation, and inflammatory cell activity [189,199]. The production of RNS, particularly nitric oxide (NO) and peroxynitrite, is also elevated in the brain. This increase in production is often caused by the overactivation of inducible nitric oxide synthase (iNOS) in inflammatory and endothelial cells [200,201].

3.1.1. Direct Damage to Endothelial Cells

BBB endothelial cells are highly susceptible to oxidative damage [195,196]. Excessive ROS and RNS can cause lipid peroxidation in the cell membranes, resulting in the loss of membrane integrity and functional alterations in endothelial cells [198,202,203]. Moreover, oxidative stress damages cellular organelles, particularly mitochondria, which are responsible for producing cellular energy [204–206]. Damaged mitochondria in turn release more ROS, creating a vicious cycle that amplifies oxidative stress within endothelial cells and weakens their barrier function [207–209].

3.1.2. Degradation of Tight Junction Proteins

Tight junction proteins, such as claudin-5, occludin, and JAMs, are crucial for maintaining the tight seal between BBB endothelial cells [21,24,25]. Oxidative stress disrupts these proteins through several mechanisms [21,24,25]. In particular, ROS and RNS can compromise BBB integrity by modifying and degrading tight junction proteins [21,41,210]. Various processes, such as nitration, carbonylation, and oxidation, can alter the structure and function of these proteins, diminishing their ability to form effective seals between cells [211,212]. Oxidative stress can also activate proteases, such as MMPs, which degrade ECM components and tight junction proteins [213–215]. Upon overactivation, MMPs cleave proteins, such as claudin-5 and occludin, causing increased BBB permeability and enhanced vulnerability to inflammation and cellular damage [216–218].

3.1.3. Activation of Inflammatory Pathways

Oxidative stress often triggers or enhances inflammatory responses, further contributing to BBB breakdown [196,219,220]. ROS and RNS can activate signaling pathways, such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, in endothelial cells, resulting in the production of proinflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF-α] and interleukin-1 beta [IL-1β]) [221–223]. These cytokines disrupt the BBB by weakening tight junctions and promoting the infiltration of peripheral immune cells [24,224,225]. Moreover, oxidative stress can upregulate cell adhesion molecules (e.g., intercellular adhesion molecule-1 [ICAM-1] and vascular cell adhesion molecule-1 [VCAM-1]) on endothelial cells, facilitating the binding and migration of inflammatory cells across the BBB [226–228].

3.1.4. Impact on Transport Mechanisms

Oxidative stress also affects the selective transport systems of the BBB, thereby disrupting the controlled passage of essential molecules [196,229]. In particular, ROS and RNS can damage carrier-mediated transport (CMT) and receptor-mediated transport (RMT) systems, lowering the efficiency of glucose and amino acid transport into the brain [198,230,231]. This deprivation of essential nutrients impairs neuronal metabolism and exacerbates neuronal vulnerability [232,233]. Additionally, oxidative stress reduces the function of efflux transporters, such as P-gp, leading to the accumulation of neurotoxic substances within the CNS [177,229,234].

3.2. Mechanisms of BBB Disruption Due to Chronic Inflammation

Chronic inflammation is a hallmark of many neurodegenerative diseases. It plays a crucial role in weakening the BBB [6,184,235]. In neurodegenerative diseases, persistent inflammatory responses disrupt BBB integrity, facilitating disease progression [4,5,188]. Activated microglia (resident immune cells in the brain) and astrocytes release proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6. These cytokines affect the structural and functional stability of the BBB, primarily by disrupting tight junctions and altering endothelial cell function [6,236,237].

3.2.1. Release of Proinflammatory Cytokines

Microglia and astrocytes are persistently activated in response to injury, protein accumulation, or environmental stress within the brain [238–240]. These activated glial cells release high levels of proinflammatory cytokines, including TNF-α, IL-1β, and IL-6 [239,241,242]. These cytokines bind to receptors on endothelial cells and trigger intracellular signaling cascades that weaken the BBB [167,224].

Proinflammatory cytokines play a significant role in compromising BBB integrity [225,243,244]. TNF-α binds to receptors on endothelial cells and activates signaling pathways, including the NF-κB pathway, which upregulates cell adhesion molecules, such as ICAM-1 and VCAM-1 [245–247]. This upregulation facilitates immune cell adhesion and migration across the BBB, resulting in heightened permeability [167,248,249]. Meanwhile, IL-1β and IL-6 contribute to inflammatory responses by upregulating MMPs and disrupting the expression of tight junction proteins, further weakening the BBB and increasing its susceptibility to inflammatory damage [12,21,244].

3.2.2. Disruption of Tight Junction Proteins Due to Inflammation

Chronic inflammation disrupts tight junction proteins that hold endothelial cells together and prevent paracellular transport [250–252]. Proinflammatory cytokines alter the expression and function of tight junction proteins, such as claudin-5, occludin, and ZO-1 [250,253,254]. Various cytokines, such as TNF-α and IL-1β, weaken the BBB by downregulating tight junction proteins at both transcriptional and translational levels, thereby reducing the tightness of the BBB and allowing toxic substances to pass more easily [21,243,255]. Additionally, inflammatory signaling can cause the phosphorylation of tight junction proteins. Consequently, they are redistributed away from cell–cell junctions [251,256]. This redistribution further compromises the BBB structure, increasing paracellular permeability and making the barrier more susceptible to infiltration and potential damage from external substances [251,256].

3.2.3. Activation of MMPs

Chronic inflammation often leads to the activation of MMPs, which degrade the ECM and basement membrane components [257,258]. Activated MMPs, particularly MMP-9

and MMP-2, break down collagen and laminin in the basement membrane, in addition to breaking down tight junction proteins [132,259,260]. This degradation not only weakens the physical structure of the BBB but also facilitates the infiltration of immune cells and inflammatory molecules into the CNS, further exacerbating neuroinflammation [261,262].

3.2.4. Increased Expression of Cell Adhesion Molecules

Inflammatory cytokines stimulate the expression of cell adhesion molecules on endothelial cells, such as ICAM-1 and VCAM-1 [263–265]. These cell adhesion molecules allow peripheral immune cells to bind to endothelial cells, enabling their passage through the BBB into brain tissue [225,226,266]. This infiltration of immune cells, including T cells and macrophages, amplifies the inflammatory response within the CNS, creating a self-sustaining cycle of BBB damage and neuroinflammation [145,267,268].

3.2.5. Microglial and Astrocytic Activation

The chronic activation of microglia and astrocytes creates a sustained inflammatory environment that can damage the BBB over time [236,238,269]. Microglia release additional ROS, RNS, and cytokines, further impairing endothelial cell function and degrading tight junction proteins [12,270,271]. Although astrocytes are typically beneficial to the BBB, they can contribute to inflammation by releasing IL-6 and other cytokines when chronically activated [272–274]. Such persistent glial activation amplifies the disruption of BBB integrity and perpetuates an environment of neuroinflammation [12,275].

3.2.6. Infiltration of Peripheral Immune Cells

Increased BBB permeability due to chronic inflammation allows peripheral immune cells, such as monocytes, T cells, and neutrophils, to infiltrate the CNS [6,276,277]. Within the brain, these cells release additional proinflammatory molecules, further promoting neuroinflammation and worsening BBB damage [12,278,279]. The resulting cycle of immune cell infiltration and inflammation creates a feed-forward loop, wherein inflammation continuously drives BBB disruption, in turn accelerating neurodegenerative processes [6,119,280].

3.3. Mechanisms of BBB Disruption by Pathological Proteins

The accumulation of abnormal proteins is a hallmark of neurodegenerative diseases and plays a significant role in disrupting BBB integrity [128,184,281]. In AD, PD, and various tauopathies, specific pathological proteins, such as amyloid-beta (Aβ), alpha-synuclein, and tau, respectively, accumulate in the brain [282–284]. These proteins exhibit toxic effects on the BBB by directly damaging endothelial cells, disrupting tight junctions, and triggering inflammatory responses. All these effects collectively increase BBB permeability and worsen disease progression [128,281,285].

3.3.1. Direct Damage to Endothelial Cells and Tight Junction Proteins

Aβ, alpha-synuclein, and tau proteins accumulate near and within BBB endothelial cells, causing cellular stress and structural damage [5,128,285]. For instance, Aβ can integrate into endothelial cell membranes, altering membrane integrity and triggering cellular stress pathways that weaken the BBB [286,287]. Similarly, excessive accumulation of alpha-synuclein and tau can disrupt cellular function, causing cellular stress and compromising the protective barrier function of endothelial cells [128,281,285].

Pathological proteins weaken tight junctions that seal endothelial cells, directly increasing BBB permeability [21,288,289]. These proteins can interfere with the expression and stability of key tight junction proteins, such as claudin-5 and occludin [184,281,290]. Aβ, for instance, can downregulate the expression of tight junction proteins by activating

inflammatory and oxidative stress pathways, which phosphorylate and degrade tight junction proteins, thereby weakening the tight seal of the BBB [165,291,292].

3.3.2. Activation of Inflammatory Response by Pathological Proteins

The accumulation of pathological proteins activates microglia and astrocytes, which release proinflammatory cytokines [238,239,269]. These cytokines disrupt BBB structure by targeting endothelial cells and promoting the activity of MMPs, which can degrade ECM components and further destabilize the BBB [11,224,261]. For instance, the accumulation of Aβ activates microglia, resulting in sustained inflammation that damages BBB integrity and increases the vulnerability of the brain to peripheral toxins and immune cells [128,271,293].

3.3.3. Impairment of Protein Clearance Mechanisms

The accumulation of pathological proteins is exacerbated by an impaired ability of the BBB to clear these toxins [128,184,294]. Normally, the BBB contains transporters and efflux mechanisms (e.g., low-density lipoprotein receptor-related protein 1 [LRP1]) to clear proteins like Aβ from the brain [295–297]. However, chronic accumulation of these proteins disrupts these clearance pathways, resulting in further accumulation of toxic proteins in the brain and exacerbating BBB permeability [295–297]. In AD, for instance, LRP1 is downregulated in response to high levels of Aβ, slowing its clearance and leading to increased deposition in the brain and around blood vessels [295,296,298].

3.3.4. Oxidative Stress Induced by Pathological Proteins

Pathological proteins also contribute to oxidative stress, further damaging the BBB [128]. Aβ, alpha-synuclein, and tau can increase the production of ROS within endothelial cells and nearby glial cells [299–301]. Such oxidative stress damages cellular structures, including tight junctions and cell membranes, promoting BBB leakage [128]. ROS can further activate inflammatory pathways, creating a cycle of inflammation, oxidative stress, and BBB damage [3,270,302].

3.4. Mechanisms of BBB Disruption Due to Vascular Dysfunction

Vascular dysfunction is a prominent feature of neurodegenerative diseases. It significantly enhances BBB disruption [6,135,183]. In neurodegenerative diseases, abnormalities in blood flow, structural remodeling of blood vessels, and direct damage to the vascular system impact BBB integrity and facilitate disease progression [4,6,184]. These vascular changes compromise endothelial cell function, reduce the supply of oxygen and nutrients to the brain, and weaken tight junctions, leading to increased BBB permeability and heightened neuronal damage [3].

3.4.1. Reduced Blood Flow to the Brain (Hypoperfusion)

Hypoperfusion is commonly observed in neurodegenerative diseases [303–305]. It deprives brain cells, including endothelial cells, of essential oxygen and nutrients, thereby creating a stressful environment that compromises BBB stability [6,305,306].

Inadequate oxygen and glucose supply leads to endothelial stress and dysfunction, causing mitochondrial impairment, increased ROS production, and a breakdown of tight junction integrity [307–309]. This stressful environment increases BBB permeability and heightens its vulnerability to damage [3,41,306]. Moreover, hypoperfusion creates hypoxic conditions within the brain. Low oxygen levels further impair cellular function and weaken tight junctions [24,305,310]. This hypoxic injury renders the BBB more susceptible to external stressors, allowing neurotoxic substances to penetrate the brain and potentially cause additional damage [19,311,312].

3.4.2. Vascular Remodeling

Blood vessels often undergo structural remodeling to adapt to the reduced blood supply resulting from chronic hypoperfusion or hypoxia [313]. While these changes are initially compensatory, they can ultimately destabilize the BBB [314–316].

In neurodegenerative diseases, structural changes in the BBB compromise its function [6,127,184]. The basement membrane surrounding blood vessels can thicken abnormally, disrupting the NVU and weakening interactions between endothelial cells, pericytes, and astrocytes, thereby weakening the protective role of the BBB [20,104,317]. Additionally, hypoxia-induced angiogenesis, primarily driven by VEGF, leads to the formation of new blood vessels [318,319]. However, these newly formed vessels are often immature and lack proper tight junctions, making them leaky and facilitating the entry of unwanted substances into the brain [21,148,320]. This increased permeability further disrupts the CNS environment and weakens BBB integrity [8,11,138].

3.4.3. VEGF and Tight Junction Disruption

VEGF is upregulated in hypoxic and neuroinflammatory conditions, commonly noted in neurodegenerative diseases [321–323]. While VEGF promotes angiogenesis, it also disrupts BBB integrity [324–326].

Moreover, VEGF facilitates the breakdown of the BBB by downregulating tight junction proteins, thereby increasing paracellular permeability and weakening BBB integrity [24,25,327]. As the expression of tight junction proteins decreases, endothelial cells become less cohesive, creating gaps that allow blood-derived toxins and inflammatory molecules to infiltrate the brain [21,24,328]. Additionally, VEGF signaling through receptors on endothelial cells promotes vascular permeability by inducing the disassembly of tight junction proteins and causing the retraction of endothelial cells [329,330]. This increased permeability allows harmful substances to cross the BBB, further exacerbating neuroinflammation and contributing to CNS dysfunction [6,12,175].

3.4.4. Pericyte Loss and Dysfunction

Pericytes play a crucial role in maintaining vascular stability and BBB integrity [34,52,331]. In neurodegenerative diseases, pericyte loss and dysfunction can contribute to vascular abnormalities [44,332,333].

Reduced pericyte coverage weakens the BBB by depriving endothelial cells of the necessary structural support, thereby compromising tight junction integrity and increasing permeability [34,60,334]. This decrease in pericyte support, observed in neurodegenerative diseases, is associated with an increase in the permeability and instability of blood vessels [335,336]. Pericytes also play a crucial role in regulating capillary blood flow in response to neural activity. When pericytes are dysfunctional, they fail to adjust blood flow adequately, resulting in impaired circulation and hypoxic conditions [68,337,338]. These hypoxic conditions further weaken BBB integrity, making the brain more vulnerable to external stressors and potential damage [339–341].

3.5. Dysfunction of Transport Mechanisms

In neurodegenerative diseases, BBB disruption is frequently accompanied by dysfunction of the transport systems responsible for the controlled exchange of nutrients, ions, and waste products between the bloodstream and the brain [5,6,184]. Two primary transport mechanisms, namely CMT and RMT, typically regulate the selective passage of essential molecules, while efflux transporters actively remove neurotoxic substances from the brain [342–344]. When these systems are compromised, as commonly seen in neurodegenerative diseases, the supply of essential nutrients to the brain is reduced and

the clearance of harmful waste products is impaired. Both these effects accelerate neuronal damage and exacerbate disease progression [4,6,119].

3.5.1. CMT Impairment

CMT systems selectively move small molecules, such as glucose, amino acids, and ions, across the BBB [154,156,343]. These transporters play a crucial role in providing neurons with the resources essential for energy and neurotransmitter synthesis [154,156,159].

In neurodegenerative diseases, dysfunctional nutrient transport across the BBB significantly impacts brain health [4,6]. The expression of GLUT1, responsible for delivering glucose, is often downregulated in these conditions, resulting in impaired glucose transport [345–347]. The resultant energy shortage makes neurons more vulnerable to stress and damage. For instance, in AD, decreased GLUT1 levels correlate with cognitive decline caused by energy deficits that hinder neuronal function and synaptic transmission [345,346,348]. Additionally, amino acid transport is compromised by the decreased function of carrier proteins, such as LAT1, which transports essential amino acids, such as tryptophan and tyrosine [159,349,350]. These amino acids are precursors for serotonin and dopamine, respectively, which are neurotransmitters crucial for mood and cognition [351,352]. Limited availability of these precursors disrupts neurotransmitter synthesis, impairing neural signaling and potentially contributing to the mood and cognitive disturbances associated with neurodegenerative diseases [353–355].

3.5.2. RMT Impairment

Larger molecules, such as hormones, growth factors, and certain proteins, rely on RMT to cross the BBB [11,153]. In neurodegenerative diseases, RMT pathways become dysfunctional, affecting the delivery of key molecules into the brain [6,356].

Insulin and other growth factors, crucial for brain function, rely on specific transport mechanisms at the BBB that can be compromised in neurodegenerative diseases [357–359]. Insulin, which crosses the BBB through insulin receptors on endothelial cells, is essential for neuronal glucose metabolism and growth signaling [360–362]. However, in AD, insulin receptors often function poorly, causing brain insulin resistance [363–365]. This reduced insulin transport results in energy deficits and impaired neural plasticity, potentially accelerating disease progression [364,366]. Similarly, transferrin receptors are responsible for transporting iron, which is vital for neuronal function [367–369]. In PD and other neurodegenerative disorders, disrupted regulation of iron transport can lead to iron accumulation in certain brain regions. This can result in oxidative stress and neurotoxicity, further exacerbating neuronal damage [370–372].

3.5.3. Efflux Transporter Dysfunction

Efflux transporters, such as P-gp, are crucial for clearing neurotoxic substances from the brain [370–372]. These ATP-dependent transporters actively pump out toxins, xenobiotics, and metabolic byproducts, helping maintain the internal environment of the brain [163,373,374]. However, in neurodegenerative diseases, the function of efflux transporters is often impaired [6,182,375].

P-gp and other efflux transporters are essential for clearing neurotoxic substances from the brain; however, their downregulation in neurodegenerative diseases leads to harmful accumulations [177,182]. P-gp expels Aβ from the brain. However, decreased expression and activity of P-gp in AD can contribute to the accumulation of Aβ, exacerbating plaque formation, neuroinflammation, and neuronal loss [376–378]. Similarly, dysfunctional efflux transporters enable the accumulation of harmful metabolic byproducts, environmental toxins, and drugs, increasing oxidative stress and damaging neurons [6,182,229]. In PD,

impaired clearance of neurotoxins intensifies dopaminergic neuron loss, worsening motor dysfunction and advancing disease progression [379–381].

3.5.4. Disrupted Ion Transport

BBB transport mechanisms also regulate ion balance, ensuring that the ionic environment of the brain remains optimal for neuronal activity [11,382,383]. In neurodegenerative diseases, the regulation of ions becomes impaired [4,6,119]. The regulation of calcium ions, K^+, and sodium ions is crucial for maintaining neuronal signaling and excitability. However, dysregulation of these ions can lead to severe neuronal stress and damage in neurodegenerative diseases [384,385]. Ion channels and transporters tightly regulate calcium and potassium concentrations in the brain; however, dysfunction of these pathways can result in abnormal concentrations of ions, causing excitotoxicity or neuronal hyperactivity that damages neurons over time [102,386,387]. Similarly, sodium–potassium ATPase, which maintains the sodium and potassium balance across the BBB, can become impaired in neurodegenerative diseases, leading to imbalances in neuronal resting potentials and the disruption of electrical signaling [388]. This dysregulation places additional stress on neurons, as seen in multiple sclerosis, wherein ion imbalance is particularly prevalent, further compromising neural health [389,390].

Table 2. Mechanisms of BBB disruption in neurodegenerative diseases.

Title	Subtitle	Contents	References
Mechanisms of oxidative stress-induced BBB damage	Direct damage to endothelial cells	Oxidative stress induces lipid peroxidation, compromising membrane integrity and endothelial cell function.	[198,202,203]
		Damaged cellular organelles, especially mitochondria, further amplify oxidative stress by releasing more ROS.	[204–206]
		This vicious cycle weakens the barrier function of endothelial cells, exacerbating BBB dysfunction.	[207–209]
	Degradation of tight junction proteins	Oxidative stress disrupts tight junction proteins through ROS- and RNS-induced modifications, such as nitration, carbonylation, and oxidation.	[21,41,210]
		Oxidative stress activates proteases such as MMPs, which degrade ECM components and tight junction proteins.	[213–215]
		Overactive MMPs cleave claudin-5 and occludin, increasing BBB permeability and vulnerability to inflammation and damage.	[216–218]
	Activation of inflammatory pathways	ROS and RNS activate the NF-κB pathway, leading to the release of proinflammatory cytokines, including TNF-α and IL-1β.	[221–223]
		Proinflammatory cytokines weaken tight junctions and promote immune cell infiltration, disrupting the BBB.	[24,224,225]
		Oxidative stress upregulates adhesion molecules (ICAM-1 and VCAM-1), enhancing inflammatory cell migration across the BBB.	[226–228]

Table 2. *Cont.*

Title	Subtitle	Contents	References
Mechanisms of oxidative stress-induced BBB damage	Impact on transport mechanisms	ROS and RNS damage CMT and RMT, reducing glucose and amino acid delivery to the brain.	[198,230,231]
		Nutrient deprivation impairs neuronal metabolism, increasing neuronal vulnerability.	[232,233]
		Oxidative stress diminishes efflux transporter function (e.g., P-gp), causing neurotoxic substance accumulation in the CNS.	[177,229,234]
Mechanisms of BBB disruption due to chronic inflammation	Release of proinflammatory cytokines	Microglia and astrocytes are activated by brain injury, protein accumulation, or stress, releasing proinflammatory cytokines such as TNF-α, IL-1β, and IL-6.	[239,241,242]
		TNF-α activates the NF-κB pathway, upregulating adhesion molecules (ICAM-1 and VCAM-1) and promoting immune cell migration across the BBB.	[245–247]
		IL-1β and IL-6 increase inflammation by upregulating MMPs and disrupting tight junction proteins, further compromising BBB integrity.	[12,21,244]
	Disruption of tight junction proteins due to inflammation	Proinflammatory cytokines such as TNF-α and IL-1β downregulate tight junction proteins (claudin-5, occludin, and ZO-1) at transcriptional and translational levels.	[250,253,254]
		Reduced tight junction protein expression weakens the BBB, allowing easier passage of toxic substances.	[21,243,255]
		Inflammatory signaling phosphorylates tight junction proteins, causing their redistribution away from cell junctions.	[251,256]
	Activation of MMPs	Chronic inflammation activates MMPs, especially MMP-9 and MMP-2, which degrade ECM and basement membrane components.	[132,259,260]
		MMPs break down collagen, laminin, and tight junction proteins, weakening the BBB structure.	[261,262]
	Increased expression of cell adhesion molecules	Inflammatory cytokines upregulate cell adhesion molecules (ICAM-1 and VCAM-1) on endothelial cells.	[263–265]
		These adhesion molecules enable peripheral immune cells to bind and cross the BBB into brain tissue.	[225,226,266]
	Microglial and astrocytic activation	Microglia release ROS, RNS, and cytokines, impairing endothelial function and degrading tight junction proteins.	[12,270,271]
		Chronically activated astrocytes release IL-6 and other cytokines, contributing to inflammation.	[272–274]
		Persistent glial activation amplifies BBB disruption and perpetuates neuroinflammation.	[12,275]

Table 2. *Cont.*

Title	Subtitle	Contents	References
Mechanisms of BBB disruption due to chronic inflammation	Infiltration of peripheral immune cells	Chronic inflammation increases BBB permeability, allowing immune cells such as monocytes, T cells, and neutrophils to infiltrate the CNS.	[6,276,277]
		Infiltrating immune cells release proinflammatory molecules, worsening neuroinflammation and BBB damage.	[12,278,279]
		This creates a feed-forward loop where inflammation perpetuates BBB disruption, accelerating neurodegenerative processes.	[6,119,280]
Mechanisms of BBB disruption by pathological proteins	Direct damage to endothelial cells and tight junction proteins	Aβ integrates into endothelial membranes, altering integrity and activating stress pathways that weaken the BBB.	[286,287]
		Alpha-synuclein and tau disrupt endothelial cell function, compromising the BBB's protective layer.	[128,281,285]
		Pathological proteins weaken tight junctions by interfering with the expression and stability of proteins such as claudin-5 and occludin.	[184,281,290]
		Aβ downregulates tight junction proteins through inflammatory and oxidative stress pathways, increasing BBB permeability.	[165,291,292]
	Activation of inflammatory response by pathological proteins	Pathological protein accumulation activates microglia and astrocytes, leading to the release of proinflammatory cytokines.	[238,239,269]
		These cytokines disrupt BBB structure by targeting endothelial cells and activating MMPs.	[11,224,261]
	Impairment of protein clearance mechanisms	The BBB normally uses transporters (e.g., LRP1) to remove proteins such as Aβ from the brain.	[295–297]
		Chronic protein accumulation disrupts these clearance pathways, increasing toxic protein buildup and BBB permeability.	[295–297]
		In AD, LRP1 is downregulated in response to high Aβ levels, slowing its clearance and promoting further deposition in the brain and blood vessels.	[295,296,298]
	Oxidative stress induced by pathological proteins	Pathological proteins increase ROS production in endothelial and glial cells.	[299–301]
Mechanisms of BBB disruption due to vascular dysfunction	Reduced blood flow to the brain (hypoperfusion)	Hypoperfusion in neurodegenerative diseases deprives brain cells of oxygen and nutrients, compromising BBB stability.	[6,303–306]
		Oxygen and glucose deprivation cause endothelial stress, mitochondrial dysfunction, and increased ROS production.	[307–309]
		Hypoperfusion-induced hypoxia weakens tight junctions and impairs cellular function.	[24,305,310]
	Vascular remodeling	In neurodegenerative diseases, abnormal thickening of the basement membrane disrupts the NVU and weakens BBB function.	[20,104,317]
		Hypoxia-induced angiogenesis driven by VEGF creates immature, leaky blood vessels lacking proper tight junctions.	[318,319]

Table 2. *Cont.*

Title	Subtitle	Contents	References
Mechanisms of BBB disruption due to vascular dysfunction	VEGF and tight junction disruption	While VEGF promotes angiogenesis, it disrupts BBB integrity by downregulating tight junction proteins.	[24,25,327]
		VEGF signaling causes tight junction disassembly and endothelial cell retraction, enhancing vascular permeability.	[329,330]
	Pericyte loss and dysfunction	Reduced pericyte coverage weakens tight junctions, increasing BBB permeability and instability.	[34,60,334]
		Dysfunctional pericytes fail to regulate capillary blood flow, leading to impaired circulation and hypoxic conditions.	[68,337,338]
Dysfunction of transport mechanisms	CMT impairment	CMT systems transport small molecules such as glucose, amino acids, and ions across the BBB, essential for neuronal energy and neurotransmitter synthesis.	[154,156,159]
		GLUT1 downregulation impairs glucose transport, causing energy deficits that increase neuronal vulnerability and hinder synaptic transmission.	[345,346,348]
		Decreased LAT1 function limits amino acid transport, reducing precursors for neurotransmitters, including serotonin and dopamine.	[159,349–352]
	RMT impairment	Larger molecules such as hormones, growth factors, and proteins cross the BBB via RMT. In neurodegenerative diseases, RMT dysfunction disrupts the delivery of essential molecules to the brain.	[6,11,153,356]
		Insulin, crucial for glucose metabolism and growth signaling, crosses the BBB through insulin receptors, but brain insulin resistance in AD impairs this process.	[360–365]
		Transferrin receptors regulate iron transport, but their dysfunction in PD and other disorders causes iron accumulation in the brain.	[367–372]
	Efflux transporter dysfunction	P-gp clears Aβ, but its downregulation in AD promotes Aβ buildup, exacerbating plaque formation, neuroinflammation, and neuronal loss.	[177,182,376–378]
		Dysfunctional transporters allow metabolic byproducts, toxins, and drugs to accumulate, increasing oxidative stress and neuronal damage.	[6,182,229]
	Disrupted ion transport	Ca^{2+}, K^{+}, and Na^{+} ion dysregulation leads to excitotoxicity and neuronal hyperactivity, damaging neurons over time.	[384,385]
		Dysfunctional ion channels and transporters disrupt Ca^{2+} and K^{+} concentrations, exacerbating neuronal damage.	[102,386,387]
		Impaired Na^{+}–K^{+} ATPase disrupts ion balance, altering neuronal resting potentials and electrical signaling.	[388]

4. Consequences of BBB Disruption

When the BBB is compromised, it sets off a cascade of pathological processes that accelerate neurodegeneration [6,119,183]. This weakened BBB allows immune cells, blood-derived molecules, and toxic substances to infiltrate the brain, triggering neuroinflammation, neurotoxicity, and abnormal protein aggregation [4,184]. These processes interact in a self-perpetuating cycle that worsens neuronal damage and accelerates disease progression [391–393].

4.1. Neuroinflammation

BBB disruption allows immune cells, such as macrophages, T cells, and B cells, to infiltrate the brain parenchyma [394–396]. Under normal conditions, the BBB acts as a selective barrier that prevents these peripheral immune cells from entering the CNS [395,397]. However, once the BBB is compromised, its increased permeability enables these cells to enter the brain, triggering a potent neuroinflammatory response [398,399].

The entry of peripheral immune cells into the brain triggers an inflammatory cascade that disrupts BBB integrity and accelerates neurodegeneration [400,401]. Immune cell infiltration activates resident immune cells, such as microglia and astrocytes, which release proinflammatory cytokines, thereby amplifying inflammation and causing further neuronal and glial cell damage [82,239,402]. Microglia enter a proinflammatory state, releasing additional cytokines, ROS, and RNS. Furthermore, astrocytes, which usually support BBB function, contribute to the inflammatory environment by releasing additional cytokines and chemokines [403–405]. This inflammatory response damages endothelial cells and disrupts tight junctions, increasing BBB permeability and allowing even more immune cells to infiltrate the brain. Consequently, a feedback loop of inflammation and barrier breakdown is created [21,24,397]. This cycle of chronic neuroinflammation accelerates neurodegeneration by directly harming neurons, increasing oxidative stress, and interfering with neuronal signaling [406,407].

4.2. Neurotoxicity from Blood-Derived Molecules

In a healthy brain, the BBB restricts the entry of blood-derived molecules [6,8,11,14,408]. However, when the BBB is compromised, these substances leak into the brain parenchyma, causing neuronal damage and exacerbating neurodegeneration [4,14,294,408,409].

When the BBB is compromised, various blood proteins, such as prothrombin, thrombin, prothrombin kringle-2 (pKr-2), fibrinogen, and albumin, also infiltrate the brain, initiating a cascade of neuroinflammatory and neurodegenerative processes [14,408]. Moreover, thrombin stimulates microglia and astrocytes to release inflammatory mediators, impairing synaptic plasticity, neuronal signaling, and overall neuronal health [14,410,411]. Prolonged exposure to thrombin and other blood proteins exacerbates neuronal dysfunction and can cause neuronal death [14,410,411]. pKr-2, a fragment of prothrombin, is indirectly neurotoxic. It specifically activates microglia and induces a proinflammatory response that results in elevated cytokine production and oxidative stress, further damaging neurons [14,408,412]. Fibrinogen is another clotting protein that is particularly detrimental to the CNS [413]. Once it crosses the compromised BBB, it activates microglia to release additional cytokines and ROS, thereby intensifying neuroinflammation and causing BBB disruption [14,413]. In AD, fibrinogen also binds to Aβ, promoting its aggregation into plaques and accelerating disease progression [414,415]. Albumin is typically restricted from entering the brain. However, upon BBB breakdown, it further contributes to neuroinflammation [12,294,398]. By disrupting neural ion balance, it causes excitotoxicity and activates astrocytes, which release inflammatory mediators that weaken the BBB and amplify inflammation [416–418]. This cycle of protein infiltration, neuroinflammation, and

oxidative stress establishes a feedback loop that progressively worsens neuronal function, potentially causing irreversible neurodegeneration [12,14,294].

4.3. Abnormal Protein Aggregation

BBB breakdown also facilitates the accumulation and aggregation of pathological proteins, such as Aβ in AD and alpha-synuclein in PD [184,419,420]. These proteins disrupt neuronal function and form aggregates, such as Aβ plaques in AD and Lewy bodies in PD [421–423]. The presence of these aggregates initiates a series of damaging processes that accelerate neurodegeneration [424,425]. The compromised BBB allows the accumulation of pathological proteins within the brain. These proteins can aggregate because of reduced clearance [127,128,184]. Upon accumulation, Aβ and alpha-synuclein are particularly prone to aggregation, forming insoluble deposits that are resistant to normal degradation pathways [426–428].

Protein aggregates in neurodegenerative diseases interfere with neuronal function and create a toxic environment that accelerates neurodegeneration [424,429,430]. These aggregates disrupt essential cellular processes, such as synaptic signaling, cellular transport, and mitochondrial function [428,431,432]. For instance, Aβ plaques disrupt calcium signaling, which is vital for neurotransmission, while alpha-synuclein aggregates impair vesicle trafficking and dopamine release, thereby affecting motor function in PD [433–435]. These aggregates also activate microglia and astrocytes, which release proinflammatory cytokines and ROS, establishing a chronic state of neuroinflammation and oxidative stress [238,436,437]. This toxic environment further damages neurons and promotes additional protein aggregation, creating a self-perpetuating cycle of degeneration [238,407,437]. The formed aggregates are resistant to degradation and persist within the brain, disrupting neuronal networks and contributing to neuronal loss over time [438–440]. The presence of these persistent structures is linked to the progressive cognitive and motor deficits characteristic of neurodegenerative diseases [135,441,442].

5. Therapeutic Approaches to Preserve BBB Integrity

The BBB is essential for maintaining a stable environment in the CNS. It regulates the exchange of substances and protects neurons from toxins, inflammation, and other stressors [6,9,11]. In neurodegenerative diseases, BBB disruption accelerates neurodegeneration. Hence, therapeutic approaches to preserve or restore BBB integrity are crucial [6,15,119]. These strategies include the use of anti-inflammatory and antioxidant therapies; modulation of tight junctions; enhancement of transport mechanisms; and use of neuroprotective agents, such as caffeine, which can support BBB stability [21,231,443] (Figure 3).

5.1. Anti-Inflammatory Therapies

Chronic inflammation is a major contributor to BBB disruption in neurodegenerative diseases [6,444]. Anti-inflammatory therapies aim to reduce the damaging effects of proinflammatory cytokines and immune cell infiltration, thereby stabilizing the BBB [243,445,446].

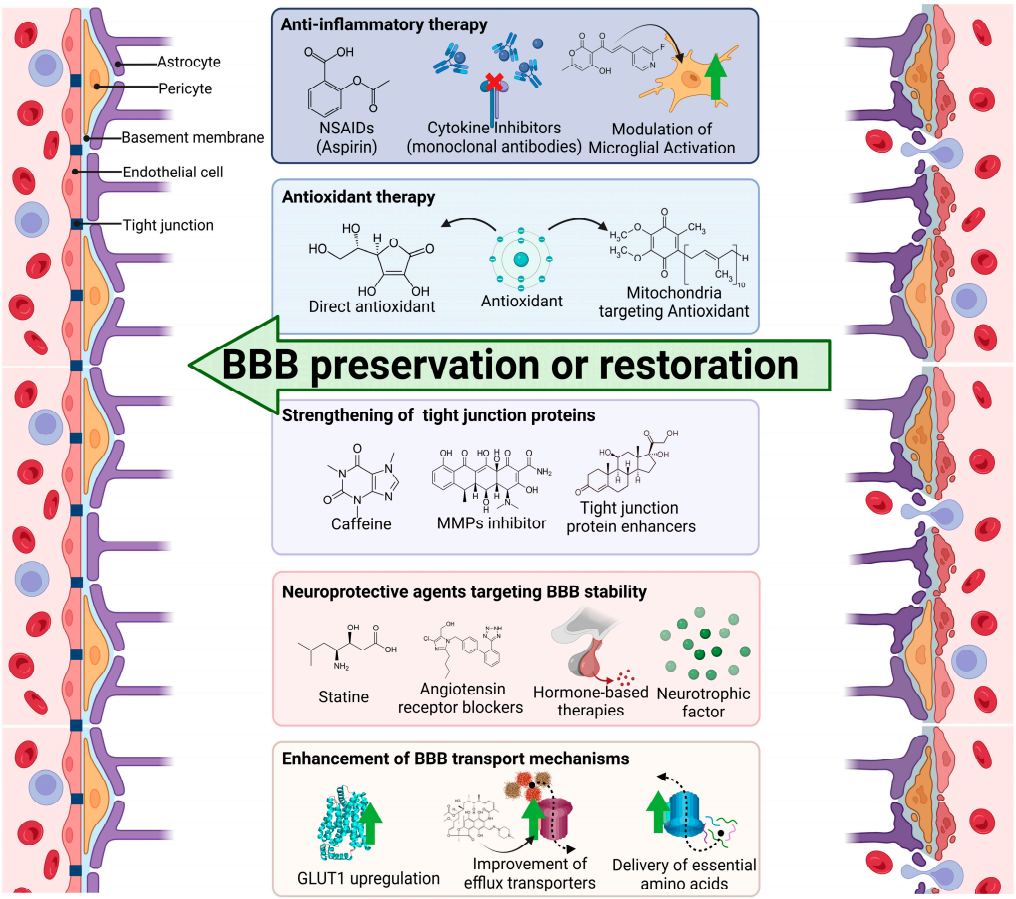

Figure 3. Therapeutic approach to preserve the BBB. In neurodegenerative diseases, BBB damage accelerates neurodegeneration. Hence, strategies to preserve or restore BBB integrity are crucial for delaying disease progression and protecting brain function. Key approaches include the use of anti-inflammatory and antioxidant therapies, strengthening of tight junction proteins, enhancement of BBB transport mechanisms, and use of neuroprotective agents. Anti-inflammatory therapies reduce BBB damage by inhibiting inflammatory cytokine and immune cell infiltration, while antioxidant therapies protect BBB components from oxidative stress caused by ROS. The upregulation of tight junction proteins decreases BBB permeability. Moreover, improved transport mechanisms ensure the delivery of essential nutrients to the brain and the clearance of toxic substances from the brain, while neuroprotective agents directly enhance BBB stability. Together, these strategies help maintain BBB integrity, creating a stable environment in the brain and protecting neural functions. Thus, multifaceted approaches to protect and restore the BBB are vital therapeutic targets for preserving brain health in neurodegenerative diseases. The figure was created using Biorender.com (Agreement number: AH27QDI3FF).

Therapeutic strategies aimed at reducing neuroinflammation and protecting the BBB are being explored to combat BBB damage in neurodegenerative diseases [13,184,447]. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit various enzymes, such as COX-2, which lowers the production of proinflammatory cytokines that can weaken BBB integrity [445,446,448]. Certain NSAIDs may exhibit neuroprotective effects in AD, potentially slowing BBB damage by reducing inflammatory signaling [401,449]. Additionally, targeting specific cytokines, such as TNF-α, IL-1β, and IL-6, with cytokine inhibitors, including monoclonal antibodies and other biologics, may directly reduce BBB permeability and neuroinflammation [175,444,450]. Modulating microglial activation is promising, as lowering the activation of these resident immune cells can help minimize neuroinflammation and prevent further BBB damage [271,279,451]. Different compounds, such as

PPAR-γ agonists and other anti-inflammatory agents, are currently under investigation to modulate microglial activity in order to reduce chronic inflammation and protect the BBB from ongoing disruption [452–454]. Moreover, emerging therapeutic approaches are focusing on more precise targets to combat inflammation-induced BBB disruption. For instance, Janus kinase inhibitors, such as tofacitinib, have shown potential in blocking key inflammatory pathways mediated by cytokines, thereby reducing endothelial activation and stabilizing the BBB [455,456]. Furthermore, NF-κB inhibitors are being developed to downregulate pro-inflammatory gene expression, which is critical in mitigating BBB damage [457]. Another promising strategy involves the use of MMP inhibitors, such as doxycycline, to prevent the degradation of tight junction proteins and basement membrane components, thereby preserving the structural integrity of the BBB [132,458,459].

5.2. Antioxidant Therapies

Oxidative stress significantly contributes to BBB breakdown by damaging endothelial cells and tight junction proteins [196,460]. Antioxidant therapies aim to neutralize ROS and RNS, protecting BBB components from oxidative damage [300,461,462].

Various antioxidant strategies are being explored to protect BBB integrity by reducing oxidative stress in neurodegenerative diseases [463–465]. Direct antioxidants, such as vitamin E, vitamin C, and N-acetylcysteine (NAC), can neutralize ROS in the brain, potentially preventing oxidative damage to BBB endothelial cells and preserving tight junctions [466–468]. Another approach is targeting the source of ROS, namely mitochondrial dysfunction, in endothelial cells. Antioxidants targeting the mitochondria, such as MitoQ and coenzyme Q10, are being studied for their potential to reduce ROS production within mitochondria and support BBB health [469,470]. Moreover, polyphenols, such as resveratrol, curcumin, and flavonoids, are plant-based compounds with antioxidant and anti-inflammatory properties [471–473]. They can cross the BBB and may further support BBB integrity by reducing oxidative stress and inflammation in the CNS [460,474,475]. Emerging antioxidant therapies are leveraging innovative strategies to combat oxidative stress and protect BBB integrity in neurodegenerative diseases. Enzyme-based antioxidants, such as superoxide dismutase mimetics and catalase formulations, directly neutralize ROS, while nanoparticle-based delivery systems enhance antioxidant bioavailability and target oxidative damage within the CNS [476–478]. Compounds that activate the Nrf2 signaling pathway, such as sulforaphane and dimethyl fumarate, promote the expression of endogenous antioxidant enzymes, providing long-term cellular protection [479,480]. Lipid-based antioxidants such as alpha-lipoic acid and hydrogen therapy, which selectively reduce toxic ROS, offer additional avenues for mitigating oxidative stress and preserving endothelial cell function [481–483]. Targeting mitochondrial dysfunction with pharmacological chaperones to reduce ROS production at its source is another promising approach [484–486]. Furthermore, combination therapies pairing antioxidants with anti-inflammatory agents, such as curcumin, show synergistic effects in reducing oxidative and inflammatory damage [487]. These advanced strategies highlight the potential for comprehensive antioxidant approaches to stabilize the BBB and slow the progression of neurodegenerative diseases.

5.3. Modulation of Tight Junction Proteins

The integrity of the BBB heavily relies on tight junction proteins, such as claudin-5, occludin, and ZO-1, which prevent paracellular leakage [21,25,216]. Strategies to strengthen or restore tight junctions are therefore promising for preserving BBB function [21,24,328].

Various therapeutic approaches are being explored to enhance BBB integrity by targeting tight junction proteins, reducing permeability, and stabilizing the barrier [21,24,328]. Agents that upregulate tight junction protein expression, e.g., glucocorticoids, can

strengthen the BBB by increasing the expression of proteins, such as occludin and claudin. However, their long-term use may be associated with side effects [488–490]. Caffeine also shows promise for BBB support; it upregulates tight junction proteins, such as claudin-5 and ZO-1, improving endothelial cell cohesion and reducing permeability [408,491]. Its antioxidant and anti-inflammatory properties also help protect tight junctions from oxidative stress and inflammation—factors contributing to BBB breakdown [492,493]. VEGF inhibition is another approach, as VEGF disrupts tight junctions and increases BBB permeability in neurodegenerative diseases. Specific antagonists or antibodies targeting VEGF may reduce leakage and support barrier stability [494–496]. Lastly, MMPs degrade tight junction proteins and basement membrane components, weakening the BBB. MMP inhibitors, such as doxycycline, reduce MMP activity, thereby preserving tight junction integrity and further promoting BBB stability [132,259,459]. Together, these interventions may help lower the progression of neurodegenerative diseases by reinforcing the BBB [6,184,497]. Emerging strategies to modulate tight junction proteins focus on enhancing BBB integrity through innovative approaches. Small molecules targeting tight junction signaling pathways, such as Wnt/β-catenin activators, and peptide-based therapies that mimic tight junction domains show promise in strengthening BBB stability [253,498]. Natural compounds such as flavonoids (e.g., baicalin and quercetin) offer dual antioxidant and anti-inflammatory benefits while enhancing tight junction expression [499–501]. These advancements offer promising avenues to preserve BBB integrity and mitigate neurodegeneration.

5.4. Enhancement of BBB Transport Mechanisms

Efficient transport across the BBB is essential for delivering nutrients and clearing waste products [19,181,502]. Therapeutic approaches to enhance or restore CMT, RMT, and efflux systems are being explored to improve BBB function [342–344].

Enhancing transporter function at the BBB is a promising strategy for supporting neuronal health and maintaining BBB integrity in neurodegenerative diseases [6,8,184]. The upregulation of GLUT1 can improve glucose transport across the BBB, restoring energy balance in the CNS. This can be particularly effective in AD, where glucose transport is often impaired [345,346,419]. Efflux transporters, such as P-gp, play a crucial role in removing neurotoxic substances from the brain. Increasing P-gp activity may help clear harmful proteins, such as Aβ, thereby reducing the brain's toxic burden and supporting BBB stability [378,503,504]. Additionally, amino acid transporters, such as LAT1, facilitate the passage of essential amino acids, which are necessary for neurotransmitter synthesis [158,159,505]. Enhancing these transporters can increase the availability of key precursors for neurotransmitter production, contributing to neuronal health and further reinforcing BBB integrity [158,159,505]. Emerging strategies to enhance BBB transport mechanisms aim to optimize nutrient delivery, waste clearance, and therapeutic drug delivery in neurodegenerative diseases. Lipid transporters, such as those facilitating omega-3 fatty acid delivery, and iron transporters, such as transferrin receptor 1, support neuronal health and prevent oxidative damage [506–508]. The modulation of efflux transporters, including P-gp and BCRP, is being investigated to balance the clearance of neurotoxins while enhancing therapeutic efficacy [509–511]. Peptide-based therapeutics that mimic natural ligands are also being studied to exploit endogenous transport systems, such as amino acid or glucose transporters [512]. Additionally, gut microbiota-derived metabolites, such as short-chain fatty acids, are being explored for their potential to influence BBB transporter activity, highlighting the interplay between diet, microbiota, and CNS health [513–515].

5.5. Neuroprotective Agents Targeting BBB Stability

Neuroprotective agents that specifically target endothelial cell health and BBB stability are being developed to protect against BBB damage in neurodegenerative diseases [5,16,516].

Several therapeutic approaches are being explored to support BBB integrity through anti-inflammatory, antioxidant, and neuroprotective mechanisms [447,517]. Angiotensin receptor blockers (ARBs), such as losartan, may help protect BBB stability by reducing oxidative stress and inflammation in endothelial cells. In preclinical studies, ARBs have shown potential in mitigating BBB disruption under chronic inflammatory conditions [518–520]. Statins, primarily known for their cholesterol-lowering effects, also exhibit anti-inflammatory and antioxidant properties. They may reduce BBB permeability by protecting endothelial cells and lowering inflammation, making them a promising therapeutic option for neurodegenerative diseases [521–523]. Moreover, hormone-based therapies, particularly estrogen-based ones, have shown potential in maintaining BBB integrity by supporting tight junction protein expression and reducing inflammation. This approach could benefit postmenopausal women at increased risk for neurodegeneration [524,525]. Additionally, neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and GDNF, support neuronal and neurovascular health, potentially reinforcing BBB integrity [188,451,526]. While direct delivery of these agents to the brain is challenging, innovative approaches, such as gene therapy and nanoparticle-based delivery systems, are being explored to deliver these neurotrophic factors effectively [527–529]. Emerging neuroprotective agents are expanding the scope of strategies targeting BBB stability in neurodegenerative diseases. Endothelin receptor antagonists, such as bosentan, reduce BBB permeability by counteracting vascular inflammation and oxidative stress [530,531]. Similarly, S1P receptor modulators such as fingolimod stabilize endothelial junctions and decrease immune cell trafficking, supporting BBB integrity [532–534]. Cerebroprotective peptides, such as angiotensin 1–7, and mitochondrial-targeted therapies, including SS-31 (elamipretide), protect endothelial cells from oxidative damage and apoptosis [535–537]. Prostaglandin analogs, such as misoprostol, and dietary nutraceuticals, including quercetin and catechins, also show promise by reducing inflammation and oxidative stress while enhancing vascular health [538–540].

5.6. Other Physical Strategies for Enhancing BBB Protection

Physical strategies for BBB protection have gained attention as potential therapeutic approaches in neurological conditions [175,541]. Focused ultrasound with microbubbles enables the temporary and targeted opening of the BBB, facilitating drug delivery while minimizing damage to surrounding tissues [542–544]. Hyperbaric oxygen therapy has been shown to enhance BBB integrity by reducing oxidative stress, inflammation, and edema [545–547]. Additionally, therapeutic hypothermia stabilizes endothelial cells and decreases inflammation, particularly during acute brain injuries such as ischemic stroke [548–550]. Emerging methods, such as electromagnetic field therapy, have demonstrated potential in modulating BBB permeability, while mechanical barriers, such as stents or implantable scaffolds, can indirectly protect the BBB by supporting vascular structures [551–553]. These strategies provide promising avenues for enhancing BBB protection and repair in various neurological disorders.

6. Conclusions

The BBB is crucial in protecting the brain from harmful substances and maintaining the precise microenvironment necessary for proper neuronal function. In neurodegenerative diseases, the disruption of BBB integrity is a critical contributor to disease progression, allowing neurotoxic molecules, inflammatory cells, and pathological proteins to infiltrate

the brain. This review highlights the BBB's central role in mitigating the progression of neurodegenerative diseases, emphasizing that preserving its function can slow neurodegeneration and improve patient outcomes. A deeper understanding of the molecular and cellular mechanisms underlying BBB breakdown, coupled with the development of targeted therapeutic strategies, is essential for protecting the BBB and reducing the burden of these debilitating conditions. Therefore, by prioritizing the maintenance of a healthy BBB, we can uncover novel approaches to prevent or delay the onset and progression of neurodegenerative diseases, offering hope for improved quality of life for affected individuals.

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