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Review

Mechanisms of Astrocyte Action in the Blood Brain Barrier: From Structural Support to Dynamic Regulation

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Abstract

The blood-brain barrier (BBB) consists of endothelial cells enmeshed by brain microvessels, surrounding basement membrane, pericytes and astrocyte pedicles. It serves as a natural barrier between the blood and brain tissue and both its structural and functional integrity play a crucial role in protecting the central nervous system (CNS) from harmful substances and maintaining the internal stability of the brain. As an important component of the BBB and a hub in the neurovascular unit that links neurons and the cerebral microvasculature, astrocytes play a key role in providing structural support and dynamic regulation of the BBB. In this review, we describe both the physiological structure and mechanistic functions of the BBB and astrocytes, and explores the role of astrocytes in the development, stabilization, destruction and repair of the BBB. Finally, we outlines the therapeutic potential of targeting these mechanisms for CNS disorders associated with BBB disruption.

Keywords: astrocyte; BBB; nervous system; glial cells

1. Introduction

1.1 Structure and Function of the Blood Brain Barrier

The blood brain barrier (BBB) is formed by the walls of the brain's capillaries and neuroglia. It constitutes one of the internal barriers involved in the immune processes of the body [1,2]. The structural core of the BBB is its unique endothelial cells (ECs) [3], which possess continuous, non-fenestrated tight junctions (TJs) composed of specific junctional proteins, as well as an intact basement membrane (BM), pericytes and extracellular matrix (ECM) [4]. Together, these structures play an important role in both protecting the central nervous system from harmful substances and maintaining the stable state of the intracerebral environment. In addition to the TJ itself, transporter proteins play a critical role in protection. These proteins are expressed in the endothelial cells of the central nervous system (CNS) and allow various nutrients to enter the brain [1]. ECs are characterised by a low transcytosis rate, with a low rate of vesicle-mediated transcellular translocation. This helps maintain the integrity of the BBB and keeps the brain microenvironment stable.

1.2 Structure and Function of Astrocytes

Astrocytes are neural cells derived from the ectoderm and neuroepithelium [5], representing the most abundant type of glial cell in the CNS. They are integral components of the neurovascular unit, playing a crucial role in the maintenance of brain homeostasis. Astrocytes display a spongiform morphology, with a diameter typically ranging from 40–60 µm [5]. Their primary structural features include the cell body, cellular processes and expression of the glial fibrillary acidic protein (GFAP). The intricate nature of their morphological architecture underpins their functional diversity, allowing them to perform a wide array of physiological roles within the CNS [6].

The most prominent structural characteristic of astrocytes is their processes, which are typically arranged in a radial pattern. These processes form tight junctions with neuronal synapses and the ECs of blood vessels [5]. Through these processes, astrocytes regulate signaling between neurons and glial cells, thereby maintaining proper function throughout CNS development and aging. Additionally, astrocytes play a pivotal role in the formation and functional maintenance of the BBB through their interactions with ECs, directly regulating the dynamic stability of the BBB [7–12]. Another key structural feature of astrocytes is GFAP, a well-established marker and structural protein [13]. As a major component of the astrocytic cytoskeleton, GFAP provides mechanical support, preserves structural integrity and facilitates stable interactions with other cells, including neurons and endothelial cells. Upon astrocyte damage, GFAP is released into the cerebrospinal fluid and blood, serving as an indicator of brain injury and neuroinflammation [14]. This release further disrupts the integrity of the BBB, exacerbating neuronal damage and inflammatory responses [15,16].

These structural and functional characteristics underscore the pivotal role of astrocytes in maintaining the stability and function of the BBB. Through their interactions with ECs via their processes, astrocytes not only provide essen-

tial structural support for BBB formation but also regulate its permeability, ensuring that harmful substances are effectively prevented from entering the brain, thus safeguarding the CNS from potential injury. Previous transplantation study has demonstrated that isolated astrocytes are capable of inducing barrier properties in newly formed blood vessels, thereby promoting BBB formation [13]. Furthermore, by examining the roles of astrocytes in various regions of the CNS, Yang *et al.* [17] have elucidated their involvement in stabilizing the internal environment of the BBB. These functions are inherently linked to the unique structural features of astrocytes. This article will further explore the underlying mechanisms involved in these processes.

1.3 Structural Support of Astrocytes in the BBB

The close apposition of astrocyte end-feet to cerebral blood vessels [1] enables astrocytes to promote the structural properties of the nascent vascular barrier [13]. This support manifests through the induction of EC barrier properties and facilitation of BM formation. Furthermore, the BBB's selective permeability and metabolic supply are mediated by diverse transport proteins (e.g., GLUT1, excitatory amino acid transporters (EAAT), P-glycoprotein (P-gp) expressed on ECs) [1]. *GLUT1* facilitates unidirectional glucose transport from the blood into the brain, providing energy essential for BBB homeostasis. *EAAT* removes excess glutamate from the brain, mitigating neurotoxicity and preserving BBB integrity. P-gp promotes efflux and restricts influx, protecting the BBB from toxic substances. Astrocytes structurally support the BBB by regulating the expression of these transporter proteins. The following sections detail the specific roles of astrocytes in maintaining BBB integrity. The structural support of astrocytes for BBB is listed in Fig. 1.

1.4 Astrocyte Induction of Endothelial Cell Barrier Properties

ECs constitute the core cellular component of the BBB, forming a low-permeability barrier that controls substance transport between blood and brain tissue. Astrocytes, positioned adjacent to ECs, secrete signaling molecules that induce and maintain EC barrier properties. Park *et al.* [18] demonstrated that optimal BBB development requires direct contact between ECs and astrocytes, indicating an astrocytic contribution to EC differentiation and barrier function.

Adjacent ECs are interconnected by TJ and adherens junction proteins, both regulated by astrocytes. TJ structures comprise transmembrane proteins (occludin, claudins, junctional adhesion molecules), actin filaments and cytoplasmic scaffolding proteins (zona occludens (ZO)) [19]. TJ formation, mediated by these proteins, is pivotal for regulating BBB permeability [17]. TJ protein expression is 1.5-2-fold higher in EC-astrocyte co-cultures compared to EC monocultures [18], reflecting the essential supportive role of astrocytes in TJ assembly. Otani *et al.* [19] found that introducing cultured astrocytes near normally leaky vessels increased TJ protein expression and EC tightening, resulting in reduced leakage. This suggests astrocytes influence both TJ formation and expression.

1.5 Astrocytes Promote BBB Basement Membrane Formation

The BBB basement membrane formation (BBB-BM), a specialized ECM [20], consists primarily of type IV collagen, laminin, nidogen (often referred to as entactin) and perlecan [1,21]. These are proteins synthesized mainly by ECs, pericytes and astrocytes. Astrocytes ensheath capillaries, arterioles and venules and secrete trophic factors that maintain EC barrier properties [22]. Astrocyte-derived apolipoprotein E (ApoE) binds the LRP1 receptor on pericytes, inhibiting cyclophilin A-mediated activation of matrix metalloproteinase-9 (MMP-9), thereby participating in BBB-BM stabilization [23]. Concurrently, astrocytes strengthen the BM via polarized end-feet expressing aquaporin-4 (AQP4), which connect to the cerebrovascular BM. Crucially, astrocytes secrete laminin, a major structural BM component [1]. Laminin not only reinforces the BM and stabilizes pericytes [20] but also induces AQP4 expression [24]. Yao *et al.* [21] demonstrated that laminin increases AQP4 expression, contributing to BBB-BM integrity. An early study by Xu *et al.* [20] revealed that astrocyte-secreted laminin deficiency leads to BBB disruption and intracerebral hemorrhage. Collectively, these findings underscore the critical role of astrocyte structure and function in BBB-BM formation.

1.6 Astrocyte Regulation of BBB Permeability via EC Transporter Proteins

1.6.1 Glucose Transporter 1 (GLUT1)

Encoded by *SLC2A1*, the glucose transporter 1 (*GLUT1*) is highly expressed at the BBB, predominantly localized within the cerebral vasculature and on astrocyte end-feet [25,26]. It transports glucose unidirectionally from blood to brain, supplying energy to neurons and glia and is essential for BBB integrity [27]. Given that astrocyte end-feet ensheath cerebral vasculature, astrocytes represent a mandatory pathway for *GLUT1*-mediated glucose transport [28–30]; astrocyte regulation of *GLUT1* is thus key to maintaining BBB integrity and function. Zheng *et al.* [31] observed vasogenic brain edema in zebrafish following *GLUT1* knockdown; *GLUT1* function is highly conserved in humans. Pearson *et al.* [32] noted that *GLUT1* deficiency impairs glucose transport across the BBB, indirectly compromising BBB stability. These findings highlight *GLUT1*'s importance in BBB homeostasis. Astrocytes regulate *GLUT1* through two primary mechanisms: (i) Releasing factors (e.g., Wnt ligands, transforming growth factor-beta (TGF-β)) that act on ECs to promote *GLUT1* transcription and protein synthesis—key regulatory path-

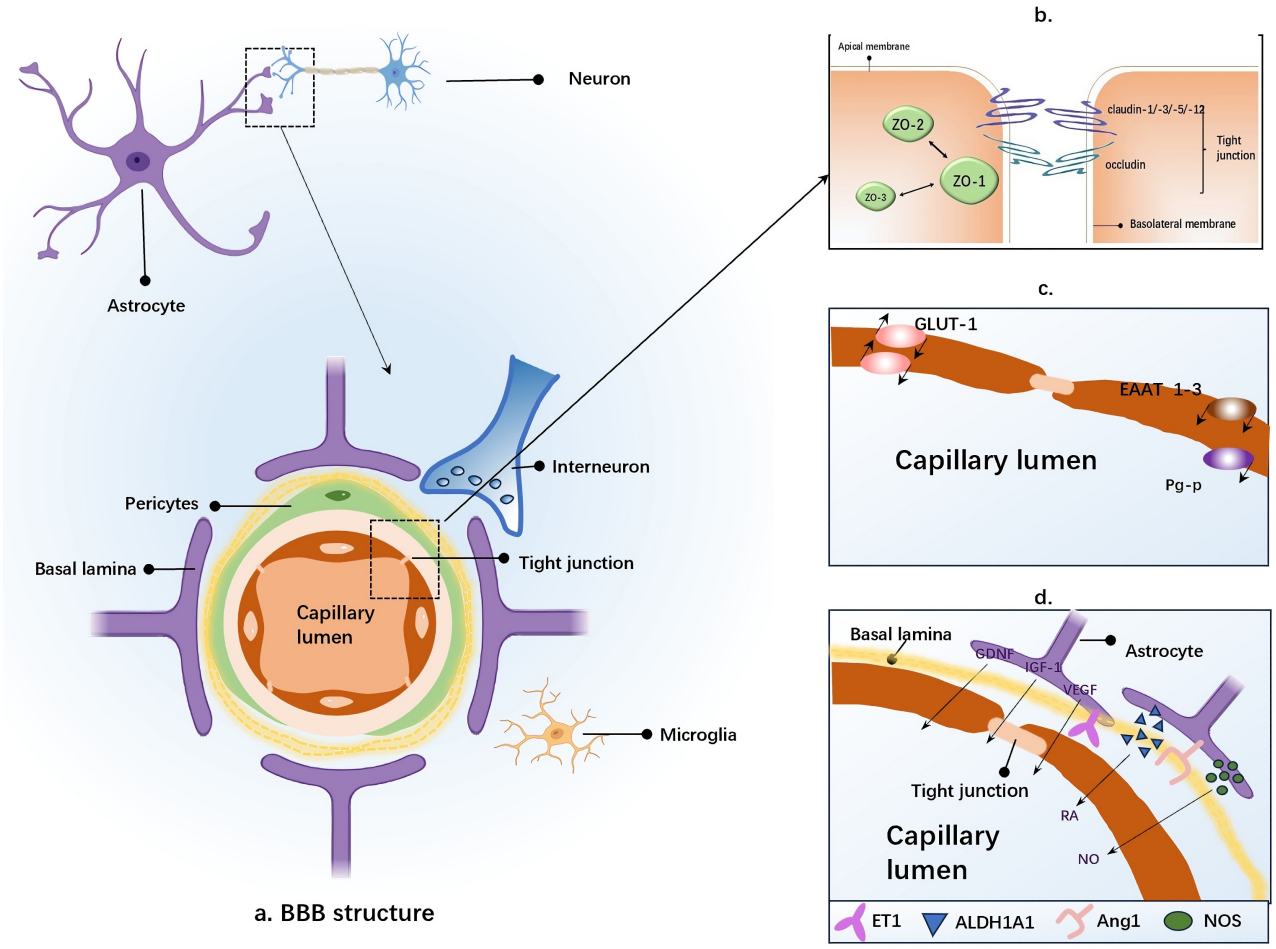

Fig. 1. Cellular Components of the BBB. (a) The structural core of the BBB is formed by capillary endothelial cells, which are encased by the basement membrane and the perivascular end-feet of astrocytes. Astrocytes establish cellular connections with neurons, while pericytes and microglia are also depicted. (b) Schematic representation of tight junction protein structure: The tight junction complex is composed of transmembrane proteins (such as claudins, occludin, and junctional adhesion molecules), actin filaments, and cytoplasmic scaffolding proteins, including zonula occludens (ZO). (c) Characteristics of brain endothelial cells observed in cell culture: These cells express various transporters and receptors, such as *EAAT* 1–3, *GLUT1*, and P-gp, which contribute to the structural support and barrier functions of the BBB. (d) Induction of BBB properties by factors secreted by astrocytes (e.g., Ang-1, ET-1, GDNF, RA, VEGF, IGF-1, NO): These factors, regulated by the brain microenvironment and astrocytes, exert distinct effects on BBB properties under different physiological or pathological conditions. ZO, zonula occludens; *EAAT*, excitatory amino acid transporters; *GLUT1*, glucose transporter 1; P-gp, P-glycoprotein; BBB, blood-brain barrier; Ang-1, Angiopoietin-1; ET-1, Endothelin-1; GDNF, glial cell derived neurotrophic factor; RA, retinoic acid; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor-1; NO, nitric oxide. The figure was created using Microsoft PowerPoint (2016, Microsoft Corporation, Redmond, WA, USA).

ways for *GLUT1* during BBB development and maintenance [33] and (ii) TGF-β-enhanced laminin deposition, which helps maintain EC polarity and stabilizes *GLUT1* membrane localization [34]. In summary, astrocytes ensure efficient brain glucose delivery and EC energy homeostasis via *GLUT1* regulation, indirectly safeguarding TJ integrity and low BBB permeability.

1.6.2 Excitatory Amino Acid Transporters (EAAT)

EAAT is a high-affinity, sodium-dependent transporter responsible for the majority of CNS glutamate uptake, compensating for the lack of extracellular catabolic enzymes [35]. Excess glutamate exerts neurotoxic effects, including neuronal death and BBB disruption. *EAAT* clears glutamate from the brain against a concentration gradient, maintaining amino acid homeostasis [36,37]. Astrocyte-derived *EAAT1* and *EAAT2* are primarily responsible for synaptic glutamate clearance at the BBB [38–41], with *EAAT2* alone accounting for ~80% of uptake [42,43]. This clearance prevents excitotoxicity, neuroinflammation and cerebral edema, thereby directly and indirectly maintaining BBB integrity [44]. Astrocytes coordinate *EAAT*-mediated glutamate metabolism [45]. Increasing *EAAT2* transcription and membrane localization via secreted TGF-β and glial cell de-

rived neurotrophic factor (*GDNF*). Estrogen and cortisol also promote *EAAT* expression and synthesis. However, dysregulation, such as excessive neuronal glutamate uptake, can saturate *EAAT*, causing astrocytic glutamate leakage into the extravascular space and inducing BBB disruption [46–48]. In summary, high astrocyte-driven *EAAT* expression and their regulatory capacity directly and indirectly influence BBB permeability.

1.6.3 P-Glycoprotein (P-gp)

P-gp, a member of the ATP-binding cassette (ABC) transporter superfamily, is localized to the luminal plasma membrane of BBB ECs during telencephalic development, serving as an early marker of BBB differentiation [49]. P-gp maintains CNS homeostasis and protects the BBB from blood-borne toxins by actively effluxing diverse substrates and restricting compound uptake into ECs [50–53]. Baello *et al*. [54] co-cultured astrocytes with ECs and observed a significant increase in P-gp levels, particularly in neonatal astrocytes. This suggests astrocytes enhance P-gp expression, thereby safeguarding efflux capacity, protecting against harmful substances and preventing BBB damage.

1.7 Co-Regulation of BBB Permeability by Astrocyte and EC Transcytosis

BBB ECs exhibit a low rate of vesicle-mediated transcytosis, a process involving endocytic uptake of material into vesicles followed by exocytic release on the opposite side. This process functions synergistically with pericytes and astrocytes [55]. At the BBB, transcytosis selectively transports macromolecules (e.g., proteins, drugs) into the brain parenchyma [1], while lysosomes degrade or return substances to the peripheral circulation, preventing toxin accumulation and sealing the BBB [55,56]. Mfsd2a, a lipid transporter highly expressed in CNS ECs, suppresses transcytosis and is associated with low BBB permeability. Evidence indicates astrocyte regulation of Mfsd2a, suggesting astrocytes modulate BBB permeability by influencing Mfsd2a-mediated transcytosis through co-regulatory mechanisms [55].

1.8 Dynamic Regulatory Mechanisms in Astrocytes

Beyond their role in inducing and maintaining long-term barrier properties, astrocytes secrete signaling factors that bidirectionally regulate EC permeability [57]. Protective factors include *Ang-1*, *GDNF*, retinoic acid (RA), and insulin-like growth factor-1 (IGF-1) [57–63], which shield ECs from apoptosis and promote functional recovery. Some EC-disrupting factors, such as astrocyte-derived ET, cause endothelial cell apoptosis and down-regulation of TJ-related proteins, leading to BBB disruption. Other specific factors have different mechanisms for regulating BBB permeability in different states. These include nitric oxide (NO) and vascular endothelial growth factor (VEGF), among others. Additionally, signaling pathways activated by astrocytes regulate BBB function. The Hh (Hedgehog), Wnt/β-catenin and TGF-β pathways have been studied in more detail and are the focus of the following sections. The effects of secreted factors from astrocytes on BBB are listed in Table 1.

1.9 Bidirectional Regulation of BBB Permeability by Astrocyte-Secreted Factors

1.9.1 Angiopoietin-1 (Ang-1)

Primarily derived from astrocytes, *Ang-1* stabilizes vascular structure, enhances TJs, inhibits inflammation, maintains BBB integrity and low permeability [64]. Mechanistically, astrocyte-secreted *Ang-1* binds the Tie2 receptor on ECs, activating the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway to upregulate TJ proteins (e.g., occludin, claudin-5). Concurrently, it inhibits the RhoA/ROCK pathway, reducing EC contraction and preventing TJ disassembly. *Ang-1* also suppresses neuroinflammation via the SNHG14/miR-223-3p/NLRP3 pathway, providing neuroprotection [65].

1.9.2 Glial Cell Derived Neurotrophic Factor (GDNF)

This astrocyte-secreted neurotrophic factor, enriched in end-feet, is a key mediator of endothelial network formation [66]. *GDNF* ensures neuronal survival and regulates EC function by activating its receptors on neurons and ECs [63]. Specifically, *GDNF* binding to the rearranged during enstransfection receptor on ECs activates the PI3K/Akt pathway, resulting in increased TJ protein expression (occludin, claudin-5), enhanced membrane localization and activity of efflux transporters (P-gp, breast cancer resistance protein (BCRP)), and modulation of the Rac1/RhoA balance to stabilize the cytoskeleton. *GDNF* also acts on pericyte receptors, enhancing vascular coverage and inhibiting leakage [67].

1.9.3 Retinoic Acid (RA)

RA, an active vitamin A metabolite, is synthesized via enzymes including ALDH1A1/A2/A3 [68]. The role of RA on the BBB is mainly in maintaining barrier integrity, regulating permeability and participating in pathological repair. Adam *et al*. [69] observed strong ALDH1A1 expression in mature astrocytes, suggesting that ALDH1A1 is highly enriched in astrocytes. Therefore, it is assumed that astrocytes regulate BBB permeability via the RA signaling pathway. Adam *et al*. [69] concluded from their analysis of human post-mortem brain tissue and *in vitro* experiments that human fetal astrocytes promote the formation of the brain endothelial barrier and increase the expression of BBB-specific genes via this pathway. To further determine the expression of BBB-specific proteins induced by RA, the Mizze experimental group performed a Western blot analysis of ZO-1 and VE-calmodulin, which are important for BBB integrity. The results indicated that the levels of these proteins increased in the group treated with RA. In

Table 1. Effects of astrocyte-secreted signaling factors on BBB permeability.

Category	Signaling factor	Abbreviation	Effect on BBB permeability
EC protection	Angiopoietin-1	Ang-1	Maintains BBB integrity and low permeability by stabilizing vasculature, enhancing TJs, and inhibiting inflammation.
	Glial-derived neurotrophic factor	GDNF	Enhances barrier function via GDNF receptor activation, supporting neuronal survival and regulating endothelial function.
	Retinoic acid	RA	Synthesized by astrocytes (ALDH1A1+), maintains barrier integrity, regulates permeability, and promotes repair.
	Insulin-like Growth Factor-1	IGF-1	Reduces BBB permeability and damage by acting as a neurotrophic factor.
	Nitric Oxide	NO	Low concentrations generated by eNOS maintain barrier integrity under homeostasis.
	Vascular Endothelial Growth Factor	VEGF	Physiological levels contribute to vascular homeostasis maintenance.
EC Disruption	Nitric Oxide	NO	Overproduction by iNOS during inflammation causes BBB destruction.
	Vascular Endothelial Growth Factor	VEGF	Secreted by reactive astrocytes in pathology, disrupts BBB integrity.
	Endothelin	ET	Astrocyte synthesis and upregulation of ET-1 exacerbate CNS inflammation, leading to BBB destruction.

eNOS, Endothelial Nitric Oxide Synthase; iNOS, Inducible Nitric Oxide Synthase; CNS, central nervous system.

summary, astrocytes participate in RA formation through ALDH1A1 and also induce EC differentiation and promote BBB formation through the RA signaling pathway.

1.9.4 Insulin-Like Growth Factor-1 (IGF-1)

Mainly sourced from astrocytes and peripheral plasma [70], IGF-1 acts as a neurotrophic factor via the IGF-1 receptor, promoting neurogenesis, neuronal survival, neuroprotection and repair [71]. Some researchers pointed out that IGF-1's anti-apoptotic effects in ECs and its reduction of Evans blue dye extravasation, suggesting BBB protection [70]. Astrocytes contribute to elevated IGF-1 levels in the infarcted cortex, partly via mesenchymal stem cell mediation [70]. Mechanistically, astrocyte-derived IGF-1 activates the MARK/ERK and PI3K/Akt pathways in ECs, inhibiting GSK-3β, upregulating TJ proteins and promoting toxin efflux to ensure normal BBB function.

1.9.5 Nitric Oxide (NO)

NO, a vasodilator involved in neurovascular coupling [72], is synthesized by NO synthase (NOS). Expression of eNOS and iNOS on astrocyte end-feet implicates astrocytes in NO-mediated BBB regulation. Physiological NO concentrations, generated by astrocytic eNOS, maintain barrier integrity via the sGC-cGMP-PKG pathway, which phosphorylates occludin and ZO-1 to stabilize TJs; eNOS also directly prevents inflammation and apoptosis [73–77]. Conversely, under inflammation, astrocytic iNOS produces excessive NO, generating peroxynitrite that degrades TJ proteins, activates MMPs to degrade the BM, and triggers NF-κB-mediated leukocyte infiltration, exacerbating inflammation and BBB disruption. Therefore, astrocytes bidirectionally regulate the BBB through differential NOS isoform expression and NO levels.

1.9.6 Vascular Endothelial Growth Factor (VEGF)

Predominantly astrocyte-derived [78], VEGF prevents EC apoptosis and protects BBB integrity under physiological conditions, but downregulates TJ proteins, increases permeability and pathologically disrupts the BBB [79–82]. Here, it is proposed that astrocyte-secreted VEGF bidirectionally regulates BBB function. Physiological VEGF maintains vascular homeostasis by activating the PI3K/Akt pathway in ECs, promoting angiogenesis and survival and transiently enhancing TJ protein expression via VEGFR2 activation [83]. Pathologically, reactive astrocytes secrete VEGF, activating the VEGFR2/PKC pathway to induce TJ protein endocytosis and degradation, increase transcytosis, inhibit P-gp (causing toxin accumulation) and amplify inflammatory infiltration, culminating in BBB damage and brain injury [79,84]. Hence, astrocyte-derived VEGF acts as a "double-edged sword": Essential for vascular development/repair at physiological levels, but destructive to the BBB when pathologically overexpressed.

1.9.7 Endothelin (ET)

ET, a potent vasoconstrictor mediating CNS inflammatory responses [85], exacerbates BBB damage, as ET blockade significantly reduces leakage [86]. Among ET isoforms (ET-1, ET-2, ET-3), astrocyte-synthesized ET-1 is upregulated and critically involved in cerebral ischemic injury pathogenesis. Cheng *et al.* [87] found astrocyte-specific ET-1 overexpression increased brain injury susceptibility following MCAO-induced ischemia. Collectively, astrocytes exacerbate CNS inflammation and BBB destruction by upregulating ET-1 expression.

1.10 Astrocyte Activation-Related Signaling Pathways Regulate BBB Permeability

1.10.1 Hh Signaling Pathway

Sonic hedgehog (Shh), secreted by astrocyte endfeet, promotes BBB formation and integrity. Shh binding to the patched-1 receptor on ECs relieves inhibition of smoothened, activating the pathway. This directly regulates transcription of target genes (e.g., *Ang-1*) via Glioma-associated oncogene (Gli) transcription factors, upregulating BBB barrier function [88].

The continuous activation of the Hh signaling pathway reduces permeability between endothelial cells by increasing the expression of tight junction proteins. This prevents toxins, immune cells, or macromolecules from infiltrating the brain parenchyma from the blood. Among these proteins, the transcription factor Gli-1 increased the expression of ECs after activation of the Hh pathway, while the TJ protein regulator SRY-box transcription factor 18 (SOX18) peaked within two hours of activation. This indicates that Gli-1 can upregulate TJ expression [88]. Thus, the Hh signaling pathway in the CNS endothelium results in increased expression of TJ proteins, which are indispensable for the maintenance and stabilization of the BBB.

The Hh signaling pathway also provides an anti-inflammatory balance within the CNS by inhibiting the NF-κB pathway, reducing the expression of pro-inflammatory mediators (e.g., tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β)) and leukocyte adherence and migration. Engelhardt *et al*. [89–91] evaluated the effects of Hh activation on cells involved in neuroinflammation, such as T helper 1 (TH1) and TH17, indicating that Shh plays a role. The specific process is as follows: In cerebral ischemia, trauma or inflammation, Shh re-induces the expression of Hh receptors in ECs, the Hh signaling pathway is re-activated and Gli-1 is up-regulated and translocated into the nuclei of ECs to promote EC proliferation and migration to accelerate BBB repair, thereby restoring the physiological and immune functions of the BBB [88]. The Hh signaling pathway also induces VEGF, which promotes neointima formation in damaged areas while restoring barrier function [58,92]. As a result, it is more difficult for these pro-inflammatory cells to enter the BBB, thus providing anti-inflammatory protection. The Hh signaling pathway is listed in Fig. 2.

1.10.2 Wnt/β-Catenin Signaling Pathway

Essential for BBB integrity and CNS homeostasis [93], this pathway centrally regulates BBB EC differentiation and function [94]. It dominates BBB formation during embryogenesis, inducing cerebral angiogenesis and barrier properties. In adults, it maintains EC TJs and low permeability, supporting post-injury repair. Astrocyte-secreted Wnt ligands (e.g., Wnt7a/7b) bind EC receptors (Frizzled, low-density lipoprotein receptor-related protein 5/6 (LRP5/6)), activating the pathway via paracrine signaling. This inhibits β-catenin degradation, enabling cytoplasmic accumulation. β-catenin then binds TCF/LEF transcription factors, forming a complex that drives EC expression of barrier-inducing molecules.

The Wnt/β-catenin signaling pathway induces TJ protein expression and maintains EC properties. Engelhardt *et al*. [89] found that claudin-5 in TJ proteins is regulated by the Wnt/β-catenin pathway *in vivo*. Claudin-3, moreover, exhibits increased expression and cell-cell contact-restricted localization with age, especially in the postnatal stage [93]. β-catenin is an important component of TJ, and Tran *et al*. [90] observed that claudin-1 and claudin-3 were downregulated in β-catenin gene knockout mice. Thus, the absence of β-catenin decreases junctional stability and increases vascular permeability.

The Wnt/β-catenin signaling pathway avoids excessive immune activation and suppresses inflammatory signals. Reuter *et al*. [91] observed that the anti-inflammatory properties of Wnt ligands depend on the cell type, the Wnt ligand and the experimental setup. Meanwhile, evidence from models of inflammation in the brain or gut has shown that Wnt ligands display immunosuppressive functions *in vivo*. In intestinal epithelial cells, the binding of β-catenin to CBP reduces the expression of pro-inflammatory genes driven by NF-κB (e.g., IL-8 and TNF-α). In diseases such as chronic inflammation and tumors, the Wnt/β-catenin signaling pathway maintains endothelial barrier function by inhibiting VEGF and inflammatory signaling to limit pathological angiogenesis [95]. The Wnt/β-catenin pathway is listed in Fig. 3.

The Wnt/β-catenin signaling pathway also works by regulating *GLUT1* and P-gp [89], optimizing the transporter function. Upon activation of the Hh signaling pathway, β-catenin directly activates the *SLC2A1* gene to safeguard EC energy supply; P-gp synergistically induces the *ABCB1* gene in conjunction with the Hh signaling pathway, which enhances the efflux of toxins (e.g., β-amyloid) and prevents BBB destruction.

1.10.3 TGF-β Signaling Pathway

Astrocytes precisely regulate BBB permeability via TGF-β signaling. They secrete latent TGF-β, activated by EC integrin αvβ6 or thrombin [96,97]. Active TGF-β binds TGF-βR1/TGF-βR2 (often denoted TGF-β1/β2 receptors) on ECs, phosphorylating the ALK5/Smad2/3 pathway, which upregulates TJ protein expression. Pharmacological ALK5 inhibition increased claudin-5 expression in endothelial cells [98], confirming TGF-β/ALK5 involvement in TJ regulation. The pathway also inhibits matrix metalloproteinase-9 (MMP-9) activity and reduces inflammatory cytokine release (e.g., IL-1β, IL-6), protecting BBB integrity. The TGF-β signalling pathway is listed in Fig. 4.

The TGF-β signaling pathway affects pericytes, maintaining BBB function and inducing differentiation into a mature phenotype through activation of the ALK5/Smad2/3

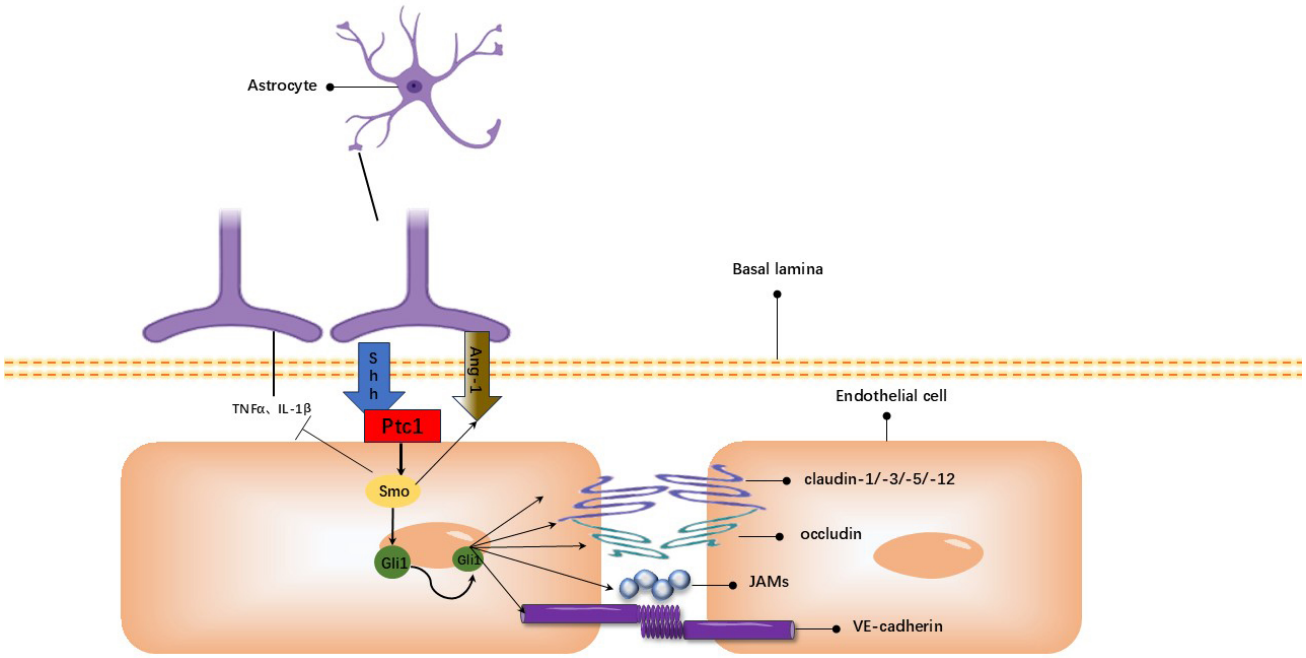

Fig. 2. Hh signaling pathway. Astrocyte-derived Shh binds Ptch-1, activating Smo. This leads to Gli1-mediated transcriptional up-regulation of Ang-1 and TJ proteins (occludin, JAMs, VE-cadherin, claudin-1/-3/-5/-12). The pathway concurrently inhibits TNF-α and IL-1β expression, exerting an anti-inflammatory effect. TJ, tight junction; JAMs, Junctional Adhesion Molecules; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta. The figure was created using Microsoft PowerPoint.

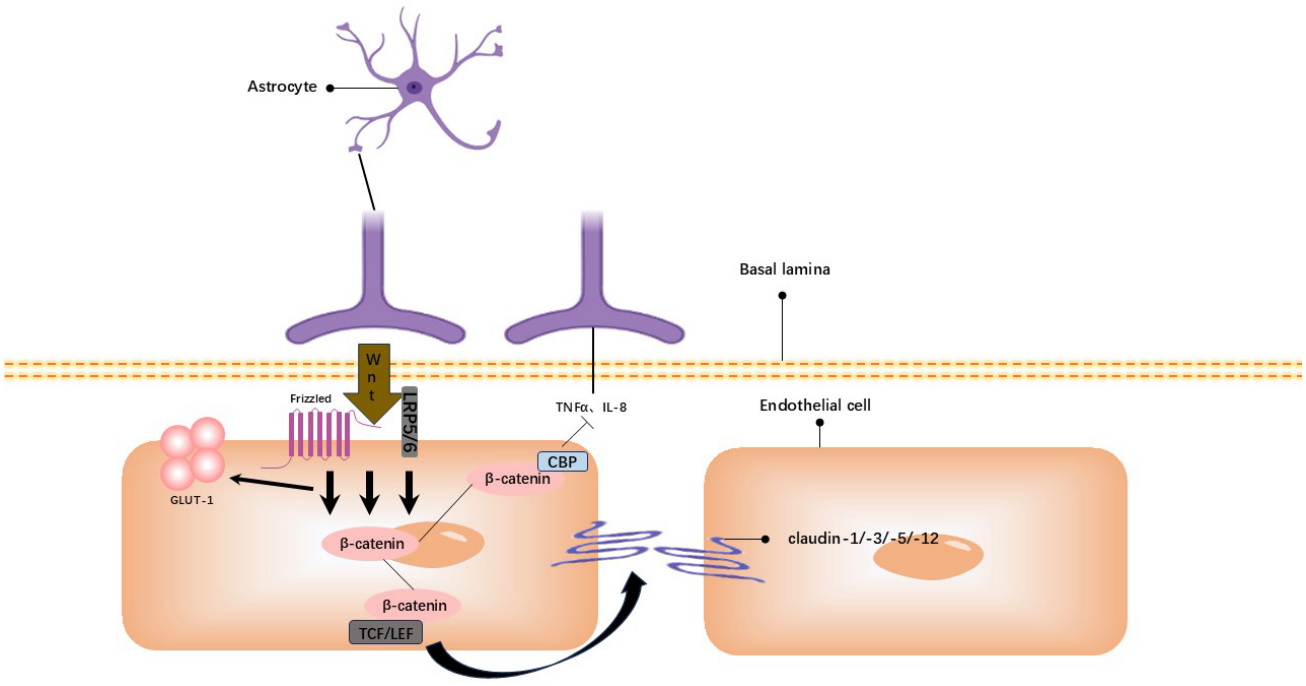

Fig. 3. The Wnt/β-catenin pathway. Astrocyte-derived Wnt ligands bind Frizzled/LRP5/6 on ECs, stabilizing β-catenin. Accumulated β-catenin binds TCF/LEF to induce TJ expression and binds CBP to repress NF-κB-driven inflammation (e.g., IL-8, TNF-α). The pathway also regulates GLUT-1 and P-gp expression, synergizing with these transporters for BBB function. ECs, endothelial cells; TCF/LEF, T-cell factor/lymphoid enhancer factor; CBP, CREB-binding protein. The figure was created using Microsoft PowerPoint.

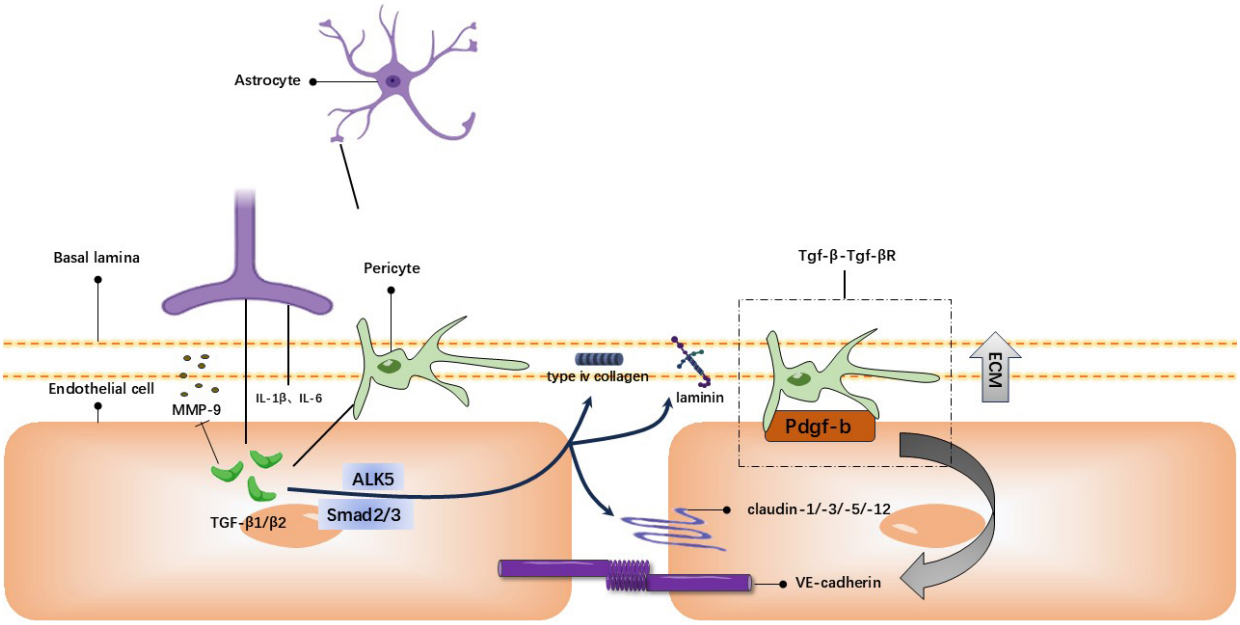

Fig. 4. TGF-β signalling pathway. Astrocyte-secreted TGF-β binds receptors (TGF-βR1/TGF-βR2) on ECs, activating ALK5/Smad2/3 phosphorylation. This upregulates TJ proteins, laminin, and VE-cadherin, while inhibiting MMP-9 and reducing inflammatory factor release (e.g., IL-1β, IL-6). The pathway also affects pericytes, promoting neovascular EC PDGF-B secretion. PDGF-B recruits pericytes, establishing bidirectional TGF-β signaling that enhances VE-cadherin-2 expression and activates pericyte secretion of ECM components, aiding BM formation. MMP-9, matrix metalloproteinase-9; PDGF-B, platelet-derived growth factor B. The figure was created using Microsoft PowerPoint.

pathway. This positively regulates the secretion of platelet-derived growth factor B (PDGF-B) by neovascularised EC. PDGF-B-expressing pericytes then assemble on the surface of the EC. The interactions between the EC and pericytes constitute bidirectional TGF-β-TGF-βR signaling transmission, which increases VE-cadherin-2 expression. Simultaneously, pericytes secrete laminin and type IV collagen to enhance the structure of the basement membrane and further stabilise the BBB [3]. TGF-β1, an isoform of TGF-β, is also an important inducer of ECM expression and Cai *et al*. [99] demonstrated that TGF-β1 reduced rt-PA-induced basement membrane degradation, BBB disruption and hemorrhagic transformation, suggesting that it protects the basement membrane.

2. Therapeutic Implications of Astrocyte-Mediated BBB Regulation in CNS Disorders

As detailed above, astrocyte involvement in BBB formation, maintenance, disruption and repair is fundamentally governed by their structural specializations, secreted signaling factors and activation of specific pathways. Critically, the pathogenesis of several CNS disorders—including multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD), ischemic stroke, and epilepsy—is intimately linked to BBB dysfunction. Below, the aforementioned astrocyte regulatory mechanisms contributing to disease pathogenesis are explored and evaluated for their potential as therapeutic targets.

2.1 Multiple Sclerosis

MS is a group of autoimmune neuroinflammatory disorders characterized by demyelination, axonal damage and ultimately neurodegeneration with progressive disability. Dysregulation of astrocytic synaptic modulation is one of the pathogenic mechanisms underlying MS [100,101]. As key regulators of neuroinflammation [102], astrocytes become overactivated under chronic inflammatory conditions, leading to glial scar formation, secretion of various chemokines (e.g., CCL2, CXCL10, CXCL12, FASL and TRAIL) and MMP-9, disruption of BBB tight junctions and interaction with immune cells to facilitate their infiltration into the brain parenchyma, thereby inducing neurotoxicity and attacking neuromyelin sheaths [103]. It has been shown that tumor necrosis factor (TNF) produced by astrocytes can directly exert cytotoxic effects by interacting with TNF receptors on neurons, thus mediating neurodegenerative processes [102,104].

Activation of astrocytic sphingosine 1-phosphate (S1P) signaling also contributes to MS pathogenesis; as a disorder of sphingolipid metabolism, its severity closely correlates with the degree of demyelination and axonal damage [105,106]. Additionally, lipolactosylceramide activates the cPLA2-MAVS-NF-κB signaling pathway in MS,

downregulating astrocytic lactate production and exerting pro-inflammatory effects, thereby perpetuating a vicious cycle in disease progression [107,108]. Furthermore, reactive astrocytes have been shown to play a dual role in MS. In an acute experimental autoimmune encephalomyelitis model using B6 mice, reduction of reactive astrocytes exacerbates neuroinflammation and disease severity [109]. Conversely, the LAMP1+TRAIL+ astrocyte subpopulation induces T cell apoptosis via TRAIL-DR5 signaling, mitigating MS progression [110]. In summary, in MS, astrocytes disrupt BBB tight junctions through mechanisms such as synaptic dysregulation, excessive release of pro-inflammatory factors and activation of the S1P signaling pathway, enabling immune cells (e.g., T cells) to breach the barrier, infiltrate the brain and attack the CNS.

2.2 Parkinson's Disease

PD is the second most prevalent neurodegenerative disorder, characterized by motor disturbances (e.g., tremor, rigidity, bradykinesia) [111]. Its pathological hallmarks include the loss of dopaminergic neurons in the substantia nigra pars compacta and aggregation of misfolded α-synuclein in Lewy bodies [112]. Accumulating evidence supports the involvement of astrocytes in PD pathogenesis. Studies have identified increased numbers of GFAP-positive A1 astrocytes in PD models [113,114]. Misfolded α-synuclein aggregates in astrocytic cytoplasm, triggering astrocyte activation with subsequent production of pro-inflammatory factors such as Interferon-gamma (IFN-γ) and TNF-α [115,116]. Moreover, α-synuclein-activated reactive astrocytes disrupt glutamate recycling, K^+ buffering and Ca^{2+} signaling, contributing to dopaminergic neuron loss [115,117]. However, astrocyte-derived factors such as NURR1, Wnt1/Fzd-1/β-catenin and GLP1R exert protective effects in PD pathology [113,118]. NURR1 (an orphan ligand-activated transcription factor) cooperates with CoREST to inhibit the NF-κB signaling pathway, suppress inflammatory responses and thereby protect dopaminergic neurons [119]. Downregulation of NURR1 expression increases CNS neurotoxic products, suggesting a role for NURR1 in inhibiting neurotoxicity [120]. Notably, inhibition of the Wnt1/Fzd-1/β-catenin pathway increases the number of reactive astrocytes, leading to neuronal damage [118]. Collectively, astrocytes exert both destructive and protective roles in PD depending on the context. Based on these mechanisms, future studies could target PD by promoting astrocyte-derived protective factors and inhibiting inflammatory responses.

2.3 Alzheimer's Disease

AD is one of the most common late-onset neurodegenerative diseases, characterized by dementia, cognitive decline and memory impairment [121]. Its pathological features include intraneuronal neurofibrillary tangles and extracellular amyloid-β (Aβ) plaques, with Aβ plaque aggregation exacerbating neuronal degeneration [119]. Following AD onset, astrocytes exhibit increased expression of beta-site amyloid precursor protein cleaving enzyme 1, a key enzyme promoting Aβ plaque formation [122]. A further study demonstrated that astrocytes pretreated with Aβ exacerbate neuronal death, indicating their role in neurodegeneration [123]. As previously noted, astrocyte-derived *EAAT1* and *EAAT2* are responsible for clearing glutamate from the synaptic cleft [117]. Reduced *EAAT* expression disrupts astrocytic glutamate uptake, contributing to neurodegeneration [124]. Mookherjee *et al*. [125] found that knockout of glutamate transporter 1 (the human homolog of *EAAT2*) leads to cognitive decline. Additionally, Aβ directly impairs astrocytic glutamate recycling *in vitro*, accelerating neurodegeneration [126]. Another mechanism by which astrocytes contribute to AD pathogenesis is through neuroinflammation: AD-associated inflammatory factors (e.g., TGF-β, TNF, IL-1β, IL-6, IFN-γ) induce astrocyte activation [113], which upregulates astrocytic Interferon-induced transmembrane protein 3 (IFITM3) expression. IFITM3 then activates γ-secretase, promoting Aβ accumulation [127] and memory impairment [128]. ApoE, an apolipoprotein expressed by astrocytes, is also involved in AD pathogenesis [129–131]; it exerts anti-inflammatory and protective effects in BBB injury [132,133], is the most upregulated apolipoprotein synthesized after brain injury [134] and shows increased expression in AD models [135]. Evidence indicates that ApoE participates in Aβ accumulation and clearance [136] and its dysfunction impairs cerebrovascular function and disrupts the BBB [113].

In summary, during AD pathogenesis, astrocytic glutamate uptake mechanisms become dysregulated. Concurrently, activated astrocytes promote inflammatory responses, driving Aβ accumulation into plaques. Furthermore, impaired BBB transport function prevents efficient toxin clearance and allows harmful substances to penetrate the brain, accelerating toxin accumulation and neuronal death. Thus, BBB protection could be achieved by upregulating *EAAT* expression and inhibiting inflammatory responses (e.g., via activation of the TGF-β signaling pathway).

2.4 Ischemic Stroke

Ischemic stroke, the second leading cause of death globally, is characterized by ischemic and hypoxic necrosis of brain tissue resulting from disrupted cerebral blood supply. In this process, astrocyte-mediated inflammatory responses play a key role. Within two to six hours of ischemic injury onset [137], activated astrocytes secrete large quantities of inflammatory factors (e.g., TNF-α, IL-1β, IL-6), which induce elevated NO expression and exacerbate brain damage. A study using cottonseed oil to inhibit astrocyte activity found significantly reduced pro-inflammatory cytokines in the ischemic penumbra post-injury. Ischemic stroke also induces the formation of A1 and A2 reactive

astrocytes: A1-reactive astrocytes, triggered by neuroinflammation, infection, or senescence, promote neuronal death and inhibit functions supporting neuronal survival and synaptogenesis, while also contributing to neurodegeneration and chronic neuropathic pain [138–141]. In contrast, A2-reactive astrocytes exhibit proliferative capacity, upregulate neurotrophic factors and presynaptic thrombospondin, promote neuronal growth and synaptic repair and are postulated to participate in glial scar formation, debris clearance and BBB repair [142–144]. Thus, inhibiting A1-type astrocytes and promoting A2-type astrocytes are pivotal for BBB protection and repair [145].

Based on these findings, mitigating post-ischemic brain damage may be achievable by inhibiting astrocyte activity (e.g., via cotton seed oil or analogous agents) or inducing A2 astrocyte polarization. Further in-depth understanding of key signaling pathways regulating A2 astrocyte differentiation and the mechanisms governing A1-to-A2 astrocyte transition (e.g., S100A10) will facilitate exploration of A2 astrocytes' roles in maintaining BBB homeostasis.

2.5 Epilepsy

Epilepsy is a chronic neurological disorder caused by highly synchronized abnormal neuronal discharges in the brain, characterized by recurrent, transient and stereotypical CNS dysfunction [146]. Following epileptogenesis, reduced *EAAT* expression in astrocytes triggers the release of pro-inflammatory cytokines and chemokines [147]. In adult epileptic rats, inhibition of IL-1β or TNF-α (e.g., via tocilizumab) reduces the frequency and duration of spike discharges, suggesting inflammation as a key driver of epilepsy [148]. Systemic inflammation induced by epileptic seizures enables ions and epileptogenic substances to cross the BBB, disrupting brain homeostasis, maintaining the epileptic state and forming a vicious cycle of "BBB disruption $\rightarrow$ epilepsy $\rightarrow$ more severe BBB disruption". In summary, preserving BBB integrity could be achieved by inducing the secretion of endothelial protective factors (e.g., *Ang-1*, *GDNF*), activating signaling pathways such as Hh and Wnt/β-catenin and upregulating tight junction expression to prevent toxic substance infiltration.

3. Discussion

3.1 Existing Research on the Effects of Astrocytes on the Blood-Brain Barrier

The BBB is a critical structural and functional component of the CNS, with its unique structural and functional properties serving to restrict the entry of harmful substances into the brain parenchyma. Additionally, it plays a pivotal role in maintaining the homeostasis of the cerebral microenvironment. Astrocytes, the most abundant glial cells in the CNS, are pivotal for maintaining BBB integrity [149]. Astrocytic perivascular endfeet are directly involved in the formation of the neurovascular unit and these endfeet act as critical nodes in cerebral metabolic processes [150]. Such functions, encompassing metabolism, cholesterol synthesis, neurotransmitter uptake and biosynthesis, represent core mechanisms underlying the maintenance of BBB microenvironmental homeostasis [151].

Astrocytes leverage their structural specializations to induce EC differentiation, upregulate TJ protein expression, enhance basement membrane integrity and regulate the BBB in coordination with transporter proteins on ECs. *GLUT1*, a key glucose transporter, is highly expressed at the BBB, with astrocytes facilitating neuronal glucose supply through *GLUT1*-mediated uptake. *EAAT*, the primary glutamate transporters, enable astrocytes to clear glutamate from the synaptic cleft, thereby preventing excitotoxicity, neuroinflammation and cerebral edema, as well as mitigating the initiation and progression of neurodegenerative diseases such as AD, PD and MS. Furthermore, P-gp actively effluxes various substrate molecules and limits compound uptake by ECs, thereby maintaining local microenvironmental homeostasis and shielding the BBB from bloodborne toxins. Moreover, astrocytes can modulate BBB permeability by regulating endothelial proteins, leveraging the BBB's intrinsic low endocytic activity.

Astrocytes also exert either protective or deleterious effects on the BBB through the secretion of diverse factors. Secreted factors such as *Ang-1*, *GDNF*, RA, and IGF-1 have been demonstrated to enhance BBB barrier properties and upregulate TJ expression. Conversely, certain factors—including VEGF, NO and ET—exert deleterious effects by inducing EC apoptosis and downregulating TJ-related proteins. These factors interact in a coordinated manner, enabling astrocytes to dynamically regulate BBB stability. Beyond secreted factors, signaling pathways are also critical: Hh, Wnt/β-catenin, and TGF-β pathways collectively protect and repair the BBB by upregulating TJ protein expression and suppressing inflammatory responses.

Astrocytes are further involved in the dynamic regulation of the nervous system and contribute significantly to the pathogenesis of neurodegenerative diseases [152]. In this review, multiple disorders have been highlighted and illustrated—including MS, PD, AD, ischemic stroke and epilepsy—as has the fact that astrocytes employ diverse mechanisms to protect, disrupt, or repair the BBB under pathological conditions, such as releasing excessive pro-inflammatory factors, modulating neuronal excitability, altering TJ protein expression and inducing reactive astrocyte polarization. Moving forward, a deeper understanding of the multifaceted roles and underlying mechanisms of astrocytes in BBB regulation may facilitate the design of more targeted therapeutic strategies aimed at BBB modulation, thereby opening new avenues for restoring BBB integrity in neurological disorders.

3.2 Limitations of Existing Research and Future Directions

Although current research has thoroughly explored the role of astrocytes in the BBB, several gaps and unresolved

questions remain to be addressed. The following outlines the limitations of current studies and potential directions for future research.

First, research into astrocyte heterogeneity is insufficient. Astrocytes are not a homogeneous cell type; rather, they exhibit functional diversity across various brain regions and physiological states. Current understanding of astrocytic heterogeneity is limited, particularly concerning the influence of distinct astrocytic subtypes on BBB stability and function. Future investigations should aim to explore the distribution and functional differences of astrocytic subtypes across brain regions, thereby elucidating their specific roles within the context of BBB regulation.

Second, the long-term effects of astrocyte functional regulation on BBB integrity are not yet fully understood. While existing studies have established the pivotal role of astrocytes in BBB formation and maintenance, there remains a significant gap in the understanding of their sustained influence, particularly in how they continuously regulate the BBB following neurotrauma or inflammatory events. For instance, while astrocytes can modulate BBB stability by secreting various signaling factors, their long-term impact on the BBB during chronic pathological conditions and the sustainability of these regulatory actions remain unclear. Moreover, the roles of astrocytes in different pathological states—whether protective or detrimental—are often time-dependent. In neurodegenerative diseases such as AD and PD, the long-term response of astrocytes may either exacerbate or alleviate BBB damage. Therefore, future research should prioritize elucidating the mechanisms underlying the long-term regulation of astrocytic function, with particular emphasis on their role in chronic diseases. Such studies will be crucial for the development of long-term therapeutic strategies aimed at stabilizing the BBB.

Finally, a gap persists between basic research and clinical application. Although numerous fundamental studies have provided valuable insights into the role of astrocytes in BBB regulation, translating those findings into effective clinical therapies remains challenging. Many studies are based on animal models or cell cultures, which do not fully capture the complexity of human diseases. Future research must place greater emphasis on clinically relevant studies, including clinical trials and human-specific models, to validate the therapeutic potential of astrocyte regulation of the BBB.

4. Conclusion

Astrocytes play an indispensable role in maintaining the integrity and function of the BBB. In terms of structural adaptation, astrocytes play a role in maintaining BBB permeability by influencing endothelial cell differentiation and regulating the expression of tight junction proteins. Meanwhile, their roles in neurotransmitter uptake, glucose transport, and protection against neurodegenerative diseases highlight their important contributions to brain homeostasis. In addition, the factors secreted by astrocytes can both protect and damage the BBB, reflecting their dual roles in health and disease. Finally, the article mentions the dynamic regulation of BBB by astrocytes under pathological conditions, highlighting their potential as therapeutic intervention targets for neurological diseases. However, after summarizing, we found that there are still some research gaps, especially in the heterogeneity of astrocytes, long-term regulatory mechanisms, and the insufficient translation of basic research into clinical applications. Future research should focus on these areas to improve strategies for stabilizing the BBB and enhancing the treatment of neurodegenerative diseases.

Author Contributions

Conceptualization, SSZ and LLW; review of the literature, DF and AYH; writing—original draft preparation, DF; writing—review and editing, SSZ and LLW. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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