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REVIEW ARTICLE

The microcirculation, the blood-brain barrier, and the neurovascular unit in health and Alzheimer disease: The aberrant pericyte is a central player

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ABSTRACT

High fidelity neuronal signaling is enabled by a stable local microenvironment. A high degree of homeostatic regulation of the brain microenvironment, and its separation from the variable and potentially neurotoxic contents of the blood, is brought about by the central nervous system barriers. Evidence from clinical and preclinical studies implicates brain microcirculation, cerebral hypoperfusion, blood–brain barrier dysfunction, and reduced amyloid clearance in Alzheimer pathophysiology. Studying this dysregulation is key to understanding Alzheimer disease (AD), identifying drug targets, developing treatment strategies, and improving prescribing to this vulnerable population. This review has 2 parts: part 1 describes the cerebral microcirculation, cerebral blood flow, extracellular fluid drainage, and the neurovascular unit components with an emphasis on the blood-brain barrier, and part 2 summarizes how each aspect is altered in AD. Discussing the neurovascular unit structures separately allows us to conclude that aberrant pericytes are an early contributor and central to understanding AD pathophysiology. Pericytes have multiple functions including maintenance of blood-brain barrier integrity and the control of capillary blood flow, capillary stalling, neurovascular coupling, intramural periarterial drainage, glia-lymphatic (glymphatic) drainage, and consequently amyloid and tau clearance. Pericytes are vasoactive, express cholinergic and adrenergic receptors, and exhibit apolipoprotein E isoform –specific transport pathways. Hypoperfusion in AD is linked to a pericyte-mediated response. Deficient endothelial cell–pericyte (PDGBB-PDGFRβ) signaling loops cause pericyte dysfunction, which contributes and even initiates AD degeneration. We conclude that pericytes are central to understanding AD pathophysiology, are an interesting therapeutic target in AD, and have an emerging role in regenerative therapy.

Significance Statement: Dysregulation and dysfunction of the neurovascular unit and fluid circulation (including blood, cerebrospinal fluid, and interstitial fluid) occurs in Alzheimer disease. A central player is the aberrant pericyte. This has fundamental implications to understanding disease pathophysiology and the development of therapies.

I. Introduction

A human brain has approximately 644 km of blood vessels, which provide brain cells with nutrients, energy metabolites, and oxygen and remove metabolic waste products such as carbon dioxide and hydrogen ions from the brain into the systemic circulation. Blood vessels also carry hormones and homeostatic information (such as plasma osmolality and pH) to the brain (Zlokovic, 2008; Kisler et al, 2017a) and distribute humoral agents synthesized in the brain to peripheral sites (Fenstermacher et al, 1988). Although the brain forms only 2% of the overall body mass, it uses 20% of the body's oxygen and glucose. It has little long-term storage of energy, and its nearly constant supply of energy is maintained through its circulatory system.

II. Blood supply to the brain

A continuous and controlled blood supply is critical for normal brain function and viability (Fantini et al, 2016). This is achieved through an extensive and well-regulated vascular network, consisting of arteries, arterioles, capillaries, venules, and veins (Sweeney et al, 2018). There is a gradual transition between the vessel types; precapillary arterioles refer to the transition between arterioles and capillaries, while postcapillary venules refer to the transition between capillaries and venules. The parenchymal arterioles, capillaries, and venules form the microcirculation system.

A. Arterial supply

The supply of the brain with arterial blood can be separated into 2 main sources: anterior circulation, originating from the 2 internal

carotid arteries; and the posterior circulation arising from the 2 vertebral arteries (Fig. 1) (Boyanova, 2022). The internal carotid arteries supply the brain with approximately 80% of the total blood supply to the brain (Agarwal and Carare, 2021). The anterior and posterior circulatory sources meet at the circle of Willis, which is located within the interpeduncular fossa of the brain. The circle of Willis allows any 1 of the 4 vessels to take over brain perfusion and provides a protective mechanism against ischemia. Major blood vessels arise from the circle of Willis and ramify extensively before traveling over the surface of the brain and end as perforating or choroidal branches to deeper structures (Chandra et al, 2017). The leptomeningeal arteries penetrate the cortex giving rise to arterioles, capillaries, and postcapillary venules that lastly drain into cortical veins that exit the parenchyma.

B. Capillaries and blood-brain barrier

Capillaries account for over 85% of the total length of cerebral blood vessels offering the greatest endothelial surface area of 12 m^2 for solute exchange from blood to brain and vice versa (Zlokovic, 2008). Approximately 56% of the total brain blood volume is held within mouse capillaries (Gould et al, 2017). The density of brain capillaries varies significantly within the brain depending on location and energy needs, with higher capillary density in gray versus white matter (Cipolla, 2009). The average density of capillaries in human brain tissue is approximately 2500–3000 capillaries per cubic millimeter, which implies a mean separation of less than 40 μm (Pardridge, 2015b). This results in virtually instant solute equilibration through the brain interstitial space as soon as molecules have crossed the capillary wall. Importantly, the capillaries in the brain are different from those in the periphery because there is no free exchange between the blood and the interstitial fluid (ISF) (Palmer, 2010). This is because the cerebral capillary walls are composed of an extremely specialized monolayer of endothelial cells whose main function is to maintain brain homeostasis by regulating the entrance of leukocytes and plasma components into the central nervous system (CNS) and exporting potential neurotoxic compounds from brain to blood (Abbott et al, 2010; Zlokovic, 2011). This is crucial for accurate neuronal and synapse function; neuronal connectivity, and information processing. Thus, the brain capillary endothelial layer has a barrier phenotype and is the site of the blood-brain barrier (BBB) (Fig. 2).

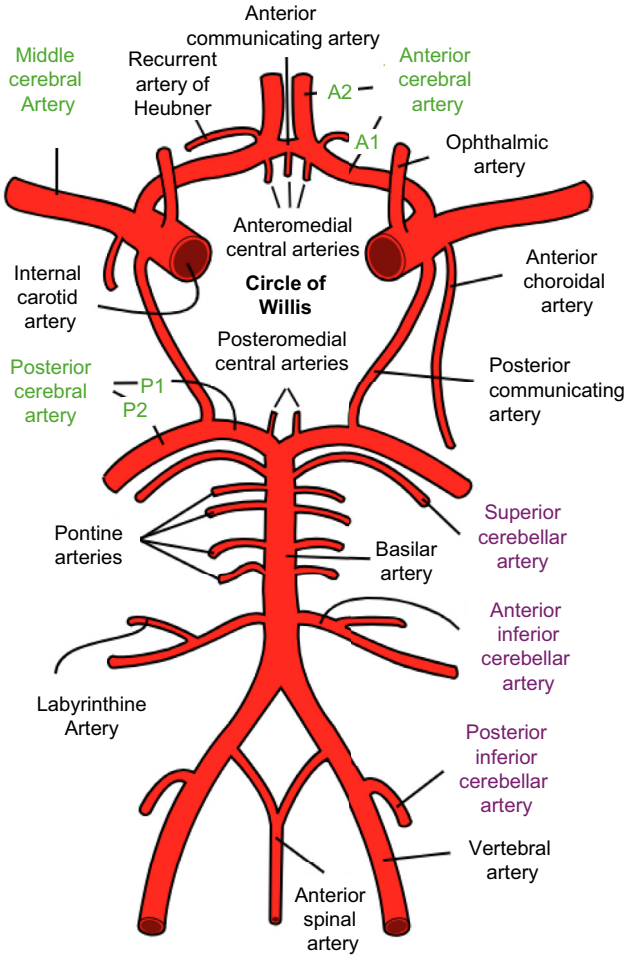

Fig. 1. The 4 major arteries (carotid and vertebral) that supply the brain merge at the circle of Willis. Arising from this arterial wreath are the anterior, middle, and posterior cerebral arteries, which give rise to the pial arteries and arterioles, which supply blood to the penetrating intracortical arterioles.

C. Venous outflow

The venous system consists of 2 networks: the more superficially located dural venous sinuses and the deeper cerebral veins (Chandra et al, 2017). The superficial veins distribute blood from the cortical and subcortical areas into 4 groups of major veins. These include the superior sagittal group; the spenoidal group; the falcine group, and the tentorial group (Rhoton, 2002; Kılıç and Akakın, 2007; Tong et al, 2018). The deep venous system consists of channels draining the third and lateral ventricular walls or the channels draining the basal cisterns and consists of the subependymal veins, internal cerebral veins, basal veins, the vein of Galen, and their tributaries (Rhoton, 2002; Kılıç and Akakın, 2007). Venous drainage in the posterior fossa exists through (1) the galenic group, (2) the petrosal group, and (3) the tentorial group (Kılıç and Akakın, 2007).

D. Cerebral vessel innervation

Adrenergic and cholinergic nerve fibres extensively innervate the entire cerebrovasculature. These fibres have both extrinsic (eg, cervical, sphenopalatine and trigeminal ganglia) and intrinsic (eg, locus coeruleus, fastigial nucleus, and dorsal raphe nucleus) origins

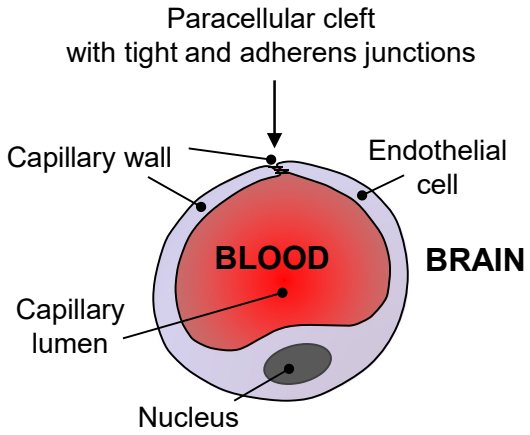

Fig. 2. The blood-brain barrier, in other words, the interface between the blood and the brain, is located at the brain capillary wall. This diagram shows a brain capillary in cross-sectional view. The capillary lumen is filled with blood. The walls of the capillary are composed of a single endothelial cell joined by tight and adherens junctions at the paracellular cleft. The paracellular cleft is indicated by an arrowhead. Created in BioRender by S.A.T. (2024) https://BioRender.com/p66u993

(Willie et al, 2014). This suggests a neural role in the regulation of cerebral blood flow (CBF).

III. Cerebral blood flow

CBF depends on the systemic control of blood pressure, cardiac output, and tissue requirements. Ultimately, the brain needs to maintain a relatively stable blood flow despite fluctuations in arterial pressure between 50 and 170 mm Hg, and because neurons lack the capacity to store significant energy reserves, it needs to match supply with use. Interestingly, despite fluctuations in cerebral perfusion pressure and changes in regional blood flow, total blood supply to the brain remains remarkably constant (Tan and Taylor, 2014). The maximum increase in CBF is less than 1-fold (approximately 14 mL/s). This contrasts to the peripheral circulation where blood flow to the muscles can increase 5- to 10-fold (Koep et al, 2022).

A. Vessel diameter

Both arterioles and capillaries take part in cerebrovascular resistance (Gould et al, 2017). The largest hemodynamic resistance occurs in the capillary bed (Koep et al, 2022). Changes in vessel diameter will drive changes in cerebrovascular resistance following the Hagen-Poiseuille equation and so affect blood flow. The smaller the vessel internal diameter, the lower the flow. Precapillary sphincters are thought to be able to generate the largest changes in resistance of all brain vessel segments (Grubb et al, 2020). The mural cells that coat the blood vessel walls are involved in changing the vessel diameter and controlling blood flow. They include smooth muscle cells and pericytes. Interestingly, vascular smooth muscle cells that surround larger vessels and pericytes may represent phenotypic variants of a continuous population of mural

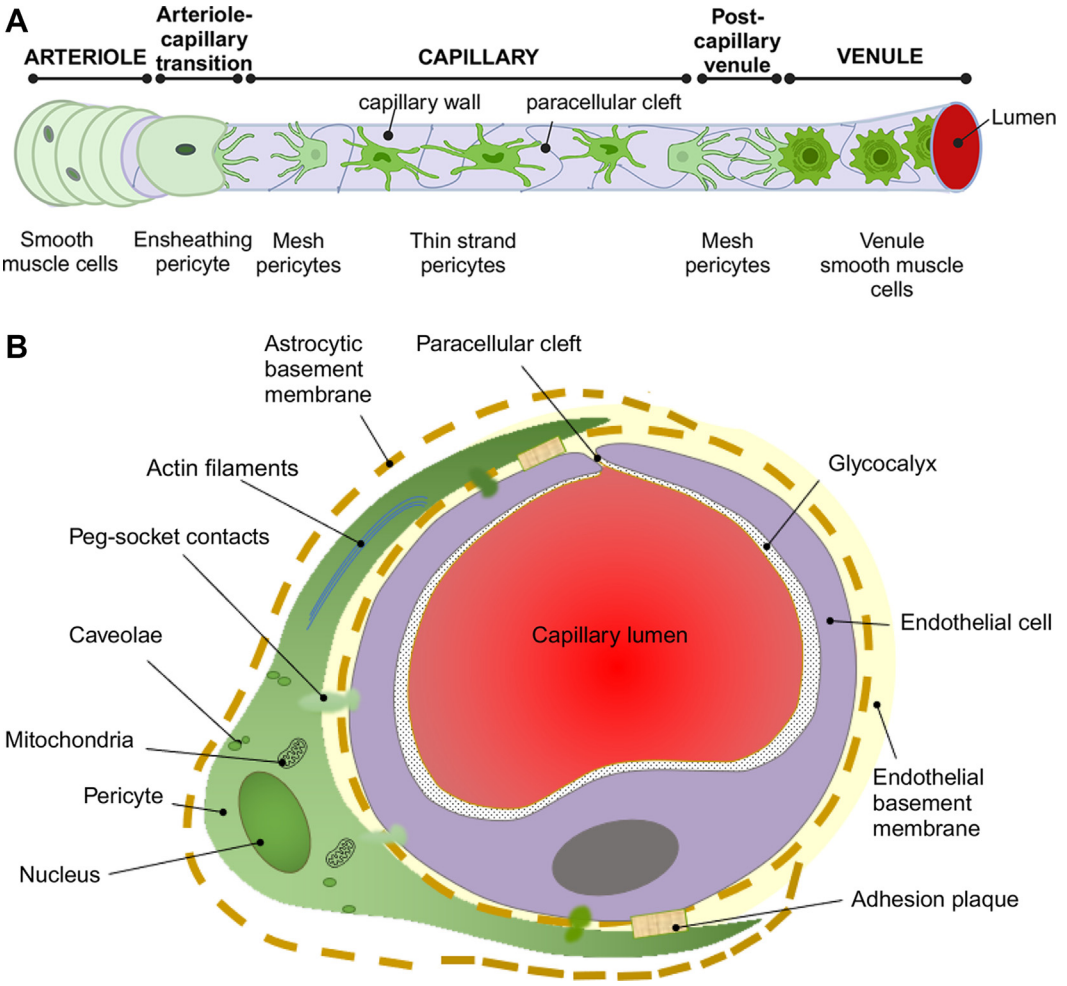

Fig. 3. (A) Schematic showing the distinct populations of pericytes, which have been identified along the cerebral vasculature and named as ensheathing, mesh, and thin-strand based on the morphology of their trunk and branches. Vascular smooth muscle cells and pericytes represent phenotypic variants of a continuous population of mural cells. Smooth muscle cells form concentric rings on arterioles. Vascular smooth muscle-pericyte hybrid cells also called ensheathing cells reside on precapillary arterioles (also called arteriole capillary transition) and interlock with mesh pericytes at the arteriole–capillary interface. Ensheathing pericytes completely encircle the vessel. However, pericytes in capillary beds typically exhibit long, meandering processes that cross the microvasculature in thin strands or pairs that twist in a helical fashion. Mesh pericytes become more prevalent again as capillaries turn into postcapillary venules, while transitioning into venules. Stellate-shaped smooth muscle cells cover the walls of parenchymal venules. Venule pericytes have many slender and shorter branching processes than capillary pericytes. Figure adapted from (Hartmann et al, 2015). It has been suggested that pericyte functions varies depending on their position in the vascular bed. Pericytes, which express α-smooth muscle actin, are found at both ends of capillaries and regulate blood flow, but pericytes in the central part of the capillary bed express less α-smooth muscle actin and maintain the characteristics of the blood-brain barrier and finally the pericytes at the end of the vascular bed regulate the passage of immune cells from the blood to the brain (Uemura et al., 2020). Created in BioRender. Thomas, S. (2025) https://BioRender.com/mmjcrhp. (B) The mature capillary pericyte has a discoid nucleus that is surrounded by cytoplasm containing mitochondria-producing and protein-producing organelles. Dense bands of microfilaments containing actin, myosin, and tropomyosin are concentrated beneath the plasma membrane, in particular, the inner surface membrane facing the endothelium. The outer, abluminal pericyte surface often shows numerous caveolae. Despite being separated by the shared basement membrane, pericytes, and endothelial cells make numerous direct contacts of different types: schematically depicted are peg-socket contacts and adhesion plaques, but other types exist including gap junctions. Based on Armulik et al, 2011. Long intercellular channels called tunneling nanotubes can be found between pericytes and other cells of the neurovascular unit including endothelial cells and astrocytes and are involved in long-distance communication (Pisani et al, 2022). Created in BioRender. Thomas, S. (2025) https://BioRender.com/v75b30b

cells (Fig. 3A) (Navarro et al, 2016). The role of the smooth muscle cells around the larger vessels being taken by the pericytes around the capillaries (Peppiatt et al, 2006).

1. Arteries, arterioles, and veins (smooth muscle)

Vascular smooth muscle forms continuous sheets around the walls of arteries, arterioles, and veins and has a major role in controlling blood flow of the larger vessels. Large extracranial and intracranial arteries have multiple contractile smooth muscle layers, which decrease to a single layer in cerebral arterioles. Constriction (or dilation) of the vascular smooth muscle cells will decrease (or increase) the vessel internal diameter to rapidly alter blood supply.

a. Myogenic tone. Resistance vessels are partially constricted at a constant pressure. This is called the myogenic tone. Importantly, this allows the smooth muscle layers of resistance vessels to respond intrinsically to changes in intravascular pressure. This is the myogenic response and is more prominent in cerebral circulation than that in many other vascular beds (Cipolla, 2009). Resting vascular tone is determined to some extent by not only the basal endothelial cell secretion of nitric oxide (NO) (vasodilator) and endothelin-1 (vasoconstrictor) (Cipolla, 2009; Davenport et al, 2016), but also extrinsic innervation from the autonomic nervous system and intrinsic innervation from subcortical neurons and cortical interneurons (MacVicar and Newman, 2015).

b. Vasomotion. Spontaneous rhythmic variations in the vessel lumen resulting from smooth muscle contraction and dilation modulate the arterial and arteriolar circulation. It occurs in the absence of neuronal activity (van Veluw et al, 2020). This is an intrinsic mechanism, called vasomotion, and has been observed in cerebral arteries and arterioles (Haddock et al, 2006).

2. Precapillary sphincters and capillaries (pericytes)

The capillary bed of the brain is comprised of a dense network of intercommunicating vessels that have no smooth muscle layers but have perivascular pericytes, some of which contain contractile machinery (eg, smooth muscle actin) and are contractile responding to increases in intracellular calcium concentration (Hamilton, 2010). It has been shown that pericytes, not endothelial cells, are responsible for capillary diameter changes (Peppiatt et al, 2006; Berthiaume et al, 2018). Pericyte contraction and relaxation can change the vessel diameter by up to 20% (Cai et al, 2018). Blood flow through the capillaries is regulated by both the contraction and dilation of (1) the smooth muscle layers at the arterial and venous end and (2) the capillary pericytes. However, the main function of the pericyte varies along the length of the capillary bed (Fig. 3A). Precapillary sphincters are considered to have pericytes (Grubb et al, 2020).

a. Myogenic tone. Capillaries are constricted at rest and the resting capillary tone is 39.4% ± 2.2% of the maximally relaxed passive diameter (Hariharan et al, 2022). Pericyte ablation has been shown to cause capillary dilation (Berthiaume et al, 2018). Therefore, capillary pericytes contribute to basal blood flow resistance (vascular tone) and slow modulation of blood throughout the brain (Hartmann et al, 2021). Pericytes control capillary vascular tone through α2-adrenergic mediated constriction or dilation (Koep et al, 2022). It is known that pericytes also express α1-adrenergic receptors and vasoconstrict in response to noradrenaline (Oishi et al, 2007). The resting vascular tone is possibly being dependent on noradrenaline release from the locus coeruleus (Hall et al, 2014). The heterogenity observed in capillary vascular tone allows blood flow to be prioritized to specific regions under basal conditions (Hartmann et al, 2021).

b. Vasomotion. Vasomotion is exhibited by ensheathing pericytes located on the arteriole–capillary transition, but has not been detected by pericytes further downstream on the capillary (Hill et al, 2015; Hartmann et al, 2022).

B. Regulation of cerebral blood flow

There are 3 effectors of cerebrovascular regulation: cerebral autoregulation, vasoactivity, and neurovascular coupling. There is some evidence of interactions between the 3 effectors (Fantini et al, 2016).

1. Cerebral autoregulation

The maintenance of a stable CBF in response to changes in blood pressure is called cerebral autoregulation and requires intact sympathetic, cholinergic, and intrinsic myogenic mechanisms (Hamner and Tan, 2014; Nizari et al, 2021). There is also likely to be other physiologic mechanisms. Autoregulation involves controlling the diameter of the cerebral arterioles and precapillary sphincters by rapid contraction of the smooth muscle layers. In this way, CBF is maintained between 40 and 60 mL/100 g/min over a wide range of mean arterial pressures (50–150 mm Hg).

Sympathetic and cholinergic nervous control mechanisms both play vital but distinct roles in cerebral autoregulation in humans, having more significant affects at different mean arterial pressures (Hamner and Tan, 2014). Sympathetic activity being a more important contributor to autoregulation than cholinergic activity at the lower to mid pressures.

Hamner and Tan (2014) suggest that neurogenic control of the cerebrovasculature is mainly responsible for maintaining a stable CBF for arterial pressures between 50 and 100 mm Hg, whereas the effects of vascular myogenic control lie outside this region (Hamner and Tan, 2014). This suggests that neurogenic control may be responsible for homoeostatic maintenance of CBF, whereas myogenic control may be neuroprotective against ischemia and hemorrhage and from rapid swings in pressure. Myogenic control playing an important role in maintaining an adequate level of tissue perfusion.

Neural activity is mediated through neurotransmitters interacting with receptors expressed on the vascular smooth muscle cells. The sensitivity, density, and distribution of α (α1 and α2) and β (β1 and β2) adrenergic receptors vary considerably throughout the cerebrovascular tree (Koep et al, 2022). Consequently, neural activity will result in differences in regional cerebral perfusion. Interestingly, the myogenic control of cerebral autoregulation is mediated through different subtypes of calcium channels, which are also variably expressed in cerebrovascular smooth muscle cells (Koep et al, 2022). In addition, the nucleus of many cells has been suggested to be a mechanosensor, suggesting a role of the pericyte nucleus in the control of blood flow (Dessalles et al, 2021).

2. Cerebrovascular vasoactivity

Alterations in arterial gas concentrations have a strong and rapid effect on global CBF. This response is referred to as cerebrovascular vasoactivity and is not considered to be a mechanistic component of cerebral autoregulation. Arterial pCO_2 is a potent vasodilator, and even small fluctuations in the physiologic range (pCO_2 of 30–50 mm Hg; 4.0–6.7 kPa) result in large changes in CBF. Hypoxia increases CBF only when systemic pO_2 is below 58 mm Hg (7.9 kPa) (Gupta et al, 1997). Carbon dioxide and hypoxia act synergistically in their control of CBF so that the delivery of oxygen to the brain is enhanced during hypoxic hypercapnia (Mardimae et al, 2012). CO_2 and hypoxia may act at different sites. The effect of CO_2 is directly on the vessel wall and is mediated by pH changes, while hypoxia is thought to be detected by specialized astrocytes (Mardimae et al, 2012). Pericytes also contract or dilate in response to changes in

local CO_2 gradients primarily as a result of changes in extracellular pH but may also be as a direct effect of CO_2 (Chen and Anderson, 1997; Matsugi et al, 1997).

3. Neurovascular coupling

Increases in local brain activity are accompanied by increases in regional blood perfusion as a result of arteriole and/or capillary dilation. This activity-dependent increase in local blood flow, or functional hyperaemia, is mediated by different mechanisms collectively known as neurovascular coupling.

The ensheathing pericytes on the precapillary arterioles, and not the smooth muscle cells of the arterioles, are the first cells to relax during neural activity, leading to capillary dilation and increased CBF to boost energy supply (Fig. 3A). In fact, the neurovascular coupling response has been shown to be initiated in first-order capillaries (Cai et al, 2018). This may simply be because most neurons are closer to capillaries (~8.4 μM) than to arterioles (70 μM) (Hall et al, 2014). Interestingly, the capillaries are capable of passing a hyperpolarizing vasodilatory signal back to arterioles via gap junctions between endothelial cells or pericytes (Hall et al, 2014). This would cause an increase in blood flow toward active areas (Gonzales et al, 2020). In addition, pericytes at capillary junctions in the postarteriole regions have been shown to differentially constrict to direct branch-specific blood flow (Gonzales et al, 2020). Interesting, capillary blood flow becomes more homogenous during functional hyperemia (Hartmann et al, 2021).

It has also been suggested that precapillary arterioles are involved in the initial stages, and the capillaries are more involved in the later stages, of neurovascular coupling (Hartmann et al, 2021). A study has demonstrated that neurovascular uncoupling in a mouse model of acute global pericyte loss was due to altered pericyte function and not changes in capillary density, endothelial cell, or neuronal cell function (Nikolakopoulou et al, 2019; Kisler et al, 2020), indicating the importance of the pericyte in the control of blood flow. In fact, capillary dilation is responsible for a large portion of the blood flow increase caused by neuronal activity. Capillary blood flow can range from 0.3 to 3.2 mm/s, which highlights the importance of local blood flow regulation (Cipolla, 2009).

Neurovascular coupling allows blood flow and oxygen to be rapidly increased to activated regions (Iadecola, 2013; Kisler et al, 2017a; Lebrun-Grandié, 1983) and involves ions, metabolic factors, neurotransmitters, and autocoids (local hormones) (Table 1). Autocoids are important in special circumstances such as inflammation (eg, histamine and bradykinin) and clotting (eg, thromboxane A2). A particularly important metabolic factor is K^+, which causes a functional hyperemia linking blood flow to activity (Ward and Linden, 2013; Hartmann et al, 2021). Adenosine is a potent vasodilator that plays a central role in neurovascular coupling (Table 1). This is partly attributable to the activation of ATP-sensitive potassium (K_{ATP}) channels downstream of adenosine 2A receptors, both of which are expressed in pericytes and endothelial cells (Sancho et al, 2022). The resulting K_{ATP} channel—mediated potassium efflux hyperpolarises the cell membranes closing voltage-gated (L-type) calcium channels and thereby inducing vessel dilation (Zambach et al, 2021; Sancho et al, 2022). Pericyte membrane hyperpolarization propagates upstream via gap junctions between pericytes or endothelial cells causing dilation of the feeding arteriole smooth muscle cells and postarteriole pericytes, which further impacts on CBF (Gonzales et al, 2020). This long-range signal is possibly amplified by inwardly rectifying potassium (K_{ir}) channels expressed on pericytes, which are electrically coupled to endothelial cells (Gonzales et al, 2020). It has recently been demonstrated that K_{ATP} channels expressed in pericytes are activated in response to a decrease in local metabolic substrate (eg, glucose) availability resulting in an increase in blood flow and restoration of glucose delivery. In fact, pericytes may be metabolic sentinels continually monitoring substrate availability to alter blood flow to maintain ongoing neuronal health and function (Hariharan et al, 2022). CO_2 produced by neurons is not thought to be involved in neurovascular coupling (Tournissac et al, 2024).

Cholinergic signaling is thought to have an important role in neurovascular coupling (Nizari et al, 2021) with pericytes possessing functional cholinergic receptors, which are thought to cause contraction via a cAMP-mediated event (Ferrari-Dileo et al, 1992). If there is an interaction between neurovascular coupling and autoregulation (Fantini et al, 2016), it is more likely to be mediated by the sympathetic nervous system than by the cholinergic pathways (Tan and Taylor, 2014).

4. Signaling pathways

Different signaling pathways are thought to be involved in the dilation of capillaries and arterioles; however, both rely on the relaxation of actomyosin (Figs. 3B and 4) (Rungta and Charpak, 2016). Capillary dilation is dependent on calcium- signaling in astrocytes triggering the release of vasodilating agents (such as prostaglandin E_2). Prostaglandin E_2 binding to the pericyte prostaglandin E_2 receptor 4 would result in vasodilation (Fig. 4). In contrast, arteriolar dilation is dependent on postsynaptic *N*-methyl D-aspartate (NMDA) receptors and neuronal NO production (Biesecker et al, 2016; Mishra et al, 2016) (Fig. 4). Interestingly, NO-mediated capillary vasodilation may also occur in specific brain regions because NO is associated with inhibition of vasoconstricting 20-hydroxyeicosatetraenois acid production (Hall et al, 2014; Mishra et al, 2016).

C. Capillary stalling

A recent observation is that in awake, healthy mice and during rest, a significant portion of cerebral capillaries experience momentary cessation of flow, otherwise called capillary stalling (Erdener et al, 2019). This is thought to be related to obstructions caused by large blood constituents (ie, leukocytes and cholesterol) failing to pass through narrow vessels. Interestingly, although some pericytes do not visibly constrict, their circumferential processes may stiffen in response to neurotransmitters (eg, ATP and noradrenaline). This would prevent dilation or prevent the changes in vessel diameter, which would allow erythrocytes to pass through (Peppiatt et al, 2006). This may actually result in the redirection of capillary blood flow. Contraction of the longitudinal processes of pericytes may also cause vessel wall stiffening without alteration of vessel diameter (Attwell et al, 2016). The obstructions are thought to be eventually cleared, but in some cases, this leads to capillary rarefaction (Reeson et al, 2018).

Table 1
Vasoactive mediators that increase cerebral blood flow (Fantini et al, 2016)

	Vasoactive Mediators
Ions	K^+, H^+, Ca^{2+}
Metabolic byproducts	Lactate, CO_2, hypoxia, adenosine
Neurotransmitters	Dopamine, γ-amino butyric acid, acetylcholine, NO
Other	Carbon monoxide

IV. Extracellular fluids of the central nervous system

The extracellular fluid of the CNS includes the brain ISF, which is the fluid that directly surrounds the brain cells, and the cerebrospinal fluid (CSF), which is within the ventricles and subarachnoid space of the CNS. The flow of cerebral blood, brain ISF, and CSF is separate but intricately connected. It is thought that the lymphatic

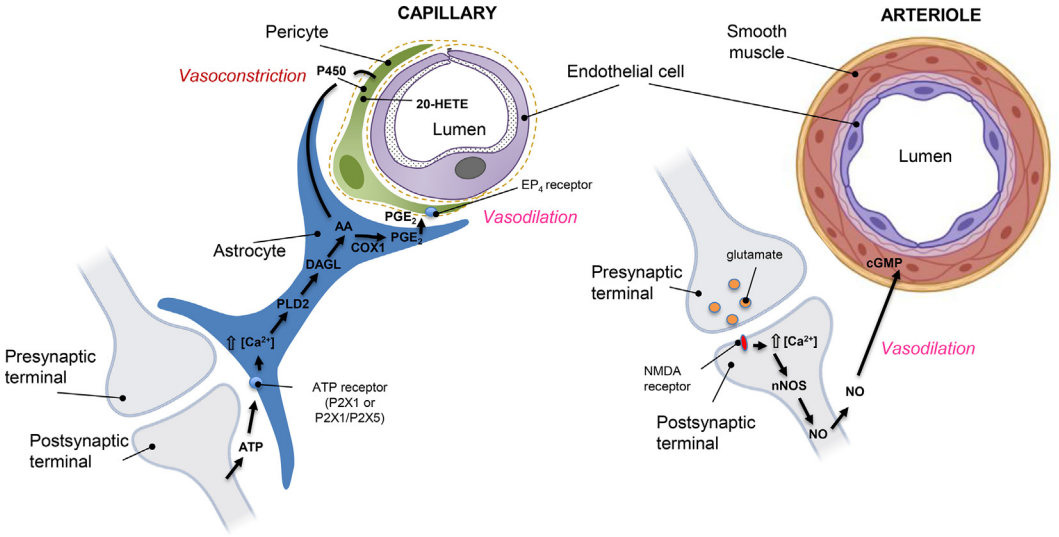

Fig. 4. Neurovascular control mechanisms link neural activity to blood supply by controlling vasodilation and vasoconstriction of the capillaries and arterioles. Neuronal activity releases ATP into the extracellular fluid and this binds to the astrocytic ionotropic ATP receptors ($P2X_1$ and $P2X_1/P2X_5$) causing calcium to enter the astrocytic processes (Mishra et al, 2016). Calcium signals propagate through the astroglial cell (and astroglial syncytium) to reach the perivascular endfoot, where Ca^{2+} triggers the release of arachidonic acid (AA). The synthesis of AA depends upon phospholipase D2 (PLD2) and diacylglycerol kinase (DAGL) activity. Depending on the brain region and local enzymatic systems, AA can be converted to vasodilatory prostaglandins (PGs, eg, prostaglandin E_2) by cyclo-oxygenase (COX)1 located in the astrocytic endfeet or to a vasoconstrictive agent 20-hydroxyeicosatetraenois acid (20-HETE) by the cytochrome P450 enzyme of the pericyte. Prostaglandin E_2 will activate prostaglandin E2 receptor (EP) 4 on pericytes to promote vasodilation. 20-HETE will modulate capillary pericyte tone via interaction with thromboxane receptor. Vasoconstriction will reduce local blood flow and vasodilation will increase local blood flow. In contrast, neurovascular signaling to cause cortical arteriolar dilation requires, at least in part, the activation of NMDA receptors and the production of NO by neuronal nitric oxide synthase (nNOS). NO can cause vasodilation of the arteriole smooth muscle via cGMP. *N*-Methyl D-aspartate (NMDA) receptors can be activated by glutamate released from the presynaptic terminals. There is evidence that glutamate transport into astrocytes may increase arteriole diameter (Jackson et al., 2022). NO may also be involved in capillary dilation by inhibiting the production of 20-HETE (Mishra et al, 2016). Created in BioRender. Thomas, S. (2025) https://BioRender.com/riubnrj

drainage of brain ISF is almost entirely separate from the lymphatic drainage of the CSF.

A. *Interstitial fluid*

The brain ISF surrounds brain cells and is produced by the BBB. Human ISF is produced at a rate of 7 μL/min, and the total volume of brain ISF is approximately 280 mL (Johanson, 2003). Consequently, the brain ISF has a very slow turnover compared with the CSF.

1. *Intramural periarterial drainage pathway*

The ISF from the CNS parenchyma can drain to cervical lymph nodes via thin and restricted basement membrane (BM) pathways close to the walls of cerebral capillaries and arteries (Carare et al, 2008). This is the so-called intramural periarterial drainage (IPAD) pathway (Fig. 5A). ISF flow through this pathway is in the opposite direction to blood flow and may be due to the intrinsic cycles of contraction and relaxation (or vasomotion) of the vascular smooth muscle cells (Aldea et al, 2019). However, CBF may also play a role in providing the motive force for the perivascular pathway (Carare et al, 2008, 2013). Net fluid flow would be in the direction of the arterial pulse, but there would be time within each cycle where the flow would be in the reverse direction (Morris et al, 2014). ISF progress from brain tissue via the periarterial route to the cervical lymph would be maintained by the compression of the BMs, which would allow them to act in a valve-like manner, preventing reflux of ISF and promoting unidirectional ISF flow (Schley et al, 2006). In addition, ISF solutes may be prevented from interacting with BM components when flow is rapid and this would also allow them to continue to progress along the drainage pathway (Schley et al, 2006).

The IPAD pathway allows passage of soluble macromolecules (up to 150 kDa; Amyloid β (Aβ) = 3 kDa) (Carare et al, 2013), but it is narrow and does not allow trafficking of cells such as large antigen-presenting cells from brain to lymph nodes (Carare et al, 2008). This would allow antigens trapped within the brain parenchyma to evade systemic immunologic recognition and would contribute to the disconnection of the brain parenchyma from the systemic immune system. ISF from the brain parenchyma can also drain into the subarachnoid space and combine with the CSF. It is thought to contribute approximately 10% to the total volume of CSF.

B. *Cerebrospinal fluid*

The meninges cover the surface of the brain and include the dura mater, arachnoid mater, and pia mater. The CSF is actively secreted by the 4 choroid plexuses at a rate of 350 μL/min and flows through the cerebral ventricles and the subarachnoid space in the meninges to its ultimate site of reabsorption into the venous blood stream (Fig. 5B). The CSF is continually replenished, and the total volume of CSF is approximately 140 mL (Johanson, 2003). Reabsorption occurs via arachnoid villi (granulations) of the dural sinuses, and the lymphatic vessels present in the dura mater, nasal mucosa and associated with the sheaths of cranial and spinal nerve roots. Recent evidence suggests that the major outflow path for CSF is in fact the lymphatics system (Ma et al, 2017). The arachnoid granulations being more involved in immune surveillance at the brain surface, rather than being a major site for CSF drainage (Shah et al, 2023). In addition, recent findings have revealed the presence of a fourth meningeal layer that separates the subarachnoid space into inner and outer layers (Møllgård et al, 2023). This so-called subarachnoid lymphatic–like membrane would reduce the efficiency of any CSF drainage via the arachnoid granulations (Wen et al, 2024). CSF in the lymphatic vessels of the dura mater and nasal mucosa appears to traffic antigen-presenting cells to lymph nodes.

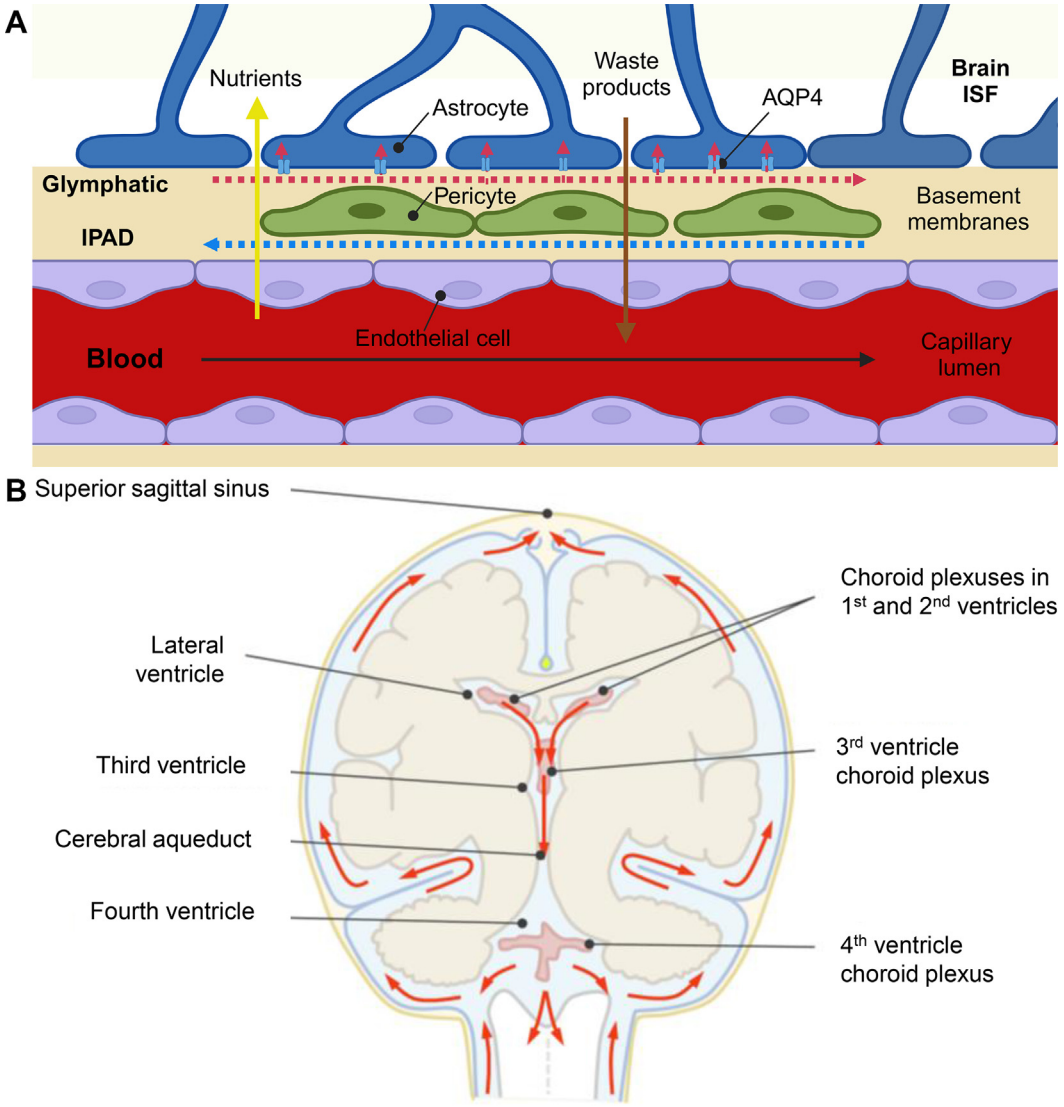

Fig. 5. (A) Cross-section through the brain capillary illustrating the direction of blood flow in the vessel lumen (black arrow) compared with the brain interstitial fluid (ISF) flow in the intramural periarterial drainage (IPAD) pathway (blue dashed arrow) and cerebrospinal fluid (CSF) flow in the glymphatic pathway (red dashed arrow). The CSF has flowed from within the subarachnoid space. The IPAD and glymphatic pathways are between perivascular astrocytic endfeet and the brain capillary endothelium. The basement membranes are maintained, in part, by pericytes, which are located within the endothelial and parenchymal basement membranes surrounding the capillary endothelium. Nutrients can cross the blood-brain barrier (BBB) located at the capillary wall and enter the brain ISF (yellow arrow). Waste products can exit the brain by crossing the BBB and entering the blood (brown arrow). The astrocytic endfeet express AQP4 water channels through which CSF can pass and mix with the intracellular fluid. The fluid can then pass through the astrocyte (and astrocyte syncytium) and enter the ISF surrounding brain cells (not shown). This fluid can exit the brain via the perivenous space and subarachnoid space (not shown). Created in BioRender by S.A.T. (2024) https://BioRender.com/g49o971. (B) Coronal section of the brain illustrating the circulation of the CSF. CSF (blue) is actively secreted by the choroid plexuses (which are located in the cerebral ventricles) before circulating in the direction of the red arrows through the ventricular cavities and entering the subarachnoid space. This diagram is based on that in (Fidanboylu, 2013). Created in BioRender. Thomas, S. (2025) https://BioRender.com/s2x2de6

1. Glymphatics and central nervous system lymphatic pathways

The CSF-filled subarachnoid space is continuous with the brain's perivascular spaces, also called Virchow–Robin spaces. These perivascular spaces of the penetrating arterioles, precapillary arterioles, postcapillary venules, and venules separate the glial and vascular BMs and are a low resistance highway for CSF influx into the brain parenchyma (Yamamoto et al, 2024). These perivascular channels are considered to be prelymphatic channels. CSF flows along the periarterial space and enters the basal lamina that surrounds brain capillaries (Fig. 5A). The subsequent transport of CSF into the brain parenchyma is facilitated by aquaporin (AQP)4 water channels expressed in astrocytic endfeet that ensheath the brain vasculature (Figs. 5A and 6). The movement of CSF through the astrocytic network allows brain ISF plus waste solutes (including proteins) to exit by bulk flow along the perivenous space into the subarachnoid space. This molecule distribution and waste clearance system is referred to as the glia–lymphatic or glymphatic system (Iliff et al, 2012; Jessen et al, 2015) because of its dependence on astroglia water transport. Flow is driven through the glymphatic system by arterial pulsation, slow vasomotion and CSF turnover (Kress et al, 2014).

The fluid in the subarachnoid space can be recirculated (again) via the glymphatic pathway, can empty into the venous blood of the dural sinuses, and/or can drain into the meningeal or perineural lymphatic system (Louveau et al, 2015).

V. Blood–central nervous system interfaces

In addition to the BBB at the brain capillary wall, there are 3 additional blood–CNS interfaces. These include the arachnoid

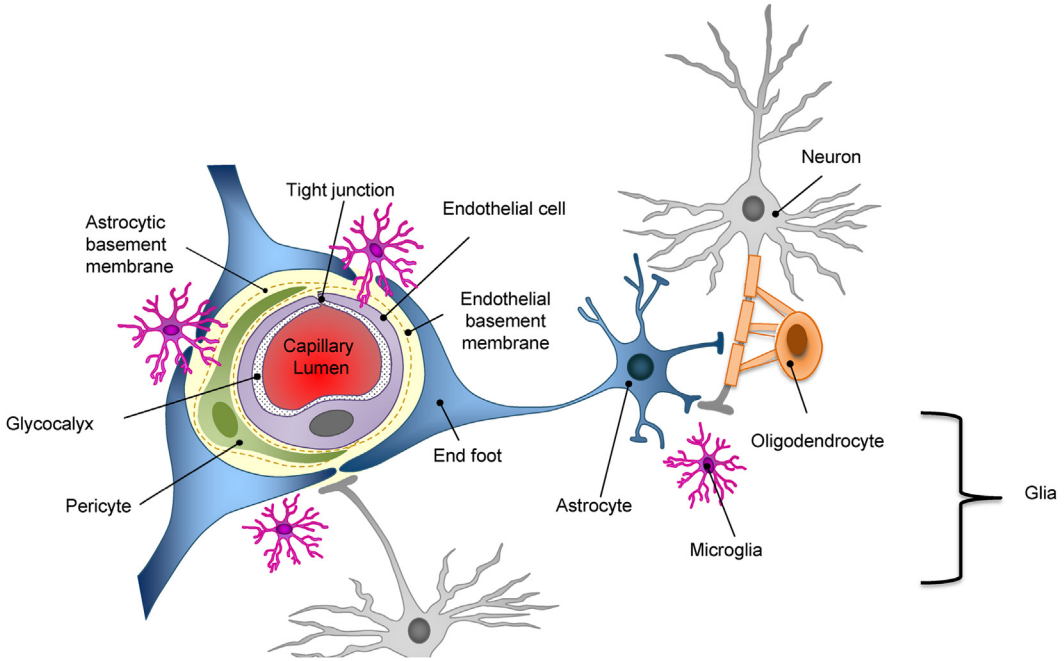

Fig. 6. The neurovascular unit. This diagram is based on that in Fidanboylu (2013). The neurovascular unit is composed of several cell types in close association, working together to maintain optimal brain function. Cerebral endothelial cells, the building blocks of the blood-brain barrier (BBB), form complex tight junctions that restrict the paracellular pathway. This cellular monolayer rests on a basement membrane, which has 2 layers: endothelial and astrocytic. Pericytes are embedded in the basement membrane and partially envelop the capillary endothelial cells. Neuronal terminals are closely apposed to capillaries and pericytes. Astroglial endfeet ensheath the microvessel wall and provide links to neurons. Microglia are CNS resident immune cells. Oligodendrocytes myelinate neuronal axons. Created in BioRender by S.A.T. (2024) https://BioRender.com/a64c483

epithelium, which separates the CSF-filled subarachnoid space from the venous blood in the dural sinuses; the choroid plexus epithelium, which actively secretes CSF, synthesizes polypeptides, and separates blood in the choroid plexus capillaries from the ventricular CSF (Segal, 2000); and the tanycytic barrier consisting of highly specialized ependymal cells forming a blood–CSF barrier at the circumventricular organs (Peruzzo et al, 2000; Mullier et al, 2010; Langlet et al, 2013). The exclusive structure of all these biological barriers encompasses a mixture of physical, metabolic, and transport barriers, which divide the neural internal environment from blood to varying degrees (Abbott et al, 2006; Zlokovic, 2008). At all sites, the physical barrier is largely influenced by the existence of tight junctions (TJs), which decrease permeability of the intercellular adhesion regions.

VI. Neurovascular unit

The BBB is at the brain capillary wall is composed of an endothelial cell monolayer and is a component of the neurovascular unit (NVU). The NVU also consists of the glycocalyx, BMs, pericytes, astrocytes, oligodendrocytes, microglia and neurons (Sweeney et al, 2016) (Fig. 6). The brain endothelial cells are in close and continual crosstalk with other components of the NVU plus mast cells and circulating immune cells. This intimate interaction refines the BBB function of supporting the requirements of the brain, while maintaining a barrier phenotype and enabling brain-body communication.

In this next section we describe each of the cellular and noncellular components of the NVU. We then report the current evidence from human studies and transgenic animal models of how BBB changes, and abnormal signal transduction during AD progression, causes BBB breakdown, neurodegeneration, and disease pathogenesis and ultimately has implications for current prescribing and future therapies for this frail population. It is hoped by separation of the key components new connections can emerge.

A. Endothelial cells

The brain capillary endothelial cells (BCECs) that make up the BBB are highly specialized. They share some characteristics with those in the periphery but, ultimately, differ because of the existence of complex TJs, selective transporters, specific ion channels (Longden et al, 2017), lack of fenestrations, minimal pinocytotic activity (Bernacki et al, 2008), high mitochondrial content (Oldendorf and Brown, 1975), and enzyme activity (el-Bacha and Minn, 1999; Strazielle and Ghersi-Egea, 2005). There is also evidence of substantial diversity at the transcriptome level between endothelial cells from different brain regions (Schaeffer and Iadecola, 2021).

1. Complex tight junctions

The low ion conductance of the brain capillary endothelium relative to endothelia elsewhere in the body is predominantly due to the presence of TJs connecting adjacent BCECs (Romero et al, 2003). In addition to limiting paracellular permeability to ions and other polar compounds, a secondary function of TJs is to separate the membranes of BCECs into brain (abluminal) and blood (luminal) sides (van Meer and Simons, 1986), facilitating the spatial segregation of functionally distinct lipids (Tewes and Galla, 2001) and proteins (Betz and Goldstein, 1978; Betz et al, 1980). Thus, the endothelial cells are polarized. TJs are intricate structures that span the intercellular space between BCECs and are formed by a complex of transmembrane proteins and cytoplasmic accessory proteins that both cluster the transmembrane proteins and serve as a platform for interacting signaling and scaffold proteins (Fig. 7) (Fidanboylu, 2013). TJs are found throughout the whole of the

paracellular cleft in BCECs. The transmembrane components of TJs include the proteins; occludin, claudin, and junctional adhesion molecules (JAMs), which attach to numerous cytoplasmic scaffold and cytoskeleton proteins (Chiba et al, 2008; Bauer et al, 2011) (Fig. 7).

a. Occludin. Occludin is a 60- to 65-kDa protein containing 4 transmembrane domains, 3 cytoplasmic domains (2 of which are the N- and C-terminal domains), and 2 extracellular loops (Fidanboylu, 2013; Furuse et al, 1993) (Fig. 7). It is the 2 extracellular loops that confer the occluding function of occludin, and particularly the second loop that determines the low ionic paracellular permeability (Feldman et al, 2005). The C-terminal domain consists of 150 amino acids and associates with the scaffold proteins zonula occludens (ZO)-1, ZO-2, and ZO-3 for anchoring onto the actin cytoskeleton (Fanning et al, 1998) and regulatory proteins such as protein kinase C (Andreeva et al, 2005). Occludin contains many phosphorylation sites on the hydroxyl groups of serine and threonine residues, with phosphorylation or dephosphorylation of these sites regulating the association of occludin with ZO proteins and consequently its membrane localization (Kale et al, 2003). The N-terminal domain of occludin also has integral roles in assembling TJs because its deletion in BCEC monolayers grown in vitro results in low transendothelial electrical resistance values and increased paracellular permeability to small polar molecules (Bamforth et al, 1999). Further studies have highlighted the important contribution of occludin trafficking from intracellular pools to the plasma membrane to maintain the restricted paracellular permeability characteristics of the brain endothelium in vivo (McCaffrey et al, 2007).

b. Claudins. Claudins are another essential structural component of TJs and are a multigene family of 20- to 34-kDa transmembrane proteins (Furuse et al, 1998). Sequence and structural homology within the claudin family is highly conserved; with 4 transmembrane domains, 2 cytoplasmic domains (a long C-terminal sequence and a short N-terminal sequence), and 2 extracellular loops (Fig. 7) (Heiskala et al, 2001). It is thought that the baseline seal of TJs arises from claudins, which is then augmented by occludin, because overexpression of claudins in fibroblasts results in TJ-like strands, and occludin only localizes to the TJ if claudin is also present (Kubota et al, 1999). Similar to the case with occludin, the C-terminal domain of claudins also binds ZO proteins (Fig. 7) (Fidanboylu, 2013). The extracellular loops of claudins from neighboring cells can interact either via homophilic (Piorntek et al, 2008) or heterophilic (Furuse et al, 1999) interactions within a single TJ. It is the extracellular loops that determine the charge and size selectivity for paracellular permeability, and it is thought that differences in the claudin content between the BBB and blood–cerebrospinal fluid barrier (BCSFB) could explain why transendothelial electrical resistance values for the BBB are typically significantly higher than those observed for the BCSFB (Matter and Balda, 2003; Van Itallie and Anderson, 2004). It is generally accepted that claudins 3, 5, and 12 are present at the BBB; however, there is some evidence that claudin 1 may also be present (Morcos et al, 2001; Nitta et al, 2003; Wolburg et al, 2003). It should be noted that while TJ strands can be formed without occludin (Balda et al, 1996; Saitou et al, 2000), the absence of claudin-5 at the BBB in double knockout (−/−) mice results in size-selective increases in paracellular permeability to molecules with a molecular weight less than 800 Da (Nitta et al, 2003). Importantly, these claudin-5 double-knockout (−/−) mice died 10

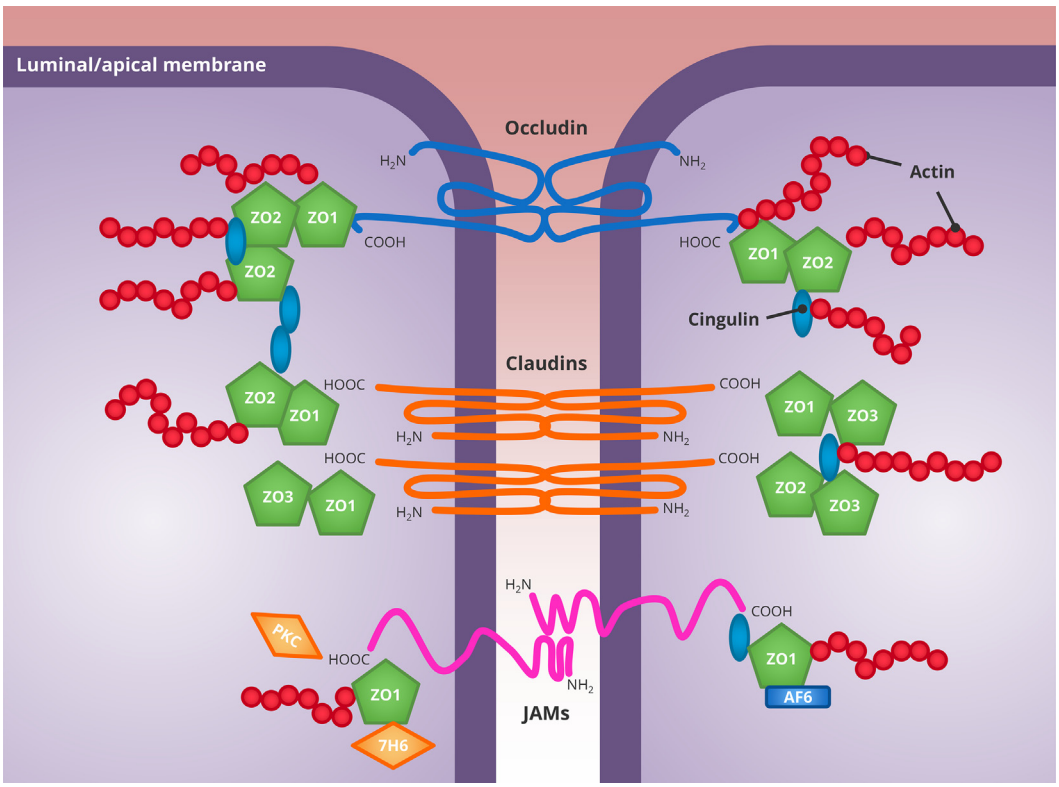

Fig. 7. Simplified schematic representation of the tight junctional complex found between the majority of brain capillary endothelial cells. This diagram is based on that by Fidanboylu (2013). Transmembrane proteins occludin, claudins, and junctional adhesion molecules (JAMs) span the intercellular cleft between adjacent endothelial cells. Scaffold zonula occludens (ZO) and cingulin proteins are closely associated and facilitate anchoring to the actin cytoskeleton and myosin, while additional regulatory proteins such as protein kinase (PK) C, 7H6, and AF6 are involved in the regulation of tight junction assembly. Created in BioRender. Thomas, S. (2025) https://BioRender.com/vvwlsg9

hours after birth, highlighting the critical role of this TJ protein at the BBB (Nitta et al, 2003).

c. Junctional adhesion molecules. JAMs are part of the immunoglobulin superfamily and contain a single transmembrane domain, a single extracellular domain, cytoplasmic C-terminal domain, and extracellular N-terminal domain (Fig. 7) (Bazzoni and Dejana, 2004; Fidanboylu, 2013). JAMs form homophilic and heterophilic interactions with other JAMs on neighboring cells to form dimers (Bazzoni et al, 2000). The C-terminal domain of JAMs typically not only associates with cingulin, ZO-1, TJ-associated protein antigen (7H6), junction-associated protein (AF6), and other scaffold proteins (Itoh et al, 2001), but also contain residues that are phosphorylated by protein kinase C (Suzuki et al, 2002). Phosphorylation of JAMs is thought to occur in the recruitment of ZO proteins and occludin into TJ complexes (Bazzoni and Dejana, 2004), while scaffold proteins such as cingulin promote binding to the actin cytoskeleton, which can also bind directly to both claudin and occludin (Huber et al, 2001).

2. Adherens junctions

Adherens junctions (AJs) form a paracellular zipper-like structure along the cell border (Dejana, 2004) and are not unique to endothelial cells. They have a critical function in the assembly of TJs and, in BCECS, consist of platelet-endothelial cell adhesion molecules and vascular endothelial (VE) cadherins. VE cadherin spans the intercellular cleft and links to the cell cytoplasm by scaffolding proteins α-catenin, β- catenin, and γ-catenin. β-Catenin binding to cadherin is essential to providing complete adhesive functioning of the AJ; this is mostly reliant on its capability to bridge cadherin with α-catenin, the actin-binding protein (Niessen, 2007). AJs are essential for forming TJs, and disturbance of AJs leads to the barrier being disrupted. AJs hold cells together, providing structural support (Bednarczyk and Lukasiuk, 2011).

3. Lack of fenestrations

Fenestrations are ultramicroscopic pores in the plasma membranes of endothelial cells that facilitate the rapid, but nonspecific, exchange of molecules between blood vessels and surrounding tissues (Fidanboylu, 2013). Fenestrations are present in highly permeable capillaries such as the glomerulus (Deen et al, 2001). However, fenestrations are very scarcely found in BCECs—no doubt an adaptation to prevent the nonspecific transcellular movement of polar molecules between the blood and brain (Fenstermacher et al, 1988).

4. Minimal pinocytotic activity

Pinocytosis is a form of endocytosis, whereby extracellular fluid (and any contents) is taken up by the cell in a nonspecific manner following membrane invagination (Fidanboylu, 2013). Pinocytic activity is low at the BBB (Brightman and Reese, 1969; Sedlakova et al, 1999). However, increased pinocytic activity is frequently observed at the BBB in pathologic conditions such as Alexander disease (Tuomanen et al, 1985; Kondo and Suzuki, 1993).

5. High mitochondrial content

BBB endothelial cells have a significantly higher density of mitochondria relative to other endothelial cells elsewhere in the body (Oldendorf and Brown, 1975) or indeed non-BBB endothelia in the brain (ie, circumventricular organ capillaries) (Fenstermacher et al, 1988). It has been proposed that this confers a large capacity for work because this greater density of mitochondria can be expected to have a higher output of ATP production (Oldendorf et al, 1977). Indeed, BCECs are highly metabolically active and express a large number of transport systems, some of which require energy (ATP) either directly (primary active transport) or indirectly (secondary active transport); making use of the ion gradients that are maintained by energy (ATP)-requiring ion pumps (Fidanboylu, 2013). Endothelial cells rely on glycolysis (glucose) for ATP production, thereby generating large amounts of lactate. In fact, lactate, as well as glucose, is important energy substrates in the brain (Lee et al, 2022).

6. Enzyme systems

In addition to serving as a physical barrier (as described above), the BBB also serves as a metabolic (enzymatic) barrier. A variety of intracellular enzyme systems have been identified in cerebral capillary endothelium, which are absent from other capillaries in the body. These enzyme systems metabolize or modify certain substances in the plasma and are associated with the metabolic, protective, and transport activities of the BBB. Both monoamine oxidase and dopa decarboxylase have been identified in the walls of the mouse brain capillaries, where they form an enzymatic protective barrier to L-dopa, as well as to 5-hydroxytryptophan (Bertler et al, 1966). These enzymes have a clearly defined enzyme substrate unlike butyryl cholinesterase and alkaline phosphatase, which are found in brain endothelial cells and are believed to hydrolyze whole classes of choline and phosphate esters. Extracellular enzymes for example peptidases and nucleotidases that metabolize peptides and ATP, respectively, have also been described at the BBB (el-Bacha and Minn, 1999).

Furthermore, both phase I enzymes (eg, cytochrome P450-1A and P450-2B) and phase II enzymes (eg, glutathione *S*-transferase and UDP-glucuronosyltransferase) have been identified at the BBB in both rodents and humans (Strazielle and Ghersi-Egea, 2005). Brain endothelial cells have also been shown to be rich Na^+-K^+-ATPase and Ca^+-ATPase. These are all thought to be more characteristic of an actively transporting epithelium than a typical endothelium (Bradbury and Lightman, 1990).

7. Signaling molecules

The capillary endothelial cells secrete a variety of important signaling molecules that interact with receptors expressed on other components of the NVU. For example, endothelial cells secrete platelet-derived growth factor (PDGF)-BB, which binds to the platelet-derived growth factor receptor (PDGFR)β on pericyte membranes, initiating multiple signal transduction pathways regulating proliferation, migration, and recruitment of pericytes to the vascular wall. There are also other paracrine signaling loops, for example, angiopoietin-1/Tie-2 receptor (Gaengel et al, 2009), which operate predominately from pericyte to endothelial cell. Other endothelial cell—pericyte signaling pathways include TGF-β/ALK1/5, and Jag1/Notch3. Other molecules secreted by the cerebral endothelial cells include a variety of vasoactive factors such as the vasodilator, NO, and vasoconstrictor such as endothelin-1 (Durieu-Trautmann et al, 1993). NO suppresses the secretion of endothelin. As such, capillary endothelial cells contribute to arteriolar and capillary vascular tone via the NO—cGMP pathway (Zambach et al, 2021). Purinergic signaling via ATP-sensitive receptors (P2Y) expressed on endothelial cells markedly influences CBF by causing NO release (Lohman et al, 2012).

B. Glycocalyx

Endothelial cells that form the BBB are coated on the luminal side with glycocalyx and on the abluminal side with BM, astrocyte endfeet, and (15%) microglial processes (Kutuzov et al, 2018; Császár et al, 2022) (Fig. 6). The glycocalyx is 0.2- to 5.0-μm thick and consists of a negatively charged layer of fibrous chains of macromolecules, including membrane-bound glycoproteins (eg,

selectins and integrins) and proteoglycans (eg, syndecans and glypicans). Hyaluronan, plasma proteins, and soluble proteoglycans are also integrated into the glycocalyx. It is an important regulator of vascular function and homeostasis, including permeability, vascular tone, leukocyte recruitment, and coagulation. The glycocalyx is a dynamic structure and can be modified by bioactive serum constituents, drugs, mechanical forces, and other factors. This affects flow resistance. It also presents as a barrier to macromolecule movement from plasma to the endothelial surface (Kutuzov et al, 2018).

C. Basal lamina and basement membrane

BCECs are completely encompassed by a basal lamina—a perivascular extracellular matrix (ECM) excreted by BCECs, which is typically between 40.0- and 50.0-nm thick and porous providing minimal resistance to CSF influx (Jessen et al, 2015). The basal lamina is predominantly made up of collagen IV, heparin sulphate, laminin, fibronectin, tenascin, and proteoglycans secreted by endothelial cells (Farkas and Luiten, 2001). The basal lamina is a constituent of the BM, which is composed of 2 layers: one separating pericytes from endothelial cells, while the other compartmentalizing pericytes from astrocyte endfeet (Fig. 6) (Fidanboylu, 2013). The endothelial BM is secreted by pericytes and endothelial cells; and the parenchymal BM is produced by astrocytes (Sixt et al, 2001; Owens et al, 2008; Baeten and Akassoglou, 2011). Although the endothelial BM is abundant in laminin α4 and α5s (Sorokin, 2010), the parenchymal BM is more enriched in laminin α1 and α2 isoforms (van Horssen et al, 2005; Owens et al, 2008). The BM is regulated and maintained by pericytes (Kose et al, 2007). The BM contributes considerably to the integrity of the BBB through multiple mechanisms. BMs anchor cells at the BBB in place and form a physical barrier enclosing the abluminal surface of endothelial cells. The BM is a source for growth factors and plays a key role in BBB regulation; the ECM facilitates varied signaling pathways between pericytes and endothelial cells (Baeten and Akassoglou, 2011). Specifically, BM compounds have been identified to control occludin cell localization in endothelial cells, therefore influencing the stability of the barrier (Savettieri et al, 2000).

The cerebrovascular basement membranes (CVBMs) allow the 2 different perivascular pathways for fluid to coexist, that is the IPAD and glymphatic pathways (Morris et al, 2016). In addition, conformational changes in the CVBM may arise as a result of the constriction and relaxation of smooth muscle cells and pericytes that occur during arterial pulsation. This may support the following reflective wave that passes along the vessel wall in the opposite direction to blood flow and so drive ISF flow in the perivascular drainage pathway (Carare et al, 2013; Morris et al, 2014). The conformational change of the BM proteins preventing ISF back flux (Schley et al, 2006).

D. Pericytes

1. Location

Pericytes were first characterized in the 1870s as spatially isolated cells present on the outside of capillaries at both straight parts and branch points (Uemura et al, 2020). In fact, pericytes extend processes around, as well as along, precapillary arterioles, capillaries, and postcapillary venules (Figs. 3 and 4). However, their most prominent location in the brain is at capillaries where the ratio of pericyte to endothelia is 1:3 (Dalkara et al, 2011). In the CNS, pericytes cover about 100% of the capillary length, which is significantly more than pericytes that cover peripheral capillaries.

2. Subtypes

Pericytes demonstrate distinct phenotypes at different capillary locations, with respect to transcriptomes, morphologies, embryonic origins, and contractile dynamics (Grant et al, 2019). The different subtypes include the ensheathing pericytes on the arteriole—capillary transition vessels and capillary pericytes (displaying mesh and thin-strand processes) on capillaries (Fig. 3A) (Hartmann et al, 2015, 2022). Mesh pericytes are also found on postcapillary venules. Interestingly, there is recent evidence that suggests that function rather than anatomical location is more important for transcriptional identity as 2 subclusters of pericytes have been identified: one that is enriched for transport activity and the other for ECM formation and regulation (Yang et al, 2022).

3. Identification

Several markers have been used to identify pericytes; however, not all pericytes express every single marker, so identification is difficult. Currently, at least 2 markers as well as morphology and cell location (in close contact with endothelial cell, embedded in the same BM) are required to unequivocally distinguish pericytes from other mesenchymal cells. Brain pericytes are often identified by expression of the tyrosine kinase receptor, PDGFRβ, and the proteoglycan, neural/glial antigen 2, a membrane coreceptor for PDGFR. PDGFRβ is not expressed in neurons, astrocytes, endothelial cells, oligodendrocytes, and/or microglia (Bell et al, 2010). However, PDGFRβ is expressed in vascular smooth muscle cells, but its concentration is higher in pericytes, and pericytes are more sensitive to PDGFRβ depletion (Nikolakopoulou et al, 2017).

4. Ultrastructure

Quiescent pericytes are embedded in the perivascular BMs and possess a cell body with a prominent nucleus and a small content of cytoplasm with several long, thin processes (Bergers and Song, 2005) (Fig. 3). The primary processes are parallel to the long axis of the vessel (longitudinal) and the smaller secondary processes encircling the vessel wall (circumferential). However, the exact morphology of the processes varies in the different pericyte subtypes (Dessalles et al, 2021). Ensheathing pericytes have short primary processes and wide secondary processes, which fully encircle the vessel. Thin-strand pericytes have very long primary processes and short secondary processes, which only partially enwrap the vessel. Mesh pericytes have thin, longitudinal processes similar to thin-strand pericytes and circumferential processes similar to ensheathing pericytes. In contrast, the processes in stellate pericytes are organized differently, having fractal-like branching processes. The cytoplasm of pericytes contains protein-producing organelles and mitochondria. Contractile protein filaments are concentrated below the membrane, which faces the endothelium.

Despite being separated by the BM, a single pericyte forms numerous contacts with several capillary endothelial cells (Fig. 3B) and integrates paracrine and juxtracrine (contact-dependent) signals along the vessel length. The majority of pericytes (83%) also receive direct microglial contact (Fig. 6) (Császár et al, 2022). There are different types of cell-to-cell contacts, including gap junctions, peg-and-socket contacts, adhesion plaques, and occluding contacts. Gap junctions provide direct connections between the cytoplasm of pericytes and other pericytes or endothelial cells and permit exchange of metabolites, ions, ribonucleic acids, and second messengers (Bergers and Song, 2005). The peg-and-socket contacts consist of pericytic cytoplasmic projections protruding into endothelial membrane pockets (sockets) via N-cadherin and connexins. The transmission of contractile force from the pericyte to the endothelium occurs through these contacts. Adhesion plaques tether pericytes to endothelial cells. Interestingly, it is thought that

pericytes along the vessel wall are in close proximity to each other but do not make stable physical contact (Berthiaume et al, 2018). However, long distance cell-to-cell communication does exist and involves thin tunneling nanotube (TNT) processes, which connect (transiently) 2 pericytes (or other cell types) and allow the intercellular transfer of vital information over long distances, for example, small molecules (eg, second messengers), micro-RNAs, macromolecules (eg, proteins such as amyloid [A]β and tau), and organelles (eg, mitochondria) (Climent et al, 2015; Alarcon-Martinez et al, 2020; Zhang et al, 2021; Pisani et al, 2022). PDGF stimulates pericyte to form TNT (Kempf et al, 2024).

5. Function

Pericytes have important functions and are thought to be involved in: (a) new blood vessel formation from pre-existing vessels (angiogenesis) and vascular homeostasis; (b) maintaining BBB integrity; (c) regulation of CBF; (d) contributing to IPAD clearance; (e) maintaining the glymphatic system; (f) elimination of materials from the brain; (g) immune function; (h) acquisition of stem cell–like properties; (i) scar formation; and (j) trophic support of neurons.

a. Angiogenesis and vascular homeostasis. Pericytes are ideally positioned to take an active part in angiogenesis and vascular homeostasis. The initial stage of angiogenesis begins with pericyte–endothelial cell detachment (pericyte activation) and BM degradation, followed by endothelial cell migration and proliferation and subsequent endothelial cell tube assembly and vessel stabilization by newly recruited pericytes.

Recent studies support the notion that pericyte-mediated signaling (eg, PDGF-BB/PDGFRβ; angiopoietin-1–Tie-2) not only may be crucial for the growth phase of angiogenesis but also has an important homeostatic role (Smyth et al, 2022; Kempf et al, 2024). Endothelial cells specifically secrete PDGF-BB, which binds to heparan sulphate proteoglycans on the basal lamina, and its concentration gradient controls proliferation of pericytes, migration, and their recruitment to the blood vessel wall via PDGFRβ receptors on the pericyte membrane. Normally binding of PDGF-BB to PDGFRβ results in PDGFR dimerization, tyrosine autophosphorylation, and subsequent activation of extracellular signal–regulated kinase (ERK), Akt, GSK-3α/β, and WNK1 intracellular pathways (Smyth et al, 2022). The main pathways that are activated are the ERK-dependent and Akt-dependent pathways.

PDGF-BB promotes the proliferation of pericytes and protection from apoptosis through ERK-dependent signaling (Smyth et al, 2022). In the healthy adult, the vessels that have been formed are quiescent, stabilized, and optimally functional. In the developing CNS, pericytes are thought to stabilize the endothelial tube and control endothelial cell number and microvessel architecture but do not determine microvessel density, length, or branching.

b. Blood–brain barrier integrity. Pericytes are vital for preserving the integrity of the BBB in the adult and the aging CNS (Armulik et al, 2010; Bell et al, 2010; Daneman et al, 2010). Studies in both adult-viable pericyte-deficient mice and in adult mice where global pericyte loss has been induced have shown an increased BBB permeability (Armulik et al, 2010; Nikolakopoulou et al, 2019; Vazquez-Liebanas et al, 2022). However, a recent study using focal pericyte ablation in adult mice did not demonstrate a significant loss of barrier integrity (Berthiaume et al, 2022). This suggests that loss of a few isolated pericytes will not result in the catastrophic loss of barrier function.

It is thought that BBB properties are not intrinsic to BCECs and they are induced, in part, by pericytes (Hori et al, 2004; Dohgu et al, 2005). For example, occludin expression is induced by factors secreted from pericytes (Hori et al, 2004) and pericytes participate in tightening the intercellular junctions and aiding P-glycoprotein (P-gp, a brain efflux transporter) function in BCECs through the production of soluble factors and cell-to-cell contact (Dohgu et al, 2005). In addition, increased BBB permeability to macromolecules has recently been shown to be linked to suppression of transcytosis by vitronectin, an ECM protein secreted by pericytes, which acts by binding to the α5-integrin receptor expressed on endothelial cells (Ayloo et al, 2022).

Other studies have revealed that PDGFRβ and PDGF-BB null mice have total loss of pericytes and diminished TJ expression, causing ruptured CNS microvessels, microaneurysms, and embryonic death (Tallquist et al, 2003; Bell et al, 2010). This highlights the importance of the PDGF-BB (endothelial cell)–PDGFRβ (pericyte) paracrine signaling loop to BBB integrity.

In addition, pericytes express SLC and ATP-binding cassette (ABC) transporters (Vanlandewijck et al, 2018) and may contribute to the selective transport of different molecules and metabolites from the blood into the brain and vice versa. In addition, endothelium-derived lactate is transported into the pericyte by monocarboxylic acid transporter isoform-12, and the pericyte uses lactate as its main energy source. The absence of lactate can lead to reduced pericyte coverage and loss of BBB integrity (Lee et al, 2022). Interestingly, smooth muscle cells do not rely on endothelial-produced lactate for energy generation (Lee et al, 2022). However, they express monocarboxylic acid transporter isoform-12.

c. Cerebral blood flow. As described in the *Cerebral blood flow* section III, pericytes are involved in the control of CBF through the capillary network. Pericytes are thought to take the role of smooth muscle, which surrounds the larger blood vessels. The contraction and dilation of pericytes can cause changes in capillary lumen diameter, thus affecting flow rate (Peppiatt et al, 2006; Dalkara et al, 2011; Cai et al, 2018). Vascular diameter responses propagating between adjacent pericytes and endothelial cells (Rucker et al, 2000; Alarcon-Martinez et al, 2018; Gonzales et al, 2020).

Pericytes are responsible for both the myogenic tone and vasomotion that occurs in capillaries. Blood flow in capillaries is regulated by cerebral autoregulation, vasoactivity, and neurovascular coupling. A study has demonstrated that neurovascular uncoupling in a mouse model of acute global pericyte loss was due to altered pericyte function and not changes in capillary density and endothelial cell or neuronal cell function (Nikolakopoulou et al, 2019; Kisler et al, 2020), confirming the critical role of the pericyte in the control of blood flow. Pericytes are also capable of stiffening vessel walls, which can cause capillary stalling and redirection of blood through the capillary network (Attwell et al, 2016).

ci. Contractile machinery. Although a topic of debate, recent insight has suggested that all pericyte types are contractile but express different amounts of contractile protein (Alarcon-Martinez et al, 2018). In fact, pericytes possess a variety of contractile proteins including α-smooth muscle actin, tropomyosin, and myosin; express ion channels (eg, K_{ATP} channels) and G-protein receptors (eg, prostaglandin E2 receptor 4, α1-adrenergic receptors, and adenosine 2A receptors) for vasoactive mediators; and respond to neuronal and metabolic signals (Fig. 4 and Table 2). Contractility of the pericyte is regulated by changes in the intracellular concentration of calcium (Zambach et al, 2021).

Significantly, capillary vascular responses are mostly initiated and peak at near arteriole capillaries (Cai et al, 2018). Rises in synaptic activity, acetylcholine, NO, cGMP, and endothelin-1 exerting far greater effects on brain precapillary sphincters and first-order capillaries than on penetrating arterioles or downstream capillaries (Zambach et al, 2021). This responsiveness is matched to

Table 2
Regulating factors involved in contraction of pericytes (Rucker et al, 2000; Hartmann et al, 2022)

Vasoconstriction	Vasodilation
Cholinergic agonists	Adrenergic agonists (β2)
Adrenergic agonists (α2)	Nitric oxide
Histamine	Atrial naturietic peptide
Serotonin	Hypoxia
Noradrenaline	Hypercapnia
Angiotensin II	Glutamate
Endothelin-1	
Hyperoxic conditions	
Thromboxane	
ATP	
Arachidonic acid derivatives	
20-HETE	

a greater expression of α-smooth muscle actin in the pericytes being associated with the precapillary sphincters and first-order capillaries. Interestingly, the differences in expression of the contractile proteins cause them to function on different timescales. A study has revealed that ensheathing pericytes contract more rapidly and cause more large-scale changes in blood flow than capillary pericytes, which are more involved in establishing resting capillary tone and flow heterogeneity (Fig. 3A) (Hartmann et al, 2022). Interestingly, the interpericyte TNT, the nanotube-like processes found between 2 pericytes, are essential for neurovascular coupling (Alarcon-Martinez et al, 2020).

d. Contributing to intramural periarterial drainage. Brain ISF can drain via perivascular spaces in the opposite direction to blood flow (Schley et al, 2006). This ISF flow may be a result of the reflection wave that follows arterial pulsation and can be aided by the constriction and relaxation of pericytes around capillaries (Morris et al, 2014). This can be regulated by neurovascular coupling, involving cholinergic receptors expressed by pericytes. The composition of the BM, and consequently the architecture of the BM drainage pathways, is regulated partly by pericytes. This may also affect the ability of solutes to interact with specific membrane proteins and form insoluble complexes, which cannot be cleared from the IPAD pathway.

e. Maintaining the glymphatic system. Pericytes secrete many of the ECM proteins and other proteins, which contribute to the formation of the BM and enrich the perivascular space creating the low resistance highway for CSF influx into the brain parenchyma or glymphatic system. Pericytes are also essential for maintaining AQP4 distribution on astrocytic endfeet (Armulik et al, 2010; Gundersen et al, 2014). In fact, AQP4 density is higher in endfeet that face pericytes. This may be linked to pericyte agrin secretion (Wolburg et al, 2011) or laminin 211 deposition in the BM and subsequent interactions with dystrophin, which anchors AQP4 to the astrocytic endfeet (Guadagno and Moukhles, 2004). AQP4 expression is critical to the mediation of CSF clearance via the glymphatic system and subsequent clearance of toxic solutes, including Aβ and tau, from the brain (Iliff et al, 2012, 2014). Pericyte loss also alters abluminal structure along the capillary bed, which may also interfere with the glymphatic clearance system (Armulik et al, 2011).

f. Elimination of materials from the brain. Pericytes internalize molecules and neurotoxic blood-derived products (ie, immunoglobulins, fibrin, and albumin) through nonspecific pinocytosis or selective receptor-mediated endocytosis. Pericytes express a high density of enzymes, which are involved in their metabolic function. This contributes to brain defence and cleans the brain extracellular fluid. In fact, CNS pericytes have been considered to be housekeeping scavenger cells (Balabanov and Dore-Duffy, 1998). The clearance of Aβ by pericytes is mainly performed through receptor-mediated endocytic pathways, not only by the low-density lipoprotein receptor–related protein (LRP)1 (Shibata et al, 2000; Zlokovic et al, 2010; Ma et al, 2018, 2022, 2024) endocytosis pathway, but also by the low density lipoprotein receptor, receptor for advanced glycosylation end products (RAGE), and the fatty acid transporter (scavenger receptor cluster [CD]36) (Wilhelmus et al, 2007) receptor pathways. Pericytes can also internalize large solid substances through phagocytosis. These internalized molecules are possibly transported to the blood circulation or to lysosomes for enzymatic degradation.

g. Immune function. Pericytes are involved in vascular immunosurveillance, responding to and mediating inflammatory signals (Duan et al, 2018). Pericytes can directly interact with inflammatory cells such as monocytes and leukocytes and regulate their entry into the brain. In addition, PDGF-BB:PDGFRβ signaling, through intracellular Akt, augments pericyte-derived inflammatory secretions (Smyth et al, 2022). Pericytes are also capable of mitigating the overall inflammatory response, and therefore tissue damage, by phagocytosis of cell debris. Pericytes clearing substances derived from the brain parenchyma, as well as around vessels. In addition, pericytes express Fc receptors, which are essential for antibody–antigen complex recognition to trigger antibody–antigen complex recognition to trigger antibody-dependent phagocytosis (Balabanov et al, 1996). Therefore, pericytes not only are players in innate immunity and inflammation but can also participate in adaptive immunity.

h. Acquisition of stem cell-like properties. Pericytes may transform into multipotent stem cells and differentiate into various cells including vascular, neural, and glial cells. Pericytes are in a constant state of differentiation (Ronaldson and Davis, 2020). The phenotype changes of pericytes could allow tissue repair after brain injury or ischemia. For example, pericytes exposed to ischemic conditions in vivo and in vitro acquire a microglial phenotype and increased phagocytic activities (Özen et al, 2014; Sakuma et al, 2016) and have the ability to clear compromised cells and/or neurotoxic substances. In so doing, they prevent BBB damage. Interestingly, pericytes, vascular smooth muscle cells, and fibroblasts are perivascular cells. Perivascular fibroblasts in the CNS are found in the Vichow–Robin spaces immediately adjacent to the vascular smooth muscle cells on arteries, arterioles, venules, and veins, but are not found by capillaries (Vanlandewijck et al, 2018). Interestingly, pericytes have an intermediate phenotype between vascular smooth muscle cells and fibroblasts and seem to have the capacity to differentiate into either cell type (Gerhardt and Betsholtz, 2003).

i. Scar formation and cell repair. Pericytes, oligodendrocyte precursor cells, as well as astrocytes are observed with glial scars. In wound healing and inflammatory processes, it has been suggested that pericytes detach from the vessel wall and differentiate into a collagen type-I–producing fibroblast-like cell (Sundberg et al, 1996). Thus, pericytes may contribute to the formation of the fibrotic components of scars, to other situations of inflammation-associated tissue fibrosis, and to fibrous tumor stroma formation. Scars are thought to protect healthy cells from being exposed to the toxic detritus of damaged cells and allow the repair of damaged cells. Pericytes have recently been shown to be able to transfer functional mitochondria to injured astrocytes via TNTs possibly to rescue them from apoptosis to allow survival and postischemic BBB repair (Pisani et al, 2022).

j. Trophic support. Pericytes provide trophic support to neurons via pleiotrophin secretion (Nikolakopoulou et al, 2019). Interestingly, PDGF-BB induces pericytes to secrete trophic factors, which are involved in pericyte endothelial communication and vascular integrity (Smyth et al, 2022).

E. Astrocytes

Astrocytes are glial cells, with a characteristic star shape; they have numerous processes that stem from a cell body and form endfeet around the abluminal surface of capillaries and below the pia mater forming the glia limitans (Oberheim et al, 2009). Astrocytes are proportionately the largest cell class in the CNS and have numerous functions, such as biochemical support of the BCECs, nutrient supply to nervous tissue, buffering of extracellular potassium, regulation of water transport via water channels (ie, AQP4), glymphatic clearance, maintenance of extracellular pH, as well as having a role in the repair and scarring process of the brain and spinal cord (Markiewicz and Lukomska, 2006; Sidoryk-Wegrzynowicz et al, 2011; Iliff et al, 2012; Rodríguez-Arellano et al, 2016). Additionally, astrocytes play a critical role in modifying CBF in response to neuronal activity (neurovascular coupling) by relaying signals (Attwell et al, 2010; Daneman and Prat, 2015) (Fig. 4). Interestingly, astrocytes constantly release adenosine, which can activate the K_{ATP} channel expressed on endothelial cells and pericytes and as a result increase CBF (Sancho et al, 2022).

Pericytes and endothelial cells can form tube-like structures in vitro only when astrocytes are also present (Ramsauer et al, 2002), suggesting that cerebral capillary differentiation requires close communication between the 3 cell types. The BBB phenotype of the cerebral capillary endothelial cells is also thought to require the presence of soluble factors released from astrocytes (Janzer and Raff, 1987; Tontsch and Bauer, 1991; Isobe et al, 1996; Hayashi et al, 1997; Sobue et al, 1999).

F. Microglia

Microglia are a type of glial cell found throughout the brain and spinal cord. They account for 10%–15% of all cells found within the brain (Lawson et al, 1990; Pessac et al, 2001). In the CNS, microglia are the resident macrophages, so are the innate immune cells that act as the first and primary immune defence (Filiano et al, 2015). Microglia are crucial in brain homeostasis and act to remove microbes, protein aggregates, plaques, and damaged neurones (Gehrmann et al, 1995).

At the BBB, 2 specialized microglial subsets can be identified: first, juxtavascular microglia that make direct contact with the parenchymal side of the CNS vascular BM, representing true intraparenchymal resident microglia; and second, perivascular cells that are contained within the basal lamina (Gehrmann et al, 1995). Microglia have been shown to dynamically contact different vessels of the vascular tree such as arterioles and capillaries. Communication between microglia and other cell types is mediated through these contacts. Microglia form purinergic (P2Y12R) contacts with endothelial cells, periarterial smooth muscle cells, pericytes, and astrocytes in the brain (Bisht et al, 2021; Császár et al, 2022). Microglia have been found to contribute to the maintenance of optimal capillary diameter, CBF, vascular responsiveness, and influence neurovascular coupling via purinergic (P2Y12R)-mediated and nonmediated actions (Bisht et al, 2021; Császár et al, 2022). Interestingly, the average lifetime of these microglia contacts ranged from 5 to 15 minutes, and microglia processes recontacted the same sites along both arterioles and microvessels. This suggests that specific sites for microglia–vascular communication exist in the brain. Interestingly, the contacts are in the site of endothelial mitochondria and endothelial pannexin1 channels, which are ATP-permeable integral membrane proteins (Császár et al, 2022). ATP release from cells of the NVU may recruit the P2Y12R-positive microglial processes. ATP is then catabolized by microglia into AMP and then adenosine. In fact, microglia are a key source of adenosine in the brain, which inhibits neuronal responses via the adenosine A_1 receptor (Badimon et al, 2020) and is a potent vasodilator in the cerebral circulation.

Microglia have 3 states: resting, activated, and phagocytic. Resting microglia are characterized by a small cell body with thin processes, which each give off numerous branches extending in all directions. Individual microglial cells each occupy their own territory around 15.0–30.0 μm in diameter, with minor overlap between adjacent territories. The term resting microglia can be slightly misleading because microglia in unperturbed brain are far from being inactive. Microglial cells constantly scan their territory; their processes are constantly moving, and each process itself sends out and retracts small protrusions, which grow and shrink by 2.0–3.0 μm/min (Verkhratsky and Butt, 2013).

Microglia can become activated by many factors in response to brain injury and immunologic stimuli. These include proinflammatory cytokines, changes in extracellular potassium (ruptured cells), lipopolysaccharides, and cell necrosis factors (Gehrmann et al, 1995).

The activation of microglia involves a stereotyped response, including proliferation, increased expression of cytokines, recruitment to the site of injury, and functional changes, such as the release of inflammatory or cytotoxic mediators (Yang et al, 2013). On activation, microglia undergo drastic changes in morphology, changing from resting to activated amoeboid microglia, which can later become phagocytic. Activated phagocytic microglia are the maximally immune responsive form of microglia (Heneka et al, 2015). Activated phagocytic microglia fight off infection, while minimizing damage to healthy brain cells, through interaction with neural cells and astrocytes (Gehrmann et al, 1995; Aloisi, 2001).

G. Oligodendrocytes

Oligodendrocytes are the myelinating cells of CNS. They are the final product of a cell lineage that undergoes proliferation, migration, differentiation, and myelination to form the functionally important insulating sheath of neuronal axons. Cerebral blood vessels are surrounded and maintained by oligodendrocytes (Burdo et al, 1999; Uranova et al, 2001; Yokoo et al, 2004), suggesting they play a role in maintenance and the integrity of the BBB (Descamps et al., 2003). ECM molecules secreted by pericapillary oligodendrocytes contribute to the permeability of BBB (Garwood et al, 2004; Beggah et al, 2005).

H. Neurons

Neurons are major components of the brain and spinal cord and of the autonomic ganglia of the peripheral nervous system. Neurons are electrically excitable cells that process and transmit information through electrical and chemical signals. These signals are transmitted between neurons and other cell types via specialized connections called synapses and membrane channels such as endothelial transient receptor potential ankyrin 1 channels, which conduct hyperpolarization to upstream arterioles more slowly that K_{ir}-2–mediated signals (Thakore et al, 2021). Transcriptome analysis of the brain has revealed numerous different subtypes of neurones (Zeisel et al, 2015). Intricate molecular interactions between 2 main cell types, the neurons and the glial cells, form the underlying basis of the critical functioning

of the nervous system (Banerjee and Bhat, 2007). The BBB has evolved to preserve the CNS microenvironment of these highly excitable neuronal cells to allow for efficient action potential generation and propagation. Neurones release both Aβ and tau into the brain ISF (Iliff et al, 2012, 2014).

VII. Transport across the blood-brain barrier

The paracellular route of transport across the BBB is practically unavailable to water-soluble compounds owing to the presence of TJs between adjacent BCECs. The BBB forms a selective transport barrier and tightly controls the transcellular movement of small hydrophilic molecules by the presence of specific transporters on the luminal and abluminal membranes of BCECs (Fig. 8A). This ensures that required nutrients for the brain are facilitated entry, whereas harmful neurotoxins are either prevented entry or are actively removed by specific transporters (Begley and Brightman, 2003).

A. Paracellular movement

In a normal, healthy BBB, TJs usually prevent the paracellular movement of hydrophilic molecules into the brain. However, some molecules, as well as immune cells, such as leukocytes, can

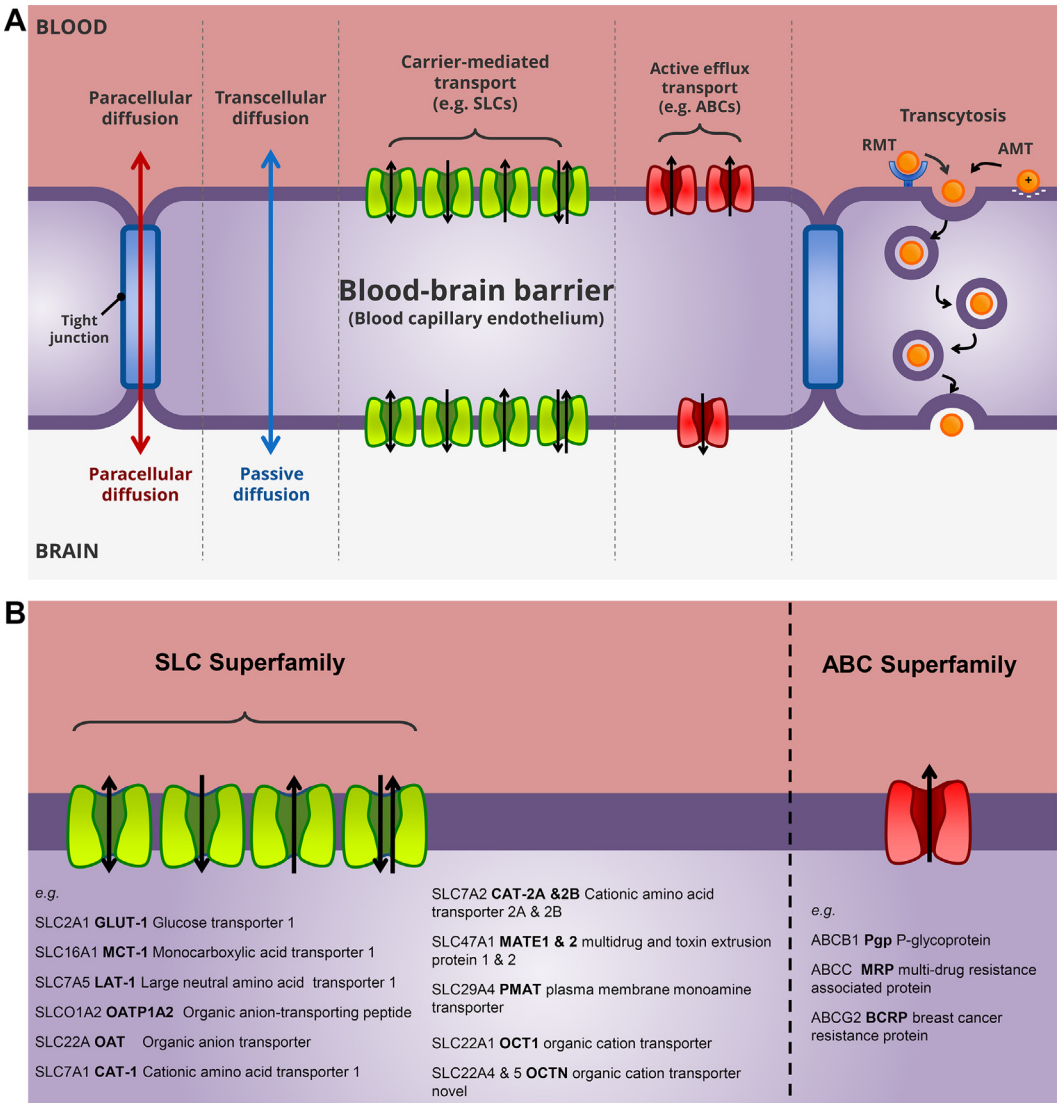

Fig. 8. w(A) Simplified schematic diagram summarizing possible routes of crossing the blood–brain barrier (BBB). This diagram is based on that by Fidanboylu (2013). Paracellular movement of hydrophilic molecules is typically blocked by tight junctions. Small lipophilic (lipid-soluble) molecules and some gases can passively diffuse across the plasma membranes of the capillary endothelial cells. Transport of specific molecules can be facilitated by transport proteins embedded in the plasma membrane that can be bidirectional, unidirectional, symport, or antiport in their transport activity, and with varying degrees of ion-dependence. Solute carriers (SLCs) can be sodium-dependent or facilitated transporters. Receptor-mediated transcytosis (RMT) can occur in the blood-to-brain and brain-to-blood directions. RMT in the brain-to-blood direction is not shown in the diagram. Transport across the BBB can be by absorptive-mediated transport (AMT) through electrostatic interactions between positively charged substances and the negatively charged glycocalyx. While RMT systems are selective pathways for trans-BBB transport because they initially necessitate the binding of a ligand to something on or in plasma membrane of BBB endothelial cells. However, AMT depends on nonspecific charge-based interactions. Initiation of AMT may be through polycationic molecules binding to negative charge on plasma membrane. However, this process has an absence of specific targeting and can cause widespread absorption. Created in BioRender. Thomas, S. (2025) https://BioRender.com/bsfz2a5. (B) Examples of proteins involved in transport mechanisms at the BBB. The transport of many essential polar molecules such as amino acids and glucose is mediated by carrier-mediated transporters belonging to the SLC transporter family. These transport mechanisms can either be facilitated (reliant on substrate concentration gradients) or secondarily active (using electrochemical/ion gradients) and can be bidirectional, unidirectional (influx or efflux), or exchangers. Members of the ABC transporter superfamily are also expressed at the BBB and rely on the hydrolysis of ATP to move substrates against their concentration gradient. Breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) are expressed on the luminal membrane, whereas multidrug resistance–associated protein (MRP) can be expressed on either membrane. The list of proteins shown in this figure is not exhaustive. Created in BioRender. Thomas, S. (2025) https://BioRender.com/r53axb8

modulate TJs to partially open the paracellular entry route into the CNS.

B. Passive diffusion

Generally, small, nonpolar, lipid-soluble molecules can passively diffuse through the BBB across the lipid bilayer of endothelial cells (Liu et al, 2004). The greater a solute's lipid solubility, the greater the rate that it enters the CNS (Clark, 2003). Factors that restrict transport of molecules into the CNS include a molecular weight above 450 Da, a high polar surface area, the presence of rotatable bonds, and a propensity to form greater than 5 hydrogen bonds—which significantly raises the free energy requirement for transitioning from an aqueous environment to the lipid environment of the plasma membrane (Clark, 2003; Gleeson, 2008). Small molecules, and the blood gases (O_2 and CO_2), can passively diffuse down their concentration gradient across the plasma membranes into and out of brain.

C. Carrier-mediated transport

The BBB prevents passive entry of essential hydrophilic nutrients such as glucose and amino acids into the brain. In order, to allow access of these substances to the brain, the BBB endothelium must contain specific transporters, also called carriers. Endogenous BBB transporters are divided into 2 large gene families: the solute carrier (SLC) superfamily and the ATP-binding cassette (ABC) superfamily (Fig. 8B). Transporters can mediate passage of molecules in the blood-to-brain direction or can mediate removal of solute (eg, waste products) from brain-to-blood (Pardridge, 2015a). There is a higher expression of transporters in brain capillaries compared with that in peripheral capillaries. In addition to transporting specific nutrients into the brain, these transporters may be exploited by drugs to cross the BBB and treat CNS disorders (Geier et al, 2013; Watson et al, 2023).

1. Solute carriers

SLCs facilitate transport of glucose, fatty acids, amino acids, carbohydrates, vitamins, hormones, nucleotides, monocarboxylic acids, cations, and organic anions across the BBB (Zlokovic, 2008; Daneman and Prat, 2015; Pardridge, 2015a). As a result, BCECs express transport proteins for numerous nutrients and solutes (Geier et al, 2013), some of which are inserted in both the luminal and abluminal membranes, whereas others are restricted to 1 membrane (Parvez et al, 2023). Some carriers rely on the exchange of 1 substance moving into the blood, for another substance to move into the BCEC from the blood. SLCs can be sodium-dependent or facilitated-diffusion transporters. Examples of SLC transporter proteins that are expressed at the BBB are listed in Fig. 8B.

2. ATP-binding cassette transporters

ABC transporters at the BBB restrict the brain entry of a considerable amount of toxins, including therapeutic agents (Miller, 2015), and are primary active transporters. With regard to the BBB, the most significant ABC transporters are P-gp (ABCB1), the multidrug resistance–associated proteins (ABCC1, 2, 4, and 5), and breast cancer resistance protein (BCRP;ABCG2) (Begley, 2004). The main role of BBB ABC transporters is to act as active efflux pumps that hydrolyze ATP to ADP and transport a variety of lipid-soluble substances out of BCECs and the CNS, removing potentially foreign neurotoxic molecules and metabolic waste products (Ha et al, 2007). In this way, they carry out a crucial detoxifying and neuroprotective function (Dallas et al, 2006). The elevated expression of ABC transporters at the BBB adds to CNS pharmacoresistance. The clinical potential of ABC transporters as targets for drug delivery improvement and disease management remains uncertain. P-gp and BCRP act to transport substances from endothelium to blood; they are expressed solely in the luminal membrane of the BBB (Cooray et al, 2002; Eisenblätter et al, 2003; Cisternino et al, 2004). There has been some debate surrounding the degree of P-gp expression at the BBB, with some groups detecting lower levels of P-gp than that of BCRP (Eisenblätter et al, 2003) and others finding that the opposite is true (Dauchy et al, 2008). Interestingly, a comparison of transporter protein expression at the BBB found that P-gp is expressed at significantly lower levels than BCRP at human BBB, while the opposite is true at the mouse BBB (Uchida et al, 2011; Storelli et al, 2021). This indicates a disparity in the relative contributions of the transporters to drug efflux from the brain between species. Some isoforms of multidrug resistance–associated proteins are expressed in both luminal and abluminal membranes of the cell and some have a polarised expression (Roberts et al, 2008), indicating that they could be involved in the efflux of substances from the BCECs to either the brain or the blood.

D. Transcytosis

Transcytosis is the process by which various macromolecules are transported across the interior of a cell within a plasma membrane vesicle. Macromolecules are captured in vesicles on one side of the cell (endocytosis), drawn across the cell, and ejected on the other side (exocytosis). It is the main route that large molecular weight solutes, including proteins and peptides, must take in order to gain access to the brain. Multiple endocytotic mechanisms operate at the plasma membrane. Endocytosis can be classified on the basis of (1) distinct processes (fluid-phase, absorptive-mediated, or receptor-mediated endocytosis); (2) the proteins involved in the initial stages of internalization (clathrin or dynamin); or (3) the other cytosolic machinery used for scaffolding, elongation, and scission (eg caveolins, flotillins, and reticulon) (Thottacherry et al, 2019; Mayya et al, 2022). The processes following endocytosis, the first step in transcytosis, are similar in each pathway, but the differences are in the binding affinity and capacity of each (Bickel et al, 1993). Transport vesicles can be directed to the Golgi complex, the plasma membrane via recycling endosomes or the late endosomes, and lysosomes for degradation. It is important to avoid the lysosomal compartment for transcytosis of an intact molecule. Interestingly, routing of the primary sorting endosome away from the degradative compartment does not seem to occur in peripheral endothelia, meaning this may be a unique feature of the BBB. In polarized cells, such as BCECs, endocytosis can occur at both the luminal and the basolateral plasma membranes. The luminal and basolateral membranes have unique early endosomal compartments, which result in endocytosed receptors being returned to the same membrane they originated from. Exocytosis is the process whereby fusion of intracellular vesicles with the plasma membrane results in the release of vesicle content into the extracellular space. Exocytosis is the energy-requiring step of transcytosis and so is ATP dependent (Bickel et al, 1993). Receptors expressed at the BBB and involved in transcytosis of specific ligands are listed in Table 3. Ligands have been developed against these receptors (eg, transferrin) to exploit the transport of linked macromolecules (eg, antibodies) across the BBB (Bien-Ly et al, 2014; Haqqani et al, 2018).

E. Ion channels

BCECs express ion channels such as K_{ir} 2.1 channels which are activated by K^+ released during neural activity, initiating a rapidly propagating hyperpolarization that drives upstream arteriolar dilation prompting rapid hyperemia at the site of the K^+ increase (Longden et al, 2017). The brain capillary endothelium thus form an electrically connected syncytium capable of directing blood flow to active brain regions. In addition, in

Table 3
Receptors present at the BBB and their ligands

Name	Abbreviation	Ligand(s)
Transferrin receptor 1	TfR1	Transferrin
Insulin receptor		Insulin
Melanotransferrin receptor	MTfR	Melanotransferrin (p97)
Lactoferrin receptor	LfR	Lactotransferrin
Apolipoprotein E receptor 2	ApoER2	Lipoproteins and molecules bound to ApoE
Low density lipoprotein receptor–related proteins 1 and 2	LRP1 and LRP2	Lipoproteins, amyloid-β, lactoferrin, α2 macroglobulin, melanotransferrin (p97), and apoE
Receptor for advanced glycosylation end products	RAGE	Glycosylated proteins, amyloid-β, S-100, and amphotericin
Immunoglobulin G receptor	Fcγ-R	IgG

contrast to endothelial cells in arteries and arterioles, capillary endothelial cells do not express calcium-activated potassium channels ensuring there is no current leak along the capillary. Interestingly, BCECs lack any type of calcium-activated ion channels. This confirms that BCECs are phenotypically distinct from their artery/arteriole counterparts.

VIII. Alzheimer disease

AD is typically characterized by a gradual decline in cognitive abilities, particularly in memory function. The central neuropathologic hallmarks of AD are (1) extracellular fibrillar Aβ in amyloid plaques, (2) intraneuronal neurofibrillary tangles consisting of aggregated hyperphosphorylated tau, and (3) elevated levels of extracellular soluble amyloid (sA)β oligomers (de Felice et al, 2008; Klein, 2012). Aβ is generated through sequential proteolytic cleavage of the amyloid precursor protein (APP) by β-site amyloid precursor protein–cleaving enzyme (BACE)1, and γ-secretase (Hardy and Selkoe, 2002). Numerous different forms of Aβ exist, but the predominant forms of Aβ in AD are the 40-amino acid peptide (<80%) and the 42-amino acid peptide (<10%), which polymerize into a variety of multimeric Aβ species and subsequently fibrillize, aggregate, and can be deposited within the parenchyma of the brain. Aβ42 is more hydrophobic than Aβ40 and has a greater propensity to polymerize and form fibrils (Walsh et al, 1997; Kirkitadze et al, 2001). Aβ40 is predominantly connected to vascular changes, whereas Aβ42 is associated with inflammation.

The deposition of insoluble fibrillar Aβ in brain parenchyma is associated with neurons and parenchymal microglial cells (Wisniewski et al, 2000); deposition in the walls of capillaries, with perivascular cells of monocyte-macrophage-microglial lineage (Wisniewski et al, 1992); and deposition in the walls of brain arteries and veins, with smooth muscle cells (Wisniewski et al, 2000). Interestingly, there are 6 specific tau isoforms in adult human brain, and the contribution of tau to AD might be isoform specific (Buchholz and Zempel, 2024). Several hypotheses have evolved to explain AD and are briefly described in the following sections.

A. Cholinergic hypothesis

Biochemical investigation of the brains of patients with AD revealed substantial neocortical deficits in the enzyme responsible for the synthesis of acetylcholine and choline acetyltransferase (Davies and Maloney, 1976). Subsequent research confirmed a substantial cholinergic (and noncholinergic) deficit could contribute to the deterioration in cognitive function in AD. Degeneration of cholinergic neurons is associated with altered CBF and increased Aβ pathology. Cholinergic deafferentation of cerebral arteries is thought to cause increased release of Aβ by deafferented neurons (Wolf et al, 1995) and to cause amyloid deposits in cerebral blood vessels and perivascular neuropil (Beach et al, 2000). The relationship among the loss of cholinergic innervation, impeded perivascular drainage of Aβ (Carare et al, 2013), and vascular dysfunction (Nizari et al, 2021) may be important in AD etiology. In fact, acetylcholinesterase inhibitors have some benefit in treating AD symptoms, possibly by preserving regional CBF and/or improving cholinergic control of cerebral autoregulation (Ceravolo et al, 2004; Hamner et al, 2012). Cholinergic-based strategies remain valid as an approach to rational drug development and have also led to neurotrophic factor studies.

B. Amyloid cascade hypothesis

The widely accepted amyloid cascade hypothesis states that AD is driven by Aβ deposition caused by an imbalance in Aβ production and clearance (Hardy and Higgins, 1992). The neurofibrillary tangles, neuronal loss, and eventually dementia follow as a direct result of this deposition (Hardy and Higgins, 1992).

Amyloid clearance is impaired in both early and late forms of AD. Specifically, carriers of early-onset AD-associated presenilin mutations show both increased Aβ production and decreased Aβ clearance (Potter et al, 2013), whereas individuals with late-onset AD exhibit decreased Aβ clearance only (Mawuenyega et al, 2010). It is now known that Aβ is cleared from the brain by multiple pathways including degrading enzymes; uptake into microglia, astrocytes, and pericytes; and transcytosis across the BBB, glymphatic, IPAD, and lymphatic drainage pathways. However, the amyloid cascade hypothesis fails to explain all the histopathologic, molecular, and biochemical abnormalities occurring in AD brain. Interestingly, the clearance of tau is thought to be much less complex than that of Aβ and mainly relies on degradation, ISF bulk flow, and CSF absorption (Tarasoff-Conway et al, 2015).

The role of Aβ clearance in the pathogenesis of AD has been studied using a multilayer mathematical 3 compartment model (Kyrtsos and Baras, 2015). The 3 compartments being the brain parenchyma, the perivascular space, and the cerebral blood vessels. It has been demonstrated that heart rate (eg, the rate of arterial pulsations) and the vessel stiffness, which is a function of the presence of atherosclerosis, cerebral amyloid angiopathy (CAA; deposition of Aβ within the brain vessels), and stiffening secondary to prolonged elevations in systemic blood pressure, are important to maintaining adequate clearance of Aβ from the brain (Kyrtsos and Baras, 2015).

C. Oligomer hypothesis

Neurotoxicity of Aβ protein in AD has been attributed to its fibrillar forms; however, there is a strong correlation between sAβ oligomer levels and the severity of neuropathologic changes in AD, and this has resulted in the oligomer hypothesis for AD (Lambert et al, 1998; Klein, 2012). The prefibrillar sAβ oligomers are found to be more toxic than their insoluble fibrillar counterparts. de Felice et al (2007) determined that sAβ oligomers induce neuronal oxidative stress through an NMDA receptor–dependent mechanism, and this has been shown to be associated with dysregulation of specific microRNAs which are known to be altered in AD (Li et al, 2014). sAβ oligomers can selectively accumulate at synapses and can rapidly induce failure of synaptic plasticity and consequently cause cognitive impairment in AD (Klein, 2012; Li et al, 2014). This loss of synaptic plasticity is caused by oligomers downregulating neuronal NMDA receptors, possibly by binding to EphB2 (Lacor et al, 2007). The NMDA receptor downregulation is linked to its own hyperactivity. Oligomers also cause a substantial loss of neuronal insulin receptors (Zhao et al, 2008). This disruption in

brain insulin signaling explains why AD is sometimes referred to as type 3 diabetes. Aβ oligomers also induce neuronal tau hyperphosphorylation (de Felice et al, 2008).

D. Vascular hypothesis

The 2-hit vascular hypothesis of AD proposes that the initiation and advancement of cognitive decline occurs because of disruption and dysfunction of neurovascular integrity and that cerebral vessels are the focus of pathologic events causing dementia (Zlokovic, 2011). According to this hypothesis, the initial insult is damage to blood vessels. Vascular damage can be initiated by genetic risk factors (eg, carriage of apolipoprotein [*APOE**ε4], environmental risk factors (including pollution), and vascular risk factors (including dyslipidemia, diabetes, and hypertension) (Sagare et al, 2012; Sweeney et al, 2015; Nelson et al, 2016). This primary disruption to the cerebrovasculature causes BBB dysfunction, pericyte degeneration, accumulation of blood-derived toxins in the brain, and diminished brain perfusion. This initiates a cascade of events, which may either (1) cause direct neuron damage and injury independent of Aβ (hit 1) and/or (2) cause acceleration of Aβ-dependent neurodegeneration (hit 2). For the Aβ-dependent pathway, disruption of the BBB causes faulty Aβ clearance from the brain, and decreased brain perfusion augments Aβ production, both leading to brain Aβ accumulation. Both hit 1, where there is a reduction in brain perfusion and hit 2, where there is Aβ accumulation, can synergistically and/or independently cause tau hyperphosphorylation and form filamentous tau pathology. Furthermore, the 2 hits can aggravate neuroinflammation (Sagare et al, 2012).

E. Inflammation and Alzheimer disease

AD has multiple associations with inflammation: being recognized as a proinflammatory disease and the long-standing finding that inflammatory events or infections can trigger or exacerbate AD (Holmes, 2013). Inflammatory pathways, when stimulated, cause the release of angiogenic cytokines such as thrombin and vascular endothelial growth factor, and contribute to pathological angiogenesis and hypervascularization (Singh et al, 2017). In addition, thrombin activates the vascular endothelia to secrete APP, and this leads to the accumulation of amyloid plaques.

Systemic inflammation may augment production of Aβ, along with inhibiting mechanisms of Aβ clearance such as efflux of Aβ across the BBB and CSF bulk flow (Jaeger et al, 2009; Erickson et al, 2012). Inflammation can affect ligand-binding affinity by making the pH more acidic, which accelerates tau hyperphosphorylation and causes conformational changes in Aβ that hinder its clearance (Tarasoff-Conway et al, 2015).

IX. CNS pathophysiology in Alzheimer disease

The following sections discuss how the NVU and barrier function seems to be compromised during the aging process and AD. Interestingly, all cell types in the NVU express APP and release biologically active APP metabolites. We summarize and examine current evidence from clinical studies that investigate CBF, microvascular anatomy, capillary perfusion, the NVU, and integrity of the BBB in patients with AD using histologic and biochemical methods in postmortem brains, CSF biomarkers, and brain imaging techniques. This is accompanied by evidence from basic science studies.

A. Changes in cerebrovascular perfusion and anatomy

1. Cerebral blood flow

Temporoparietal CBF reduction is often considered to be a defining pathologic feature of AD, and there is evidence that chronic cerebral hypoperfusion/hypoxia, a consequence of aging and a variety of vascular conditions, may initiate the degenerative process (Guglielmotto et al, 2009). Indeed, postmortem studies have shown coexisting cerebrovascular disease in most patients with AD (di Marco et al, 2015b). The 4D-flow magnetic resonance imaging studies have demonstrated a general reduction in the total arterial blood flow in major cerebral arteries and an increase in arterial pulsatility in patients with AD (Rivera-Rivera et al, 2016, 2017). In addition, regional blood flow is impaired in AD resulting in hypoperfusion. This may be due to neurovascular uncoupling, impaired myogenic autoregulation, impaired vasoreactivity, loss of vascular innervation, and endothelial dysfunction (Cantin et al, 2011; Hunter et al, 2012). The endothelial dysfunction is associated with dysregulation of vascular NO production, which affects microvessel tone and consequently CBF (de la Torre and Aliev, 2005; Navarro et al, 2016). Of particular interest is that chronic loss of endothelial NO is an important contributor to Aβ-related pathology within the brain because of it causing an increase in APP and BACE1 expression as well as Aβ production (Austin et al, 2010, 2013). Aβ can also affect vascular NO production by inhibiting endothelial NO synthase enzyme activity and altering cytosolic Ca^{2+} homeostasis (Gentile et al, 2004) and blood flow. Numerous pathologic factors associated with AD also stimulate endothelial cells to produce the vasoconstrictor (endothelin). These factors include inflammation, ischemia, reactive oxygen species, and amyloid (Deane et al, 2003).

Importantly it has been suggested that the reduced blood flow observed in AD causes the development of capillary alterations and BBB damage and, consequently, prevents the optimal transport of sufficient nutrients to the neural tissue and subsequent neuronal dysfunction (Farkas et al, 2000). As such, the dysfunction of the BBB could mediate a defective circle in which cerebral perfusion is decreased further and the neurodegenerative process is accelerated (Nunomura et al, 2006).

2. Capillary density

Structural alterations of the brain capillaries are now recognized to occur with AD. Capillary density declines in both aging and dementia (Bell and Ball, 1981). In fact, in brains of people with AD, the overall capillary diameters and densities do not differ from those of age-matched controls. However, similarity in microvascular density does not necessarily translate into functional equality. For instance, microbleeds and infarcts are more prevalent in patients with AD (Kapasi and Schneider, 2016).

3. Capillary stalling

Capillary stalling caused by capillary obstruction perturbs blood flow (Reeson et al, 2018). The incidence of capillary obstructions is likely to be increased in dementia (Reeson et al, 2018). The cause of the obstruction is not only due to increased adhesion of leukocytes to capillary endothelial cells but also associated with increased constriction of actin containing pericytes preventing the flow of blood cells (Crumpler et al, 2021). Neutrophil plugging likely caused by increased neutrophil interaction with the inflamed endothelium has been shown to contribute significantly to CBF decreases in AD mouse models (Cruz Hernández et al, 2019). Neutrophils, monocytes, and erythrocytes contribute to producing capillary blocks near pericytes in AD mice and may lead to capillary loss (Korte et al, 2024).

4. Narrowing of vessels

In the brains of patients with AD, microvessels have an irregular diameter and are often narrowed especially in the vicinity of the senile plaques (Kitaguchi et al, 2007). Studies have suggested that endogenous amyloid causes vasoconstriction of capillaries, and not arterioles or venules, suggesting that hypoperfusion in AD is due to a pericyte-mediated response and not a vascular smooth muscle

response (Nortley et al, 2019). To cope with the decrease in blood flow, the brain has evolved a compensatory mechanism whereby it increases the formation of blood vessels resulting in hypervascularity in postmortem samples of patients with AD (Pfeifer et al, 2002). It is possibly caused by amyloidogenesis and disruption of TJ integrity causing pathologic angiogenesis (Biron et al, 2011).

5. Cerebral amyloid angiopathy

In AD, the aggregates of Aβ can be found both around arteries and capillaries as CAA and in the brain parenchyma as neuritic plaques (Miyakawa et al, 1982; Vinters, 1987; Weller et al, 2008). CAA is associated with the accumulation of insoluble Aβ40 deposits in the outer BM close to the neuropil of the capillary wall (Natté et al, 1999; Thal et al, 2002). Using multiphoton laser scanning microscopy, Aβ deposits were shown wrapped around arteriole walls in patches in a mouse model of CAA (Kim and Jeong, 2015). CAA was not observed around the veins or dura vessels in the relatively young mice (7 months). However, older mice exhibited complete rings of CAA. From brain autopsy, CAA has been found in 30%–40% of elderly individuals without dementia and 60%–95% of patients with AD (Vinters, 1987; Prelli et al, 1988; Haan et al, 1991; Jellinger, 2002). CAA predominantly occurs in cortical and leptomeningeal arteries but additionally affects cerebral capillaries (Vinters, 1987; Roher et al, 2003). A key characteristic of sporadic CAA is a failure of Aβ clearance from the brain. It has been hypothesized that CAA is linked to the failure of the ISF clearance mechanism along the CVBM (Weller et al, 2008) of the periarterial wall, but not the perivenous wall (Kim and Jeong, 2015). This is the so-called IPAD pathway.

In a mouse model of CAA, capillary CAA was associated with capillary occlusion and CBF disturbances/hypoperfusion (Thal et al, 2008). The vascular amyloid deposits are thought to have a brain-based origin. Aβ40 is more commonly observed in CAA, and parenchymal plaques are made up predominantly of Aβ42 (Suzuki et al, 1994). It has been hypothesized that platelets contribute to the formation of CAA because platelets play a role in repairing blood vessels damaged as a result of hypoperfusion, contain large amounts of APP, and produce predominately Aβ40 (Davies et al, 1998; Simons et al, 1998).

Recent research supports the importance of cholinergic innervation and vascular function in CAA progression (Nizari et al, 2021). CAA develops topographically, presenting initially in the occipital lobe, followed by the temporal, frontal, and parietal lobes, then in the entorhinal cortex and hippocampus at later stages (Attems et al, 2007).

6. Changes to intramural periarterial drainage

Failure of IPAD is a key element in CAA pathology (Weller et al, 2008; Carare et al, 2013). IPAD moves solutes and ISF from the brain parenchyma to the cervical lymph nodes via CVBM pathways. Movement is in the opposite direction to the blood flow. The driving force that underlies IPAD is thought to be due to arterial pulsation, vasomotion, and neurovascular coupling (Schley et al, 2006). Although the relative contribution of each is debated, these mechanisms are reduced in AD (di Marco et al, 2015a). The slower the arterial pulse cycle, the longer time molecules (such as Aβ) have to form interactions with BM proteins (Schley et al, 2006). In addition, BM composition changes (Morris et al, 2014) and the deposition of immune complexes and insoluble amyloid deposits may block, possibly temporarily, perivascular lymphatic drainage in aging arteries and in AD (Carare et al, 2013). This would further exacerbate IPAD failure.

Importantly, in AD, there is a decrease in the amount of both Aβ40 and Aβ42 in the CSF. This is possibly related to the trapping of Aβ in the IPAD pathways as CAA. Consequently, less Aβ is able to reach the CSF via the IPAD pathways. In contrast, there is a corresponding increase in total and phosphorylated forms of tau in CSF (Höglund et al, 2017; Albargothy et al, 2018). This suggests that the more soluble tau can pass more readily than Aβ along the BMs surrounding smooth muscle cells (Albargothy et al, 2018).

7. Changes to glymphatic and lymphatic drainage pathways

The glymphatic system facilitates the clearance of solutes, including Aβ and tau, from the brain (Iliff et al, 2012, 2014; Harrison et al, 2020). In fact, it is believed to drain approximately 60% of the brain Aβ to cervical lymph nodes (Kyrtsos and Baras, 2015). Glymphatic transport is suppressed before significant accumulation of Aβ (Peng et al, 2016). This suggests that lack of glymphatic function renders the brain susceptible to the accumulation of neurotoxic substances. Glymphatic pathway function is dramatically impaired in the aging brain and contributes to cognitive decline among the elderly (Kress et al, 2014). The olfactory bulb is particularly prone to age-related glymphatic dysfunction (Li et al, 2022b). The decline in glymphatic function is related to a reduction in arterial pulsatility, arteriole vasomotion, and CSF turnover as well as changes to the expression of astrocytic AQP4 and lymphatic dysfunction. The changes in vasoreactivity may be related to loss of innervation of perivascular mural cells, loss of smooth muscle cells, and the progression of CAA in specific brain regions (van Veluw et al, 2020; Nizari et al, 2021). Aβ is deposited in BM drainage pathways in CAA and may impede elimination of Aβ and ISF from the brain in AD (Carare et al, 2008). The changes to CSF turnover may be due to a reduction in CSF secretion by the choroid plexuses and/or an increase in CSF volume (Matsumae et al, 1996; Preston, 2001). Failure in CSF bulk flow permitting Aβ accumulation.

There is a significant decline in CSF lymphatic outflow in aged mice compared with that in young mice. This suggests that changes to the lymphatic system may also be associated with age-associated neurologic conditions (Ma et al, 2017). Experimental damage to the meningeal lymphatic system leads to accumulation of protein aggregates in the brain parenchyma including AD-associated Aβ and tau (da Mesquita et al, 2018; Patel et al, 2019). Impairment of either the glymphatic channels or dura mater and cervical lymphatics may be a risk factor for neurodegenerative disease.

B. Changes to blood–brain barrier integrity

Normal age-related decline may be the mechanism causing BBB disruption (Verheggen et al, 2020). New biomarker and imaging studies indicate BBB breakdown and vascular dysregulation is an early event in AD occurring before cognitive decline, neurodegeneration, or brain atrophy (Sweeney et al, 2015; Montagne et al, 2016; van de Haar et al, 2016; Kisler et al, 2017b; Nation et al, 2019). Early involvement of cerebral vessel disease in AD is also supported by neuropathologic studies (Toledo et al, 2013; Arvanitakis et al, 2016). Carriers of the *APOE*ε4* allele, the main genetic risk factor for AD have the most pronounced evidence of BBB breakdown. In fact, recent evidence suggests BBB breakdown contributes to the cognitive decline in *APOE*ε4* carriers independent of AD pathology (ie, Aβ and tau) (Nation et al, 2019; Montagne et al, 2020). Conversely, individuals who are homozygous for the commonest allele, *APOE*ε3*, have a lower AD risk and display a reduced degree of BBB breakdown (Nishitsuji et al, 2011; Bell et al, 2012, 2023; Alata et al, 2015). Aβ can also alter BBB permeability (Deli et al, 2010; Kook et al, 2012).

1. Blood-derived molecule leakage

Over 20 individual postmortem human studies have confirmed BBB breakdown in patients with AD showing blood-derived

proteins (hemosiderin, IgG, albumin, thrombin, and fibrinogen) in the hippocampus, entorhinal, and prefrontal cortex (Zipser et al, 2007; Cortes-Canteli et al, 2010; Hultman et al, 2013; Sweeney et al, 2015; Halliday et al, 2016; Nelson et al, 2016; Miners et al, 2018). These blood-derived proteins are potential causes of brain injury, for example, thrombin is neurotoxic and hemosiderin generates reactive oxygen species. These blood-derived proteins are often found in microvascular segments colocalized with deposits of AD-associated Aβ, senile plaques, and CAA in AD brains (Ryu and McLarnon, 2009; Hultman et al, 2013; Sengillo et al, 2013). Additionally, the cerebellum of patients with AD have higher levels of hemoglobin-derived peptide, in contrast to control patients who had no significant neuropathology (Slemmon et al, 1994). Raised prothrombin levels in AD postmortem tissues has also been measured, the level of which showed positive correlation with Braak staging (Zipser et al, 2007). These findings together implicate the disruption of the BBB in AD.

However, some studies have shown conflicting results. Immunohistochemical staining for C1q, C3c, immunoglobulin, prealbumin, albumin, or fibrinogen showed levels of serum protein extravasation in AD brains were similar to those of controls (Alafuzoff et al, 1987; Tomimoto et al, 1996). However, variations in the procedures for immunohistochemical staining and sample preparations could be possible factors causing inconsistency in the results (Rozemuller et al, 1988). Furthermore, the diversity of concurrent vascular pathology in AD brain could be accountable for the discrepancy in results. Additional studies with optimized methodology and larger cohorts are required to establish whether parenchymal accumulations of peripheral blood–derived molecules are intensified in brains of patients with AD, signifying BBB disruption.

2. Cellular infiltration

Peripheral monocyte/macrophages and lymphocytes can migrate through a disrupted BBB into human AD brains (Hultman et al, 2013). Macrophages were localized around sites of disruption of the endothelial TJ protein, ZO1. Macrophages also infiltrate endothelial plaques, which partly encircle the walls of Aβ-containing vessels in amyloid angiopathy (Fiala et al, 2002). The adherence and transmigration of monocytes across the BBB was increased by Aβ (Giri et al, 2000, 2002; Gonzalez-Velasquez and Moss, 2008). This was mediated by the transcription factor, nuclear factor-κB (Gonzalez-Velasquez et al, 2011). Neutrophils can also cross the BBB in AD (Zenaro et al, 2015). The extravasation of red blood cells has been identified in AD (Cullen et al, 2005). Taken together, these results suggest that in AD, BBB disruption not only causes activation of the innate immune response in the brain but also allows extravasation of red blood cells, which leads to microbleeds and deposition of hemosiderin.

3. Increased cerebrospinal fluid/blood albumin ratio

Patients with AD show an increase in the CSF:plasma or CSF:serum ratio of albumin, which is frequently used as a measure of BBB breakdown, because albumin is a blood-derived protein (Algotsson and Winblad, 2007; Halliday et al, 2013; Janelidze et al, 2017; Skillbäck et al, 2017). Some studies, however, report that only patients with AD with vascular lesions or vascular risk factors (such as ischemic heart disease, diabetes mellitus, mild arterial hypertension, or dyslipidemia), exhibit alterations in CSF markers and that these alterations were not evident in patients with AD without them (Blennow et al, 1990, 1991; Bowman et al, 2012; Sweeney et al, 2015). However, the majority of patients with AD have some extent of vascular pathology present; 80% of patients aged 85 years and 65% of patients aged 65 years have vascular risk factors with AD (Iadecola, 2013; Montine et al, 2014; Snyder et al, 2015). A meta-analysis of 31 BBB permeability studies including 1953 patients found that BBB permeability parameters as measured by biochemical techniques or imaging were increased in normal aging, to a greater extent in patients with vascular dementia and AD, in vascular dementia compared with AD, and with worsening leukoarasiosis (Farrall and Wardlaw, 2009). Therefore, vascular pathology, instead of tauopathy or senile plaque deposits, could affect the CSF:serum albumin ratio in AD. Consequently, disruption of the BBB in patients with AD should be characterized by taking into consideration the amount of concomitant vascular factors. Additionally, because patients with AD demonstrate disturbed CSF protein turnover (Silverberg et al, 2001; Chen, 2011) and CSF is produced by the choroid plexuses (the blood-CSF barrier), the CSF:plasma albumin ratio might not be a precise representation of BBB permeability in AD.

C. Capillary endothelium alterations

There is considerable evidence that cerebral endothelial cell dysfunction and toxicity underlies the neuropathogenesis observed in AD, including the loss of BBB integrity. Loss of barrier integrity can be due to changes in the paracellular (TJs or AJs) or transcellular (transporter or receptor) permeability of the cerebral capillary endothelium. The following section describes the ultrastructural features that are altered in AD and the specific nature of the changes to BBB permeability.

1. Ultrastructural changes

In patients with AD, brain vasculature is characterized by increased incidence of degenerated and collapsed endothelium, along with more severely impaired BBB transport systems, in contrast to age-matched controls (Kalaria and Hedera, 1995). There is evidence from clinical and basic studies that the mitochondria in cerebral capillary endothelium are damaged and dysfunction. Reduced mitochondrial density and size (but the same mitochondrial volume) in cortical capillaries from patients with AD, compared with that in control subjects, has been reported (Stewart et al, 1992). Mitochondrial damage has also been observed in the form of broken cristae, membrane disruptions, swelling, and mitochondrial DNA deletions (Aliev et al, 2002). Clusters of mitochondria-derived lysosomes, large-sized lipid vacuoles, and necrotic structures have been observed in cerebral microvessel endothelium of AD brains and are absent in age-matched controls (Table 4) (Aliev et al, 2002). Aβ1–42-induced ultrastructural changes in cultured rat brain endothelial cells have been reported and include vacuolization, decreased number of caveolae and Golgi bodies, and shrunken mitochondria (Deli et al, 2010). Mitochondrial dysfunction will cause deficient ATP production, which affects the proper functioning of primary and secondary active transport mechanisms and ultimately disrupt the homeostasis of the cerebral fluids. The consequent dysregulation of intracellular calcium concentrations may result in apoptosis (Fonseca et al, 2015). In addition, deficient ATP production would also cause reduced lactate production (Lee et al, 2022). Table 4 summarizes the brain endothelial cell alterations observed in AD.

2. Tight junction protein changes

Changes in the expression of TJs that are found between the cerebral capillary endothelial cells will increase the paracellular permeability characteristics of the BBB. This would increase the delivery of molecules to the brain in a nonselective manner and may allow for the passage of large molecules such as the large blood-derived proteins into the brain, which is observed in AD. Interestingly, a study has also suggested that sAβ1-40 transiently

Table 4
Overview of cerebral endothelial cell changes in Alzheimer disease

Change	Specific	Causes
Ultrastructural changes	Large lipid-laden vacuoles. Swollen mitochondria. Increased cytoplasmic inclusions. Increased pinocytotic vesicles.	Oxidative injury.
Mitochondria dysfunction	Deficient ATP production.	Mitochondria dysfunction. ATP-pump dysfunction and consequent dysregulation of calcium concentration and signaling. Primary and secondary active transporter dysfunction.
Altered gene expression	Reduced mesenchyme homeobox 2 expression. Altered AβPP expression.	Reduced cerebral blood flow. Reduced capillary density. Endothelial LRP degradation.
Altered protein expression	Intracellular Aβ accumulation.	Cerebral amyloid angiopathy.
Aβ-induced changes	Reduced NO production. Endothelial nitric oxide synthase inhibition. β-Site amyloid precursor protein–cleaving enzyme 1 increases. Increased endothelin-1 production. Intracellular calcium homeostasis dysfunction.	Activation of inflammatory response. Production of neurotoxic molecules. Vasoconstriction. Impairs regional cerebral blood flow. Endothelial cell degeneration and apoptosis.
Altered tight junction expression	Reduced claudin-5, occludin , ZO-1 and ZO-2 expression Linked to increased expression of MMP-1 and MMP-9.	Extravasation of macromolecules and mononuclear cells.
Altered receptor-endocytosis pathways	Reduced expression of LRP1, RAGE, and *PICALM*	Reduced Aβ clearance.
Altered transporter expression	Reduced ABCB1 (P-gp) expression Reduced SLC2A1 (GLUT1) expression Reduced SLC29A4 (PMAT) expression	Reduced Aβ clearance Altered nutrient delivery Altered drug delivery

AβPP, Aβ-protein precursor; LRP, low density lipoprotein receptor–related protein; MMP, matrix metalloproteinase; RAGE, receptor for advanced glycosylation end products; ZO, zonula occludens.

decreases claudin-5 and occludin expression at the BBB and allows for autoregulated paracellular clearance of amyloid monomers from brain to blood. Importantly, high molecular weight oligomers of amyloid would be too large to traverse the BBB and thus (if present) would accumulate in the ISF space (Keaney et al, 2015).

There is evidence from multiple studies that demonstrate and suggest that there are changes in the expression of the TJ proteins, ZO-1, ZO-2, claudin 5, occludin, and JAM-C in AD. Capillaries of postmortem human brains in individuals with CAA showed a substantial reduction in the TJ proteins, ZO-1, and claudin-5, which was associated with elevated fibrinogen leakage into the brain parenchyma (Carrano et al, 2012). Additionally, in the amyloid model of 5x FAD mice, alterations in cerebral TJs were observed. Electron microscopy revealed that in the 5xFAD mice, the lengths of TJs were considerably shorter compared with those in the littermate control mice (Kook et al, 2012). Another study showed Aβ1–42 oligomers caused disruption to TJs and increased vascular permeability by inhibiting claudin-5, occludin, and ZO-1 expression through increased expression of matrix metalloproteinases (MMP)-9 and MMP-1 in cultures of mouse brain endothelial cells (bEnd.3) (Wan et al, 2015). Individuals who are *APOE4* carriers have increased activity of the BBB degrading cyclophilin A–MMP-9 pathway in CSF compared with noncarriers (Montagne et al, 2020), suggesting the barrier may be more permeable in *APOE4* carriers. Further studies also revealed a decrease of occludin by administering Aβ42 and Aβ40 into brain endothelial cells isolated from rat cerebral cortex microvessels (Marco and Skaper, 2006) and human brain endothelial hCMEC/D3 cells (Tai et al, 2010), respectively. A highly sensitive water-exchange magnetic resonance imaging method has detected subtle BBB permeability alterations associated with reduced occludin expression in a rat model of AD (Dickie et al, 2019). Hypoxia stress has been shown to modulate occludin oligomeric assemblies and cause alterations in TJ integrity (McCaffrey et al, 2009; Lochhead et al, 2010). Aβ42 has also been shown to cause a disrupted plasma membrane pattern of claudin 5 and ZO-2 with relocation to the cytoplasm in rat brain endothelial cells (Marco and Skaper, 2006; Kook et al, 2012) found that Aβ42 induced changes in ZO-1 were mediated by RAGE.

Another TJ protein, JAM-C expression, has been shown to be downregulated by Aβ42 in human umbilical vein endothelial cells in vitro; however, it is uncertain whether this is the case in vivo (Chao et al, 2016). Therefore, JAM involvement in AD remains to be fully elucidated. Furthermore, in a mouse model of hyperhomocysteinemia, a pathology that can be associated with cognitive disorders such as AD, a considerable reduction of VE-cadherin in brain vessels and increased BBB permeability was noted, along with enhanced cerebrovascular Aβ and fibrinogen deposition. This suggests Aβ disturbs the barrier function of endothelial cells, by disrupting the organization of TJs and AJs (Muradashvili et al, 2014).

3. *Changes to receptor-mediated endocytosis pathways*

Cells of the NVU are capable of endocytosing Aβ and removing it via lysosomal degradation (Kanekiyo and Bu, 2014). Endothelial cells are thought to facilitate the transport of Aβ across the BBB through receptor-mediated endocytosis. The receptors involved include RAGE and LRP1.

RAGE mediates Aβ influx into the CNS and LRP1 mediates the efflux of unbound Aβ and Aβ bound to apoE2, apoE3, or α2-macroglobulin from the brain to the periphery (Deane et al, 2004; Pflanzner et al, 2010; Sagare et al, 2012). On the abluminal side of endothelial cells, LRP1 can internalize Aβ, from where it is transported via transcytosis to the luminal side, effluxed via ABCB1 (P-gp), or targeted to the lysosome for degradation (Pflanzner et al, 2011; Candela et al, 2015).

Preclinical and clinical studies have shown that Aβ accumulation within the brain and AD pathology correlate with higher RAGE levels and lower LRP1 levels within the brain parenchyma (Shibata et al, 2000; Deane et al, 2004, 2012; Donahue et al, 2006; Zlokovic, 2008; Storck et al, 2015; Osgood et al, 2017). A gene associated with LRP1 (rs541458, *PICALM*) also has a reduced expression in AD (Zhao et al, 2015, 2024). Syndapin-2 stabilizes the tubulation mechanism associated with LRP1 transcytosis of amyloid and expression of syndapin-2 in the brain endothelium declines in aging and AD (Leite et al, 2022). The changes in receptor expression could be linked to the progressively toxic brain extracellular fluid environment (as ISF and CSF dynamics waver), to inflammation (Erickson

et al, 2012), to defective endogenous neurogenetic programming in those who are susceptible (Johanson and Johanson, 2016), or to diminished glucose transporter (GLUT)1 expression (Winkler et al, 2015). Additionally, systemic inflammation modifies P-gp function and expression and increases influx of Aβ in the absence of a change in RAGE expression within brain microvessels (Jaeger et al, 2009).

In contrast to brain microvessels, within the choroid plexus epithelium of the BCSFB, expression of LRP1 appears to be maintained or possibly even increases with aging or AD (Pascale et al, 2011). LRP1 is found on the choroid apical membrane and clears Aβ from CSF (Fujiyoshi et al, 2011). In patients with advancing AD in contrast to aging controls, increasing Aβ in the cortex is commonly accompanied with concomitant reduced CSF Aβ concentration. This consistent finding has been puzzling, but recent observations elucidate BCSFB versus BBB transport mechanisms on differing Aβ levels in separate CNS regions (Johanson and Johanson, 2016). Aging along with disease associated differential expression in BBB versus BCSFB of the Aβ reabsorptive transporter, LRP1, is crucial in understanding this evident paradox of how CSF Aβ concentration is reduced in the face of lowered BBB removal of Aβ, with resulting Aβ brain retention (Silverberg et al, 2010).

4. Transporter expression changes at the blood–brain barrier

There is evidence that ABC (P-gp, BCRP) and SLC (GLUT1, multidrug and toxin extrusion protein [MATE]1, and plasma membrane monoamine transporter [PMAT]) transporter activity at the BBB changes in AD. Both P-gp and BCRP transport Aβ (Do et al, 2012).

Compromised function of P-gp has been reported in aging and more significantly in AD (Vogelgesang et al, 2002; Wijesuriya et al, 2010; van Assema et al, 2012; Deo et al, 2014; Boyanova et al, 2023). Interestingly P-gp cerebrovascular expression was inversely correlated to the number of Aβ plaques in elderly without dementia (Vogelgesang et al, 2002). In an animal study, it was revealed that a deficiency in P-gp prevents clearance of Aβ and increases Aβ brain accumulation (Cirrito, 2005). Aβ plaques act to suppress P-gp expression in brain endothelium of 5xFAD mice (Park et al, 2014). Exposure of mouse brain capillaries to Aβ40 causes degradation of P-gp, thus decreasing its transport activity (Hartz et al, 2016). This suggests that P-gp function continues to deteriorate during AD. In contrast BCRP expression is increased in Alzheimer brain with CAA and may act as a gatekeeper to prevent blood Aβ from entering the brain (Xiong et al, 2009). However, a reduced expression of BCRP has also been observed in AD brain capillaries with CAA than in AD brain capillaries without CAA (Carrano et al, 2014). These discrepancies in expression are likely related to differences in method, region, age, and staging (Kannan et al, 2017).

Many studies have revealed that in humans, glucose (and oxygen) extraction form the cerebral microcirculation decreases with aging and in dementia (Kalaria and Harik, 1989). Glucose is transported into the brain via the GLUT1 (SLC2A1) expressed in the plasma membrane of the cerebral capillaries.

GLUT1 expression is considerably decreased in brain capillaries of patients with AD (Horwood and Davies, 1994; Mooradian et al, 1997) and AD mouse models, compared with that in those of aged-matched controls, signifying AD brains experience chronic shortages of energy-rich metabolites (Hooijmans et al, 2007; Merlini et al, 2011). It has recently been proved that GLUT1 is essential for correct maintenance of BBB integrity, blood flow, the brain capillary network, and neuronal function. GLUT1 deficiency in BCECs resulted in BBB deterioration with extravascular accumulation in brain parenchyma of IgG and fibrin and decreased expression of TJ proteins in AD mice. Further, deficiency of GLUT1 also causes degeneration of the cerebral microvasculature, followed by an acceleration of Aβ pathology in an amyloid mouse model (Winkler et al, 2015). Hence, this suggests a role for the reduction of GLUT1 on endothelial cells during AD pathogenesis. Overall, changes in the expression and function of specific ABC transporters (eg, P-gp and BCRP) and SLC transporters (eg, GLUT1) in AD is related to reduced clearance of Aβ and shortages in the delivery of energy-rich metabolites to the brain and so is directly related to the pathophysiology of AD.

Recently, our group has reported that there is also a reduced expression of the SLC transporters, PMAT (SLC29A4) and MATE1 (SLC47A1), in AD cases (Sekhar et al, 2019). These previously unreported changes in SLC transporter expression in patients with AD require further research to characterize the pathogenesis and implications of these findings.

5. Clinical importance

It is important to note that changes in ABC and SLC transporter expression may alter drug distribution to the CNS and therefore efficacy of CNS active drugs. This maybe especially relevant to understanding the importance of prescribing lower doses of antipsychotics (and other psychotropics) to patients with dementia (Uchida et al, 2009; Gareri et al, 2014) and so preventing side effects including sedation, postural hypotension, and fall-related injuries. Table 5 lists the commonly prescribed psychotropics used in older people and those with dementia. These drugs are all either positively charged or have no charge (neutral) at physiologic pH so are all candidates for transport by either transporters for organic cations (eg, OCT, MATE1, and PMAT) and/or P-gp. Risperidone, 9-hydroxyrisperidone, quetiapine, olanzapine, aripiprazole, citalopram, and sertraline are known to be P-gp substrates (Akamine et al, 2012).

6. Changes to enzyme systems

Alkaline phosphatase is enriched in the capillary endothelium and is upregulated in the brains and plasma of patients with AD (Vardy et al, 2012). This may alter the ability of molecules to cross the BBB.

D. Alterations to the glycocalyx

Located at the interface between capillary endothelium and the blood, the glycocalyx is prone to disruption by inflammation and oxidative stress. Aging is associated with glycocalyx thinning and components of the glycocalyx are promising biomarkers of vascular disease. For example, Nägga et al (2014) demonstrated increases in the CSF concentration of the glycocalyx glycosaminoglycan, hyaluronic acid, with AD. A recent study has shown that cerebral endothelial glycocalyx mediates capillary stalling and impacts CBF and is involved in the pathogenesis of subcortical vascular dementia (Yoon et al, 2022).

Table 5
A table listing the commonly used psychotropics in both community dwelling and care home–based older adults

Antipsychotics	Antidepressants	Sedating	Hypnotics
		Benzodiazepines	Z-drugs
Risperidone	Mirtazapine	Temazepam	Zolpidem
9OH-Risperidone	Citalopam	Lorazepam	Zopiclone
Amisulpride	Sertraline		
Olanzapine	Trazodone		
Quetiapine			
Clozapine			
Aripiprazole			

E. Alteration to the basement membrane

Thickening, duplication, splitting, and abnormal inclusions in the CVBM have been found in the brains of elderly animals and humans; these changes occur to a larger extent in the AD brain (Perlmutter, 1994; Kalaria et al, 1996; Farkas and Luiten, 2001; Szpak et al, 2007; Shimizu et al, 2009; Baloyannis and Baloyannis, 2012). Alterations of the biochemical composition of the CVBM (eg, collagen IV and agrin) have been reported and support a proamyloidogenic environment (Berzin et al, 2000; Morris et al, 2014). Immunohistochemical analysis demonstrated that expression of the BM components such as fibronectin, perlecan, and collagen IV increased in the temporal and frontal cortexes in both patients with subclinical AD and patients with AD in comparison with that in controls; however, between subclinical AD and AD cases, no significant difference was detected (Lepelletier et al, 2017). Further, the degree of collagen IV staining did not correlate with the CAA severity in the occipital or frontal cortex of patients with AD (Tian et al, 2006). Using Western blotting, cerebral microvessels isolated from patients with AD showed an increase in collagen IV levels and total collagen, compared with controls (Kalaria and Pax, 1995). However, conflicting evidence reported elevated collagen I and III, but reduced collagen IV, in AD cerebral microvessels (Christov et al, 2008). This may be related to methodologic differences between the 2 studies, but we can conclude that changes in the amount of collagen occur in AD.

The *APOE*ε4* allele, the most significant genetic risk factor for late-onset AD, has also been found to alter CVBM development in *APOE*ε4*-targeted replacement mice, disrupting perivascular removal of Aβ40 (Hawkes et al, 2012). The route of ISF drainage occurs through the CVBMs surrounding the arterioles and capillaries (Morris et al, 2016). Significantly, it was found that the removal of Aβ through the ISF drainage pathway, when injected into mouse hippocampus was impaired by aging, most probably due to the thickening of the CVBM with changes to ECM components (Hawkes et al, 2013), but another possibility is a change in amyloid degradation within the ISF. Aβ is broken down in the ISF by combinations of proteases such as insulin-degrading enzymes and neprilysin (Saido and Leissring, 2012). Reduced elimination of Aβ along the CVBM could be a trigger for the amyloid cascade driving the formation of amyloid plaques and neurofibrillary tangles in the brain of AD (Weller et al, 2015).

A mouse model has revealed that the CVBM also plays a crucial function in IPAD drainage of ISF into cervical lymph nodes from brain parenchyma and with glymphatic drainage of CSF into the ISF (Morris et al, 2016). Further studies are needed to establish how the CVBM is altered during AD and how its changes impact disease pathogenesis by affecting Aβ removal through the cerebral vasculature.

F. Pericyte injury, degeneration, and loss in Alzheimer disease

Injury, degeneration, and loss and altered function of brain pericytes has been demonstrated in AD. Pericyte injury and degeneration occurs in mild dementia (Hall et al, 2014; Montagne et al, 2015) and AD (Halliday et al, 2016). Patients with AD have been found to experience a substantial loss of microvessel coverage by pericytes in both the hippocampus and cortex in contrast to control subjects (Sengillo et al, 2013; Hase et al, 2024). Pericyte loss is significantly higher in *APOE4* carriers compared with that in *APOE3* carriers in human AD (Halliday et al, 2016), although pericyte loss does occur in normal aging (Procter et al, 2021).

Pericyte loss in AD is associated with dysfunction of the PDGF-BB—PDGFRβ axis (Sagare et al, 2015). PDGF-BB is secreted from brain endothelial cells and is the main ligand for PDGFRβ, which is expressed on pericyte membranes. Soluble PDGFRβ is released from damaged pericytes, and its presence in the CSF is a surrogate marker of pericyte degeneration. It has been reported by several groups that levels of both plasma and CSF PDGF-BB and soluble PDGFRβ were increased in patients with AD, thus reflecting not only pericyte injury but also dysfunction of the PDGF-BB—PDGFRβ axis (Sagare et al, 2015). The increase in PDGF-BB is due to increased nonvascular expression (Smyth et al, 2022). However, a reduction in the local vascular PDGF-BB levels due to reduced endothelial cell abundance is thought to result in pericyte loss in AD (Smyth et al, 2022). Pericyte loss possibly occurs through decreased ERK-dependent signaling and increased apoptosis.

1. Ultrastructural changes

Pericytes from AD brains are disorganized and exhibit pinocytotic vesicles, mitochondrial abnormalities, and amyloid deposits (Szpak et al, 2007; Baloyannis and Baloyannis, 2012). Some pericytes also showed a swollen cytoplasm. It remains to be seen whether there is loss of interpericyte TNT in pericytes from AD brains (Alarcon-Martinez et al, 2020; Pisani et al, 2022).

2. Altered pericyte function

There is evidence that the degeneration and loss of pericytes causes pathologic angiogenesis, loss of BBB integrity, brain hypoperfusion, reduced IPAD and glymphatic clearance, reduced clearance of amyloid, and altered trophic support in AD (Fig. 9). This will now be described and the clinical significance summarised.

a. Pathologic angiogenesis. Pathologic angiogenesis takes place in numerous diseases including AD possibly because of chronic inflammation (Singh et al, 2017). Chemokines produced by pericytes have a key role in inflammation-associated angiogenesis. Pathologic angiogenesis results in vessels that are in a continuous dynamic state of growth, regression, and remodeling. Common characteristics of pathologic neovascularization include abnormal permeability and defective vascular remodeling and maturation, which promote leakage, hemorrhaging, and inflammation. Neuroinflammation is associated with deficient PDGFRβ signaling and prevention of PDGF-BB—mediated pericyte proliferation and migration (Jansson et al, 2016). Disrupted PDGF-BB—PDGFRβ signaling will affect the growth phase of angiogenesis.

b. Damaged blood—brain barrier integrity. BBB impairment in AD appears to be associated with the degeneration of pericytes (Nation et al, 2019). Aβ can be taken into the pericytes via CD36 and the mechanism by which Aβ1—40 destroys the BBB involves the induction of pericyte mitophagy-dependent ferroptosis through the CD36/PINK1/Parkin pathway (Li et al, 2022a).

PDGF-BB plays a role in BBB maintenance by signaling TJ redistribution (Harhaj et al, 2002). Because soluble PDGFRβ is shed from damaged pericytes, PDGFRβ levels in the CSF are associated with disrupted PDGF-BB—PDGFRβ signaling and increased BBB permeability. Greater amounts of soluble PDGFRβ were found in patients with mild cognitive impairment in comparison with those in controls (Montagne et al, 2015) irrespective of tau or Aβ changes (Nation et al, 2019). Montagne et al (2015) discovered a positive correlation between CSF PDGFRβ levels and BBB permeability in the hippocampus with increased permeability in individuals with mild cognitive impairment ($n = 17$) compared with cognitively healthy individuals ($n = 14$). CSF PDGFRβ levels correlate with BBB dysfunction. This suggests a relationship between pericyte degeneration and BBB permeability. An elevation of soluble PDGFRβ has also been found in the CSF in preclinical AD (Wang et al, 2022). In fact, high baseline CSF levels of soluble PDGFRβ can predict future cognitive decline in APOE4 carriers, but not in noncarriers

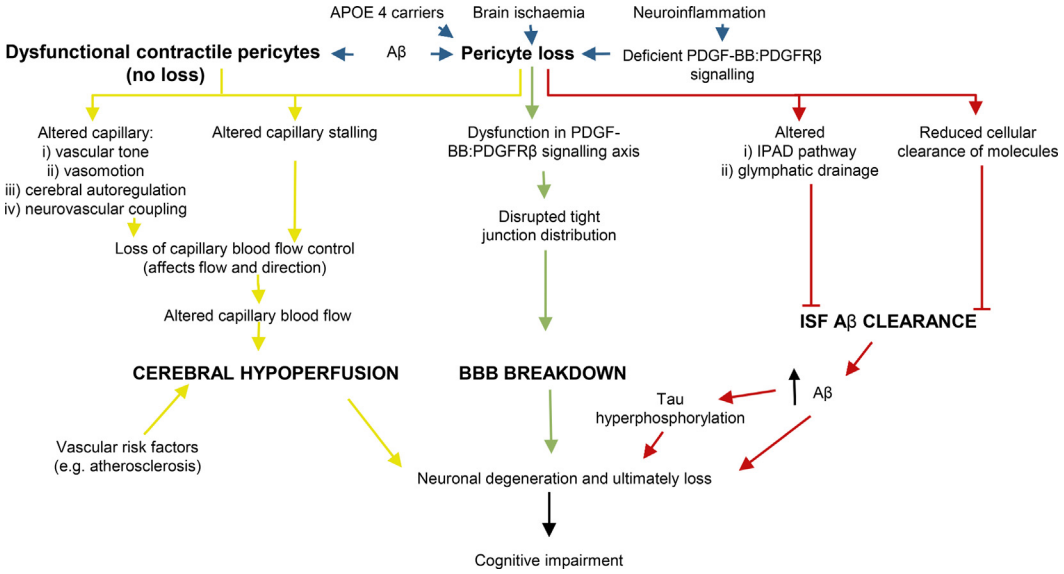

Fig. 9. Summary of the causes and consequences of pericyte loss and dysfunction particularly impaired amyloid β clearance (red), blood–brain barrier (BBB) breakdown (green), and reduced cerebral blood flow (yellow). The myogenic tone, vasomotion, cerebral autoregulation, neurovascular coupling, and capillary stalling will all be affected by pericyte loss and dysfunction. This will alter the rate and direction of blood flow through the capillary network and contribute to cerebral hypoperfusion. Created in BioRender. Thomas, S. (2025) https://BioRender.com/xgc7euo

(Montagne et al, 2020). *APOE4* carriers develop accelerated pericyte loss and degeneration and BBB breakdown compared to *APOE*3 carriers (Halliday et al, 2016).

c. Altered blood flow. Studies have suggested that endogenous amyloid causes vasoconstriction of capillaries, and not arterioles or venules, suggesting that hypoperfusion in AD is due to a pericyte-mediated response and not a vascular smooth muscle response (Nortley et al, 2019). Significantly, endothelin secretion from endothelium is increased because of inflammation, ischemia, and reactive oxygen species, all of which are associated with AD. Interestingly, first-order capillaries near the precapillary arterioles are the most ischemia-sensitive region of the vasculature (Cai et al, 2018). Endothelin binds to endothelin A receptors, which are specifically expressed by pericytes and can cause aberrant sustained contraction (Nortley et al, 2019). This would cause a reduction in capillary blood flow. In contrast, some inflammatory mediators can cause pericytes to increase expression of inducible NO synthase and generate NO, which would cause vasodilation and an increase in capillary blood flow. Cholinergic receptors are expressed on pericytes and are thought to be involved in neurovascular coupling. Cholinergic agonists causing the capillaries to constrict. AD is associated with cholinergic deficits causing vascular dysfunction. Pericyte degeneration and loss would therefore contribute to dysregulation of neurovascular coupling. In fact, a study has demonstrated that neurovascular uncoupling in a mouse model of acute global pericyte loss was due to altered pericyte function and not changes in capillary density, endothelial cell, or neuronal cell function (Nikolakopoulou et al, 2019; Kisler et al, 2020). Importantly, pericyte loss would also induce vasodilation due to loss of capillary vascular tone (Peppiatt et al, 2006; Choe et al, 2022) and interrupt capillary vasomotion. Pericyte loss is also associated with CBF downregulation due to capillary stalling that is caused by a reduced glycocalyx and reduced angiopoietin 1–Tie2 signaling altering the homeostasis of the vasculature (Choe et al, 2022). It is possible that swollen pericytes that have been observed in AD could also affect capillary lumen diameter (Szpak et al, 2007). Thus, both contractile pericytes without loss and pericyte loss can contribute to impaired blood flow in AD and disruption of optimal flow through the brain capillary network.

d. Reduced intramural periarterial drainage and glymphatic clearance. The expression of the subtype of pericytes involved in ECM regulation is reduced in AD (Yang et al, 2022). This will affect normal IPAD and glymphatic clearance by changing the architecture of the CVBM pathways and/or expression of AQP4 in astrocytic endfeet. Reduced expression of astrocytic AQP4 is associated with AD.

In an amyloid mouse model, pericyte deficiency caused an acceleration in brain Aβ accumulation and formation of CAA, along with impairment in removal of soluble Aβ42 and Aβ40 (Sagare et al, 2013). Indeed, CAA causes dysfunction and death of mural cells. The decrease in pericytes in AD could promote increased vascular and parenchymal Aβ buildup and has this been attributed to decreased Aβ clearance rather than increased Aβ production (Sagare et al, 2013).

e. Reduced elimination of materials from the brain. Pericytes have been suggested to have a phagocytic role in AD (Baloyannis and Baloyannis, 2012). However, degenerating pericytes fail to clear amyloid and Aβ accumulation is toxic to pericytes. Brain capillary pericytes from patients with AD have been shown to accumulate Aβ42 unlike control brain capillary pericytes (Ma et al, 2018, 2022, 2024). An increase in the CSF PDGFRβ levels has been observed to occur earlier than the decline of Aβ42 in CSF, suggesting that pericyte damage occurs before amyloid deposition in AD (Wang et al, 2022).

There is evidence to suggest that Aβ42 accumulation into mouse pericytes is due to an LRP1-dependent apolipoprotein E (apoE) isoform–specific mechanism (Ma et al, 2018) and/or an autophagy-mediated internalization. LRP1 expression in pericytes has been shown to increase on exposure to Aβ (Wilhelmus et al, 2007). Pericyte injury is also associated with accelerated Aβ-mediated tau hyperphosphorylation, tau pathology, and neurodegeneration (Wang et al, 2022).

f. Reduction in trophic secretions. Impaired PDGF-BB/PDGFRβ signaling in AD may cause a reduction in trophic secretions, which result in loss of pericyte—endothelial communication, reduced vascular integrity, and activation of local immune cells (Smyth et al, 2022).

g. Clinical importance. Pericyte loss leads to BBB breakdown, altered CBF, and impaired Aβ clearance, which are changes associated with AD pathogenesis (Fig. 9). The subtypes of pericytes that contribute most to the pathophysiologic characteristics of AD are likely to be contractile pericytes, particularly the ensheathing pericytes and those on first-order capillaries nearest the precapillary arterioles. This is because they can cause large changes in blood flow (Hartmann et al, 2022), they are thought to initiate the neurovascular coupling response (Cai et al, 2018), and they are associated with the most ischemia-sensitive region of the vasculature (Cai et al, 2018). Contractile pericytes could cause the capillaries to constrict during and after ischemia (Attwell et al, 2016), preventing vessel reperfusion and causing loss of BBB integrity and ultimately neuronal cell death. Attempts have already been made to restore pericyte function to prevent and treat AD (Wang et al, 2022). For example, aberrant pericyte contraction by Aβ was prevented by applying the vasodilator, C-type natriuretic peptide (Nortley et al, 2019). In addition, pericyte transplantation into the brain of an amyloid model mouse has already shown promise in reducing amyloid and related pathology (Tachibana et al, 2018). Pericytes are an interesting target to improve perfusion of ischemic tissues, and infusion of exogenous pericytes may be a novel regenerative therapy in the future (Cathery et al, 2018; Zhang et al, 2020). Improving the main energy (lactate) supply to pericytes may attenuate some pathophysiological changes. Nutritional therapy in mouse models of AD has been explored (Pawlosky et al, 2017; Dienel, 2019).

G. Changes to perivascular astrocytes

Throughout the development of AD, distinct ultrastructural changes in astrocytes have been identified in postmortem human brains (Hoshi et al, 2012; Sengillo et al, 2013; Zeppenfeld et al, 2017) and amyloid mouse models (Merlini et al, 2011; Yang et al, 2011). Histologically, AD is characterized by astrodegeneration and astrogliosis, which are dependent on both the region of the brain and the stage of the disease (Verkhratsky et al, 2010). In murine models, astrodegeneration and astrogliosis have been shown to precede the classical hallmarks, including neurofibrillatory tangles and amyloid plaques (Heneka et al, 2005; Olabarria et al, 2010).

Aβ can be removed from the brain by reactive astrocytes, which can be found close to amyloid plaques. ApoE, an extracellular chaperone protein, is produced primarily by astrocytes in the brain and has been implicated in the degradation of Aβ. ApoE may also compete with Aβ for binding to LRP1 and subsequent uptake in astrocytes, and this could impact on Aβ clearance (Verghese et al, 2013).

Decreased mRNA expression of the water channel AQP4 on astrocytic endfeet was observed in the temporal cortex of patients with AD, along with activation of the astrocyte marker glial fibrillary acidic protein correlating with the degree of CAA pathology (Wilcock et al, 2009). During aging and in AD, global immunoreactivity of AQP4 rose in the frontal cortex; however, localization of perivascular AQP4 was considerably diminished independent of age, in comparison with cognitively healthy controls. The reduced AQP4 perivascular localization was related to a high severity of AD pathology, as measured by Aβ accumulation and Braak staging (Zeppenfeld et al, 2017). Additionally, in amyloid mouse models, relocation of AQP4 from astrocytic endfeet membranes to nonendfeet membranes was discovered, probably as a result of astrocyte depolarization due to deposition of Aβ in the brain (Yang et al, 2011). Importantly, water transport through AQP4 of astroglia not only aids CSF influx to the brain parenchyma but also supports the removal of solutes though ISF drainage and so has a key role in glymphatic clearance and IPAD. A deficiency of AQP4 resulted in impaired clearance of Aβ40 and tau in mouse brain parenchyma (Iliff et al, 2012, 2014). Therefore, disruption of astrocyte endfeet during the advancement of AD could increase accumulation of Aβ by reducing cerebrovascular Aβ removal via the ISF drainage pathway.

In amyloid mouse models, astrocyte endfeet surrounding vascular Aβ deposits showed morphologic change such as swelling and retraction, along with reduced GLUT1 and lactate transporter expression (Merlini et al, 2011). These changes occur at an early stage of AD and are suggestive of NVU uncoupling. This suggests dysfunction of astrocytes can lead to cognitive impairments and early behavioral changes. Importantly, reactive astrocytes express BACE1, APPs, and γ-secretase at sufficient levels to generate Aβ and can significantly contribute to the amyloid load (Frost and Li, 2017).

H. Microglia involvement

Microglia play a pivotal role in the maintenance of brain homeostasis but lose homeostatic function during neurodegenerative disorders and become chronically inflammatory. For example, extracellular Aβ is internalized by microglia and then degraded via the autophagic/lysosomal system. This homeostatic function is reduced during AD progression. In fact, microglia cells start manufacturing amyloid fibrils of Aβ plaques in the neuropil (Wisniewski et al, 1992; Wegiel et al, 2000).

AD is characterized by a microglial-driven inflammatory response, during which there are alterations in the morphology, activation state, and distribution of microglia. The binding of microglia to the Aβ fibrils in senile plaques is mediated via a B-class scavenger receptor CD36, $\alpha_6\beta_1$-integrin, and the integrin-associated protein CD47 complex and initiates microglia activation into the reactive proinflammatory phenotype (Bamberger et al, 2003). The resulting disease-associated microglia (DAM) have a neurodegenerative phenotype and can be found clustered around amyloid plaques. This is thought to represent an attempt to clear the misfolded and aggregated Aβ peptides from the brain. The clustering of DAM around plaques is mediated by the triggering receptor expressed on myeloid cells (TREM)2—*APOE* pathway (Keren-Shaul et al, 2017; Krasemann et al, 2017) and receptor-interactive protein kinases (RIPK)1 (Ofengeim et al, 2017). Interestingly, phagocytosis of Aβ by microglia requires TREM2 (Akhter et al, 2021) and RIPK1 is involved in lysosomal degradation of Aβ. *TREM2* mutations on microglia are associated with an increased risk of dementia. The levels of RIPK1 in postmortem samples from individuals with late-onset AD are increased compared with those in control and positively correlate with the Braak staging. In addition, the ability of microglia to switch to a DAM phenotype appears essential to limit Aβ plaque—mediated tau pathogenesis in AD (Gratuze et al, 2021).

The neurodegenerative phenotype results in the increased release of proinflammatory cytokines and other key inflammatory mediators that can contribute to neuronal loss (Wang et al, 2015). A potent proinflammatory cytokine is interleukin-1β. Higher concentrations of interleukin-1β have been measured in the brain tissue of patients with AD (Cacabelos et al, 1994) and in microglia surrounding Aβ plaques (Hunter et al, 2012). Sustained elevations of interleukin-1β have been suggested to play a key role in AD pathogenesis (Wang et al, 2015).

Cholesterol-25-hydroxylase (CH25H) is an enzyme that catalyses the synthesis of 25-hydroxycholesterol (25-HC) from

cholesterol and has been identified as 1 of the upregulated genes featured in the DAM subcluster (Keren-Shaul et al, 2017; Krasemann et al, 2017). Another study has revealed that CH25H is upregulated in the AD brain and AD transgenic mouse brain and that 25-HC is produced by activated primary microglia (Wong et al, 2020). *APOE4*-expressing microglia express more 25-HC than *APOE2*-expressing or *APOE3*-expressing microglia. 25-HC amplifies microglial interleukin-1β production in an apoE isoform–dependent manner (Wong et al, 2020). These findings indicate that 25-HC may be involved in AD pathogenesis (Wong et al, 2020). *Cst7* is a gene that encodes an endosomal/lysosomal cathepsin inhibitor named cystatin F in microglia. CH25H and *Cst7* expression is regulated by RIPK1. Increased *Cst7* in AD microglia may cause dysfunction of the lysosomal amyloid degradation pathway.

Microglia of *APOE4* transgenic mice produced more NO compared with that of APOE3 transgenic mice (Colton et al, 2002). The mechanism for this isoform-specific difference in NO production is not known, and multiple sites in the NO production pathway may be affected. One of the affected components is known to be arginine transport, which is greater in microglia from *APOE4* transgenic mice compared with that in microglia from *APOE3* mice. This may be linked to cationic amino acid transport (CAT2B) transporter expression (Colton et al, 2002). Overall, the greater NO production in human *APOE4* carriers, who characteristically have high levels of oxidative/nitrosative stress, provides a mechanism that potentially explains the genetic association between *APOE4* and AD.

Microglia have recently been shown to be involved in modulation of CBF during neurovascular coupling (Császár et al, 2022). Altered microglia activity is observed in AD and could contribute to the impaired CBF and neurovascular coupling associated with the disease.

I. Changes to oligodendrocytes

Myelination-related genes in oligodendrocytes and oligodendrocytes precursor cells have been shown to be recurrently perturbed in AD. This suggests myelination has an important role in AD pathogenesis (Mathys et al, 2019).

J. Changes to neurons

Neuronal hyperexcitability has been detected in the early stages of AD and is thought to contribute to not only memory failure but also disease progression (Lam et al, 2020; Horvath et al, 2021). Seizures, which are a result of hyperexcitability, may be the first symptom of the disease and are reported in 10%–22% of patients with AD (Sarkis et al, 2016).

Glutamate is the major excitatory neurotransmitter in the CNS. Hyperexcitability in AD has been related to an impaired neuronal glutamate uptake/recycling mechanism and modulation of the glutamate receptor (NMDA) function by elevated Aβ concentrations (Wang and Reddy, 2017). Cellular toxicity being mediated by excessive Ca^{2+} entry into the postsynaptic neurone via NMDA receptors. Interestingly, cellular hyperexcitability can stimulate the release of tau into the ISF, enhancing transfer between neurones transneuronally and transsynaptically, and can also exacerbate tau pathology (Wu et al, 2016).

Severe neuronal loss is a key feature of AD affecting multiple brain regions. Cell death can be divided into 2 main types: apoptosis (programmed form of cell death) and necrosis (uncontrolled lysis of the cell). Necroptosis is a programmed form of necrosis and is triggered by RIPK1 and RIPK3 in AD (Caccamo et al, 2017).

Neuronal apoptosis is a rare event in human AD (Stadelmann et al, 1999). However, focal apoptosis (synaptosis) and necroptosis commonly occurs on neuronal processes, dendrites, or synapses (Mattson et al, 1998; Caccamo et al, 2017; Ofengeim et al, 2017). In fact, synaptic loss is an early feature in AD and the major correlate of cognitive impairment, much stronger than the presence of plaques or tangles (Terry et al, 1991). Presynaptic, but not postsynaptic, changes have been identified, supporting the possibility of presynaptic failure in AD (Haytural et al, 2021). Senile plaques contain dystrophic neurites (Grutzendler et al, 2007), Aβ is known to trigger progressive synapse loss correlating with cognitive impairment (Spires-Jones and Hyman, 2014). This synapse loss may be mediated by Aβ interacting directly with neuronal synaptic receptors such as α7 nicotine acetylcholine receptor α7nAChR (Wang et al, 2009), cellular prion protein (Laurén et al, 2009), or metabotropic glutamate receptor 5mGluR5 (Um et al, 2013). Others suggest that microglial cells activated by Aβ are responsible for destroying the synapses (Hong et al, 2016). There is also evidence to suggest that synaptic dysfunction associated with AD is due to dysregulation of P2X receptor–mediated neurotransmission (Chen et al, 2014; Sáez-Orellana et al, 2016, 2018; Francistiová et al, 2020). Loss of BBB integrity induces neuronal stress related to leaked blood-derived neurotoxic proteins such as hemosiderin followed by neuronal dysfunction and loss of synaptic proteins (Montagne et al, 2020).

Loss of the neuronal surface receptor, heparan sulphate proteoglycans, has been shown to reduce amyloid and amyloid deposition by enhancing Aβ clearance (Liu et al, 2016). In fact, these receptors colocalize with amyloid plaques. Altered amounts and distribution of heparan sulphate proteoglycans in AD brains may contribute to amyloid aggregation and plaque formation.

X. Conclusion

The central pathological hallmarks of AD comprise extracellular Aβ deposition, forming as senile plaques in the brain parenchyma and as CAA in vessels (Ellis et al, 1996; Shinohara et al, 2016). Additionally, AD is characterized by neurofibrillary tangles consisting of an accumulation of hyperphosphorylated tau protein inside neurons, normally accompanied by glial activation and neuronal loss (Serrano-Pozo et al, 2011; Spires-Jones and Hyman, 2014; Heneka et al, 2015). Although these both form the principal pathologic hallmarks in AD brains, NVU alterations, and cerebrovascular lesions often coexist. A growing body of literature suggests that AD pathology in preclinical models and human patients alters the structure and function of each component of the NVU and detrimentally affects each of the CNS pathways involved in the circulation of blood, CSF, and ISF, and the barrier phenotype of the brain capillary wall.

In this literature analysis review, we explored the roles of cerebral autoregulation, vasoactivity, and neurovascular coupling in the control of CBF and described the cellular and noncellular components of the NVU and how they contribute to CBF, IPAD, glymphatic drainage pathways, and the integrity of the BBB. We then describe how NVU function is compromised in AD. We conclude that 1 of the most important cell types in AD pathophysiology are the pericytes. Pericyte injury, degeneration and loss is associated with mild dementia and AD. Pericyte dysfunction can contribute to the existing hypotheses to explain AD (Table 6). However, because it plays a central role in the key characteristics of AD such as reduced clearance of neurotoxins, cerebral hypoperfusion, and loss of BBB integrity (Fig. 9), it may help to highlight their importance and consider a separate aberrant pericyte hypothesis.

To summarize, pericytes have a central location and are critically located in the BMs between the brain capillary wall and astrocyte

Table 6
The different hypotheses to explain Alzheimer disease and how pericytes are implicated

Hypothesis	Key issues	Pericyte involvement
Cholinergic hypothesis	Loss of cholinergic innervation. Reduced neurotransmitter (acetylcholine). Causes vascular dysfunction.	Express functional cholinergic receptors. Respond to acetylcholine. Involved in control of blood flow (myogenic tone and neurovascular coupling and capillary stalling). Involved in control of flow of ISF in IPAD drainage and CSF in glymphatic drainage pathways.
Amyloid cascade hypothesis	Imbalance of Aβ production and clearance.	Aβ elimination (via cellular accumulation) and Aβ clearance (via IPAD and glymphatic pathways). Regulate and maintain basement membranes, which allow the 2 different fluid pathways to coexist. Pathway sensitive to *APOE4* allele. Pericyte contraction and relaxation contribute to conformational change of basement membranes supporting ISF flow in IPAD pathways.
Oligomer hypothesis	Soluble Aβ oligomers more toxic than insoluble fibrillar counterparts. Large oligomers of Aβ fail to cross BBB and accumulate in ISF.	Aβ clearance via IPAD and glymphatic pathways. Regulate and maintain basement membranes, which allow the 2 different fluid pathways to coexist.
Vascular hypothesis	Loss of neurovascular integrity due to blood vessel damage.	Maintain BBB integrity. Control capillary blood flow. Endothelial cell (PDGFR-BB)/pericyte (PDGFRβ) signaling.
Inflammation	Proinflammatory disease causing pathological angiogenesis and hypervascularization.	- Respond to inflammatory mediators. - Activate local immune cells. - Cause pathological angiogenesis. - Endothelial cell (PDGFR-BB)/pericyte (PDGFRβ) signaling.

BBB, blood-brain barrier; CSF, cerebrospinal fluid; ISF, interstitial fluid; IPAD, intramural periarterial drainage; PGDFR, platelet-derived growth factor receptor.

endfeet. They form contacts with different neuronal cells (including microglia) and have region specific functions. Some pericytes express smooth muscle actin and are contractile. In fact, capillary pericytes and the smooth muscle cells of the larger vessels may represent phenotypic variants of a continuous population of mural cells. The contractile and stiffening ability of pericytes allows them to control and direct blood flow through the capillary network. Pericytes are responsible for the capillary myogenic tone and capillary vasomotion and are involved in the regulation of capillary blood flow by cerebral autoregulation, vasoactivity, and neurovascular coupling. Stiffening of pericyte processes contributes to capillary stalling without changes in vessel diameter. This not only is likely related to redirection of blood flow through specific capillaries but may also influence flow in the IPAD and glymphatic drainage pathways due to less flexible BMs. The main function of the pericyte is likely dependent on its location along the capillary vessel wall and, because they can communicate via TNT, could even be variable depending on local conditions. Pericytes respond to blood-borne signals (acting as a metabolic sentinel), endothelial cell signals (such as PDGF-BB), and neuronal signals (including acetylcholine) and can respond to stretch (acting as a mechanosensor). Pericytes influence BBB integrity in part by maintaining TJ expression. Additionally, they maintain BM proteins and astrocytic AQP4 expression and so have a role in fluid and neurotoxin clearance via the IPAD and glymphatic drainage pathways. Interestingly, the main genetic risk factor for AD is the *APOE*ε4* allele and pericytes directly remove Aβ through a pathway, which is apoE isoform sensitive. Pericytes are also implicated in tau hyperphosphorylation.

Hence, it follows that pericyte degeneration and loss is associated with impaired CBF and altered BBB integrity and may accelerate Aβ and tau accumulation in the brain and CAA formation around vessels. A central and early component in the pathophysiology of AD may therefore be the aberrant pericyte, and there is evidence to suggest that this is related to deficient PDGF-BB—PDGFRβ signaling. With regard to clinical applications, not only pericytes are an important therapeutic target, but also infusion of exogenous pericytes could be the regenerative therapy of the future.

Abbreviations

Aβ, amyloid β; ABC, ATP-binding cassette; AD, Alzheimer disease; AJ, adherens junction; *APOE*, apolipoprotein E gene; apoE isoforms, apolipoprotein E isoforms; APP, amyloid precursor protein; AQP, aquaporin; BACE, β-site amyloid precursor protein—cleaving enzyme; BBB, blood-brain barrier; BCSFB, blood-cerebrospinal fluid barrier; BCEC, brain capillary endothelial cell; BCRP, breast cancer resistance protein; BM, basement membrane; CAA, cerebral amyloid angiopathy; CBF, cerebral blood flow; CD, scavenger receptor cluster; CH25H, cholesterol-25-hydroxylase; CNS, central nervous system; CSF, cerebrospinal fluid; CVBM, cerebrovascular basement membrane; DAM, disease-associated microglia; ECM, extracellular matrix; ERK, extracellular signal—regulated kinase; HC, hydroxycholesterol; IPAD, intramural periarterial drainage; ISF, interstitial fluid; JAM, junctional adhesion molecule; K_{ir}, channels, inwardly rectifying potassium channels; LRP, low density lipoprotein receptor—related protein; MATE, multidrug and toxin extrusion protein; MMP, matrix metalloproteinase; NMDA, *N*-methyl D-aspartate; NO, nitric oxide; NVU, neurovascular unit; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PMAT, plasma membrane monoamine transporter; P-gp, P-glycoprotein; RAGE, receptor for advanced glycosylation end products; RIPK, receptor-interactive protein kinase; sA, soluble amyloid; SLC, solute carrier; TNT, tunneling nanotubes; TJ, tight junction; TREM, triggering receptor expressed on myeloid cells; VE, vascular endothelial; ZO, zonula occludens.

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Conflict of interest

The authors declare no conflicts of interest.

Data availability

The authors declare that all data supporting the findings of this study are contained within the paper.

Authorship contributions

Wrote or contributed to the writing of the manuscript: Thomas, Divecha, Rampes, Tromp, Boyanova, Fleckney, Fidanboylu.

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