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Endothelial dysfunction in neurodegenerative disease: Is endothelial inflammation an overlooked druggable target?

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ABSTRACT

Neurological diseases with a neurodegenerative component have been associated with alterations in the cerebrovasculature. At the anatomical level, these are centred around changes in cerebral blood flow and vessel organisation. At the molecular level, there is extensive expression of cellular adhesion molecules and increased release of pro-inflammatory mediators. Together, these has been found to negatively impact blood-brain barrier integrity. Systemic inflammation has been found to accelerate and exacerbate endothelial dysfunction, neuroinflammation and degeneration. Here, we review the role of cerebrovasculature dysfunction in neurodegenerative disease and discuss the potential contribution of intermittent pro-inflammatory systemic disease in causing endothelial pathology, highlighting a possible mechanism that may allow broad-spectrum therapeutic targeting in the future.

1. Neurodegeneration and the cerebrovasculature

The prevalence of neurological disease with a neurodegenerative component is rapidly increasing due to the aging global population (Wyss-Coray, 2016). This collection of primarily sporadic diseases affecting the central nervous system (CNS) are often characterised by neurodegeneration of neuronal populations or axonal processes, across a lifespan (Heemels, 2016). The most common examples include Alzheimer's disease (AD), Parkinson's disease (PD) and Multiple Sclerosis (MS) (DeTure and Dickson, 2019; Simon et al., 2020; Mey et al., 2023). In addition, secondary neurodegeneration can arise following a large vascular injury such stroke (Ong, 2022). Neurological diseases with a substantial degenerative component (from here on termed neurodegenerative diseases, NDDs), are diverse in presentation and pathology, causing an array of life altering symptoms including memory impairment, cognitive deficits, loss of motor function and respiratory complications (Erkkinen et al., 2018). Treatment options for these conditions are primarily limited to symptom management (Wareham et al., 2022). New therapies directly targeting disease processes have recently been identified for AD, though it remains unclear how efficacious these will be in clinical practice given limitations of diagnostic capacity (Larkin, 2023; van Dyck et al., 2023). There is, therefore, a pressing need for novel therapeutic approaches.

Alterations within the cerebral microvasculature may contribute to neurodegenerative disorders *via* several processes (reviewed by Wareham et al., 2022), and have been suggested to play a critical role in the aetiology of these conditions (Drouin-Ouellet et al., 2015; Hatate et al., 2016). More work is required to definitively support this link, which is partly strengthened by the increasing evidence that vascular dysfunction is an early part of disease pathophysiology (Kelleher and Soiza, 2013; Apátiga-Pérez et al., 2022; Yuan et al., 2023). If true, a renewed focus on the cerebrovascular contribution to NDDs may add to our understanding of disease aetiology and treatment options. As the interface between the brain and the rest of the body, the endothelial cells (ECs) that make up the cerebrovasculature are exposed to a plethora of minor (and major) insults across a lifetime that may alter their function and disrupt the neuronal cells they protect. Equally, the ECs of the blood-brain barrier (BBB), unlike the neuronal cells beyond this barrier, are a highly druggable target and therefore may represent a future theragnostic target, exploitable both as a diagnostic biomarker and for a disease modifying treatment.

In this broad review, we discuss the role of ECs in regulating cerebrovascular function, summarise the evidence for cerebrovascular dysfunction in NDDs and suggest mechanisms by which ECs may contribute to this. We also make a link between systemic disease and endothelial injury, a mechanism through which repeated peripheral inflammation may contribute to NDD severity and progression that could be exploited in the future to diagnose and treat patients.

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2. The endothelium, blood-brain barrier, and neurovascular unit

The endothelium, a monolayer of ECs, lines the luminal surface of all blood vessels within the body, forming the critical interface between the blood and the tissue, and orchestrating vascular function. ECs have a heterogeneity of structure and function which has been described at the morphological, functional, and genomic levels (Aird, 2012; Jambusaria et al., 2020). Signals from within the tissue microenvironment, such as those generated through cell-cell interactions, together with release of growth factors, can influence tissue-specific adaptations of ECs (Potente and Mäkinen, 2017), enabling them to perform various physiological roles in tissues including the modulation of vascular tone, platelet aggregation, angiogenesis, leukocyte trafficking and other responses to inflammation (Ait-Oufella et al., 2010; Sturtzel, 2017).

In terms of their contribution to vascular tone, and therefore regional blood flow, healthy ECs produce multiple vasoactive mediators that act on surrounding contractile cells to either constrict or dilate the blood vessels (see Sandoo et al., 2010 for a review on the molecular regulation of these processes). Many of these actions typically occur in arterioles and post-capillary venules through modulation of smooth muscle cell function, regulating blood flow at a mesoscale, and are common across vascular beds. In the cerebrovasculature, there is additional regulation of blood flow *via* neurovascular coupling at the level of the capillary which is utilised to regulate and maintain regional cerebral blood flow (CBF) in response to local activity (Otsu et al., 2015; Iadecola, 2017; Ahmad et al., 2020; Stackhouse and Mishra, 2021).

Within the neurovascular unit (NVU; Fig. 1), the ECs are specialised compared to those in most peripheral vascular beds and form the BBB, the regulated interface between the peripheral circulation and the CNS (Macdonald et al., 2010; Koizumi et al., 2016). ECs exhibit continuous junctions between adjacent cells, sealed by tight junction complexes, which are important for creating a functional anatomical barrier into the brain (Liu et al., 2012). There is a substantial body of work on the nature of these junctions (for a recent review see Lochhead et al., 2020), with the presence and structural organisation of claudin and occludin proteins considered particularly essential for junctional integrity. ECs within the CNS also demonstrate low rates of vesicle transport, due to the inhibition of caveolae-mediated transcytosis regularly utilised in the periphery (Andreone et al., 2017) and have a high presence of efflux transporters which restrict access of specific lipophilic molecules to the brain (Qosa et al., 2015). As a counter to this restrictive barrier, brain ECs express multiple transporters to support the active movement of specific solutes in and out of the brain and consequently have a high mitochondrial density (Kadry et al., 2020). Together, these specialisations allow the ECs of the BBB to protect the CNS from fluctuations in the systemic environment (Lansdell et al., 2022), and disruption in these mechanisms are hallmarks of neurodegenerative conditions.

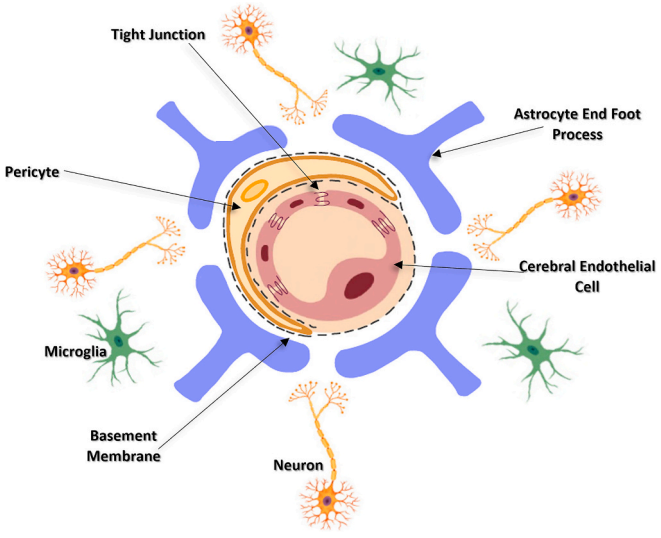

Fig. 1. The Neurovascular Unit.
Schematic illustration of the neurovascular unit (NVU) at the microvascular level. The NVU is comprised of endothelial cells, the basal lamina, pericytes, astrocyte endfeet, neurones and microglia. These different components work together to maintain homeostasis of the brain microenvironment (Adapted from Dubois et al., 2014).

While there are many factors that may lead, at a cellular level, to altered vascular function or disruption of the BBB, this review focuses on inflammation as a process with important commonality to systemic disease and NDDs. Many systemic conditions that are associated with vascular injury in the periphery, such as diabetes and high serum cholesterol, result in increased circulating inflammatory mediators that will inevitably interact with the cerebral ECs (Que et al., 2018; Sheikh et al., 2022). When sufficiently severe, systemic inflammation results in acute, transient inflammation of the cerebral endothelium (Verma et al., 2006) and altered function of the cerebrovasculature and the BBB (Sheikh et al., 2022; Banks et al., 2015). Normal aging and neurodegeneration also cause inflammation of systemic and cerebrovascular ECs (see Finger et al., 2022), and acute systemic inflammation can reactivate dormant neuroinflammatory lesions (Serres et al., 2009) and affect amyloid clearance from the brain (Erickson et al., 2012), suggesting a complex interplay between (systemic) inflammation and neurological injury.

The vascular endothelium is a key modulator of the acute inflammatory response, promoted by abnormal physiological stimuli, damage, or infection (Leick et al., 2014). A recent analysis of peripheral and cerebral endothelial inflammatory responses suggests that a subset of ECs may even have a specific immunomodulatory role (Amersfoort et al., 2022), possibly contributing to immune surveillance as well as tissue pathology. During acute inflammation, there is increased release of pro-inflammatory cytokines and upregulation of cellular adhesion molecule (CAM) expression. These processes occur in all vascular beds, the underlying molecular mechanisms at the BBB have been well described (Dietrich, 2002; Müller, 2019; Wimmer et al., 2019). Numerous transcriptomics studies in rodent models of acute systemic inflammation have added to our understanding of the early (Kodali et al., 2020; Struck et al., 2024) and later stages (Munji et al., 2019) of endothelial inflammatory signalling. These studies show that at baseline, genes associated with chemokine signalling, antigen presentation and leukocyte diapedesis (*e.g.* ICAM-1, VCAM-1, CCL2) are more highly expressed in peripheral vessels compared to cerebral ECs (Munji et al., 2019). Cerebral ECs up-regulate pathways associated with nuclear factor- kappa B (NF-κB) signalling within 15 min of a peripheral inflammatory stimulus followed, at later time points, by genes governing cytokine and chemokine production and leukocyte migration (Kodali et al., 2020), similar to changes observed in peripherally derived ECs (Struck et al., 2024). Overall, current evidence implied that cerebral ECs appear adopt a phenotype comparable to that of peripheral ECs following systemic challenge, with down regulation of BBB-enriched genes and increases in inflammatory genes (Munji et al., 2019). It should be noted that the majority of studies in models of vascular inflammation utilise high concentrations of lipopolysaccharide (LPS) or TNF. As a result, the timing, magnitude and composition of the endothelial inflammatory response would likely vary in more disease specific injury models or in patient responses.

Generally, the acute inflammatory response is confined and beneficial, providing protection from pathogenic stimuli, particularly in the periphery. However, if inefficient resolution occurs, detrimental chronic inflammation can develop. At the microvascular level, endothelial dysfunction is evident, characterised by a prolonged increased in the release of pro-inflammatory cytokines, impaired production of vasodilators, increased generation of vasoconstrictor molecules as well as upregulated expression of CAMs (Steyers and Miller Jr, 2014; Bennett

et al., 2018). In the periphery these changes have been well-described as contributing to increased vasoconstriction and to enhanced leukocyte migration, capillary permeability, and platelet aggregation (Pober and Sessa, 2007). Combined, these altered functions are responsible for the extensive damage exhibited in chronic inflammatory diseases in the periphery such as atherosclerosis and rheumatoid arthritis (Murdaca et al., 2012; Nikpour et al., 2013; Steyers and Miller Jr, 2014).

Leukocyte transmigration, following increases in cytokine signalling and upregulation of CAMs, is recognised to occur in the brain and contributes to neurological disease, particularly in MS and stroke (Juurlink, 1998; Schmitt et al., 2012; Sienel et al., 2022; Fig. 2). While these pathways are not as active in physiological or low-inflammatory states as in the periphery, leading to the original hypothesis of immune-privilege in the brain, they can be substantially upregulated in the brain under pathological conditions (recently reviewed in detail in Ludewig et al., 2019). The signalling pathways regulating transmigration, and the downstream consequences of this for cerebrovascular and parenchymal damage have been extensively reviewed elsewhere (Man et al., 2007; Larochelle et al., 2011; Takeshita and Ransohoff, 2012).

The structural and functional alterations in the cerebral endothelium have been shown to lead to increased inflammation and oxidative stress, which together severely impair neurovascular function (Lehner et al., 2011; Liu et al., 2012). Dysfunction of the BBB is characterised by the loss of tight junction integrity, increased permeability, upregulated transcytosis and increased CAM expression leading to an influx of inflammatory mediators into the brain (Daneman, 2012; Koizumi et al., 2016).

The data from patients with neurodegenerative disease, as well as animal and cell models of these diseases is currently fragmentary (discussed in detail below). In order to reduce endothelial dysfunction in neurodegenerative diseases, it is important to understand and determine how and when processes of endothelial dysfunction occur, whether the common inflammatory pathways are activated equally in each condition, and if early-life injuries or systemic disease may alter the timing or magnitude of the cerebral endothelial response. This knowledge can be used to identify early markers of the disease process and to investigate vascular targeted therapies as disease modifying agents. Therapeutic agents are already available that could be used to counter the detrimental effects of a range of inflammatory mediators *e.g.* TNF (Chou et al., 2016) and IFNGR1 (Yetkİn and Gültekin, 2020), if stronger evidence for their involvement in the disease process merges.

3. Evidence for and against altered cerebral blood flow in cerebrovascular and neurodegenerative diseases

In the absence of accessible and effective methods for measuring CBF, many studies investigating vascular dysfunction in neurodegenerative disease have focused on measuring peripheral endothelial function using flow-mediated dilation (FMD), a non-invasive ultrasonography technique that measures endothelium-dependent relaxation of the brachial artery following reactive hyperemia. The difference in diameter in the brachial artery compared to the basal diameter is considered to be the FMD, with an FMD value <7.8% being the cut-off for the diagnosis of endothelial dysfunction (Korkmaz and Onalan, 2008; Mućka et al., 2022). In PD, FMD has been found to be significantly lower in patients

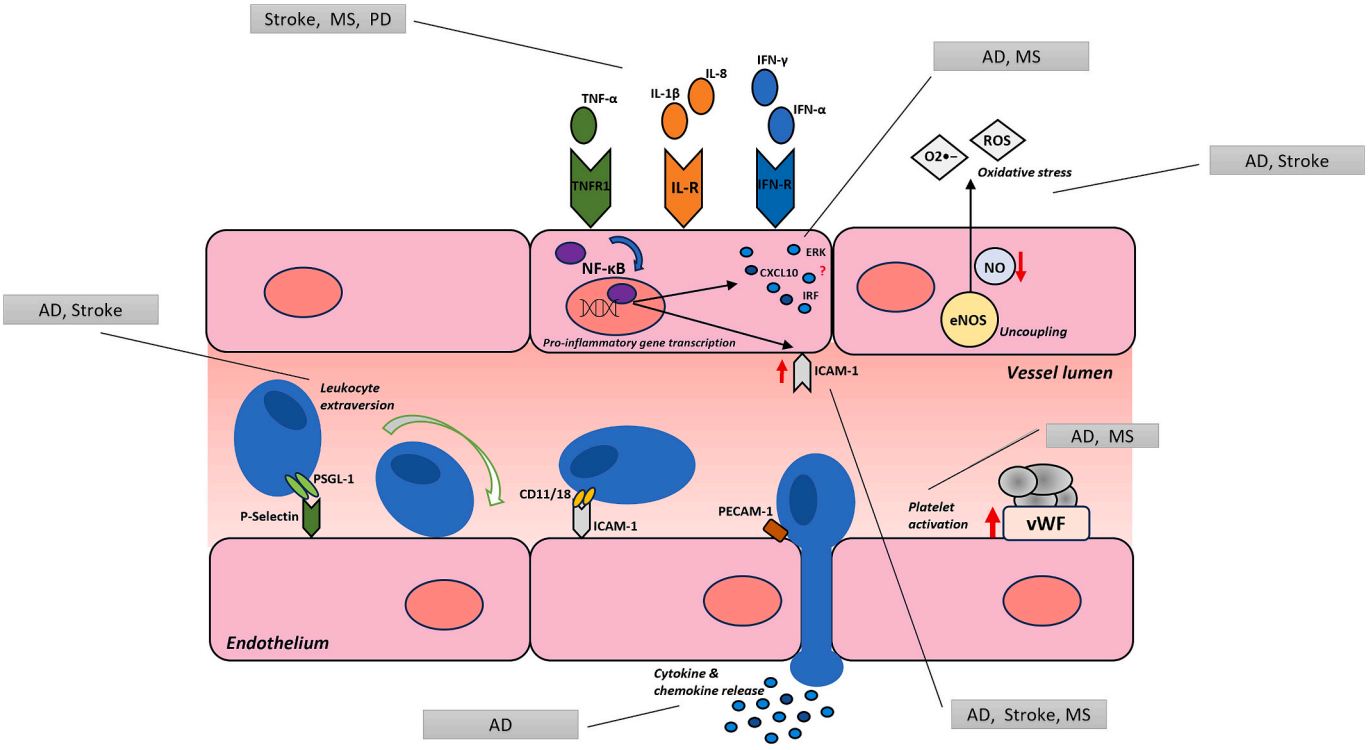

Fig. 2. Mechanisms of endothelial inflammation in NDDs.
Multiple mechanisms of endothelial inflammation have been confirmed to be present in different NDDs. Pro-inflammatory cytokines (*e.g.* TNF, IL-6) bind to their corresponding receptors on the endothelial cell surface (Aref et al., 2020; Magliozzi et al., 2021), shown to lead to the activation and translocation of NF-κB to the nucleus. As a consequence, this initiates transcription of genes hypothesised to be involved in the downstream functional changes arising from endothelial cell inflammation (Srinivasan et al., 2017; Zhou et al., 2023). The activation of the NF-κB pathway can also lead to the upregulation in the expression of cellular adhesion molecules (CAMs) such as ICAM-1 (Frohman et al., 1991; Lindsberg et al., 1996). Upregulation of CAMs facilitates the transmigration of leukocytes into the tissues (Brock et al., 2015; Quan et al., 2019), alongside the release of pro-inflammatory mediators (Grammas and Ovase, 2001). Additionally, inflammatory expression of von-Willibrand factor (vWF) mediates platelet activation and aggregation within the vessel (Mari et al., 1996; Sevush et al., 1998; Morel et al., 2015). The release of reactive oxygen species (ROS) occurs due to the uncoupling of endothelial nitric oxide synthase (eNOS), consequently leading to a decrease in nitric oxide (NO) and a state of oxidative stress (Szolnoki et al., 2005; Tan et al., 2015).

compared to age matched control subjects (7.1% compared to 8.1% respectively) (Yoon et al., 2015). A small case-control study found AD patients free of vascular risk factors to have lower FMD values than those of control patients (3.45% compared to 8.41%, respectively) (Dede et al., 2007). Disease severity, in particular lower scoring on cognitive tests, has also been reported to correlate with the decreased FMD values found in AD patients (Dede et al., 2007; Tachibana et al., 2016). Overall, these findings suggest that peripheral endothelial dysfunction, assessed by FMD, is associated with multiple risk factors of AD.

With respect to the brain, the obvious limitation of FMD is that it is a measurement of peripheral endothelial dysfunction, and does not directly indicate CBF or indeed other regional changes in brain blood flow associated with disease states. Technological advances in arterial spin labelling magnetic resonance imaging (ASL-MRI) have allowed the detection of a posterior hypoperfusion condition in PD patients within the parietooccipital cortex and posterior cingulate cortex (Kamagata et al., 2011; Arslan et al., 2020). A broader pattern of altered blood flow has been reported by others (Wei et al., 2016), although not specifically within the substantia nigra. These studies have shown that regional hypoperfusion occurs in cognitively normal PD patients, and the degree of hypoperfusion is strongly correlated with mild cognitive impairment or dementia in addition to the PD diagnosis (Kamagata et al., 2011; Arslan et al., 2020).

Regional changes in CBF have also been measured using ASL-MRI in AD patients, with a recent meta-analysis indicating that reductions in blood-flow occur with normal aging and are exacerbated in AD, though with high variability in the affected brain regions reported between studies (Graff et al., 2023; Swinford et al., 2023). Altered regional CBF has also been demonstrated using neuroimaging in patients following stroke (Nakaoku et al., 2018), or who have been diagnosed with MS (Zhang et al., 2018). However, it is difficult to make definitive statements as to the location and magnitude of these changes given the variation in presentation and evolution of these conditions compared to those studies conducted in PD and AD patients.

In AD, there has been a greater depth of research into the nature of vascular disruption leading to altered regional CBF (reviewed by Korte et al., 2020). There is clear evidence that damage to the capillaries can occur as a secondary response to amyloid deposition in AD patients (Kimura et al., 1991), and cerebral amyloid angiopathy (CAA), the deposition of amyloid beta (Aβ) plaques on the walls of both brain arterioles and capillaries, is present in 90% of AD cases (Grinberg and Thal, 2010). This Aβ deposition can directly reduce CBF in both *ex vivo* and *in vivo* AD models (Suo et al., 1998; Dietrich et al., 2010) by evoking vasoconstriction through increased reactive oxygen species (ROS) production by the cerebral arteries (Niwa et al., 2001). In turn, this reduction in CBF increases the production of Aβ *in vivo*, forming a damaging feedback loop (Sun et al., 2006; Zhang et al., 2007). At the capillary level, Aβ acts at pericyte-dense locations to cause constriction (in both human AD and mouse models) *via* a mechanism involving NOX-4-dependent reactive oxygen species (ROS) production and downstream release of endothelin-1 (Nortley et al., 2019). The molecular and cellular mechanisms responsible for the reduced CBF in other NDDs remain to be determined.

4. Evidence for structural reorganisation of the cerebrovasculature and blood-brain barrier in neurodegenerative disorders

Altered CBF in a pathological scenario may result from changes in vascular wall structure, affecting the compliance to modulatory signals from the endothelium. It is likely that these pathological alterations in tissue structure, along with associated modifications in local endothelial signalling, contribute to the measured changes in regional CBF discussed above.

The clearest data in this area come from investigations into the initiating factors of stroke. In addition to vascular disruption occurring in the brain after stroke, there is substantial evidence of systemic vascular dysfunction contributing to the risk of stroke. Specifically, atherosclerotic vascular changes (Libby et al., 2019), are a well-established risk factor for (non-cardioembolic) ischemic stroke, with ~70% of patients showing a substantial aortic plaque burden, and ~20% having severe internal carotid artery stenosis (Serena et al., 2015). The combination of high body mass and diabetes (both risk factors for atherosclerosis), as well as the presence of symptomatic peripheral artery disease and intracranial artery stenosis, have all been identified as common risk factors for further stroke events occurring within a 12-month period (Serena et al., 2015).

While atherosclerosis is a systemic condition, and in part contributes to stroke risk by increasing the chance of a thrombotic event, the data overall suggest that there may also be early changes occurring within the cerebral vascular beds that increase the risk of an ischemic occlusion. This idea is supported by data from a meta-analysis that followed stroke free individuals over a 5–12 year period, assessing the retinal vessels as biomarkers for stroke risk. Altered vessel calibre, specifically increased venular calibre was shown to be an independent risk factor for stroke (McGeechan et al., 2009). As many of the factors that contribute to atherosclerosis also affect local vessel function (*e.g.*, inflammatory cytokines, increased ROS, enhanced leukocyte and platelet adhesion, reduced nitric oxide production; Roquer et al., 2009), it is possible that while atherosclerotic burden can increase the risk of stroke, much of this risk arises directly from altered reactivity within the cerebrovascular beds. Current preventative treatments for cerebral small vessel disease and their sequalae are largely focused on reducing risk factors, such as clot formation and reducing cholesterol (Smith and Markus, 2020). The assessment of retinal vessel calibre provides proof-of-principle that assessing vascular structure can provide insights into disease risk and could lead to identification of more focused biomarkers related to vascular function, probably as part of a multi-tiered screening for early diagnosis and preventative therapy. In line with this aim, trials of allopurinol and cilostazol are currently being performed in patients with cerebral small vessel disease to reduce endothelial inflammation and increase the capacity to regulate vascular tone (reviewed in Smith and Markus, 2020). A similar change in therapeutic approach may be useful in AD, where research utilising vessel size imaging to quantify vessel structure in an AD mouse model found decreased density and abnormal morphological changes in the microvessels at both early and late stages of disease (Xu et al., 2020).

Substantial disruption of BBB integrity is evident in most neurodegenerative disorders and commonly results in increased leakage of serum proteins into the brain. In PD patients, post-mortem analysis or *in vivo* MRI have specifically shown altered BBB permeability in the striatum and substantial nigra (Gray and Woulfe, 2015; Al-Bachari et al., 2020). A recent study has reported increased BBB leakage in a PD mouse model with global overexpression of human alpha-synuclein (α-syn), a key protein involved in PD pathology (Gómez-Benito et al., 2020; Elabi et al., 2021). This was accompanied by localisation of α-syn within ECs, inappropriate pericyte activation, and dynamic alterations in vessel density starting relatively early in the aging process (Elabi et al., 2021). Interestingly, the authors showed increased vessel density at 8-months and decreased density at 13-months, potentially explained by an initial increase in compensatory angiogenesis in the early stages of disease followed by vascular regression in the later stages (Elabi et al., 2021). These observations clearly place alterations in the cerebrovasculature as an early part of PD disease pathophysiology.

The use of advanced neuroimaging in both human AD patients and AD animal models has identified breakdown of the BBB in early disease states (van de Haar et al., 2016; Alkhalifa et al., 2023). Deposition of Aβ plaques has been directly associated with an increase in BBB permeability (Roher et al., 2003; Carrano et al., 2011; Zenaro et al., 2017). Similarly, in a rat BBB *in vitro* model, treatment with human tau increased endothelial permeability (Kovac et al., 2009). Decreases in both claudin-5 and occludin expression have been found in post-mortem

analyses of AD patient brains and are associated with increased permeability of the BBB (Yamazaki et al., 2019). In addition, a single intravenous injection of claudin-5 produced acute improvements in both learning and memory in the APP/PS1 mouse when assessed 1–4 days post treatment (Zhu et al., 2022).

BBB disruption has been recognised as a key component of MS pathophysiology (Claudio et al., 1995; Werring et al., 2000; Vos et al., 2005a, 2005b; Cramer et al., 2015), typically considered a consequence of the high level of leukocyte diapedeses. Investigations using gadolinium (Gd)-MRI to assess MS lesions recognised intense focal disruptions within the BBB, primarily centred around sites of extensive neuroinflammation (Grossman et al., 1986; Miller et al., 1998). A study using dynamic-contrast MRI revealed a correlation between BBB disruption and the appearance of MS lesions with disease relapse (Cramer et al., 2013). Gd-enhancing MRI techniques have also documented BBB breakdown in the normal white matter as well as white matter lesions in MS patients (Lund et al., 2013; Choi et al., 2021), indicating a broader cerebrovascular dysfunction in this condition than the acute inflammatory lesions might suggest. Consistent with these MRI studies, post-mortem histology has shown a decrease in the expression of the tight junction proteins occludin and ZO-1 in the microvessels within active MS lesions. Abnormalities in the structure of these tight junctions were identified in ~40% of the vessels, including in white matter with a normal appearance (Plumb et al., 2002; Kirk et al., 2003). Tight junction abnormalities are associated with an increased leak of serum fibrinogen within MS lesions (Vos et al., 2005a, 2005b; McQuaid et al., 2009). It has been suggested that increased entry of mediators such as fibrinogen into the CNS, resulting from continuously increased BBB permeability, can lead to the progressive demyelination characterising MS pathology, and exacerbates neuroinflammation (Kirk et al., 2003). While there is clear evidence of loss of tight junction proteins in MS, a longitudinal case-control study of tight junction proteins in the blood of MS patients showed increased circulating levels of these proteins, but there was no clear correlation with MS disease severity (Olsson et al., 2021), limiting their potential use as diagnostic biomarkers in this condition. There is, therefore, need of further work in this, as in other neurodegenerative conditions, to identify biomarkers of disease that can facilitate diagnosis and monitoring of disease progression and treatment. A more detailed understanding of vascular injury may provide candidates for these new biomarkers.

5. Evidence for inflammatory injury as a driver of endothelial cell dysfunction in neurodegenerative disorders

In common with BBB breakdown, neuroinflammation has been identified in the cerebrovasculature in all the NDD conditions discussed, though the body of evidence is greater in some than others. In MS, increased expression of CAMs and the associated leukocyte diapedesis are well recognised. This is due in part to the presence of high levels of ICAM-1 and VCAM-1 in chronically active brain lesions (Cannella and Raine, 1995; Kuenz et al., 2005). The role of ICAM-1 and VCAM-1 upregulation has been investigated in the commonly used experimental autoimmune encephalomyelitis (EAE) *in vivo* model of MS, confirming that these molecules assist in the penetration of leukocytes through the BBB and exacerbate neuroinflammation (Doerck et al., 2010). Moreover, a meta-analysis of MS genome-wide association studies identified key CAM biological pathways to be highly enriched and linked to MS susceptibility (Damotte et al., 2014). In contrast, work in this area in PD patients is limited to one recent small, and therefore underpowered, study (Yu et al., 2020). The study found abnormally high expression of vascular inflammatory markers, including VCAM-1, in the peripheral blood. This correlated with disease severity and with specific regional brain atrophy (Yu et al., 2020). In AD, there has been substantial assessment of CAMs (ICAM-1 and VCAM-1) in the plasma and CSF (reviewed by Custodia et al., 2023), that appear to correlate with rapid progression of cognitive impairment (Drake et al., 2021). Microvessels isolated from the brains of AD patients also show high levels of pro-inflammatory cytokines (Grammas & Ovase), and histological studies in tissue from AD patients have reported elevated ICAM-1 (reviewed in Grammas, 2011).

While vascular inflammation is evident in these conditions, the onset and extent of inflammation in the aetiology of neurodegeneration remains a point of discussion. While many of the findings described above reflect the response to cerebral injury and degeneration, there is also evidence of vascular inflammation indirectly contributing to the disease process and driving neuronal damage. Data in support of this are accumulating from studies on AD and stroke. In particular, cerebral ECs isolated from AD patients have been reported to release toxic factors, causing neuronal injury (Kelleher and Soiza, 2013), although the identity of these factors is yet to be confirmed. *In vitro* studies using microvessels from AD patients showed that vascular-mediated neuronal death occurred when naïve neurons were cultured directly with AD microvessels, or with their conditioned media (Grammas, 2000). Additional *in vitro* work investigating pro-inflammatory cytokine-mediated activation of cerebral ECs has also demonstrated the release of neuron-toxic factors from ECs, leading to death of cholinergic neurons. These studies indicate a role for the cerebral vasculature in contributing to the degeneration of cholinergic neurons observed in AD (Moser et al., 2006). These *in vitro* approaches suggest a direct role for the endothelium in the neuronal death that underpins NDD aetiology. There is research in animal models that have investigated the effects of systemic inflammation on the cerebral vasculature, as discussed below (Marottoli et al., 2017), or the contribution of inflammation to neurodegeneration (Kitazawa et al., 2005; Catorce and Gevorkian, 2016; Huang et al., 2024). However, further research into the involvement of early life vascular inflammation and its link to neurodegenerative disease in later life is now warranted.

6. Does altering endothelial cell or vascular function affect neurodegenerative disease outcomes?

To date, improvements in vascular function in NDDs have been assessed following treatment of the non-vascular related elements of the disease process, thereby reducing the secondary vascular injury that occurs following neurodegeneration. For instance, a study using a mouse model of AD showed preservation of BBB integrity when tau is suppressed (Blair et al., 2015). Similarly, in an *in vitro* study using human brain ECs Aβ was shown to influence the integrity of the BBB primarily through the disruption of tight junction proteins such as claudin-5 (Griffin et al., 2016). Current therapies targeting the Aβ-induced neuropathology such as Lecanemab (an immunotherapy, targeting Aβ to slow AD progression; van Dyck et al., 2023) may therefore be effective both through reducing primary disease and limiting exacerbation that would otherwise follow amyloid-induced alterations in BBB integrity. A question remaining, is whether therapies aimed at directly reducing BBB breakdown or other early stages of endothelial dysfunction, could improve vascular function and prevent subsequent neurodegeneration.

In MS and stroke, where the role of the vasculature in the early stages of disease is clearer, there have also been some direct clinical and pre-clinical trials of drugs aimed at reducing endothelial inflammation and thereby limiting neurodegeneration. Major targets of these approaches are the CAMs and this has already been shown to be therapeutically effective in MS, where Natalizumab, a monoclonal antibody which blocks interaction of VCAM-1 with its ligand very-late antigen-4 (VLA-4), is one of the main therapeutic agents used (Brandstadter and Katz, 2017). This therapy reduces disease progression, as well as the number of relapses and development of brain lesions in relapsing remitting MS (Polman et al., 2006; Rudick et al., 2006; Nicholas et al., 2022). However, it is not authorised for use against secondary-progressive MS due to lack of efficacy (Kapoor et al., 2018), implying a primary function in preventing neurological damage following initial neuroinflammatory events.

Post-mortem tissue from ischemic stroke patients (collected between

15 h and 18 days post-stroke), exhibits a substantial increase in cerebral endothelial ICAM-1 expression (Lindsberg et al., 1996). The role of ICAM-1 in neurodegeneration following stroke is supported by a rodent study using a middle cerebral artery occlusion (MCAO) model of stroke, where treatment with an anti-ICAM-1 antibody significantly reduced brain damage and the presence of leukocytes within lesions (Zhang et al., 1994). However, it should be noted that ICAM-1 is also expressed by some immune cells (macrophages and lymphocytes) so ICAM-1 inhibition, unless targeted to ECs alone, will also affect these cell types. Elevated ICAM-1 concentrations have also been reported in the sera of acute ischemic stroke patients and associate with poor prognosis (Wang et al., 2021). Despite these data, reducing CAM activation is not universally protective. A clinical trial evaluating the treatment of ischemic stroke patients with Enimomab, an anti-ICAM-1 therapy, showed that treatment led to more adverse events and a higher chance of death (Enlimomab Acute Stroke Trial, 2001). This variance is likely due, at least in part, to the limitations of the real-world clinical environment, where treatment is not given immediately after stroke (delayed until as late as 6 h post stroke onset in this example); earlier initiation of treatment may have led to a different outcome. Delayed treatment of mice with anti-VCAM-1 in a model of ischemia-induced vascular dementia found significant reductions in neuroinflammation and cognitive decline, although early intervention with anti-VCAM-1 did not produce the same effects (Zera et al., 2021). Together, these data indicate a time-dependence in the use of CAMs as a therapeutic target. Furthermore, no protection against ischemic stroke, nor a difference in accumulation of inflammatory cells was found when the MCAO model was applied to transgenic ICAM-1^{null} deficient mice (Enzmann et al., 2018), suggesting the existence of a more complex relationship between adhesion molecules, leukocyte infiltration and injury severity than is currently recognised.

7. Can systemic disease push endothelial cells to dysfunction and affect the incidence, severity or onset of neurodegenerative disorders?

The association between chronic systemic inflammation and vascular disease is one that has been well documented (Petek et al., 2022). Findings from studies using models of NDDs alongside clinical data suggest that ongoing systemic inflammation may also exacerbate the occurrence and progression of neurological disorders *via* actions on the cerebrovasculature. This may occur *via* a number of mechanisms (some of which are discussed below), but more epidemiological studies are required to understand how systemic disease affects an individuals' risk burden for neurological disease. Specifically, it is not yet clear whether systemic disease has a contribution of sufficient magnitude to increase the number of people who may later develop a neurodegenerative condition, or whether it interacts with other risk factors to affect the severity and/or timing of disease onset.

One mechanism by which inflammation may lead to cerebrovascular dysfunction and NDDs is through the production of ROS, leading to a state of oxidative stress (Song et al., 2020). Systemic oxidative stress has been associated with reduced ocular hemodynamic flow, linked to increased vascular permeability in patients with glaucoma (Himori et al., 2015). Neurodegeneration in NDD mouse models and patients, is associated with changes in oxidative stress and mitochondrial dysfunction (Henchcliffe and Beal, 2008; Elstner et al., 2011; Grammas et al., 2011; Reeve et al., 2013; Chang and Chen, 2020; Ahn et al., 2023). Similarly, oxidative stress in ischemic stroke it has been proposed to heighten neuroinflammation through release of ROS, increasing programmed cell death following ischemic injury. Although the molecular mechanisms behind this interplay are not known (reviewed by Wu et al., 2020).

There is an accumulation of evidence linking diabetes, a primary metabolic disorder, to cerebrovascular and cognitive disorders. Diabetes is characterised by dysregulated insulin signalling and is a recognised risk factor for NDDs (Li et al., 2015; Verdile et al., 2015). Insulin signalling is imperative for optimal cerebral EC and neuronal function (Rhea and Banks, 2019). Decreased expression of insulin receptors in the brain microvasculature of mice *in vivo* alters insulin signalling within the brain (Konishi et al., 2017). Disruption to insulin signalling is common to both diabetes and AD pathology (Arnold et al., 2018). In addition, hyperglycaemia-induced production of compounds such as methylglyoxal, a harmful oxoaldehyde, exacerbate endothelial dysfunction due to increased cellular apoptosis and oxidative stress, therefore increasing the risk of PD (Sabari et al., 2023). A murine model of type 2 diabetes has shown extensive damage to BBB structure, occurring due to the increased presence of pro-inflammatory mediators and an altered immune response (Sheikh et al., 2022). The *in vitro* and *in vivo* models of type-2 diabetes studies in the work of Sheikh et al. (2022) both show a loss of tight junction protein expression and an increased influx of neutrophils into the brain parenchyma (Li et al., 2022). These effects were reversed by either pharmacological intervention with recombinant ANXA1 (a mediator of glucocorticoid anti-inflammatory mechanisms, known to reduce BBB leakage) or dietary reversion of the diabetes phenotype (Sheikh et al., 2022). If early stages of metabolic disease, such as diabetes, can cause systemic inflammation and BBB damage, then it is possible that undiagnosed or poorly controlled diabetes may results in prolonged injury to the brain. This chronic systemic challenge to the cerebrovasculature may also have other actions to increase risk to cerebral disease (see below) and warrant further investigation.

Studies utilising animal models of chronic systemic inflammation have reported increased cognitive impairment and enhanced expression of dementia-associated risk factors (Sy et al., 2011; Marottoli et al., 2017). The effect of systemic inflammation on the BBB has been modelled in mice using peripheral injections of LPS (Nonaka et al., 2005; Qin et al., 2007; Franciosi et al., 2012; Banks et al., 2015; Zhao et al., 2019). There is evidence that neuroinflammation can significantly alter multiple BBB transport systems, such as those for insulin, TNF and amyloid beta peptide, and that these changes are further exaggerated with repeated exposure to LPS *in vivo* as opposed to a single high-dose LPS exposure (Xaio et al., 2001; Pan et al., 2008; Jaeger et al., 2009). In a transgenic animal model of AD, repeated low-medium dose LPS administration (0.5 mg/kg) over a 2-month period produced significant cerebrovascular injury, including increased vessel leakage and protein deposition in the parenchyma, alongside cognitive deficits (Marottoli et al., 2017). More work is required to understand the links between systemic inflammation and subsequent neurodegeneration, including the level of plasticity and repair possible within the cerebrovasculature, how early irreparable vascular damage occurs, and the role of molecular priming of endothelial inflammatory response as a contributor to the severity of later injury. Processes of tolerance and sensitisation are known to affect inflammatory signalling following repetitive exposure (Gillen et al., 2021; Nürnberger et al., 2021; De Zuani et al., 2022; Li et al., 2023). Which of these, if any, occur in cerebral ECs following repetitive or chronic (peripheral or central) inflammation has not yet been established, but the outcomes of such studies will be critical for understanding mechanisms of endothelial dysfunction and whether elements of the endothelial signalling pathways referenced above are potential candidates for effective therapeutic targeting.

As an additional factor, aging also affects the immune response and the cerebral vasculature (Malaguarnera et al., 2001). Aging is accompanied by an increase in cellular senescence, where cells undergoing senescence release pro-inflammatory cytokines, promoting a chronic inflammatory state (Childs et al., 2015). Increasing proportions of senescent cells appears to be a driving force in the progression of age-associated disorders which include atherosclerosis and NDDs (Saez-Atienzar and Masliah, 2020; Wissler Gerdes et al., 2020). Yamazaki et al. (2016) using an *in vitro* BBB model comprised of senescent primary cells, highlighted an exacerbation of senescence in ECs, leading to decreased tight junction coverage and increased BBB disruption (Yamazaki et al., 2016). Additionally, in a senescence prone mouse model, it was found

that altered CBF arising from aging and vascular insult, correlated with a decline in cognitive dysfunction (Zhang et al., 2013).Therefore the association between EC senescence, cerebrovascular inflammation, and increased BBB permeability is one that is well-established and requires further exploration in the context of early-life systemic disease and the subsequent risk burden for NDDs (Graves and Baker, 2020; Han and Kim, 2023).

Given the interplay between systemic inflammatory disease, acute and prolonged cerebrovascular dysfunction and risk of NDD, there needs to be increased focus on how events throughout the lifespan contribute to the risk burden for neurodegenerative disease. New epidemiological cohort studies are shedding light on the contribution of extremely early life events, such as low birth weight or preterm birth, to cerebrovascular disease and aging (Backhouse et al., 2021; Crump et al., 2021). There is clear evidence, as described here, that aging, diabetes, and atherosclerosis alter systemic inflammatory status and reactivity of the cerebrovasculature, but it is, as yet, unclear how they interact. The commonality of molecular signals may allow biomarker monitoring of (cerebro-) vascular health and earlier diagnosis of risk, as well as the identification of therapeutic targets. While we have suggested some possible therapeutic approaches based on existing knowledge, it is likely that more effective strategies will be identified if we can better understand the nature and consequences of repeated inflammatory activation on cerebral ECs.

8. Conclusion and perspectives

The emerging role of cerebrovascular dysfunction in the early and progressive pathogenesis of NDDs has led to an increase in research exploring alterations in vascular function and how increased leukocyte transmigration, atherosclerosis, and loss of BBB integrity contribute to NDD onset and progression. There is accumulating evidence that inflammation is a mediator of the vascular alterations seen in NDDs, and that systemic inflammation across a lifetime is a major contributor to cerebrovascular dysfunction. The common pathways and processes leading to impaired BBB function and subsequent cerebrovascular injury resulting from low grade systemic inflammatory insult are currently underexplored and underexploited. There is a need for the development of appropriate *in vitro* models for investigating molecular regulation mechanisms, priming and plasticity and their contribution to neurovascular pathology, as well as further exploration of *in vivo* models and clinical disease. Monitoring the evolution of the endothelial inflammatory responses over a lifetime may support biomarker development and early diagnostic potential. Targeting the cerebral endothelium to achieve neurovascular stabilisation could provide a broad-spectrum therapeutic for an array of neurodegenerative diseases, irrespective of underlying pathology, or be utilised in unison with disease-specific screening.

CRediT authorship contribution statement

Megan Ritson: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Caroline P.D. Wheeler-Jones:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Helen B. Stolp:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization.

Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

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