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REVIEW

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Dysfunction of the blood–brain barrier in Alzheimer's disease: Evidence from human studies

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Abstract

The pathological processes leading to synapse loss, neuronal loss, brain atrophy and gliosis in Alzheimer's disease (AD) and their relation to vascular disease and immunological changes are yet to be fully explored. Amyloid-β (Aβ) aggregation, vascular damage and altered immune response interact at the blood–brain barrier (BBB), affecting the brain endothelium and fuelling neurodegeneration. The aim of the present systematic literature review was to critically appraise and to summarise the published evidence on the clinical correlations and pathophysiological concepts of BBB damage in AD, focusing on human data. The PubMed, Cochrane, Medline and Embase databases were searched for original research articles, systematic reviews and meta-analyses, published in English language from 01/2000 to 07/2021, using the keywords Alzheimer*, amyloid-β or β-amyloid or abeta and BBB. This review shows that specific changes of intercellular structures, reduced expression of transendothelial carriers, induction of vasoactive mediators and activation of both astroglia and monocytes/macrophages characterise BBB damage in human AD and AD models. BBB dysfunction on magnetic resonance imaging takes place early in the disease course in AD-specific brain regions. The toxic effects of Aβ and apolipoprotein E (ApoE) are likely to induce a non-cerebral-amyloid-angiopathy-related degeneration of endothelial cells, independently of cerebrovascular disease; however, some of the observed structural changes may just arise with age. Small vessel disease, ApoE, loss of pericytes, proinflammatory signalling and cerebral amyloid angiopathy enhance BBB damage. Novel therapeutic approaches for AD, including magnetic resonance-guided focused ultrasound, aim to open the BBB, potentially leading to an improved drainage of Aβ along perivascular channels and increased elimination from the brain. In vitro treatments with ApoE-modifying agents yielded promising effects on modulating BBB function. Reducing cardiovascular risk factors represents one of the most promising interventions for dementia prevention at present. However, further research is needed to elucidate the connection of BBB damage and tau pathology, the role of proinflammatory mediators in draining macromolecules and cells from the cerebral parenchyma, including their contribution to cerebral amyloid angiopathy. Improved

insight into these pathomechanisms may allow to shed light on the role of Aβ deposition as a primary versus a secondary event in the complex pathogenesis of AD.

KEYWORDS
Alzheimer dementia, beta amyloid protein, blood–brain barrier, brain–blood barrier, cerebral amyloid angiopathy, clearance, neurovascular unit, small vessel disease

INTRODUCTION

The blood–brain barrier (BBB) represents a unique structure of the central nervous system (CNS), consisting of cerebral endothelial cells, perivascular mural cells (pericytes), glial cells (astrocytes and microglia) and neurons (Figure 1).[3] Under physiological conditions, the interplay of the different cell types at the BBB regulates the neuronal and glial cell environment and is crucial for cell function and survival.[11,12] In Alzheimer's disease (AD), there is increasing evidence that the BBB represents a link between neurodegeneration (particularly the accumulation of proteins), vascular damage and inflammatory processes.

The deposition of amyloid-β (Aβ) in extracellular plaques and the abnormal folding and aggregation of tau to intraneuronal fibrils are key upstream pathological characteristics of AD.[13] Further downstream, those changes are associated with synaptic and neuronal loss, brain atrophy, gliosis and white matter degeneration.[14] There is consensus that these events lead to cognitive deterioration and dementia, but the exact mechanisms remain to be clarified. The most influential pathogenetic concept of sporadic AD—the amyloid hypothesis—posits that an imbalance between the production and clearance of Aβ causes an accumulation of insoluble extracellular Aβ aggregates.[13,15–19] (Figures 2 and 3). The BBB facilitates the clearance of proteins such as

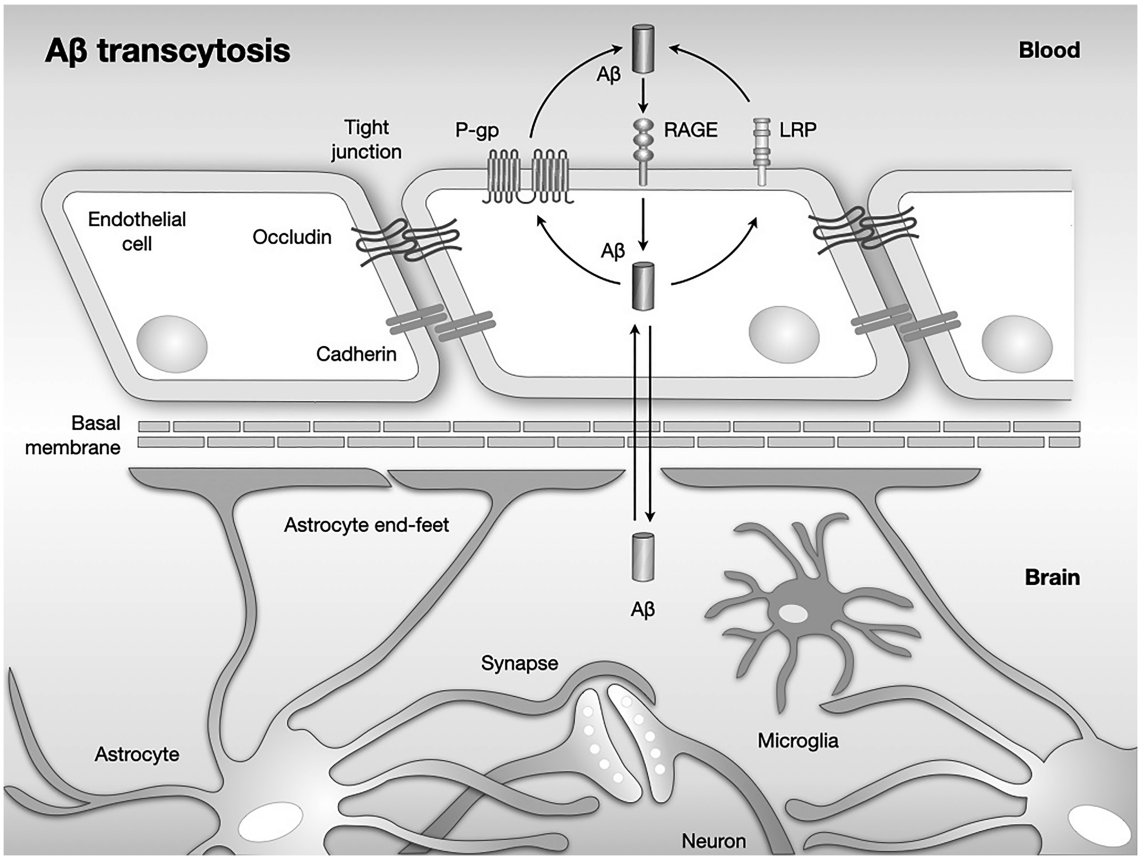

FIGURE 1 The BBB is a unique characteristic of the central nervous system (CNS) and composed of highly specialised cell contacts—continuous tight junctions (e.g., occludin and claudin)[1]—and adherens junctions (cadherins) between brain endothelial cells.[2] Together with perivascular mural cells—pericytes[3]—the brain endothelium acts as a dynamic barrier limiting transcellular and paracellular movement and separates circulating blood from the CNS.[1,4] The BBB regulates brain homeostasis especially by removing catabolites and preventing (re)uptake of neurotoxic mediators.[5–8] Furthermore, brain endothelial cells act as a gatekeeper of neuroinflammation signalling blood-borne leukocytes (not) to adhere, migrate and invade.[9] Some small lipophilic molecules are able to passively diffuse across the BBB; however, tight junctions prevent paracellular transport of most hydrophilic molecules.[10] Because of the presence of tight junctions, large molecules are transcytosed from the blood to the brain by uptake via active transcellular transport proteins (e.g., LRP-1, P-GP, and RAGE)[10]

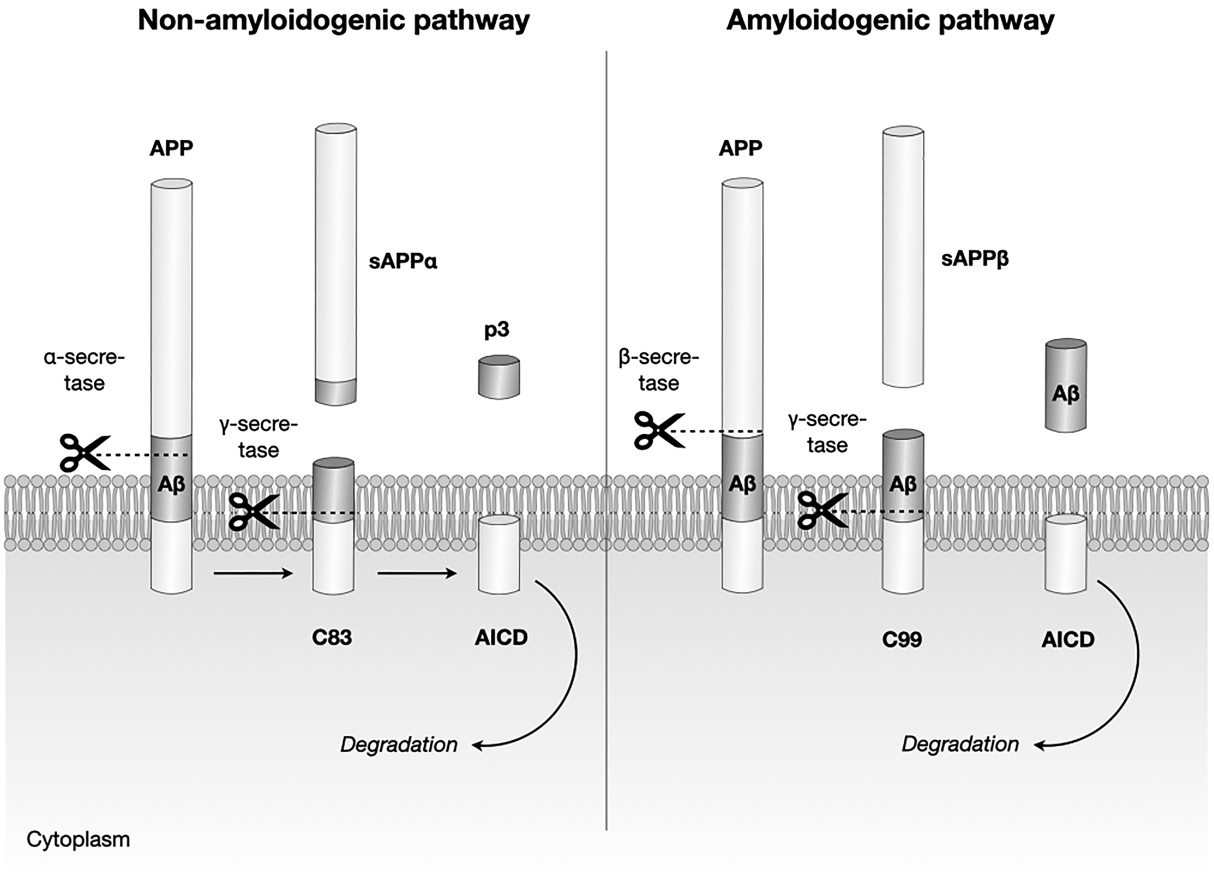

FIGURE 2 Amyloid and its derivates undergo a complex cycle: Different amyloid peptides derive from its precursor protein—the transmembrane protein amyloid precursor protein AβPP[20] by sequential β- and γ-secretase cleavage.[11] Amyloid peptides are produced by a variety of cells, including neurons, glial cells, but also human blood–brain barrier endothelial cells, cerebrovascular smooth muscle cells[20] and circulating platelets.[1] Furthermore, AβPP is expressed in different cell compartments (cell surface, endosomes).[21] Depending on the splicing site of secretases, an "amyloidogenic"—"Aβ"—pathway leading to insoluble amyloid peptides and a "non-amyloidogenic"—"non-Aβ"—pathway leading to soluble amyloid peptides exist.[1,21] Splicing by β-secretases produces Aβ peptides ranging from 39 to 43 amino acids[21,22]

Aβ via the cerebrovascular system, but its connection to other intracerebral Aβ drainage systems, such as the intramural periarterial drainage (IPAD) pathway, remains to be clarified.[11,12,23] Advancing age and carrying the apolipoprotein (ApoE) ε4 (*APOE* ε4) genotype, both related to enhanced cerebral amyloid angiopathy (CAA) risk,[23,24] may alter this drainage pathway (Textbox 1). In contrast to the plaques mainly composed of Aβ42 in the brain parenchyma of older healthy individuals, Aβ40 accumulates predominantly in the vessel walls and presents as CAA, a type of small vessel disease (SVD) affecting small arteries, arterioles, venules and capillaries of the brain.[25,26] (Figure 3). During the formation of CAA, Aβ aggregates in the tunica media and adventitia, with affected vessels showing a distinctive "double barrel" lumen.[27] Later, Aβ infiltrates all layers of the vessel replacing smooth muscle cells in the tunica media.[27] In capillaries, Aβ concentrates in the perivascular basement membrane and as globular deposits in the capillary walls.[28,29] Aβ shows inconsistent effects at the BBB, including oxidation,[30] proinflammatory signalling[31,32] and endothelial damage, but also[20,33,34] neuroprotective and neurotrophic,[21,30] and vasoactive effects,[35,36] such as promoting blood clotting[36,37] and sealing BBB leaks.[38,39]

Vasculopathic effects of Aβ may enhance vascular disease, lead to inefficient clearance and disease progression. Prevention of vascular disease could represent an approach to mitigate BBB dysfunction and decelerate neurodegenerative processes. In this systematic literature search, the available literature on the relationship between BBB function and AD pathology in humans or in vitro models with human cells was summarised for different methodological approaches and analysed concerning its significance.

Textbox 1. From the pool of multiple Aβ species, Aβ1–40 and Aβ1–42 mainly contribute to the histopathological hallmarks of AD, with Aβ1–40 being the most abundant Aβ species in the brain[30]; however, Aβ1–42 has a higher propensity to aggregate.[40] Aβ1–42 represents the major component of neuritic plaques (Aβ plaques in the centre of dystrophic neurites[41] with frequent phospho-tau immunoreactivity[14]). Neuritic plaques mainly develop in the grey matter[42] and are histopathologically differentiated from other forms such as diffuse plaques.[14] Aβ deposits are also found in the vessel walls

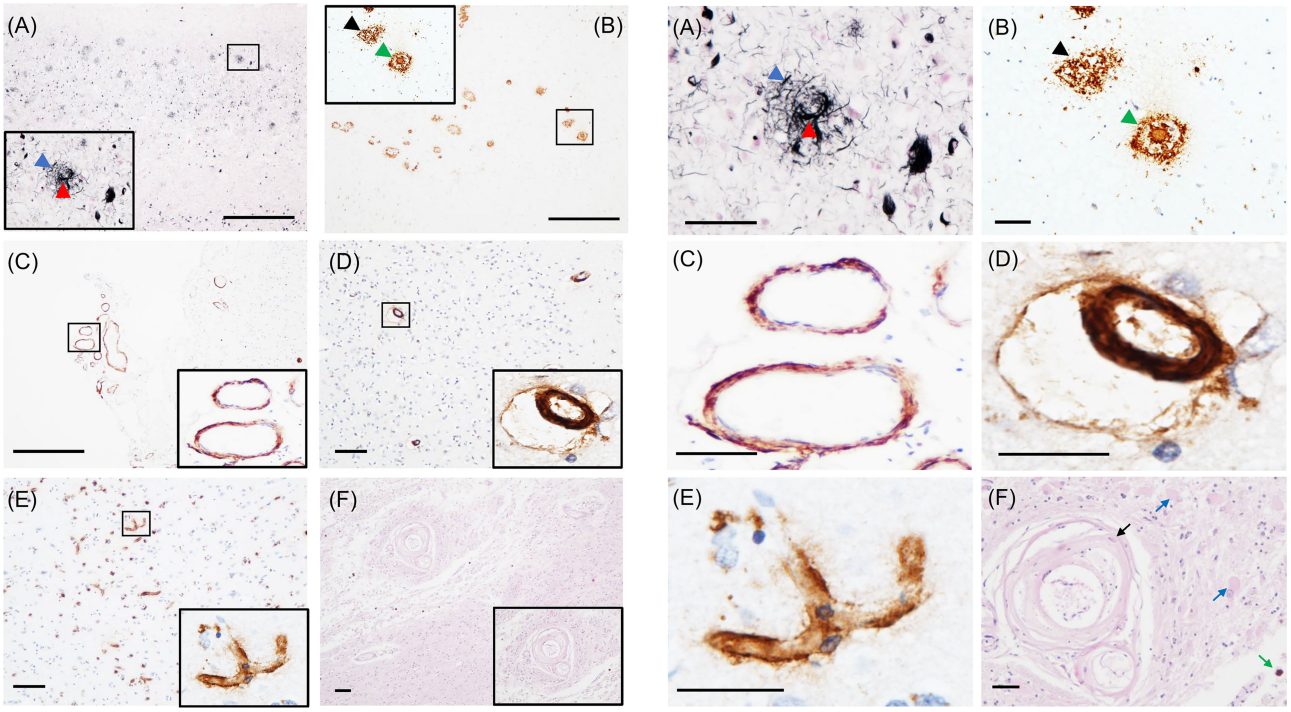

FIGURE 3 Alzheimer's disease (AD) related pathology

of the cerebrovascular system, referred to as cerebral amyloid angiopathy (CAA) which is a common (90%[43]) vascular pathology of AD.[20] In CAA, predominantly Aβ1–40[35] is deposited in the basement membranes of capillary walls followed by Aβ deposits in the tunica media of smooth muscle cells,[44,45] followed by an affections of the connective tissue elements and a focal or complete replacement of artery walls by Aβ.[46] Two regional distributions are distinguished: CAA type 1 with Aβ deposits in cortical capillaries, leptomeningeal and cortical arteries, arterioles, veins and venules[47] and CAA type 2 with Aβ deposits in leptomeningeal and cortical vessels, with the exception of cortical capillaries.[47] In general, CAA is very sparse in subcortical white matter.[48] Apart from primary proteinopathies and CAA, arteriosclerosis, small vessel disease (SVD) in particular, is considered as an additional vascular pathology in the AD process, contributing to cognitive decline in ageing and AD.[41] SVD is a systemic vasculopathy and leads to a loss of smooth muscle cells from the tunica media, to deposits of fibro-hyaline material, to narrowing of the lumen and to thickening of the medial layer in cerebral arteries.[49]

MATERIALS AND METHODS

We conducted a comprehensive search of the published literature between 2000 and 2021 (last updated on 7 July 2021) using the databases Cochrane, Embase, Medline and Pubmed. Relevant articles were considered if they reported original research, were published in English and included individuals diagnosed with AD[50] or mild cognitive impairment (MCI)[51] or in vitro models with human cells. Articles without peer-review (e.g., conference abstracts), review articles and publications on nonhuman studies were excluded (e.g., animal model or cell culture studies with nonhuman cells). The search terms were[3] Alzheimer* (*root expander, title/abstract) AND "brain blood barrier" (title/abstract) OR "blood brain barrier" (title/abstract), amyloid-beta OR beta-amyloid OR abeta (title/abstract) AND brain blood barrier OR blood brain barrier (title/abstract). In the first step, relevant literature was preselected based on the abstract, followed by an evaluation of the preselected full text papers. Randomised-controlled trials, cohort studies, case–control studies and diagnostic studies were analysed following the Scottish Intercollegiate Guidelines Network (SIGN) recommendations (www.sign.ac.uk) with regard to internal validity, overall assessment and description of the studies.[52] After screening the abstracts, only articles with high or moderate quality (internal validity concerning the selection of subjects, the assessment, report of confounders and statistical analysis) were included. The literature search was performed by one experienced reviewer (CK). Out of $n = 641$ identified articles, $n = 71$ met the inclusion and quality criteria, after removal of duplicates (Supporting Information).

RESULTS

All findings on BBB dysfunction are subdivided according to the analytical method and source of information.

Evidence from histopathological studies

Structural and vascular alterations

In histopathology, BBB damage is characterised by extravasation of plasma proteins (fibrinogen, immunoglobulin G) or patchy expression of endothelial markers, basement membrane proteins and tight junction proteins (claudin, occludin).[53–55] On post-mortem examination, these alterations were described in AD patients especially in advanced stages,[38,54–58] and in cortical areas (prefrontal,[38,56] frontal and parietal,[59] orbitofrontal, inferior temporal, posterior cingulate and entorhinal cortex[56]), but not in subcortical regions.[56] Significant loss of cortical tight junction proteins was observed in AD patients compared with normal ageing and showed an association with the severity of CAA.[56] Aβ accumulation in brain pericytes of AD cases, but not of controls, indicated that pericytes not only regulate BBB permeability and cerebral blood flow but are also involved in the clearance of Aβ.[60] Hallmarks of AD pathology (Aβ load, Braak stages) and the extent of BBB damage were positively associated with expression of the vasoactive mediator (vasoconstrictor) endothelin.[59] Cerebral hypoperfusion (increase in vascular endothelial growth factor-A [VEGF] and reduced ratio of myelin-associated glycoprotein to proteolipid protein-1) were more pronounced in mixed dementia (AD/vascular) compared with AD, vascular dementia and controls,[59] pointing towards an additive effect of AD and SVD pathology.

Immunological changes

While the glial barrier, formed by astrocytic end-feet, appears to be intact in AD patients,[61] capillary pericytes were significantly reduced,[54,58,62] correlating closely with BBB damage.[54] Activation of astrocytes and reduced number of microglia around capillaries were reported as specific features of BBB damage in AD.[61] The hippocampus and mid frontal gyrus of patients with advanced AD showed perivascular infiltration of T[63] and B lymphocytes.[64,65] Macrophages accumulate in the walls of Aβ-containing vessels (referred to as CAA),[32,64] the ability of macrophages from AD patients to phagocytise Aβ and to emigrate across the BBB was reduced.[66] Furthermore, macrophages from AD patients seem to be particularly susceptible to caspase-induced apoptosis from different assembly states of Aβ,[66] which in turn may contribute to CAA by releasing Aβ into the vessel walls.[66]

Relation to cerebral amyloid angiopathy

CAA is part of AD pathology[56] and present in approximately 80% of AD cases.[67] Histopathological data suggests an association of BBB damage and CAA type 1 (capillary type), but not CAA type 2 (non-capillary type).[33,38,53,56] BBB damage (measured by fibrinogen extravasation) correlated with SVD and CAA pathology, and to a lesser degree with cortical AD-related pathology.[67] It remains to be clarified whether a synergistic mechanism promotes both endothelial and BBB damage or whether BBB dysfunction interferes with the clearance of Aβ resulting in CAA pathology.[56]

Transcellular transport proteins

Histopathological work-up of patients with AD[68,69] and with AD/CAA pathology[33,70] revealed an association of local Aβ plaque burden and deposition of neurofibrillary tangles[68] with reduced expression of transendothelial transport proteins involved in the brain-to-blood clearance of Aβ, including lipoprotein-related protein 1 (LRP-1)[3,69] and P-glycoprotein (P-gp).[69] In contrast, a recently published study described no differences between AD patients and controls in the expression of LRP-1, P-gp and other transendothelial drug transporters (BCRP, OATP2B1 and ENT1).[71] However, increased expression of LRP-1 in AD patients compared with controls was interpreted as an active, though inefficient, transendothelial transport mechanism of Aβ,[68] compensating the failure of other clearance mechanisms. In line with this, an association of Aβ with upregulation of transport proteins involved in the blood-to-brain uptake (receptor for advanced glycosylation end-products [RAGE][33,68]) and an upregulation of alternative efflux transporters at the BBB (ATP-binding cassette G2—ABCG2—transport protein[70]) was demonstrated. These findings underline the dysfunctional clearance of Aβ in AD and indicate an increased Aβ influx from the periphery, leading to an interstitial accumulation of Aβ (Figure 1).

ApoE deposition

Apolipoprotein E (ApoE) is the most important susceptibility gene for AD (and for CAA[72]), encoding the lipid and Aβ carrier protein ApoE (Textbox 2). ApoE was detected in pericytes but not in endothelial cells or smooth muscle cells[72] and together with Aβ in perivascular astrocytes.[73] The accumulation of ApoE within the perivascular space, especially of SVD-altered vessels, points to a role in perivascular drainage of Aβ across the BBB and a common pathway in the development of AD and SVD.[73]

> **Textbox 2.** Apolipoproteins regulate the generation, metabolism, transport and clearance of different lipoproteins—including the high-density lipoproteins (HDL)—and are lipidated with cholesterol and phospholipids by the membrane-bound ATP-binding cassette transporter A1 (ABCA1).[74,75] ABCA1 transporter transfers cholesterol from cells onto lipid-poor apolipoproteins.[76] The major pool (70–90%) of CNS cholesterol is found in the myelin sheaths of oligodendroglia and the second pool of cholesterol derives from plasma membranes of neurons and glia, especially astroglia.[76]

Apolipoprotein E (ApoE) is primarily synthesised by liver cells, astrocytes and neurons and to a lesser extent by microglia.[11,73,77] As a lipid carrier, ApoE regulates lipid homeostasis, regulates synaptic plasticity, signal transduction and owns immunological functions[76] but is also a constituent of amyloid plaques.[77] Depending on its lipidation status (lipidated or lipid-free) apolipoproteins promote Aβ aggregation.[74] ApoE-bound Aβ can be internalised by neurons and astrocytes via lipoprotein-receptor-related protein (LRP).[11,73,77] ApoE exists in three major ApoE isoforms: ε2, ε3 and ε4.[3] Carrying the ApoE ε4 allele is the strongest and most highly replicated genetic risk factor for sporadic late-onset AD.[3] Individuals with one copy of ApoE ε4 have a 3.7-fold increase in AD risk and individuals with two copies of ApoE4 a 12-fold increase in AD risk compared with ApoE ε3/ε3 carriers.[3]

Evidence from CSF studies

An increase in cerebrospinal fluid (CSF)/serum IgG ratio characterises BBB dysfunction, but is prone to measurement errors[12] and showed no association with AD CSF markers.[78] Therefore, the CSF/serum albumin (Qalb) index was introduced as a more reliable measure, with values of >9 indicating BBB dysfunction.[4] Pathological Qalb was described ranging from 16%[4] to 22% in patients with mild to moderate AD dementia.[79] The significance of this finding is unclear as one study reported no difference in Qalb between MCI and controls,[78] while another study showed 30% higher Qalb for the same comparison.[80] Two studies did not find an association of Qalb with cognitive performance (Mini-Mental-State Examination, MMSE) in both AD and MCI patients,[78,79] but with markers of disease progression (annual change on the MMSE and the Clinical Dementia Rating Sum of Boxes [CDR-SOB]).[79] Furthermore, the association of Qalb with vascular risk factors remains to be clarified: While in one study Qalb levels were not associated with vascular risk factors (presence of high blood pressure and Hachinski ischaemia score),[79] another study found an association of Qalb with a composite vascular risk factor score, but not with white matter hyperintensity volumes.[78] A systematic review concluded that BBB permeability measured by Qalb and brain imaging increases with normal ageing and was pronounced in vascular dementia.[12] While CSF/serum IgG ratio is not useful as a marker of BBB damage in AD and the significance of Qalb remains to be clarified, CSF levels of platelet-derived growth factor receptor β (PDGFRβ) may represent an alternative and sensitive marker of BBB damage: Biomarker-defined (positron emission tomography [PET] or CSF) Aβ-positive AD patients exhibited increased levels of PDGFRβ compared with healthy controls, even in the absence of Qalb differences, and CSF PDGFRβ levels correlated strongly with clinical disease severity,[57] especially in at risk patients (APOE ε4 allele carriers).[81,82]

Evidence from brain imaging

Three different approaches to examine BBB dysfunction by contrast-enhanced magnetic resonance imaging (MRI) were described:

I. Pericortical enhancement (defined as brighter than the proximal parenchymal signal intensity, occurring in the subarachnoid space) was compared between precontrast and postcontrast FLAIR images.[83–85] However, the significance of this technique remains unclear as it generates patchy signal changes,[84] did not consistently differentiate between AD patients and healthy controls and therefore was discussed to reflect increasing age or vascular pathology.[84,85]
II. Gadolinium flow from the intravascular to the extravascular space was detected in disease-specific regions (hippocampus and parahippocampal gyrus)[80,81,86,87] and in the whole cerebral cortex.[86] This technique discriminated AD and MCI patients from controls.[80,86] The extent of intravascular to extravascular gadolinium flow correlated negatively with cognitive performance on the MMSE,[80] dementia severity on the CDR,[86,87] with Qalb[80] and CSF PDGFRβ levels—even in early-stage individuals without hippocampal atrophy.[87]
III. The wepcast technique labels water by arterial spin labelling and measures the extraction fraction in the superior sagittal sinus in relation to global cerebral blood flow.[78] Wepcast distinguished MCI patients from controls,[78] and correlated negatively with cognitive performance (episodic memory and language) and CSF Aβ42/Aβ40 ratio, but not with vascular pathology.[78]

There is only limited data on the utility of PET in visualising BBB dysfunction. Two published studies showed a decreased binding potential of the Aβ carrier P-gp in AD patients compared with controls[88,89] in disease-specific regions (parietotemporal, frontal, posterior cingulate cortices and hippocampus).[89]

In small case series, transient opening of the BBB by magnetic resonance-guided focused ultrasound was discussed to improve Aβ clearance from the brain without significant side effects.[90–94] After sonication of the hippocampus, contrast enhancement along the course of draining veins in the hippocampus[94] and perivenous enhancement towards the dural venous sinuses[95] were interpreted as glymphatic efflux.[94] The enhanced drainage along veins does not affect CAA, which mainly occurs along arteries. A reduction in Aβ load on PET after sonication was also shown, but cognitive outcomes were not reported.[92,93,95]

Evidence from genetic studies

In histopathology, *APOE* ε4 allele carriers showed acceleration of pericyte and BBB damage and increased accumulation of proinflammatory cytokines,[3,38,58] in line with increased BBB permeability in the hippocampus of cognitively normal apolipoprotein *APOE* ε4 allele carriers on MRI.[81] BBB permeability in APOE ε4 carriers was

reported to emerge independently of tau and Aβ amyloid pathology.[96] Contrarily, a recent study did not reveal differences in BBB permeability and Qalb between *APOE* ε4 carriers versus noncarriers.[78]

Genetic polymorphisms involved in the transcytosis of Aβ across the BBB (*PICALM*, *BIN1*, *CD2AP* and *RIN3*) increased the risk of AD, vascular dementia and stroke, and a cumulative effect of polymorphisms was observed.[97] Polymorphisms in the *ABCB1* gene, encoding the Aβ-carrier P-gp correlated with disease status.[88,98] Reduced expression of genes involved in differentiation of vascular cells (*MEOX2*[99]) and BBB integrity (*CLDN5*[100]) was described in autopsy cases. The transcription factors ABCC4, RELA, LAMA4, CCNE2, CCNA2 und NCF2 were associated with genes regulating T-cell-migration, cell cycle regulation (proliferation, differentiation and cell death) and astrocyte-derived inflammatory response and were significantly expressed in the regulatory networks of BBB injury-related genes.[101]

Taken together, there is evidence for increased BBB damage in *APOE* ε4 carriers, potentially arising from the vascular effects of ApoE.[72,73] Genetic studies point to an altered expression of transcellular transport proteins in the development of AD, but only one of them was adjusted for *APOE* status.[97]

Evidence from in vitro BBB models

BBB models using human cerebral microvascular endothelial cells (hCMEC/D3,[102] TY-10 cells[31]) or human brain endothelial cells differentiated from induced pluripotent stem cells (iPSC) indicated effects of Aβ on the regulation of tight junctions and transmigration of immune cells (Figure 1).[10] BBB models can form a polarised monolayer with an abluminal ("brain") and luminal ("blood") side, express tight junctions and exhibit receptor-mediated transport of macromolecules.[102] BBB models reveal higher permeability for smaller molecules such as Aβ, probably caused by incomplete formation of tight junctions[103] and of transendothelial electrical resistance.[104]

In BBB models, a bidirectional movement through the BBB of Aβ1–40 was demonstrated (Figure 2); endocytosis[105] and abluminal to luminal transcytosis (clearance from the brain) was mediated by LRP-1[105,106] P-gp[105] and PICALM.[106] Luminal to abluminal transcytosis was mediated by RAGE[105,106] and caveolin.[106] The presence of Aβ was associated with an increase in permeability,[10,102,106–110] disruption of tight junctions (claudin-5)[32] and increased expression of leukocyte adhesion molecules.[31] These effects were possibly mediated by proinflammatory and vasoactive substances including matrix metalloprotease 9 (MMP9), VEGF,[107,111] tumour necrosis factor,[31] interleukins (IL-6, IL-8[32] and IL-1β[108]). There is evidence that vascular adhesion proteins and Aβ interact, enhancing their vasculopathic effects and contributing to CAA.[112] Transcytosis of Aβ and immunological response were potentially linked via Aβ carriers, including RAGE, belonging to the immunoglobulin superfamily[109] and possessing an immunomodulatory function (activating cytokines).[20] Astrocytes modulated the endothelial response to Aβ and reduced Aβ-related expression of leukocyte adhesion molecules.[31,113]

A dose-dependent toxic effect of Aβ on endothelial cells and astrocytes[20,32–34,108] via caspase-mediated apoptosis[108] and a dose- and time-dependent growth inhibiting effect on endothelial cells[110] were reported. The oligomerisation status of Aβ affected BBB permeability and survival of endothelial cells: while all Aβ species inhibited angiogenesis in vitro, oligomeric Aβ fragments (Aβ1–42) induced endothelial cell apoptosis, whereas fibrillar aggregates disrupted tight junctions (claudin) without apoptotic effects.[114]

RNA-binding proteins (RBPs) including TAR DNA-binding protein 43 (TDP43) and transformer 2 alpha homologue (TRA2A) and pseudogenes (DNA fragments) were reported to modulate BBB permeability (ZO-1, occludin and claudin-5 expression)[115,116] via transcription and translation processes and were enriched in endothelial cells of AD patients and in vitro after incubation with Aβ1–42.[115,116]

DISCUSSION

Based on the evidence from a systematic literature search, BBB damage in AD is characterised by specific changes in (inter)cellular structures (tight junctions), altered expression of transendothelial Aβ carriers, apoptosis of endothelial cells, astrocytes and pericytes, induction of vasoactive mediators and activation of both astroglia and monocytes/macrophages. Furthermore, post-mortem, in vivo and in vitro studies indicated non-CAA- and non-SVD-related vasculopathic and proinflammatory effects of both Aβ and ApoE and an impairment of cellular Aβ degradation by microglial cells and astrocytes.

While in histopathology, BBB breakdown was detected in patients with advanced AD,[38] brain imaging studies observed BBB breakdown already present at early stages, particularly in the hippocampus.[80,81,87] This discrepancy is partly explained by the nature of autopsy, mainly being performed in advanced cases. However, it remains unclear if structural changes of the BBB may be age related; during ageing, several alterations of the BBB have been observed including a loss of tight junctions, accumulation of extracellular matrix components in the vascular basement membrane, changes in the astrocytic end feet and stiffening of the vessel.[117] Similarly, CAA can be found in the brains of nondemented older controls,[48] and an age-related failure of Aβ elimination from the brain is possible.[46,48] Although the pathogenesis of CAA is not completely understood, it is likely multifactorial, since hypertensive angiopathy (HA) (a non-Amyloid SVD) frequently co-occurs with CAA in the ageing brain (Figure 3). HA develops in early stages as endothelial failure with basement membrane changes and results in BBB breakdown and collapse in vessel wall integrity.[118,119] In histopathology, HA can appear with vessel fibrosis, infiltrating foam cells, astrogliosis and hemosiderin laden macrophages (Figure 3). Whether the co-existence of pathologies is due to shared common risk factors, such as ageing, or whether there is a more causal relationship is yet to be fully determined.[120,121]

Endothelial damage may also arise because of SVD.[122,123] However, the existing evidence is inconsistent, with some studies describing an intact endothelial layer even in severe SVD[9,79,80,124] and white matter lesions occurring secondary to cortical AD pathology.[125] At

the same time, other studies argued for loss of BBB integrity being an early pathogenic step in SVD caused by multiple factors, including hypertension, diabetes, inflammation, smoking and increased sodium intake.[122] Despite these ambiguities, increased and additive risk for vascular dementia, stroke and AD when carrying (one or more) mutations in transendothelial transport protein genes,[97] increased BBB permeability in *APOE* ε4 carriers[3,38,58,81,82] and reduced expression of genes involved in the differentiation of vascular cells in AD cases (*MEOX2*[99]) point towards a common pathway in both neurodegenerative and cerebrovascular disease. Both pathogenetic concepts (Aβ first or vascular changes first) would support the idea of preventing neurodegenerative processes by minimising vascular changes.

While in vitro studies suggested that Aβ deposition preceded proinflammatory changes such as increased leukocyte and monocyte adhesion[20,31,64,109,113,126]—possibly even as an initially neuroprotective reaction to remove Aβ deposits[64]—in vivo PET studies suggested that glial activation occurred prior to Aβ deposition.[127] Moreover, there is evidence that tau pathology is also associated with an increase in BBB permeability via release of cytokines from activated microglial cells and[128] changes in the activity of transcellular transport proteins.[129,130]

Implications for treatment

Changes of the brain endothelium caused by Aβ or tau aggregation may lead to inefficient protein clearance via perivascular spaces and contribute to AD pathogenesis in a synergistic fashion. Approaches to achieve therapeutic effects at the BBB were proposed, including influencing the expression of ApoE via calcineurin[72] and the lipidation status of ApoE via ABCA1 activity.[76,131] Studies with BBB models indicated that treatment with simvastatin and lovastatin lowered the secretion of cytokines and improved BBB function.[32] Somatostatin reduced Aβ-induced increase in BBB permeability and was associated with an upregulation of neprilysin, an Aβ-degrading enzyme.[108] Vasoactive mediators, such as epidermal growth factor, were found to ameliorate Aβ-induced vessel degeneration.[132] Furthermore, Aβ clearance was enhanced by oleocanthal, a component of olive oil[133] and by magnesium.[106] The BBB may obstruct Aβ clearance especially in the presence of vascular changes (lypohyalinosis or CAA or both). Recent research implicated the possibility of enhancing Aβ clearance, for example by transient opening of the BBB using magnetic resonance-guided focused ultrasound.[90–93] Focused ultrasound was also suggested to enhance glymphatic efflux, potentially facilitating the physical removal of pathologic proteins[95] and the transport of immunotherapeutics to the CNS in sufficient concentrations.[10]

Limitations

We might have missed relevant papers by applying our search strategy; furthermore, findings from in vitro studies should be interpreted with caution.

CONCLUSIONS

This systematic review summarises the current evidence on BBB dysfunction in AD. Taken together, the available evidence strongly suggests an interaction between Aβ deposition and clearance, vascular changes and dysregulation of the immune system in the disease process. The downstream effects of the Aβ peptide are elusive and may comprise transmigration of immune cells, downregulation of transcellular transport proteins and increase in BBB permeability but also vasculopathic effects. Further research is also required to elucidate the interaction of brain endothelial cells, pericytes, glial cells and neurons, the role of co-factors such as proinflammatory mediators in draining macromolecules and cells from the cerebral parenchyma, and connections to the glymphatic and the cerebral lymphatic system.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

1. Research Project: A. Conception, B. Organisation, C. Execution. 2. Manuscript Preparation: A. Writing the First Draft, B. Preparation of figures, C. Review and Critique. Carolin Kurz 1 A, 1 B, 1 C, 2 A, 2 B; Lauren Walker 1 A, 2 B, 2 C; Boris-Stephan Rauchmann 2 A, 2 C; Robert Perneczky 1 A, 1 B, 1 C, 2 C. All authors have read and agreed to the published version of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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