Blood-brain barrier alterations in ageing and dementia

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A B S T R A C T
The current pathogenic scenarios of different types of dementia are based on a number of common mechanisms of neurodegeneration, such as accumulation of abnormal proteins (within or outside cells), mitochondrial dysfunction and oxidative stress, calcium homeostasis dysregulation, early synaptic disconnection and late apoptotic cell death. Ageing itself is associated with mild cognitive deterioration, probably due to subtle multifactorial changes resulting in a global decrease of a functional brain reserve. Increased age is a risk factor for neurodegeneration and key pathological features of dementia can also be found in aged brains. One of the underexplored brain structures in ageing and dementia is the blood-brain barrier (BBB), a complex cellular gate which regulates tightly the transport of molecules into and from the central nervous system. Disruption of this barrier is now increasingly documented not only in brain vascular disease but also in ageing and neurodegenerative disorders. To date, such evidence points mainly at an association between various dementia forms and disruption of the BBB. But, in reviewing such results, and taking into account the exquisite sensitivity of neuronal function to the composition of the interstitial brain fluid (IBF), which is regulated by the BBB, we would like to propose the existence of a possible causal link between alterations of BBB and conditions associated with cognitive decline.

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1. Introduction
In order to function properly, the central nervous system (CNS), and the neurones in particular, require the maintenance of ionic concentrations (Na⁺, K⁺ and Ca²⁺) within narrow ranges and of adequate metabolic substrates. In addition, the neural function is also very sensitive to the effects of a wide variety of circulating substances (both proteins and non-proteins) that are not harmful to the peripheral organs. Such strict separation between the neural milieu and the circulatory space is achieved through the properties of a unique biological structure, essentially composed of capillary endothelial cells, basal lamina and astrocytes, and acting as a two-way diffusion barrier — the blood-brain barrier (BBB). Pericytes, the least studied BBB constituents, are mesenchymal-like cells surrounding the endothelial cells and able to contract brain capillaries and to change the blood flow [1,2]. The peculiarity of BBB (Fig. 1) is given, at least in part, by a specific phenotype of the endothelial cells, with adherens junctions as cell–cell interaction stabilizers, and tight junctions (TJs) that limit the paracellular flow of water, ions and larger molecules into the brain (gate function) and organize the cell membrane in apical–basal domains (fence function) [3]. The ‘sealing’ feature of the TJs is conferred by the expression in endothelial cells of transmembrane proteins such as occludin [4], claudins [5] and junction adhesion molecules [6], anchored via accessory proteins to the cytoskeleton [7]. This ‘BBB phenotype’ of endothelial cells is characterized by a low pinocytic activity and is also much more effective in limiting the paracellular flow of ions as compared to that in peripheral capillaries, as reflected by a ~100 fold higher transendothelial electrical resistance in the CNS [8]. Therefore, the molecular traffic at the BBB level takes place mostly by transcellular means. Gases, such as O₂ and CO₂, are exchanged through the lipid membranes, as a result of gradient diffusion, while the influx of amino acids and glucose is regulated through specific transporters. Larger molecules such as peptides (e.g. leptin, insulin, and transferrin) are transported by receptor-mediated transcytosis. With the exception of the receptor-guided molecules, passage of all other hydrophilic compounds, including drugs, is highly restricted under normal conditions. Size generally represents another passage criterion, substances with a molecular weight higher than 500 Da being unable...
endothelial cells, pericytes and astrocyte end-feet. Endothelial cells are sealed by tight and adherens junctions. The tight junctions are composed of transmembrane proteins such as occludin, claudins and junction adhesion molecules (JAM), which grasp actin-anchored cytoplasmic proteins such as ZO1, ZO2 and ZO3. Transport through the BBB mostly takes place by transcellular means: diffusion of gases (\(O_2, CO_2\)), transporters (e.g. GLUT-1 for glucose), or receptor-mediated transcytosis (e.g. insulin). P-glycoprotein (P-gp) operates the endothelial efflux of different compounds, including drugs, and aquaporin 4 (AQP-4) modulates the water flow into the brain. Physiological regulation of BBB permeability is probably regulated by both blood-borne and astrocytic factors, such as growth factors (transforming growth factor beta 1 — TGF\(\beta\)), vascular endothelial growth factor — VEGF, the basic fibroblast growth factor — bFGF, glial cell line-derived neurotrophic factor — GDNF, tumour necrosis factor (TNF) family members and calcium signals. Extracellular signal-regulated kinases (ERK) are activated through TNF receptors and are able to influence transcription via transcription factors. In BBB endothelial cells, localization of many proteins at the luminal and abluminal membranes differs, thus creating a ‘polarization’ (e.g. P-gp is expressed only in luminal capillary membranes; GLUT-1 is present at both cellular versants but asymmetrically). Moreover, there are proteins important for BBB transport expressed only in astrocytes, and not in endothelial cells, and vice versa (e.g. AQP-4 is abundant in glial endfeet but is absent in endothelial cells). Mobilization of cytosolic calcium (Ca\(^{2+}\)) in astrocytic endfeet occurs as a result of purinergic receptors (P2Y) signalling; however, how endothelial cells respond to these Ca\(^{2+}\) waves is not elucidated.

to cross the BBB [7]. Some of the transporters are specialized for endothelial efflux, for instance P-glycoprotein, which acts as an active, ATP-dependent pump [9]. Water flow into and out of the brain tissue is regulated by aquaporins (AQP). AQP-4 being expressed in astrocyte perivascular endfeet [10] to form water channels and to enable fluid homeostasis in the brain. In contrast, the brain endothelial cells do not express AQP channels [11]. Besides the physical and transport barriers described above, an enzymatic barrier made of nucleotidases and peptidases is active in the proximity of the capillaries [12].

Another potentially important theoretical issue is the physiological regulation of BBB permeability. The current view is that under normal circumstances the tightness and transport properties of the BBB are relatively constant, and this is in agreement with the need for a conserved extracellular milieu allowing normal CNS functioning. However, the major features of the endothelial cell phenotype in the BBB are dependent on astrocytes [13], indicated by the fact that protein expression and distribution in endothelia are induced by astrocyte-derived signals, and thereby being adaptable. In mixed culture conditions for instance, astrocytes induce the differentiation of endothelial cells and pericytes partly via secretion of transforming growth factor beta 1 (TGF\(\beta\)) [14], which also alters the expression of basement membrane-related molecules [15]. Moreover, there is evidence showing that other growth factors are synthesized and secreted by astrocytes, such as the vascular endothelial growth factor (VEGF) [16,17], the basic fibroblast growth factor (bFGF) [17,18] and the glial cell line-derived neurotrophic factor (GDNF) [19], are involved in modulation of BBB permeability. Recent reports also suggested that calcium signals originating in astrocytes can be transferred to capillary endothelial cells and mediate BBB transport processes [20]. Mobilization of cytosolic calcium (Ca\(^{2+}\)) in astrocytic endfeet occurs as a result of purinergic receptors (P2Y) signalling; however, how endothelial cells respond to these Ca\(^{2+}\) waves is not elucidated [21]. Endothelial cells bear also receptors of tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) receptor superfamiliy, such as TNFR1, Fas and DR5, but their ligands do not trigger cell death in this cell type. Instead, they are able to upregulate chemokines and adhesion molecules and to activate the extracellular signal regulated kinases [22]. Besides, TNF-\(\alpha\) can induce an upregulation of the efflux transporter P-glycoprotein in endothelial cells [23]. However, the regulation of occludin and claudins in endothelial cells and the factors inducing their low pinocytic phenotype, key features of the BBB gate function maintenance, are not yet clarified.

### 2. Ageing impact on blood-brain barrier

Dysfunction of the BBB in the ageing brain was documented by various studies and is at least in part responsible for pathological alterations such as white matter lesions [24], which in turn correlate with progressive cognitive deterioration [25]. In a recent review, Farrall and Wardlaw extensively document the increase in BBB permeability with ageing in healthy individuals. The commonly used methods to analyze the BBB function in studies in humans are either linked to brain imaging or biochemical. By means of assessment of the cerebrospinal fluid (CSF)/plasma albumin ratio, different studies demonstrated significantly higher albumin leakage through the BBB in old healthy as compared to young healthy individuals, and these
results were also confirmed by studies using brain imaging (computed tomography — CT, magnetic resonance imaging — MRI or positron-emission tomography — PET) [26].

In a rodent model of senescence, morphological changes of BBB [27] and leakage of endogenous albumin [28] and IgG [29] to the brain parenchyma were selectively demonstrated for brain regions involved in cognition, such as the hippocampus. The senescence-accelerated prone mouse strain 8 (SAMP8), which shows age-related learning and memory deficits [27], exhibits increased oxidative stress at an early age [30], before other pathological features are reported. Decreased levels of superoxide dismutase [31,32] and glutathione peroxidase [33] seem to be responsible for this modification. An age-related increase in amyloid precursor protein (APP) expression without plaque formation was described in the brain of the SAMP8 mice [34]. These results suggest that oxidative stress in brain parenchyma can trigger alterations of the BBB, possibly by cell death, gloosis and signalling changes. Moreover, in aged Wistar rats, which show impairment in short term-memory, leakage through the BBB was found to be associated with microglial activation [35]. The latter is a source of oxidative damage [36] possibly not only to neurons, but also to glial and endothelial cells. Leakage of BBB can induce microglial activation by letting abnormal molecules pass into the brain parenchyma and in turn free radicals released from the microglia may further alter the BBB, in a vicious cycle. In addition, passage of neuroimmune factors to the brain also changes with senescence. Furthermore, increased transport of TNF-α has been shown in some brain regions of old SAMP8 mice, suggesting that beyond modulating BBB properties, TNF-α is able to cross the BBB more efficiently with age [37], while passage of interleukin-1β (IL-1β) through the BBB decreases with age [38]. It was also suggested that the aged BBB is not able to transfer glucose properly to the brain, since expression of the glucose transporter GLUT-1 is reduced, both in physiologically aged [39] and in SAMP8 mice [37]. Neurotrophin-like peptides are able to reverse this modification [40], suggesting that protein expression at the BBB level could be influenced by neurotrophines during ageing.

Another effect of brain ageing is the accumulation of iron in astrocytes [41] and one suggested mechanism for this is the reduction of ceruloplasmin expression in the CNS [42]. Iron in excess can generate free radicals and harm cells [43], therefore its increase in the perivascular astrocytes could participate in alterations seen in BBB with ageing. Transferrin mRNA levels have been shown to increase in the brain with age, independent to blood-borne factors [44]. However, the reverse scenario, i.e. an increased passage of iron to the brain due to improper barrier function, cannot be excluded [45].

A different mechanism for BBB dysfunction in the elderly is the decreased activity of the efflux transporter P-glycoprotein that may result in decreased extrusion of toxins from the brain to capillaries. Toornvliet and coauthors measured P-glycoprotein activity in young and elderly healthy volunteers by (R)-(11)C verapamil and PET and found a significantly increased grey substance distribution for the ligand in the aged subjects [46], suggesting a decreased P-glycoprotein activity.

A decline in estrogen levels may also be involved in age-related malfunction of BBB and may result in sensitization to neurodegenera-
tion. Thus, Bake and Sohrabji found that BBB leakage is 2 to 4 times increased in senescent ovariectomized rats as compared to the young adult controls. Surprisingly, estrogen replacement resulted in a further increase of leakage at the hippocampal level [47]. Moreover, a recent study showed that mid-life adiposity factors correlate with BBB leakage in late life and suggested a sex-hormone mediated mechanism for this alteration [48]. In turn, an altered transfer through the aged BBB of leptin [49], a hormone of adipose tissue origin linked to obesity, could induce its deleterious central effects, which may be reversible [50]. Furthermore, ageing and obesity are both associated with reduced sensitivity to insulin in the brain [51,52], which can decrease the clearance of β-amylloid (Aβ) peptide by a mechanism linked to BBB [53].

3. Blood-brain barrier in cerebrovascular disease and vascular dementia

Vascular dementia (VD) is a syndrome with different etiologies and different pathogenic mechanisms, which associates with some common vascular risk factors [54]. Such a risk factor, perhaps the most important, is arterial hypertension. In epidemiological studies, antihypertensives showed a robust effect as protectors against development of dementia [55]. It was hypothesized that changes in brain microvasculature in response to chronic hypertension, for instance lipohyalinosis and fibrosis, may induce BBB failure, which further contributes to lacunar strokes, leukoaraisis and dementia [56]. Indeed, a recent report showed that hypertension can induce BBB alterations by modulation of protein expression level. In this study, spontaneously hypertensive rats (SHR) displayed lower levels of the TJ protein zonula occludens-2 (ZO-2) and higher levels of the ion transporter, Na⁺/H⁺ exchanger 1, as compared to control rats which maintained normal blood pressure values. In contrast, the expression of ZO-1, occludin, claudin-5 in endothelial cells at the BBB level remained unchanged [57]. The most acute and threatening effects of hypertension on BBB may occur in hypertension encepha-
lopathy, a condition in which the cerebral perfusion is elevated beyond the limits of autoregulation. In Dahl salt-sensitive rats, the most commonly used model for hypertension encephalopathy, BBB leakage is massive and can be reversed by treatment with α V-1, a selective peptide inhibitor of α protein kinase C (αPKC) [58,59]. Therefore, αPKC could be a promising therapeutic target for the protection of BBB under vascular stress [60] and possibly for the prevention of cognitive impairment in cardiovascular patients. Other PKC inhibitors were also previously reported to reduce the endothelial permeability induced by deleterious factors such as oxidative stress [61,62] and therefore it can be claimed that basic cell signalling mechanisms regulate endothelial transfer properties at least in patholo-
gical conditions. Besides kinase inhibitors, magnesium sulphate has been shown to reduce BBB permeability and brain oedema in an animal model for eclampsia by an AQP-4-independent mechanism [63]. More-
over, hypertension is not only able to alter BBB properties per se, but can also aggravate the BBB leakage and cognitive decline triggered by environmental factors, such as heat stress [64].

Type 2 diabetes mellitus appears to be a risk factor for developing VD, particularly if treated with insulin [65,66]. Despite being a peripheral disease, diabetes is able to induce alterations in BBB permeability [67], and this may be a mechanism for its role in VD caused by small vessels disease. In a rat model of diabetes it has been shown that the expression of GLUT-1 and GLUT-3 is downregulated, probably by an adaptive mechanism of protection against sustained high blood glucose levels [68]. Furthermore, in an in vitro BBB model and in streptozotocin-induced diabetic rats, the efflux transporter P-glycoprotein was found to be upregulated by high glucose through a NF-κB-dependent mechanism [69]. Hawkins and colleagues showed that in experimental rat diabetes BBB permeability to sucrose increased in parallel to a decrease in the level of the TJs proteins occludin and ZO-1 [70]. Interestingly, occludin expression in neurons is elevated in VD brains, suggesting an additional biological role for this protein [71]. Moreover, a recent study showed that in diabetic rats the BBB permeability is progressively increased despite normalization of blood glucose levels by insulin treatment [72]. Based on the molecular weight passage pattern, the authors suggested that the BBB failure in diabetes mellitus is mainly due to a loosening of the paracellular path. Besides affecting the properties of endothelial cells, diabetes may act on astrocyte phenotype, which is the other important regulator of molecular transport of the BBB [73].

High cholesterol and dyslipidemia are well-known vascular risk factors that associate with cognitive decline, stroke, VD and Alzheimer’s disease (AD), even though the molecular basis needs clarifying [74]. Brain cholesterol represents a quarter of the total cholesterol in the human body. It is synthesized locally and exchange with circulating cholesterol is normally prevented by the BBB [75]. The main carrier of...
Akt pathway [83]. Endothelial cells through inhibition of the phosphoinositide 3 kinase (PI3K)/protein kinase C (PKC) axis may be explained by a decreased interaction of monocytes with the endothelium [82]. The protective effect of statins on BBB permeability in diabetic rats, however, appears not to be a protective effect on endothelial permeability in diabetic rats, however, [79]. A sw e l l a si nn e u r o n a l oxidant protein NAD(P)H:quinone oxidoreductase (NQO1), which was induced by a low-density lipoprotein receptor-related protein (LRP) downregulation [103,109]. Even though there is no unifying theory that is able to fully explain the neuropathological lesions and the progression of the neurodegenerative process in AD, this disease is still best defined by dementia with a peculiar accumulation of Aβ peptide and hyperphosphorylated tau in the brain [91]. The ApoE genotype is a known factor for AD [92], and inflammation [93], vascular factors [94], oxidative stress and synaptic dysfunction [95], alterations in cell signalling [96] and sensitization to cell death [97] all appear to be important pathogenic mechanisms. Many of these factors are encountered in other dementia types, mainly in VD, therefore giving rationale for the concept that most of the dementia cases in fact have a mixed origin [54]. The importance of BBB alterations in AD is well established [98] and it is worthy to notice that many of the above mentioned disease mechanisms also affect the BBB (e.g. oxidative stress, vascular factors, inflammation). Furthermore, one crucial link between ageing and AD can be an altered management of Aβ at the BBB level [99]. First, since Aβ is produced not only in the brain but also in the periphery, leakage of Aβ from capillaries to the brain may occur both in aged and in pathologically altered BBB. Moreover, it was suggested that the receptor for advanced glycation end products (RAGE), which mediates transfer of Aβ to the brain through the endothelial cells [100], can be upregulated during ageing [101]. Second, a diminished extrusion of Aβ from the brain occurs during ageing, by a decreased low-density lipoprotein (LDL) receptor-related protein (LRP)–mediated endothelial transcytosis of Aβ [102]. Moreover, in P-glycoprotein null mice, clearance of Aβ from the brain falls by 50%, suggesting that not only LRP, but also P-glycoprotein is important in Aβ clearance [103]. As already mentioned, the activity of P-glycoprotein decreases with age [46] and therefore excessive accumulation of Aβ due to BBB impairment could be one of the links between ageing and AD. Indeed, a proof that BBB alteration precedes accumulation of senile plaques came from work performed in AD transgenic mice, in which a breakdown of BBB was demonstrable before Aβ deposits were seen in the brain [104]. In current therapeutic approaches, treatment of Aβ accumulation by means of RAGE or LRP may not be efficient enough to protect the brain from Aβ toxicity.

Table 1

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Possible intervention</th>
<th>Ageing or disease</th>
<th>Model/human</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased oxidative stress</td>
<td>Antioxidants, gene therapy to target SOD</td>
<td>Ageing</td>
<td>SAMP 8 mice</td>
<td>[30–33]</td>
</tr>
<tr>
<td>Microglia activation</td>
<td>Anti-inflammatory drugs</td>
<td>Ageing</td>
<td>Physiologically aged rats</td>
<td>[35]</td>
</tr>
<tr>
<td>Increased transport of TNF through BBB</td>
<td>Anti-TNF antibodies</td>
<td>Ageing</td>
<td>SAMP 8 mice</td>
<td>[37]</td>
</tr>
<tr>
<td>Decreased expression of GLUT-1</td>
<td>Neurotrophines, neurotrophic-like peptides</td>
<td>Ageing, diabetes (risk factor for VD)</td>
<td>Physiologically aged and SAMP 8 mice, SDR</td>
<td>[39,40,68]</td>
</tr>
<tr>
<td>Iron accumulation</td>
<td>Iron chelators</td>
<td>Ageing, high cholesterol (risk factor for VD), PD</td>
<td>Human, physiologically aged mice, cholesterol-enriched rabbits</td>
<td>[41,42,78,119]</td>
</tr>
<tr>
<td>Decreased activity of P-gp</td>
<td>Gene therapy targeting P-gp</td>
<td>Ageing, AD, PD</td>
<td>Human, P-gp null transgenic mice, SDR</td>
<td>[46,103,118]</td>
</tr>
<tr>
<td>Decreased estrogen level</td>
<td>New methods of estrogen replacement</td>
<td>Ageing</td>
<td>Senescent ovariectomized rats</td>
<td>[47]</td>
</tr>
<tr>
<td>Reduced sensitivity to insulin</td>
<td>Insulin, IGF-1</td>
<td>Ageing</td>
<td>Human, physiologically aged mice</td>
<td>[51,52]</td>
</tr>
<tr>
<td>Reduced occludin expression</td>
<td>Insulin, gene therapy, statins</td>
<td>Diabetes (risk factor for VD)</td>
<td>SDR</td>
<td>[70]</td>
</tr>
<tr>
<td>Decreased ZO-1 expression</td>
<td>Insulin, gene therapy, statins</td>
<td>Diabetes (risk factor for VD)</td>
<td>SDR</td>
<td>[70]</td>
</tr>
<tr>
<td>Decreased ZO-2 expression</td>
<td>Antihypertensives, gene therapy</td>
<td>Hypertension (risk factor for both AD and VD)</td>
<td>SHR</td>
<td>[57]</td>
</tr>
<tr>
<td>Increased endothelia–monocytes interaction</td>
<td>Inhibition of PI3K/Akt</td>
<td>Diabetes (risk factor for VD)</td>
<td>SDR</td>
<td>[82,83]</td>
</tr>
<tr>
<td>Activation of iκB kinase</td>
<td>iκB kinase specific inhibitors</td>
<td>Hypertension (risk factor for both AD and VD)</td>
<td>DSSR</td>
<td>[58,59,60]</td>
</tr>
<tr>
<td>Alteration of adhesions and TJs function</td>
<td>Calcium blockers</td>
<td>Stroke (risk factor for both AD and VD)</td>
<td>in vitro BBB model, rats</td>
<td>[85,86]</td>
</tr>
<tr>
<td>RAGE upregulation</td>
<td>RAGE blockers</td>
<td>Ageing, AD</td>
<td>AD transgenic mice</td>
<td>[101]</td>
</tr>
<tr>
<td>LRP downregulation</td>
<td>Gene therapy, other Aβi clearance strategies</td>
<td>Ageing, AD</td>
<td>AD transgenic mice</td>
<td>[102,109]</td>
</tr>
</tbody>
</table>

**SOD** = superoxide dismutase, **SAMP** = senescence-accelerated prone mice strain 8, **TNF** = tumour necrosis factor, **BBB** = blood-brain barrier, **GLUT-1** = glucose transporter 1, **VD** = vascular dementia, **SDR** = streptozotocin-induced diabetic rats, **PIN1** = phosphoinositide 3 kinase, **PKC** = protein kinase C, **DSSR** = Dahl salt-sensitive rats, **RAGE** = receptor for advanced glycation end products, **LRP =** low-density lipoprotein receptor-related protein, Aβ = β-amyloid peptide.
approaches it has been shown that antibodies to Aβ can induce clearance of Aβ from the brain, through the BBB [105]. ApoE4 is the main genetic risk factor for sporadic AD [92]. Mice deficient in apoE show a compromised BBB function, demonstrated by a spontaneous leakage of dyes into the brain [106], which progresses with age [107]. Mulder and colleagues showed that a high-fat diet is an important inducer of both atherosclerosis and BBB disruption in apoE KO mice suggesting that protective isoforms of apoE may protect the brain from pathological lesions induced by high-fat diet and BBB leakage [108]. Interestingly, apoE KO mice also show a decreased expression of LRP receptor [109].

A recent systematic review concluded on the existence of BBB disruption in patients with AD or VD. The authors reported that BBB permeability, as assessed by biochemical and imaging methods, significantly increases in both AD and VD as compared to ageing controls. Furthermore, the BBB leakage was more pronounced in VD patients as compared to AD patients [26], and this is in agreement with the experimental evidence that vascular factors are able to modify the BBB phenotype and properties (see the previous chapter). Bringing an argument that not only vascular factors could affect the BBB, Algotsson and Winblad recently reported on an altered BBB integrity in a subgroup of AD patients without noticeable vascular lesions [110]. Interestingly, men were primarily affected. However, in a recent report in Neurology, Bowman and colleagues followed a population of AD patients for one year and found that BBB impairment is present and constant in a subgroup of AD individuals, but with no correlation with age, gender, ApoE genotype or Mini-Mental State examination [111].

It is our view that BBB changes found in AD are not explained only on the basis of vascular lesions. The degeneration of neurones and activation of glial cells may also affect the endothelial cell phenotype and transport properties. For instance, BBB disruption has been shown to develop in a transgenic mouse model for taupathies [112], supporting the concept that the BBB is affected not only by vascular factors, but also by degeneration of brain-residing-cells. Dickstein and coworkers have also shown that expression of an AD-linked mutation in APP in transgenic mouse is sufficient to compromise the BBB integrity [113]. Moreover, astrocytes and neurones secrete trophic factors such as FGF2 and VEGF [114] that regulate BBB function and can be depleted in dementia [115]. Thus, it is conceivable that the BBB alteration in AD is due both to vascular factors and to cell degeneration and abnormal signalling. Moreover, disruption of BBB may accelerate the pathology of the disease, resulting in a vicious cycle. Some of the molecular mechanisms associated with BBB disruption in ageing and different dementia types and proposed protective treatments are presented in Table 1.

5. Blood-brain barrier in Parkinson's disease

Except for AD and VD, there is little known regarding BBB alterations in other neurodegenerative diseases associated with cognitive decline and dementia. However, a recent review analyses malfunction of BBB in Parkinson’s disease (PD) [98]. Recent data from animal experiments support a pathogenic link between BBB disruption and degeneration of dopaminergic neurones. Rite and colleagues found that increased permeability by injection of VEGF into the substantia nigra resulted in a subsequent loss of dopaminergic neurones [116]. Moreover, there is increasing interest in inflammation as a pathogenic mechanism in PD and possibly through alterations in BBB properties, as shown in many different experimental paradigms [117]. The first evidence of increased permeability of the BBB in PD came from a PET study, showing a significantly increased uptake of 11C-verapamil in the midbrain of PD patients relative to controls, suggested to be due to a decreased function of P-glycoprotein [118]. It was also speculated that an increased BBB passage of metals, such as iron or manganese, may be involved in PD pathogenesis [119].

6. Conclusions and perspectives

In this review we presented some of the evidence that is rapidly accumulating and which implicates dysfunctions of the blood-brain barrier in a variety of instances connected to cognitive decline, from
the normal ageing phenotype to various forms of dementia. Although these observations are currently mainly associated, the fact that both in ageing and during early neurodegenerative states the neurons are working in regimens of reduced homeostatic reserve [120] and thus become extremely sensitive and vulnerable to an altered composition of the extracellular milieu, raise the potentially very important question of whether BBB lesions could trigger, or at least accelerate, brain pathology, particularly when superimposed on a favorable genetic background (Fig. 2). This view was until now mostly applicable to understanding the etiopathology of multiple sclerosis or neuroinfections, rather than dementia. Nevertheless, there is increasing data showing that neurodegeneration per se can induce BBB disruption. Therefore, we conclude that an aggression to any component of the neurovascular unit can ultimately result in brain degeneration, pathological lesions and cognitive decline. Moreover, in the future it may be of interest to target the BBB with specific therapeutic approaches that could be complementary to strategies designed for neuronal protection or glia.

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