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The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia

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Abstract

There is increasing evidence that cerebrovascular dysfunction plays a role not only in vascular causes of cognitive impairment but also in Alzheimer's disease (AD). Vascular risk factors and AD impair the structure and function of cerebral blood vessels and associated cells (neurovascular unit), effects mediated by vascular oxidative stress and inflammation. Injury to the neurovascular unit alters cerebral blood flow regulation, depletes vascular reserves, disrupts the blood–brain barrier, and reduces the brain's repair potential, effects that amplify the brain dysfunction and damage exerted by incident ischemia and coexisting neurodegeneration. Clinical-pathological studies support the notion that vascular lesions aggravate the deleterious effects of AD pathology by reducing the threshold for cognitive impairment and accelerating the pace of the dementia. In the absence of mechanism-based approaches to counteract cognitive dysfunction, targeting vascular risk factors and improving cerebrovascular health offers the opportunity to mitigate the impact of one of the most disabling human afflictions.

Introduction

Alzheimer's disease (AD) and vascular dementia are the most common forms of cognitive impairment in the elderly [28]. The pathogenic mechanisms underlying these two conditions have traditionally been considered separate, even mutually exclusive [23]. At the time of Alois Alzheimer, dementia was most often attributed to vascular insufficiency or syphilis [70]. Over the next several decades, the emergence of AD as a distinct clinical-pathological entity established this condition as the prevailing cause of dementia. Biochemical, cellular, and molecular studies provided evidence that AD is caused by a neurodegenerative process leading to neuronal dysfunction and death related mainly to the amyloid- β peptide (A β) and hyperphosphorylation of the microtubule-associated protein tau [85]. Diagnostic criteria were drafted and widely applied, establishing AD as the predominant cause of senile cognitive impairment, a course of action aptly referred to as "alzheimerization" of dementia [70]. On the other hand, vascular dementia evolved from the concept of "arteriosclerotic dementia", in which hardening of cerebral arteries leads to diffuse ischemia and neuronal loss [70], to "multiinfarct dementia", caused by multiple infarcts resulting in cognitive impairment due to progressive brain loss [36]. In the early 1990s, the broader term "vascular cognitive impairment" (VCI) was introduced to encompass the wide spectrum of cognitive alterations associated with cerebrovascular pathologies, including more subtle deficits that would not fulfill AD criteria [35]. Standards for the diagnosis of VCI were established [13,34,86], and vascular causes of cognitive impairment have regained the attention of the basic and clinical neuroscience communities [23,49]. In addition, it has become widely

recognized that a large proportion of dementias is caused by mixed AD and vascular pathology, especially in older individuals [28,50]. Importantly, coexistence of ischemic and neurodegenerative pathology was found to have a profound impact on the expression of the dementia, suggesting reciprocal interactions between ischemia and neurodegeneration [75,102]. These observations, in concert with epidemiological studies indicating that AD and cerebrovascular diseases share the same risk factors [10], has revived the interest in the idea that vascular factors may play a role in the pathogenesis of AD [17,43,56]. This hypothesis has received support from experimental studies indicating that A β has potent cerebrovascular effects, and that hypoxia–ischemia is a powerful modulator of cerebral amyloidogenesis [41]. Both A β and vascular risk factors target the structure and function of cerebrovascular cells, glia, and neurons (neurovascular unit), resulting in neurovascular dysfunction. This brief review examines the neurovascular alterations underlying AD and VCI, and discusses their implications for the prevention and treatment of vascular and neurodegenerative dementia.

The neurovascular unit: the guardian of cerebral homeostasis

Neurons, glia, perivascular, and vascular cells, collectively termed the *neurovascular unit*, are closely interrelated and work in concert to maintain the homeostasis of the cerebral microenvironment (Fig. 1). Thus, the neurovascular unit regulates blood flow, controls the exchange across the blood–brain barrier (BBB), contributes to immune surveillance in the brain, and provides trophic support to brain cells.

Blood flow regulation

The brain's structural and functional integrity depends on a continuous and well-regulated blood supply, and interruption of cerebral blood flow (CBF) leads to brain dysfunction and death [74]. Consequently, the brain is equipped with control mechanisms that assure that the brain's blood supply is well matched to its energetic needs [44]. Thus, neural activity induces a powerful increase in CBF (functional hyperemia) that is thought to deliver energy substrates and remove toxic byproducts of brain activity [83]. Astrocytes, whose end-feet encircle the outer wall of cerebral microvessels (arterioles, capillaries, and venules), act as a link between synaptic activity and the cerebrovascular cells mediating the increase in CBF [44]. Cerebrovascular autoregulation holds CBF relatively constant despite changes in perfusion pressure and protect cerebral perfusion from potentially damaging fluctuations in arterial pressure [114]. Specialized receptors on the endothelial cell membrane initiate intracellular signaling cascades in response to mechanical (shear stress), chemical (neurotransmitters and neuromodulators) and cellular (circulating immune cells) stimuli, and release potent signaling molecules, like nitric oxide, endothelin, and prostanoids [124]. These endothelial mediators contribute to local flow distribution [3] and to other functions of the neurovascular unit as well (see below).

Blood–brain barrier exchange

Owing to the tight junctions between cerebral endothelial cell, highly specialized endothelial membrane transporters regulate the trafficking of macromolecules, ions, amino acids, peptides, neurotransmitters, and other signaling molecules between the blood and the brain, which is at the basis of the BBB [1]. Transporters on the abluminal side of the vessel regulate the removal of metabolic byproducts from the brain. Relevant to the mechanisms of AD and VCI, the BBB plays a critical role in the transport of A β to and from the brain [132]. Thus, circulating A β is transported into the brain via receptors for advanced glycation products (RAGE) on endothelial cells [18]. Intracerebral A β , normally produced by synaptic activity [15], is cleared from the brain through vascular mechanisms involving the

lipoprotein receptor protein 1 (LRP1) and P-glycoprotein, a process controlled by the serum response factor and myocardin [8,14,93].

Immune surveillance

Endothelial cells are able to detect blood-borne immune signals and express adhesion molecules (P- and E-selectin, intercellular adhesion molecule, vascular cell adhesion molecule, etc.) that recognize cognate molecules on circulating immune cells leading to the attachment and transmigration of these cells into the brain [118]. Cytokines produced by perivascular macrophages, endothelium, and glia regulate the expression of adhesion molecules, cytokines, and chemokines, and promote the trafficking of leukocytes across the BBB [64]. This process is vital both for immune surveillance in the normal brain and for the immune response of the brain to injury.

Hemostatic balance

Cells in the neurovascular unit play a critical role also in hemostatic balance. Whereas the prothrombotic effects of collagen and tissue factor in the vascular wall protect the tissue from hemorrhage, antithrombotic and profibrinolytic factors in the endothelium (NO, prostacyclin, CD39, plasminogen activators, etc.) prevent vascular occlusion [29]. Furthermore, the cerebrovascular endothelium is involved in the removal of intravascular clots, a process that may reestablish flow after microvascular embolism [65].

Trophic function

Endothelial cells exert trophic actions that are essential to the well-being of neurons and glia [128]. In turn, neurons and glia produce growth factors that provide trophic support to vascular cells. Such reciprocal trophic interaction is critical during development when ephrins, slit ligands, semaphorins, and netrins act as guiding cues for both migrating axons and vessels [119]. Furthermore, after brain injury, growth factors released from endothelial cells like brain derived neurotrophic factor (BDNF), vascular endothelial derived growth factor (VEGF), stromal-derived factor 1, and angiopoietin-1 orchestrate the migration and differentiation of neuroblasts [16,78,101]. Therefore, the survival of vascular cells neurons and glia relies on reciprocal trophic interactions, and the proper functioning of the neurovascular unit depends on the health of all its cellular constituents.

The neurovascular unit in VCI and AD

The structure and function of the neurovascular unit are profoundly impaired in VCI and AD [9,41]. These alterations disrupt the homeostasis of the cerebral microenvironment and promote the neuronal dysfunction underlying the impairment in cognition.

Structural alterations

Both VCI and AD are associated with marked alterations in cerebrovascular structure [57,92,120]. Large intracranial vessels exhibit atherosclerotic plaques not only in VCI but also in AD [7,40]. At the microvascular level, arterioles and capillaries are reduced in number, tortuous, and have thickened basement membranes [11,27,92,125]. The arteriolar wall exhibits degenerative changes and, in cases associated with hypertension, undergoes hyaline degeneration (lipohyalinosis), causing microhemorrhages [92]. In the periventricular white matter, a region prone to injury, reactive astrocytosis and microglial activation are associated with expression of hypoxia inducible genes, suggesting local energy deficit [27,99]. In AD or in cerebral amyloid angiopathy (CAA), accumulation of A β in the media of cortical arterioles leads to weakening of the vessel wall, increasing the chance of lobar hemorrhages [120].

Cerebrovascular dysregulation

Animal and human studies indicate that risk factors for VCI and AD, such as hypertension, aging, dyslipidemia, and diabetes, have profound effects on cerebrovascular regulation, and disrupt endothelium-dependent vasodilatation, functional hyperemia, and autoregulation [42,53,60,66,73,80,91]. Similarly, A β is a potent vasoconstrictor [111], and impairs the fundamental mechanisms regulating the cerebral circulation [45,76,77]. CBF is reduced, and functional hyperemia is attenuated in patients with AD [6,47,54,72,⁸⁴,87,108,117,127]. Furthermore, endothelial-dependent responses are impaired in systemic vessels of patients with AD [20]. Cerebral smooth muscle cells have a hypercontractile phenotype [12], which increases the constrictor tone of cerebral arteries and contributes to reduce resting CBF and its reactivity [41]. Vascular oxidative stress and inflammation have emerged as key pathogenic factors in neurovascular dysfunction [25,42,98]. In particular, experimental studies suggest that free radicals produced by the enzyme NADPH oxidase are responsible for the cerebrovascular alterations induced by VCI risk factors and A β [59,61,80,81]. Free radicals can trigger inflammation by activating redox sensitive transcription factors, like NF κ B and AP1. In addition, the endothelial dysfunction induced by oxidative stress can lead to release of VEGF and prostanoids, which promote vascular leakage, protein extravasation, and inflammation [71]. Inflammation, in turn, enhances oxidative stress by upregulating the expression of free radical-producing enzymes and by downregulating antioxidant defenses [30]. Inflammation and oxidative stress not only affect CBF regulation, but, as discussed below, have a profound impact on the other functions of the neurovascular unit as well.

Blood–brain barrier dysfunction

Alteration of the BBB is an early finding in white matter lesions associated with VCI and AD [26,132]. Extravasation of plasma protein triggers vascular inflammation, oxidative stress, perivascular edema, and axonal demyelination [26] (Fig. 2). Demyelination slows the transmission of nerve impulses, and contributes to the neural dysfunction that underlies cognitive impairment. In addition, in models of multiple sclerosis, the loss of saltatory conduction between nodes of Ranvier induced by demyelination, coupled with the expression of leaky Na⁺ channels on denuded axons, increases the inefficiency of action potential conduction [113]. Therefore, demyelination increases the oxygen demands of axons and enhances the local energy deficit and hypoxia [113]. A similar process could take place in the white matter lesions observed in AD and VCI [28], but additional evidence of demyelination with axonal preservation is needed to establish this point more firmly, especially in AD [46].

Alterations in BBB transport processes may also have an impact on the brain accumulation of A β in patients with AD [55,132]. The downregulation of the BBB receptors LRP-1 and P-glycoprotein promotes vascular A β deposition and may worsen the vascular dysfunction [8]. Furthermore, elevated circulating levels of A β in patients with VCI and AD could also promote cerebrovascular insufficiency, inflammation, and oxidative stress, and play a role in the white matter alterations observed in both conditions [31,33] (Fig. 2).

Loss of trophic support

Vascular oxidative stress, aging, and inflammation disrupt neurovascular trophic function [16]. Pro-inflammatory cytokines impair growth factor signaling inducing a state of “neurotrophin resistance” [112,115]. Furthermore, oxidative stress attenuates the growth factor support provided by endothelial cells to oligodendrocyte precursors [4]. Loss of trophic support may impede the proliferation, migration, and differentiation of oligodendrocyte progenitor cells, and compromise the repair of the damaged white matter in AD and VCI [5,79,96,97] (Fig. 2). Loss of neurovascular trophic support is also observed in AD. Inflammation and oxidative stress can result in neurotrophin resistance (see above), but

other factors also contribute to impair trophic support at the microvascular level. For example, the homeobox gene MEOX, critical for vascular differentiation, is suppressed in patients with AD and may mediate the cerebral microvascular rarefaction observed in this disease [125]. A β induces endothelial cell autophagy [37], and inhibits vasculogenesis, effects mediated by inhibition of VEGF signaling [82]. In AD patients, the perivascular accumulation of endostatin, a neurally derived antiangiogenic factor, may also contribute to the vascular damage [21]. Although CSF levels of VEGF are increased in AD [109], brain VEGF is sequestered by amyloid plaques [126], reducing its bioactivity. Furthermore, BDNF levels are low in AD brains [94]. Collectively, these alterations in growth factors expression, localization, and signaling are likely to have a major impact not only in the vascular alterations observed in AD and VCI, but also in the brain atrophy associated with these conditions [88,106].

Interactions between ischemia and neurodegeneration

The profound effects of cerebrovascular risk factors and A β on the neurovascular unit suggest a pathogenic link between ischemia and neurodegeneration [48]. The pathological changes characteristic of AD, i.e., amyloid plaques and neurofibrillary tangles, are observed together with vascular pathology (subcortical white matter lesions, lacunes, infarcts, etc.) in more than 40% of elderly demented individuals [49]. This finding is not surprising since both neurodegenerative and ischemic changes are common in the elderly and would be anticipated to coexist in a large number of cases [48]. Volume of ischemic lesions and their location play a critical role in the expression of the dementia in mixed cases [49]. Nevertheless, the coexistence of ischemic and neurodegenerative pathologies raises a number of questions related to their effects on cognition, and has important implications for the prevention, diagnosis, and treatment of VCI and AD.

Does vascular insufficiency promote neurodegenerative changes and vice versa?

Ischemia may promote A β accumulation by reducing the vascular clearance of this peptide, its major elimination pathway [15,19]. In addition, hypoxia and/or ischemia promote the cleavage of A β from the amyloid precursor protein (APP) by upregulating β -secretase expression and activity [62,69,107,110,121,131]. These experimental findings indicate that increased production and reduced clearance could enhance A β deposition in brain and favor the formation of amyloid plaques and CAA (Fig. 3). Indeed, brain A β levels and amyloid plaques are elevated in patients with cerebrovascular insufficiency and VCI [68]. On the other hand, the cerebrovascular dysfunction induced by A β could threaten cerebral perfusion, reduce vascular reserves, and increase the propensity to ischemic damage. Consistent with this hypothesis, focal cerebral ischemia produces larger infarcts in mice overexpressing APP [63,130], an effect associated with A β -induced vascular dysregulation, reduced collateral flow, and more severe ischemia [130]. Similarly, patients with AD have heavier burden of cerebrovascular lesions [51]. Paradoxically, some cardiovascular risk factors can increase the risk of AD without aggravating neurodegenerative pathology. For example, diabetes mellitus doubles the risk of AD without a corresponding increase in plaques and tangles [58,104]. Rather, a prominent increase in microinfarcts is observed [58], suggesting that the effect of diabetes on AD risk is related to microvascular lesions that amplify the consequences of the neurodegenerative pathology [58]. The interaction between vascular lesions and neurofibrillary tangles is less well understood. Focal cerebral ischemia promotes tau phosphorylation in animal models [122], and hypertension increases neurofibrillary tangles in the hippocampus of non-demented elderly persons [105], suggesting a link between tau hyperphosphorylation and vascular factors. But, in triple transgenic mice expressing plaques and tangles, transient cerebral hypoperfusion, a more global yet milder ischemic insult, reduces tau levels [62]. Although this finding is reminiscent of the reduced neurofibrillary tangles observed in patients with mixed dementia

[32,75], to what extent ischemia modulates neurofilament dynamics and phosphorylation remains unclear. Therefore, while there is evidence that ischemia promotes A β accumulation by enhancing production and reducing its clearance, the impact that ischemia exerts on tau pathology is less well understood.

Does the vascular pathology worsen the cognitive dysfunction in AD?

Ischemic lesions enhance the severity of the dementia in AD patients. Thus, most studies, with notable exceptions [67], found that moderate AD pathology has a much greater cognitive impact in patients who also exhibit basal ganglia lacunes, ischemic white matter lesions, symptomatic, or silent infarcts [39,75,89,102,103,116,123]. The effect of vascular lesions is more pronounced in patients in the early stages of AD [24,90]. In addition, ischemic lesions and vascular risk factors also accelerate the tempo of the dementia [38]. AD patients with a reduced cerebrovascular reactivity to hypercapnia, an index of cerebrovascular function, have a more rapid cognitive decline [95], linking disease progression with cerebrovascular dysfunction. Therefore, coexisting cerebrovascular disease or incident ischemic lesions may shorten the preclinical stage of AD and accelerate disease progression.

Are the cognitive effects of vascular and AD pathology additive or synergistic?

In mixed dementias, the vascular pathology may worsen the cognitive effects of neurodegeneration by different mechanisms. Neurodegeneration and ischemic lesions could contribute independently to the dementia, the cumulative cognitive decline being the sum of the deleterious cognitive effects exerted by each pathology (additive effects). Alternatively, the vascular pathology could interact synergistically with the neurodegenerative changes resulting in a cognitive decline greater than that produced by each pathology alone (synergistic effects). Furthermore, there could be a “pathogenic” synergy between the two disease processes, such that the tissue damage produced by vascular factors could enhance the damage produced by neurodegeneration and vice versa. The evidence reviewed above indicates that synergistic pathogenic interaction between vascular and neurodegenerative pathologies is biologically plausible because in animal models ischemia promotes A β accumulation and, in turn, A β aggravates ischemic injury (Fig. 3). The observation that patients with AD have more cerebrovascular lesions at autopsy [51] would support this possibility. Furthermore, with exceptions [2], cerebrovascular insufficiency has been reported to promote formation of amyloid plaques [52]. On the other hand, synergistic effects on cognition are suggested by clinical-pathological studies demonstrating that minimal cerebrovascular pathology worsens the cognitive impact of mild AD pathology [24,102,129]. However, in patients with more severe vascular and AD lesions, the cognitive effects seem to be additive [90]. Therefore, it is likely that both additive and synergistic effects can be observed depending on the magnitude of vascular and neurodegenerative pathology and the stage of evolution of the disease process.

In conclusion, vascular lesions are detrimental to cognitive function either by directly damaging neural pathways involved in higher integrated functions or by worsening the impact of AD pathology. Considering that modifiable vascular risk factors can be controlled, approaches to treat dementia should rely heavily on strategies to preserve cerebrovascular health. In support of this approach, treatment of vascular risk factors in AD patients slows down the cognitive decline [22]. A healthy diet and exercise can help minimize the deleterious effects of cardiovascular risk factors and have a positive effect on cognition [16,100]. In the absence of specific interventions targeting the mechanisms of vascular or neurodegenerative dementia, lifestyle modification and risk factor control may be valuable initial steps to mitigate the cognitive decline associated both with AD and VCI.

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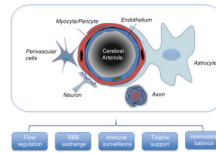


Fig. 1.

The neurovascular unit is constituted by endothelial cells, myocytes, neurons and their processes, astrocytes, and perivascular cells (microglia, macrophages, mast cells, etc.). In arterioles and capillaries, the foot processes of astrocytes envelop the majority of the abluminal vascular surface. In capillaries, myocytes are replaced by pericytes. The function of the neurovascular unit is to maintain the homeostasis of the cerebral microenvironment. Thus, the neurovascular unit is involved in cerebral blood flow regulation, blood–brain barrier (*BBB*) exchange, immune surveillance, trophic support, and hemostatic balance. Cardiovascular risk factors and $A\beta$ alter the structure and function of the neurovascular unit leading to neurovascular dysfunction

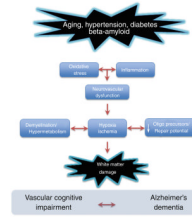


Fig. 2.

Mechanisms of white matter damage produced by cardiovascular risk factors and A β . Oxidative stress and inflammation induced by these factors are responsible for disruption of the functions of the neurovascular unit (see Fig. 1), which, in turn, leads to local hypoxia–ischemia, axonal demyelination, and reduced repair potential of the white matter by altering oligodendrocyte progenitor cells. Data in autoimmune models of demyelination suggest that loss of myelin increases the energy consumption of the affected axons and aggravates local hypoxia. The resulting white matter damage contributes to both VCI and AD

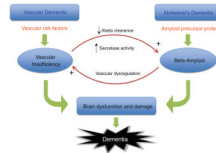


Fig. 3.

In vascular dementia, cerebrovascular risk factors induce neurovascular dysfunction (see Fig. 2), leading to cerebrovascular insufficiency, which, in turn, leads to brain dysfunction and damage. In AD, cleavage of the amyloid precursor protein by β - and γ -secretases leads to $A\beta$ accumulation, which also causes brain dysfunction and damage. Although individually these pathways are capable of inducing cognitive impairment, their interaction enhances their pathogenic effects. Thus, $A\beta$ induces vascular dysregulation and aggravates the vascular insufficiency, thereby enhancing the brain dysfunction and damage associated with vascular risk factors. On the other hand, the hypoxia–ischemia resulting from the vascular insufficiency increases $A\beta$ cleavage from APP and reduces $A\beta$ clearance through the cerebral vasculature, promoting $A\beta$ accumulation and the attendant deleterious effects on the brain