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Hypertension, dietary salt and cognitive impairment

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Abstract

Dementia is growing at an alarming rate worldwide. Although Alzheimer disease is the leading cause, over 50% of individuals diagnosed with Alzheimer disease have vascular lesions at autopsy. There has been an increasing appreciation of the pathogenic role of vascular risk factors in cognitive impairment caused by neurodegeneration. Midlife hypertension is a leading risk factor for late-life dementia. Hypertension alters cerebrovascular structure, impairs the major factors regulating the cerebral microcirculation, and promotes Alzheimer pathology. Experimental studies have identified brain perivascular macrophages as the major free radical source mediating neurovascular dysfunction of hypertension. Recent evidence indicates that high dietary salt may also induce cognitive impairment. Contrary to previous belief, the effect is not necessarily associated with hypertension and is mediated by a deficit in endothelial nitric oxide. Collectively, the evidence suggests a remarkable cellular diversity of the impact of vascular risk factors on the cerebral vasculature and cognition. Whereas long-term longitudinal epidemiological studies are needed to resolve the temporal relationships between vascular risk factors and cognitive dysfunction, single-cell molecular studies of the vasculature in animal models will provide a fuller mechanistic understanding. This knowledge is critical for developing new preventive, diagnostic, and therapeutic approaches for these devastating diseases of the mind.

Keywords

Alzheimer disease, cerebrovascular disease, dementia, endothelial dysfunction, neurovascular coupling

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Introduction

Dementia is an umbrella term referring to a progressive and irreversible decline in cognitive abilities sufficient to interfere with activities of daily living, typically associated with aging.[1] It affects approximately 50 million people worldwide, a number expected to grow by nearly 9.9 million new cases each year due to demographic shifts and lack of effective therapies.[2] While Alzheimer disease (AD) is the leading cause, dementia on vascular basis is the second leading cause of cognitive impairment.[3] However, up to 50% of clinically diagnosed AD have a mixed pathology at autopsy including cerebrovascular lesions[4] (Figure 1). Therefore, vascular pathology once considered to be linked exclusively to vascular cognitive impairment, has emerged as a key contributor also to other forms of dementia.[3,5]

Hypertension (HTN) is the major vascular risk factor of cognitive impairment.[3] Based on new diagnostic guidelines, HTN afflicts almost 50% of the population in the US.[6] Owing to its key role in vascular cognitive impairment, the World Health Organization has set a global target of 25% relative reduction in the prevalence of HTN by 2025 as a key measure to reduce the risk of cognitive decline.[2] High dietary salt is associated with HTN in many patients, but the effects of salt go beyond its role in blood pressure (BP) elevation. Specifically, a high-salt diet has been independently linked to increased risk of cerebrovascular disease and dementia.[7,8] Therefore, dietary salt, although not currently identified as one of the risk factors targeted for

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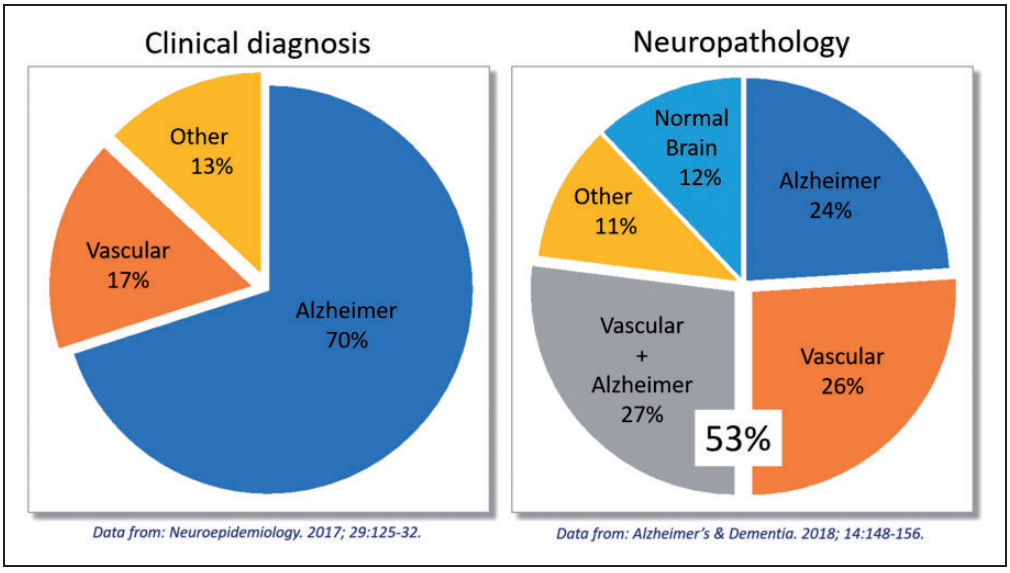

Figure 1. Over 50% of cases of clinically diagnosed Alzheimer disease (AD) feature vascular pathology. AD represents 70% of cases of late-life dementia, diagnosed according to clinical criteria. However, post-mortem neuropathological analysis reveals that only 24% of dementia cases feature exclusively AD pathology (amyloid plaques and neurofibrillary tangles), while over 50% feature vascular pathology, either alone (26%) or mixed with AD pathology (27%).

prevention of dementia,[2] may also contribute to cognitive impairment.[9]

The purpose of this brief review is to evaluate the current evidence identifying potential mechanisms underlying the damaging effects of HTN and dietary salt on the brain. First, we will discuss the importance of maintaining adequate perfusion to the brain, and the link between reduced cerebral blood flow (CBF) and cognitive impairment. Then, we will examine the structural and functional cerebrovascular alterations caused by HTN, as well as the recently emerged connection between dietary salt and cognitive dysfunction. Finally, we will seek to identify outstanding questions that need to be addressed and related challenges to overcome.

CBF regulation and impact on cognitive function

The brain relies upon a continuous blood supply to deliver essential nutrients to support its dynamic and regionally diverse energetic needs, and to clear potentially toxic byproducts of brain activity.[10] Vascular, perivascular, and brain cells work together as a unit, termed the "neurovascular unit" (NVU), to assure adequate blood perfusion to the brain and maintain the homeostasis of the brain's internal milieau.[10] Here, we will briefly review the main mechanisms involved in CBF regulation, and provide evidence linking inadequate cerebral perfusion to cognitive impairment.

Cerebrovascular autoregulation

Cerebrovascular autoregulation maintains CBF relatively constant in response to BP changes within a certain range, normally from 60 and 150 mmHg.[11] Autoregulation ensures adequate perfusion despite changes in perfusion pressure, while protecting downstream microvessels from excessive transmural pressure. Autoregulation is mainly dependent on the property of vascular smooth muscle cells to contract in response to increased transmural pressure (myogenic tone). Thus, a rise in BP results in vasoconstriction, while a decrease in BP leads to vasodilation. This key protective mechanism is mediated by complex molecular events that finely regulate intracellular Ca^{2+} and the Ca^{2+} sensitivity of the contractile apparatus to induce assembly of contractile proteins and ultimately induce constriction.[12] Bayliss' myogenic hypothesis of autoregulation[13] has been extensively investigated since its original proposal and focuses on mechanoreceptors on vascular smooth muscle cells.[14] For example, several members of the transient receptor potential (TRP) channel superfamily are found in vascular smooth muscle cells and have been shown to be mechanosensitive, and TRPC6 and TRPM4 have been shown to have a critical role in cerebral autoregulation. One hypothesis is that TRPC6 increases Ca^{2+} entry in response to mechanical stress, which in turn activates TRPM4 channels to allow Na^{+} entry leading to further depolarization, activation of voltage dependent Ca^{2+} channels, and constriction of the smooth muscle cell.[15]

Additionally, mechanoreceptors on endothelial cells have been proposed to contribute to autoregulation by modulating the response to shear stress and transmural pressure by releasing both constricting and relaxing-factors.[14,16] These mechanisms, in addition to the release of vasoactive metabolites due to reduced cerebral perfusion, may also contribute to the smooth muscle relaxation underlying the lower limit of autoregulation.[14]

Endothelial cells: Vasoregulatory function and the blood–brain barrier

Endothelial cells regulate vasomotor tone by releasing vasoactive signals which include both constrictor (endothelin-1, thromboxane A2, prostaglandin H2, etc.) and relaxing factors (nitric oxide [NO], bradykinin, endothelium-derived hyperpolarization factor [EDHF], prostacyclin [PGI2], prostaglandin E2, etc.).[17] The precise nature of EDHF remains elusive and could be either a chemical or an electrical signal.[18] Perhaps the most studied endothelium-dependent mechanism is NO-mediated vasodilation. NO is produced in endothelial cells by endothelial NO synthase (eNOS), and its diffusibility allows it to freely permeate membranes to reach vascular smooth muscle cells.[19] Then, NO activates soluble guanylate cyclase (sGC), which in turn leads to the generation of the second messenger cyclic guanosine monophosphate (cGMP).[19] Thus, vasodilation is ultimately induced by intracellular cGMP through a reduction in intracellular Ca^{2+} concentration, activation of K^+ channels leading to hyperpolarization and relaxation of the smooth muscle cell, and cGMP-dependent protein kinase 1 activation of myosin light chain phosphatase.[20] The endothelium participates in regulating blood flow, as laminar sheer stress and mechanical stretch stimulate production of NO and reactive oxygen species (ROS), major determinants of NO bioavailability.[21] Endothelial cells are also involved in the retrograde propagation of the vasodilation evoked by neural activity (discussed in the next section).

The cerebral endothelium is the site of the blood–brain barrier (BBB), which restricts the molecular exchange between blood and brain.[22] There are three main mechanisms by which the BBB regulates the entry and removal of molecules into and from the brain: tight junctions, active bidirectional transporters, and vesicular transport (transcytosis). Adjacent endothelial cells are linked by junctional complexes (tight junctions) which prevent paracellular passage of blood borne substances. Astrocytic end-feet play a crucial role in the development and maintenance of integrity of the tight junctions. Cerebral endothelial cells express transporters for the bidirectional transfer of molecules across the BBB.[22] Transcytosis is normally very limited in cerebral endothelial cells, which has been attributed the expression of the omega-3 fatty acid transporter Mfsd2a.[23] Pericytes, mural cells that replace smooth muscle cells at the level of the capillaries, may also be involved in the regulation of transcytosis.[24] Additionally, plasmalemma vesicle-associated protein (plvap), normally associated with high vesicular transport in peripheral vessels, has been found to be negatively correlated with BBB development, so that as the BBB is established during development, the expression of plvap decreases.[25]

Neurovascular coupling

Neural activity increases local CBF through complex mechanisms involving neurons, astrocytes, and vascular cells known as neurovascular coupling.[26] The increase in blood flow is coupled to meet the energetic demands of the brain by increasing the delivery of glucose and oxygen, while also clearing the byproducts of cellular metabolic activity.[27] Vasoactive mediators are released during brain activity and act on the cerebral vasculature to induce vasodilation at the activated site and also in upstream vascular segments. This requires a concerted effort involving various cell types along the cerebrovascular tree. We will discuss the contributions of these cells to neurovascular coupling only briefly since the topic has been recently reviewed.[10]

Synaptic activity is the initiating factor triggering neurovascular coupling. Glutamate binding on both NMDA and AMPA receptors on neurons elicits the release of potent vasodilators, including NO and prostanoids, through the activation of calcium-dependent enzymes such as neuronal NOS (nNOS) and cyclooxygenase (COX) 2. Glutamate could also bind to metabotropic glutamate receptors on neighboring astrocytes to induce vasodilation through the release of arachidonic acid metabolites through COX and cytochrome p450 epoxygenase pathways,[26] but this mechanism remains controversial.[10] Release K^+ ions mediated by calcium-activation of BK channels in astrocytic end-feet has also been implicated in neurovascular coupling.[26] K^+ ions then induce vascular smooth muscle relaxation through Kir channels.[10] However, the contribution of this mechanism also remains unclear since deletion of BK channels does not impair neurovascular coupling.[10] Interneurons, cells endowed with powerful vasoactive agents, can also have a profound effect on local CBF, and there is evidence that they could contribute to CBF regulation during neural activity.[28] In addition, adenosine, a metabolic messenger produced during ATP hydrolysis, also contributes to the increase in CBF during neuronal activity. Finally, changes in O_2 and CO_2 concentrations in the brain, as a result of

cellular aerobic catabolism, are able to modulate cerebral perfusion.[26] Therefore, multiple vasoactive factors are involved in linking neural activity to local cerebral perfusion.

Adding to the complexity of neurovascular coupling, the mechanisms involved vary depending on the segment of the cerebral vasculature. The role of astrocytes seems to be restricted to capillaries, and not upstream arterioles, whereas in arterioles, neurovascular coupling seems to be mediated by NMDA receptor-induced neuronal NO production.[29] Microvascular endothelial cells may play a unique role in the retrograde propagation of activity-induced neurovascular signals.[30] This retrograde propagation of vasodilation is necessary, as upstream vessels must also relax in order to adequately supply increased flow to the vascular segment of the activated regions downstream and prevent "flow steal" from neighboring interconnected vascular territories. The mechanisms of retrograde propagation in cerebral vessels have not been fully elucidated, but in peripheral vessels, it is known to be driven through a fast Ca^{2+}-activated K^+ (K_{Ca}) channel-mediated component, and a slow NO and prostanoid-mediated component.[10,31] In the cerebral vasculature, the endothelial Kir channels have been implicated in mediating the fast component, instead of the K_{Ca} channel involved in the peripheral vasculature.[32] Thus, neurovascular coupling results from a concerted effort involving various cell types and vasoactive modulation on different segments of the cerebrovascular tree to increase flow in the activated areas.

Cerebral perfusion and cognitive function

Adequate brain perfusion is critical for optimal brain health. Several cellular events occur with gradual reductions in CBF. First, protein synthesis is inhibited at CBF of 35–55 ml/100 g/min.[33] Next, metabolism switches to anaerobic glycolysis at CBF at 20–35 ml/100 g/min,[34] and overall glucose metabolism declines at CBF 20–25 ml/100 g/min.[35] Finally, cellular ion homeostasis fails below 10–12 ml/100 g/min[36] leading to irretrievable cell damage and death. Concerning the impact of hypoperfusion on cognition, reduction in CBF from 47 to 37 ml/100 g/min produced a transient deterioration of sustained attention. However, patients whose CBF dropped to 27 ml/100 g/min suffered from impaired sustained attention which persisted until the carotid obstruction was reversed.[37] It is important to note that these are average CBF levels, and there was substantial variability within the groups, indicating that these are not hard-drawn lines identifying how much CBF needs to be reduced in order to lead to cognitive impairment.

Cognitive impairment is observed across a wide range of conditions associated with reduced cerebral perfusion. In patients with transient ischemic attack (TIA), acute perfusion deficits in the carotid artery territory leads to decreased cognitive performance after 90 days.[38] The link between TIA and subsequent dementia is clinically relevant, since it suggests that TIA may lead to cognitive impairment independently of the increased risk for future strokes. Chronic carotid stenosis caused by atherosclerosis increases the risk of cognitive deterioration.[39,40] Furthermore, in heart failure, low ejection fraction is associated with reduced verbal memory,[41] as well as impaired cerebral autoregulation, vasomotor tone,[42] and reduced CBF.[43]

Reduced CBF may precede the development of dementia.[44] CBF and cerebrovascular reactivity are reduced in patients with mild cognitive impairment.[45] In elderly adults, low CBF is associated with faster brain atrophy[46] and cognitive deterioration.[47] Most importantly, a recent prospective study linked cerebral hypoperfusion with accelerated cognitive decline and an increased risk of dementia in the general population.[48] Although previous cross-sectional studies found an association with hypoperfusion in mild cognitive impairment and AD cohorts,[49] this is the first study to extend these findings to pre-symptomatic individuals in the general population, thus providing further evidence of the importance of adequate cerebral perfusion for maintenance of brain health. These findings, collectively, highlight the dependence of cognitive function on cardiovascular and cerebrovascular health and on adequate cerebral perfusion.

HTN is a major cause of CBF dysfunction

The brain is a major target of end-organ damage in HTN. HTN has profound effects on the cerebral vasculature leading to both structural and functional alterations affecting the NVU at all levels of the cerebrovascular tree.[27] These alterations may promote vascular insufficiency, leading to neuronal dysfunction and cognitive impairment.[50] This section will discuss the effects of HTN on the cerebral vasculature. Selected papers describing the alterations in cerebrovascular function induced by HTN are present in Table 1.

Structural alterations

Cerebral blood vessels undergo several adaptive changes in response to the increase in arterial pressure in an attempt to protect microvessels from the increased pulsatile and mechanical stress.[51] Vascular smooth muscle cells undergo a rearrangement of their organization leading to a decrease in the wall-to-lumen ratio without major changes in cross-sectional area (eutrophic remodeling). On the other hand, smooth muscle cells hypertrophy leads to a drastic increase in

Table 1. Selected examples of cerebrovascular alterations in models of hypertension.

Model		Cerebrovascular effects	Method	References
Genetic	SHR	Impaired autoregulation	Cranial window (LDF)	Toyoda et al.[144]
		Impaired neurovascular coupling	Cranial window (LSF) Thin skull (2PLSM)	Calcinaghi et al.[96]
		Endothelium-independent responses		
		Enhanced constriction (Ser)	Basilar artery rings	Winquist et al.[145]
		Reduced calcium sensitivity		
		Endothelium-dependent responses		
		Impaired dilatation (ACh)	Pressurized MCA	Toth et al.[146]
			Cranial window (LSF)	Freitas et al.[147]
	SHR-SP	Impaired autoregulation	Cranial window (LDF)	Smeda et al.[148]
		Endothelium-independent responses		
		No effect (Adenosine)	Cranial window (pial a. Ø)	Mayhan et al.[149]
		Endothelium-dependent responses		
		Impaired dilatation (ACh)	Cranial window (pial or basilar a. Ø)	Mayhan et al.[149] Kitazono et al.[150]
		Impaired dilatation (BK)	Cranial window (pial a. Ø)	Yang et al.[151]
		Impaired dilatation (A23187)		Yang et al.[152]
	BPH	Impaired neurovascular coupling	Cranial window (LDF)	Faraco et al.[88]
		Endothelium-independent responses		
		No effect (Adenosine)	Cranial window (LDF)	Faraco et al.[88]
		Endothelium-dependent responses		
		Impaired dilatation (ACh)	Cranial window (LDF)	Faraco et al.[88]
Salt-sensitive	Dahl SS	Impaired autoregulation	Cranial window (LDF) Pressurized MCA Ø	Fan et al.[153] Smeda et al.[154]
	DOCA-salt	Impaired neurovascular coupling	Cranial window (LDF)	Faraco et al.[119]
		Endothelium-independent responses		
		Enhanced constriction (Ser)	Basilar artery strips	Soltis et al.[155]
		No effect (Adenosine)	Cranial window (LDF)	Faraco et al.[119]
		Endothelium-dependent responses		
		Impaired dilatation (ACh)	Cranial window (LDF)	Faraco et al.[119]
			Pressurized MCA/Pen. Art. Ø	Matin et al.[156]
Ang II	Topical neocortex	Impaired neurovascular coupling	Cranial window (LDF)	Kazama et al.[95]
		Endothelium-dependent responses		
		Impaired dilatation (ACh)	Cranial window (LDF)	Faraco et al.[119]
	Acute i.v.	Impaired neurovascular coupling	Cranial window (LDF)	Kazama et al.[93]
		Endothelium-independent responses		
		No effect (Adenosine)	Cranial window (LDF)	Girouard et al.[72]
		Endothelium-dependent responses		
		Impaired dilatation (ACh)	Cranial window (LDF)	Girouard et al.[72]
			Carotid rings	Didion et al.[157]
		Impaired dilatation (A23187)	Cranial window (LDF)	Capone et al.[98]
	Slow pressor	Impaired neurovascular coupling	Cranial window (LDF)	Kazama et al.[95]
		Endothelium-independent responses		
		Enhanced constriction (Ser)	Carotid rings	Ryan et al.[158]
		No effect (Adenosine)	Cranial window (LDF)	Capone et al.[94]
		Endothelium-dependent responses		
		Impaired dilatation (ACh)	Carotid rings	Schrader et al.[77]
			Pressurized basilar a. Ø	Chrissobolis et al.[70]
			Cranial window (LDF)	Capone et al.[94]
		Impaired dilatation (BK)	Cranial window (LDF)	Capone et al.[94]
		Impaired dilatation (A23187)	Cranial window (LDF)	Capone et al.[94]
			Pressurized basilar a. Ø	Johnson et al.[159]

SHR: spontaneously hypertensive rat; SHR-SP: Stroke-prone SHR; SS: salt sensitive; LDF: laser Doppler flowmetry; LSF: laser speckle flowmetry; 2PLSM: 2-photon laser scanning microscopy; Ser: Serotonin; ACh: Acetylcholine; BK: Bradykinin; A23187: calcium-ionophore; Ø: diameter; MCA: middle cerebral artery.

cell size in conjunction with the accumulation of extracellular matrix components, ultimately resulting in a decreased lumen size (hypertrophic remodeling). Deposition of collagen and fibronectin causes stiffening of the vessel walls,[27] which is associated with clinically silent brain lesions in patients with HTN, and has been identified as a predictor of both stroke and cognitive decline.[3] Additionally, HTN-induced vessel hypertrophy leads to increased vascular resistance as the lumen diameter is reduced, and is a potential risk factor for cerebrovascular disease in patients.[52] These alterations have a profound effect on cerebral perfusion as they lead to increased vascular resistance and stiffening of arteries, but may also affect autoregulation (see next section). Furthermore, HTN promotes build-up of atherosclerotic plaques in cerebral blood vessels, which may compromise CBF by causing stenosis and nonlaminar flow.[53] Atherosclerotic lesions are commonly found at sites of turbulent flow, including the carotid bifurcation,[27] potentially due to a combination of free radicals and shear stress leading to vascular damage, inflammation, and immune cell accumulation.[53]

Small vessel disease (SVD) affecting deep white matter small arteries and arterioles is another major cerebrovascular consequence of HTN.[27] SVD is characterized by arteriolosclerosis, marked by loss of smooth muscle cells, narrowing of the lumen, thickening of the vessel wall, and hyaline deposits (lipohyalinosis).[54] These microvascular alterations are particularly damaging since: (a) the subcortical white matter is located at the border-zone between two arterial territories, i.e. descending terminal branches from the pial microcirculation and ascending branches arising from the first segment of the middle cerebral artery, and (b) the affected vessels are terminal arterioles with little or no potential for a compensatory collateral flow.[27] Therefore, SVD often leads to white matter lesions (white matter disease), which remain the leading cause of cognitive impairment of vascular bases.[3]

Functional alterations

Cerebrovascular autoregulation. HTN has a detrimental effect on autoregulation, as it shifts the autoregulatory pressure-flow curve to the right. Although the autoregulation shift is intended to protect the microvessels from the mechanical impact of the elevated transmural pressure, this adaptive response may ultimately increase the risk for cerebral hypoperfusion if BP falls.[27] The mechanisms underlying the detrimental effects of HTN on cerebrovascular autoregulation have not been fully elucidated, but they may involve both structural and functional factors. While the structural remodeling induced by HTN may impair cerebral autoregulation by altering the mechanical properties of cerebral blood vessels, functional alterations may also play a role. For example, the myogenic tone is increased in several models of HTN, which may results in vasoconstriction and contribute to the shift of the autoregulatory curve.[27] The importance of cerebral autoregulation is highlighted by the fact that the magnitude of autoregulatory dysfunction correlates with the severity of periventricular white matter injury.[55] Experimental data suggest that these alterations may be modulated by anti-hypertensive medication. Specifically, animal studies have shown that normalizing BP with ACE inhibitors normalizes the lower limit of the CBF autoregulation,[56] suggesting that the dysfunction induced by HTN on autoregulation is not permanent and may be amenable to treatment.[57]

Endothelial function. Major cardiovascular risk factors (HTN, diabetes, hypercholesterolemia, etc.) have the common effect of disrupting endothelial function.[58] Brain endothelial dysfunction has been extensively described in HTN. In the cerebral circulation, responses to endothelium-dependent vasodilators appear to be impaired in several models of HTN (see Table 1). One main mechanism is the impairment of NO signaling and bioavailability. Alterations of eNOS may underlie the impairment in various models, varying from decreased expression,[59] mislocalization,[60] altered phosphorylation[61] and eNOS uncoupling.[62] eNOS uncoupling refers to a dysfunctional state of the enzyme induced by a lack of cofactors that lead to the production of the free radical superoxide instead of NO.[63] One of such cofactors, tetrahydrobiopterin (BH_4) may facilitate L-arginine binding to eNOS, enabling electron transfer from the reductase to the oxidase domain, minimizing oxidative decay of the heme prosthetic group,[64,65] and stabilizing eNOS dimerization.[66] In the presence of ROS, BH_4 is oxidized to dihydrobiopterin (BH_2) so that the conversion of L-arginine to L-citrulline leads to production of $O_2^{\cdot -}$ instead of NO.[63] Thus, reduced BH_4 in HTN may lead to eNOS uncoupling resulting both in reduced NO production and exacerbation of vascular oxidative stress.

A major source of vascular ROS responsible for endothelial dysfunction is NADPH-oxidase.[53] This enzyme usually requires assembly of cytosolic and membrane-bound subunits for its catalytic activity, i.e. reduction of molecular oxygen to superoxide.[53] The catalytic subunit (Nox) includes five main isoforms (Nox1-5). Nox 1, 2, 4, and 5 have all been reported in brain tissue and blood vessels.[67–70] However, single-cell RNA sequencing data indicate that only Nox2 is expressed in brain endothelial and myeloid cells, and, that although Nox1 and Nox4 are expressed in peripheral vessels, neither is detected in brain vascular smooth

muscle or endothelial cells.[71] In HTN induced by sustained administration of low doses of the octapeptide angiotensin II (Ang II; slow pressor HTN), ROS production occurs predominantly through Nox2, and superoxide is the main contributor to impaired cerebral endothelial function.[72] However, Nox1 was found to play small role as well.[72] Superoxide could impair NO-dependent responses by scavenging NO, leading to the production of peroxynitrite.[73] Indeed, our previous studies have identified an important role for peroxynitrite. Slow pressor Ang II infusion induced 3-nitrityrosine (3-NT) immunoreactivity, a peroxynitrite marker, in cerebral blood vessels, and topical application of peroxynitrite scavengers or decomposition catalysts reduced 3-NT immunoreactivity and prevented the neurovascular dysfunction.[74] The source of the superoxide involved in 3-NT production is likely to be Nox2, since mice lacking Nox2 did not show elevated ROS production, 3-NT immunoreactivity, or neurovascular impairment.[74,75]

Given that HTN is associated with a systemic immune response[76] and endothelial cells are in direct contact with the blood circulation, it is conceivable that immune mediators may affect cerebrovascular function. For example, interleukin (IL)-6 is an important mediator of endothelial dysfunction in carotid arteries of mice with HTN induced by Ang II.[77] On the other hand, the anti-inflammatory cytokine IL-10 protects endothelial function in carotid arteries following Ang II HTN.[78] Recently, IL-17 has been implicated in both CNS and cardiovascular diseases, including Ang II HTN.[79] Increased levels of IL-17 have been observed in Ang II HTN[79] and the production of IL-17 is elevated in human $CD4^+$ T cells of hypertensive patients.[80] Chronic infusion of IL-17 in mice increased BP and caused endothelial dysfunction in aortic rings.[81] Additionally, IL-17 knockout mice[79] and germ-free mice lacking the IL-17 response to Ang II infusion[82] are protected from endothelial dysfunction. However, in the mouse cerebral microcirculation, IL17 infusion induces endothelial dysfunction in the absence of HTN.[9] Therefore, the role of IL-17 in the cerebral vasculature during HTN remains to be determined.

BBB. HTN has profound effects on BBB permeability. Several animal models of HTN are associated with disruption of the BBB.[83,84] Disruption of the BBB has also been observed in patients with HTN[85] and in white matter damage associated with SVD.[86] The cellular and molecular mechanisms underlying the disruption of the BBB in HTN have not been elucidated. Early studies in which acute changes in BP were induced in laboratory animals suggested a role of mechanical effects of elevated pressure on cerebral blood vessels.[87] However, more recent studies in models of sustained HTN produced by chronic Ang II administration have shown that the breakdown of the BBB is independent of the BP elevation.[88] A loss of tight junction components, including occludin and claudin-5, has been described, but only in aged mice.[89]

Pericytes have been implicated in BBB alterations in models of AD,[24] and may also be involved in HTN. Pericyte migration and contraction are stimulated by Ang II,[90] suggesting that they respond to hypertensive stimuli. Human brain pericytes upregulate Nox4 expression in response to Ang II stimulation,[91] suggesting that these cells may be a contributing cellular source of ROS in human HTN. One study indicated an increase in "granular" pericyte size and activity accompanied by a degeneration of "filamentous" pericytes during HTN in stroke-prone spontaneously hypertensive rats (SHR-SP).[92] However, recent single-cell RNA sequencing studies have failed to molecularly identify pericyte subtypes in the brain microvasculature.[71] Therefore, the functional implication of different pericyte morphology remains unclear. Of note, the RNAseq studies mentioned above were performed in normal mice and the possibility that HTN alters pericyte structure and function cannot be ruled out, and this presents a new opportunity to identify molecular and genetic changes in individual vascular cell types in HTN.

Neurovascular coupling. Neurovascular coupling was first shown to be attenuated in mice with acute or slow pressor Ang II HTN.[93] Interestingly, the cerebrovascular dysfunction in slow-pressor Ang II HTN actually precedes the onset of HTN and persists following normalization of BP at the end of infusion.[94] Attenuation of neurovascular coupling could also be induced by topical neocortical application of Ang II,[95] indicating that it was not a result of the BP elevation. In support of this hypothesis, sustained elevation of BP with the alpha-adrenergic agonist phenylephrine did not induce a dysfunctional response.[95] Similarly, preventing the BP elevation during Ang II infusion or administration of Ang II at subpressor doses significantly attenuated the neurovascular coupling response during whisker stimulation.[94] Thus, in this model of HTN, the dysfunction can be attributed to Ang II signaling, rather than the BP elevation. However, as described in the previous section, chronic effects of BP elevation on arterial structure cannot be discounted. Neurovascular coupling to whisker stimulation is also impaired in genetic models of lifelong HTN, including blood pressure high (BPH) mice[88] and spontaneously hypertensive rats (SHR),[96] which also exhibit elevated levels of circulating Ang II. Importantly, neurovascular dysfunction has also been reported in human HTN. Hypertensive patients showed an attenuated increase in CBF in response to

brain activation during memory tasks, compared to normotensive subjects.[97]

The mechanisms underlying the effects of Ang II HTN on neurovascular coupling are not completely clear. The response is not explained through direct effects of Ang II on neuronal activity, as Ang II does not affect the shape or amplitude of the field potentials induced by whisker stimulation when delivered either acutely[95] or chronically.[94] A central component to the neurovascular dysfunction has been shown by studies indicating that chronic Ang II infusion acts on the subfornical organ (SFO), one of the circumventricular organs, leading to activation of hypothalamic pathways releasing vasopressin and inducing expression of the potent vasoconstrictor endothelin-1 in cerebral arterioles.[98] In this model, AT1R inhibition by losartan superfusion over the neocortex improves neurovascular dysfunction only partially, indicating that other mechanisms are also at play.[98] Scavenging radicals in the SFO with CuZnSOD viral gene transfer prevents the neurovascular dysfunction, indicating the critical role of ROS in the SFO.[98] Topical application of an ET_A receptor blocker partially improves the neurovascular dysfunction and the residual deficit is completely rescued by losartan, implicating both local AT1R and ET_A receptors in its mechanisms[98] (Figure 2). Thus, unlike acute administration of pressor doses or neocortical application of Ang II, SFO activation of central pathways is necessary for the neurovascular dysfunction induced by slow-pressor Ang II HTN. In addition, a contribution of COX-1 mediated production of PGE_2 acting on EP1 receptors has also been reported in this model.[99]

Perivascular macrophages. As discussed in the previous section, vascular oxidative stress is ultimately responsible for neurovascular dysfunction in models of Ang II HTN, but the cellular source(s) of the ROS remained unclear. Although capable of producing ROS,[100] smooth muscle cells do not seem to be a major source of oxidative stress in the cerebral circulation.[101] Furthermore, the ability of cerebral endothelial cells to produce toxic amounts of ROS is relatively limited compared to "professional" ROS producing cells such as macrophages.[102]

Recent data have revealed that perivascular macrophages (PVMs) are the major source of ROS mediating the neurovascular dysfunction. Brain PVM are innate immune cells closely apposed to cerebral arterioles and have emerged as critical constituents of the NVU.[103] PVM and meningeal macrophages represent the bulk of macrophages in the normal brain. PVM reside in the Virchow-Robin space, delimited by the glia limitans and the vascular basement membrane, and are attached to the outer wall of intracerebral arteries and veins. They are distinct from other perivascular cells and microglia for their immune phenotype ($CD45^{high}$, $Iba1^{low}$, CD206+, CD163+) and propensity to phagocytosis. Their origin and function has been recently reviewed.[103]

In addition to their role in immune surveillance, recent data indicate that PVM are a major source of ROS with a negative impact on cerebrovascular function.[88,103] Due to their myeloid origin, PVM express functional AT1R and have the potential to produce large amounts of ROS through Nox2.[104] This is of interest, because, as discussed above, cerebrovascular dysfunction in slow-pressor Ang II HTN is mediated by vascular oxidative stress from a Nox2-containing NADPH-oxidase.[93,98] Therefore, we recently tested the hypothesis that PVM are a source of ROS mediating the cerebrovascular and cognitive dysfunction induced by Ang II HTN. We found that in Ang II HTN, AT_1 receptors on PVM mediate ROS production through Nox2-derived radicals leading to impairment in endothelium-dependent vasodilation and neurovascular coupling.[88] This is in agreement with data showing that PVM depletion with clodronate in SHRSP improves the remodeling and endothelium-dependent vasodilation of middle cerebral artery.[105] PVM depletion also improved cognitive function assessed in BPH mice, a model of lifelong HTN.[88] These data indicate that PVM are a critical source of ROS responsible for the deleterious neurovascular and cognitive effects of HTN (Figure 3). Given that the cerebral endothelium, but not arteriolar smooth muscle, also express AT1R and Nox2,[71,93] it is possible that these cells play a contributing role to the radical production during Ang II HTN. However, their contribution is assumed to be smaller because single-cell RNA sequencing data indicate that the expression of Nox2 in endothelial cells is limited compared to that in microglia and PVM.[71] Furthermore, the observation that removal or genetic modification of PVM completely abolishes vascular ROS production,[88] suggests that the endothelium and vascular smooth muscle cannot be the primary source of ROS. In contrast, in the HTN induced by acute Ang II administration, PVM do not participate in the neurovascular dysfunction[9] implicating the endothelium in the ROS production (Figure 3).

Dietary salt, cerebrovascular dysfunction and cognitive impairment

A diet rich in salt has been linked to increased incidence of cerebrovascular diseases, an effect first attributed to the elevation in BP observed with high-salt intake.[106] However, subsequent studies revealed that high-salt intake had detrimental effects independent of BP.[107] Thus, dietary salt is now recognized as an independent risk factor for stroke and dementia.[7,8]

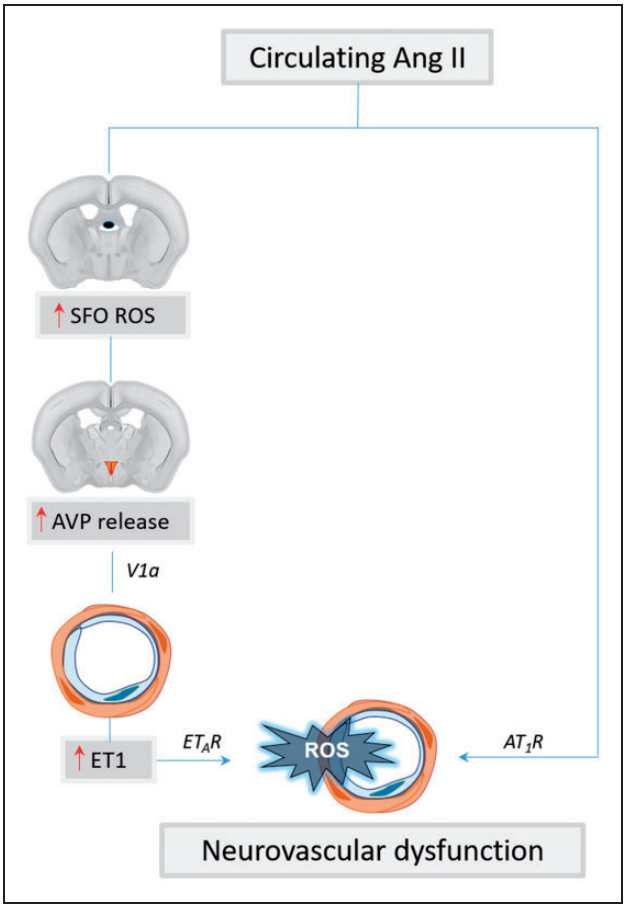

Figure 2. Mechanisms of slow-pressor Ang II HTN-induced neurovascular dysfunction. Circulating Ang II activates ROS production in the subfornical organ (SFO) leading to increased vasopressin (AVP) release from the hypothalamic paraventricular nucleus. AVP, in turn, leads to upregulation of endothelin-1 (ET1) in cerebral arterioles. ET1 and Ang II contribute to vascular oxidative stress and neurovascular dysfunction through ET_A and AT1 receptors, respectively.

Effects of salt on the cerebral vasculature

High dietary salt can result in arterial stiffness in animal models of HTN, an effect independent of the BP elevation.[108] In peripheral vessels, this effect has been attributed to salt-induced increases in the pro-fibrotic effects of transforming growth factor beta (TGFβ).[109,110] In agreement with these experimental data, arterial stiffness was found to be lower in patients on a low-salt diet versus normal-salt diet.[111] Furthermore, reducing sodium consumption in HTN patients lowered stiffness in large peripheral arteries.[112] Whether a similar reversal occurs in cerebral vessels remains to be established. High-salt diet also results in functional alterations in systemic vessels. For example, the mesenteric arteries of rats fed a high-salt diet show enhanced vasoconstriction to norepinephrine[113] and effect attributed to an increase in the contractile properties of the vascular smooth muscle.[114]

Relatively little is known on the effect of dietary salt on the cerebral vasculature. Rats fed a high-salt diet have an impaired cerebral smooth muscle cell response to prostacyclin.[115] Following short-term high-salt diet, rat pial arterioles exhibit impaired responses to ACh and to the prostaglandin I_2 receptor agonist iloprost.[116] A subsequent study in the same model found that the impaired ACh-induced vasodilation of MCA could be attributed to the suppression of peripheral Ang II and brain Cu/Zn SOD.[117] Additionally, high-salt intake in rats abolished ADP-induced vasodilation,[118] suggesting the involvement of eNOS-independent mechanisms. Neurovascular coupling during whisker stimulation and endothelium-dependent responses are impaired with a model of salt retention associated with HTN (DOCA-salt model),[119] but the BBB is not affected.[120] Similarly, chronic administration of a high-salt diet (8% NaCl) does not alter the BBB in normal mice,[9] but it enhances BBB dysfunction in SHR-SP[121] which already have BBB alterations at baseline.[122] Therefore, the evidence suggest that dietary salt may induce endothelial dysfunction without affecting the BBB, unless there is pre-existing vascular damage, such as in SHR-SP.

Dietary salt, endothelial dysfunction and cognitive impairment

High-salt intake has long been associated with elevated BP, and the deleterious cardiovascular effects of salt-rich diets have traditionally been attributed to HTN.[123] However, epidemiological data have unveiled a link between dietary salt, stroke, dementia and white matter damage independently of HTN.[124] In a recent study, we examined the effect of dietary salt on cerebrovascular function and cognition. We found that high-salt diet (4–8% NaCl, 8–16 times the salt content of the normal mouse chow) for two to six months leads to cerebral endothelial dysfunction in the absence of HTN, without affecting neurovascular coupling.[9] Uncertainties concerning basal salt requirements and consumption in humans notwithstanding,[125] a 4–8% salt diet approaches the highest levels of estimated salt consumption in humans.[126] Dietary salt-induced endothelial dysfunction is associated with a global reduction in CBF and cognitive impairment, attesting to the key role of the cerebrovascular endothelium in maintaining cognitive health. Therefore, this study provides evidence that endothelial dysfunction is sufficient to produce cognitive impairment in the absence of neurovascular coupling dysfunction. However, the relative contribution of neurovascular coupling and endothelial dysfunction to cognitive health in humans as in animal models is not clear.

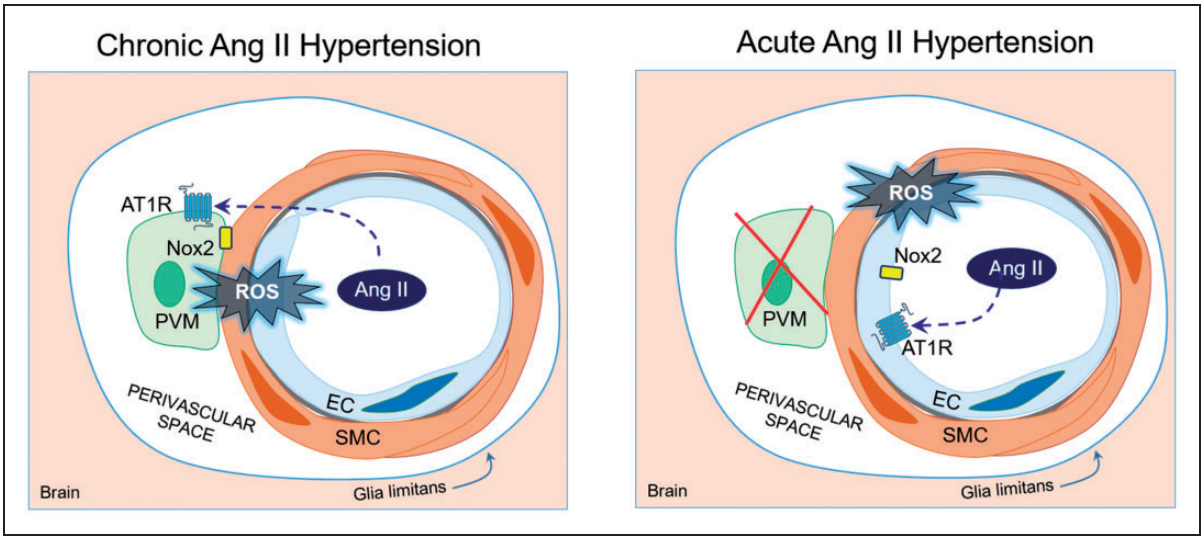

Figure 3. PVM mediate cerebrovascular dysfunction in slow-pressor Ang II HTN but not acute Ang II HTN. In slow-pressor Ang II HTN and BPH mice (left), circulating Ang II crosses the BBB and acts on AT1R on PVM to increase production of ROS by activating a Nox2-containing NADPH oxidase. Nox2-derived radicals, in turn, cause neurovascular dysfunction and cognitive deficits. ET1 also plays a role in the dysfunction (see Figure 2), but it remains unclear how this peptide contributes to ROS production in PVM. In contrast, in acute administration of pressor doses of Ang II (right), circulating Ang II activates AT1R and Nox2 on endothelial cells to increase ROS production and induce neurovascular dysfunction.

We then explored the potential mechanisms of the cerebrovascular and cognitive effect of salt. In humans as in mice, a high-salt diet acts on the gut adaptive immune system leading to expansion of T-helper lymphocytes producing IL-17 (Th17).[127–129] We found that this adaptive immune response induces the endothelial dysfunction and cognitive deficits. In particular, the Th17 response led to an increase in circulating IL-17, which, in turn, induced inhibitory eNOS phosphorylation (at Thr495) and reduced the bioavailability of endothelial NO. The inhibitory phosphorylation is mediated by Rho-kinase (ROCK), and ROCK inhibition prevented high-salt diet-induced Thr495 phosphorylation, cerebrovascular dysfunction, and cognitive impairment.[9] The key role of IL-17 was confirmed by the observation that increasing circulating IL-17 to the same level reached with the high-salt diet reproduced the neurovascular and cognitive dysfunction induced by high-salt diet.[9] Additionally, mice lacking IL-17 or treated with IL-17 neutralizing antibodies were protected from the detrimental effects of high dietary salt.[9] Attesting to the cellular specificity of the neurovascular alterations induced by high salt, PVM, which are critical for the cerebrovascular effects of Ang II HTN, are not involved in the mechanisms of the endothelial dysfunction.[9] These findings unveil a new gut-brain axis in which an adaptive immune response initiated in the gut by dietary salt acts on the cerebral endothelium to induce NO deficit and, consequently, cognitive impairment (Figure 4). The pathways downstream of endothelial NO leading to cognitive impairment remain to be established and are presently being investigated.

Clinical considerations

HTN is by far the most important modifiable risk factor for cerebrovascular disease leading to stroke and dementia.[50] Mounting evidence has also linked HTN to the risk of AD, the leading cause of dementia in the elderly.[130] An important consideration is that approximately 50% of clinically diagnosed AD feature vascular pathology (Figure 1), thus targeting vascular risk factors as a preventive measure for AD is increasingly important. Midlife HTN increases the risk of clinical diagnosis of AD later in life[131] and at autopsy the brains of hypertensive patients have more amyloid plaques and neurofibrillary tangles, pathological hallmarks of AD, than normotensive subjects.[132] Recent imaging studies using markers of amyloid or tau and positron emission tomography have shown that HTN increases amyloid and tau deposition.[133–135] Furthermore, arterial stiffness, a correlate of HTN, is also associated with greater accumulation of amyloid markers.[136] These findings have raised the possibility that HTN promotes AD pathology, but the mechanisms by which HTN and other vascular risk factors may exert this effect remain to be established. Experimental studies have shown that slow-pressor Ang II HTN promotes amyloid-β deposition in mouse models of amyloid accumulation, an effect due to enhancement of amyloid-β cleavage from the amyloid precursor protein

through the enzyme β-secretase.[119] Similarly, experimental HTN has been shown to induce tau phosphorylation,[137,138] but the mechanism of the effects is not entirely clear. Furthermore, the role of AD pathology in the cognitive deficits of HTN in animal models as in humans remains to be established. Highlighting the complexity of the link between HTN and AD is the clinical observation that the association between these conditions is age dependent, such that later in life HTN no longer correlates with AD risk.[139] This is probably due to the fact that, as dementia develops, reduced activity, nutritional factors and possibly central autonomic dysfunction lead to BP lowering.

Given that many of cardiovascular risk factors have recently also been linked to cognitive impairment, cardiovascular health is now recognized as a key requirement for optimal brain health.[140] Indeed, the recommendations for promoting and maintaining optimal brain health are similar to those proposed for cardiovascular health, and include a combination of physical exercise, healthy diet (with reduced sodium consumption), and control of vascular risk factors (such as HTN) as a strategy.[140] Physical exercise reduces the risk of cardiovascular disease and improves endothelial function, thus potentially reducing the risk for dementia.[58] Importantly, reducing sodium consumption remains an important recommendation for BP and cardiovascular risk management.[123]

Although anti-hypertensive medications remain the cornerstone of therapy, definitive evidence that HTN treatment reduces the risk of dementia is lacking.[50] Several observations studies have suggested that treatment of HTN reduced the risk of dementia,[50] but only one double-blinded, randomized and placebo controlled clinical trial has thus far shown a clear benefit of treatment of HTN on subsequent cognitive impairment,[141] while other trials have not.[50] A major problem has been that midlife HTN increases the risk of late-life dementia decades later, and studies to date have lacked the length of follow up or the proper cognitive assessment to assess the impact of HTN treatment on cognitive outcomes. Another challenge has been that it has been difficult to differentiate between direct effects of BP lowering on the development of dementia, and indirect effects resulting from the associated reduction in the risk of stroke, in itself a significant cause of cognitive impairment (post-stroke dementia).[50]

A related question is whether certain classes of anti-hypertensive agents are superior in terms of dementia prevention. In animal models, angiotensin receptor blockers have been found to be neuroprotective.[142] However, strong evidence is lacking in patients with HTN. Although some studies have suggested certain drug classes superiority,[143] their findings are weakened by underpowered design and lack of equivalent cognitive end points.[50] Therefore, additional double-blinded clinical trials with extended follow up and assessment of cognitive outcomes are needed to address these critical questions. In this regard, results from the SPRINT-MIND trial are eagerly awaited in the hope that they may provide guidance on the use of antihypertensive medications to prevent that deleterious effects of HTN on cognition.

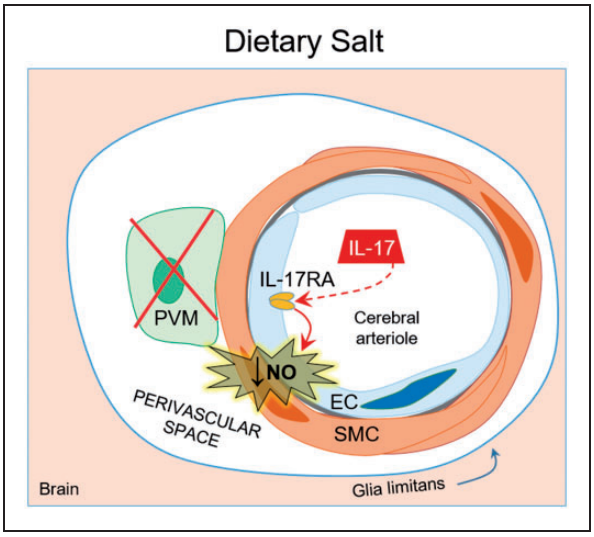

Figure 4. Dietary salt induces endothelial dysfunction and cognitive deficits. High dietary salt stimulates Th17 polarization in the gut leading to increased circulating IL-17. IL-17 acts on the cerebral endothelium to induce inhibitory phosphorylation of eNOS through Rho-kinase, thus reducing NO production and bioavailability. The resulting endothelial dysfunction in the cerebral vasculature is associated with cognitive impairment. Remarkably, neurovascular coupling is not affected. Of note, PVM do not play a role in the cerebrovascular dysfunction of dietary salt.

Conclusions

We have examined the damaging effects of HTN and dietary salt on the brain, focusing on microvascular dysfunction and its negative impact on cognition. The evidence suggests that HTN and dietary salt alter cerebrovascular structure and function profoundly, resulting in vascular insufficiency and cognitive impairment. Vascular oxidative stress has long been known to be a major culprit, especially in HTN, but the sources and targets of ROS remain to be clearly identified. While PVM have emerged as a previously unappreciated cellular source of ROS in the vasculopathy of Ang II HTN, the potential contribution of other vascular cells remains unclear. How radicals interact with cerebrovascular cells to induce vascular and neuronal dysfunction also remains to be fully established. Reduced NO bioavailability may play a role, but considering the multitude of neurovascular mediators interacting with

the cerebral vasculature, other agents are also likely to be involved.

A remarkable specificity in the cellular bases of vascular dysfunction has also emerged. For example, PVM are critical for the neurovascular and cognitive dysfunction in HTN, but are not involved in the cerebrovascular effects of dietary salt, which is exclusively mediated by endothelial cell dysfunction (Figures 3 and 4). Single cells RNAseq studies of cerebrovascular cells in health and disease would provide important clues to unveil the earliest disease-linked molecular change in vascular cells that may yield novel diagnostic and therapeutic insights.

The downstream events linking the vascular dysfunction to the synaptic dysfunction underlying cognitive impairment remain to be defined. How does alteration of specific vascular cells drive neuronal dysfunction in brain regions critical for cognition? Is a mismatch between energy supply and demands due to hemodynamic insufficiency the sole factor? Or, are there yet-undiscovered neurovascular links through which vascular cells can directly influence neuronal function? The role of vascular growth factors in neuronal development and survival is well described, but are there also disease specific processes at play?

These are some of the outstanding questions that remain to be addressed. Rapid advances in neurovascular biology and a host of new methodological approaches and disease models promise to expand our understanding of these damaging processes and to identify predictive biomarkers and viable therapeutic targets. These preclinical studies are essential for subsequent clinical efforts to better define the natural history of the pathogenic impact of HTN and dietary salt on cognitive function and develop disease-modifying treatments for age-related dementia, one of the greatest public health challenges of our times.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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