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The Hippocampal Vascular Supply and Its Role in Vascular Cognitive Impairment

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Abstract

The incidence of age-related dementia is increasing as the world population ages and due to lack of effective treatments for dementia. Vascular contributions to cognitive impairment and dementia are increasing as the prevalence of pathologies associated with cerebrovascular disease rise, including chronic hypertension, diabetes and ischemic stroke. The hippocampus is a bilateral deep brain structure that is central to learning, memory and cognitive function and highly susceptible to hypoxic/ischemic injury. Compared to cortical brain regions such as the somatosensory cortex, less is known about the function of the hippocampal vasculature that is critical in maintaining neurocognitive health. This review focuses on the hippocampal vascular supply, presenting what is known about hippocampal hemodynamics and blood-brain barrier function during health and disease, and discusses evidence that supports its contribution to vascular cognitive impairment and dementia. Understanding vascular-mediated hippocampal injury that contributes to memory dysfunction during healthy aging and cerebrovascular disease is essential to develop effective treatments to slow cognitive decline. The hippocampus and its vasculature may represent one such therapeutic target to mitigate the dementia epidemic.

Introduction

Alzheimer's disease (AD) is the leading cause of clinically diagnosed dementia, with vascular contributions to cognitive impairment and dementia being the second leading cause of age-related dementia.[1] However, emerging evidence suggests that the majority of patients with AD have mixed dementia, with both classic AD neurodegenerative pathology as well as cerebrovascular pathology.[2] Therefore, the incidence of vascular-related cognitive impairment may be underestimated. Vascular cognitive impairment (VCI) is a broad term that encompasses a spectrum of cognitive dysfunction across multiple cognitive domains due to cerebrovascular pathology, including ischemic stroke (i.e., strategic infarcts) and/or cerebral small vessel disease that damages the cerebral microvasculature, resulting in white matter lesions and microinfarcts.[1, 3–6] Therefore, understanding cerebrovascular function in

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None.

health and disease is important, particularly in brain regions central to learning, memory and cognition, such as the hippocampus.

Pathologies that impact the cerebral circulation and contribute to VCI have been extensively studied, including chronic hypertension, diabetes and ischemic stroke.[1, 7] Importantly, the vast majority of animal studies have been completed almost exclusively in the vasculature supplying the sensorimotor cortex and striatum (e.g. lenticulostriatal branches of the middle cerebral artery, MCA). However, reductions in hippocampal blood flow occur during healthy aging, and contribute to several pathologies that involve hippocampal neuronal atrophy and memory decline, including VCI, demonstrating a need to better understand hippocampal vascular function in health and disease.[8–12] Despite the importance of the hippocampus in memory function and its high susceptibility to injury, we know remarkably little about the function of the hippocampal vasculature. VCI has recently been reviewed extensively elsewhere.[1, 6, 13] For the purposes of this review, the term VCI (vascular cognitive impairment) will be used as it includes mild cognitive impairment due to cerebrovascular disease up to its most severe form, vascular dementia.[1, 6] Although recent criteria no longer require memory impairment for a VCI diagnosis which is more characteristic of AD, memory is an important cognitive domain that can be disrupted, having a tremendous impact of the patient's quality of life.[14] Further, the hippocampus and its vasculature may be particularly important in dementia patients with mixed vascular and AD pathologies. This review will focus on the hippocampal vascular supply and discuss evidence that supports its contribution to VCI.

The purpose of this review is to introduce the hippocampal vascular supply as a potential contributor to VCI. An in-depth review of what is known about hippocampal arteriole (HA) function, hippocampal hemodynamics and blood-brain barrier (BBB) function, including properties that are unique from other cerebrovascular territories that increase the susceptibility of the hippocampus to hypoxic/ischemic injury will be discussed. The structure and function of the hippocampal vasculature under physiological (e.g. healthy aging) and pathological conditions will be presented, predominantly focusing on chronic hypertension and ischemic stroke that are primary contributors to VCI.

The Vascular Supply of the Hippocampus

The hippocampus is part of the archicortex and is a bilateral brain structure deep within the temporal lobes centrally involved in learning and memory. The blood supply to the hippocampus is dependent primarily upon the collateral branches of the posterior cerebral artery (PCA) with some contributions coming from the anterior choroidal artery (AChA).[15–17] Common vascularization patterns of the hippocampus have been identified through histological studies, neurosurgical autopsy studies and more recently by an *in vivo* study using MRA (magnetic resonance angiography). Erdem et al. (1993) microsurgically characterized 30 fixed brain hemispheres post-mortem and reported that the most frequent pattern of vascularization of the hippocampus was a mixed supply of branches of the PCA and AChA, occurring in 17/30 hemispheres (57 %).[15] Spallazzi et al. (2019) used high resolution 7 Tesla time-of-flight MRA to assess hippocampal vascularization patterns in 62 hemispheres *in vivo* in healthy, young adults that were 19 – 34 years old. They found that

31 (50 %) of hemispheres had a mixed vascular supply from both the PCA and AChA.[17] The next most common patterns of the origin of the hippocampal arteries identified were predominantly PCA branches, including inferior temporal branches of the PCA (27 – 34 %) and the anterior inferior temporal branch of the PCA (10 – 11 %).[15, 17] The least common vascularization pattern was the hippocampus being supplied only by branches of the AChA, occurring in 3 – 5 % of subjects.[15, 17] Demené et al. (2016) used ultrafast Doppler tomography with high resolution imaging to reconstruct the rat brain vasculature in 3D (Figure 1A).[18] Figure 1B shows the bilateral hippocampal vasculature in blue as it sits deep within the brain compared to the cortical vasculature shown in red.[18]

Although it is generally accepted that the majority of the hippocampal blood supply comes from the PCA, there are variations in the regional contributions of blood flow to the PCA and therefore the hippocampus due to heterogeneity of the Circle of Willis. Smaller mammals (e.g. cats, sheep, gerbils) tend to have a greater proportion of hippocampal blood flow from the anterior circulation, with the PCA being largely supplied by the carotids via the posterior communicating artery.[19, 20] In humans, the PCA is more often supplied by the vertebrobasilar system, making the posterior circulation the dominant source of hippocampal blood supply. However, it is estimated that ~ 20 – 30 % of the population has a fetal PCA in which the posterior communicating artery is larger than the P1 segment of the PCA, or a hypoplastic P1 segment, resulting in the anterior circulation supplying the majority of blood flow to the PCA.[21–23] Thus, there is variability in the contributions of anterior vs. posterior circulation to distal branches of the PCA perfusing the hippocampus. A transient MCA occlusion (tMCAO) in gerbils and mice that lack a P1 segment of PCA and rely more heavily on anterior circulation for hippocampal blood flow have infarction that includes in portions of the hippocampal region.[24, 25] Thus, the source of PCA blood flow becomes important if/when these people with an anterior-dominated PCA have a cerebral ischemic stroke. A large vessel occlusion in the carotid system or MCA could disrupt blood flow to the hippocampus, resulting in hippocampal ischemia and post-stroke memory loss. This is likely compounded by the fact that the hippocampus is one of the most susceptible brain regions to hypoxic and ischemic injury.[26, 27] Thus, maintenance of appropriate hippocampal perfusion, including basal blood flow and activity-dependent changes in blood flow is critical to preserving healthy memory and cognitive function.

The Microarchitecture of the Hippocampal Vasculature Promotes Hypoxia and Ischemia

The hippocampus is distinct from cortical brain regions comprising the neocortex (i.e. sensorimotor cortex) from architectural and functional standpoints, both of which are important to consider to understand regional differences in susceptibility to hypoxia and ischemia. The hippocampal formation is formed by the infolding of the dentate gyrus, forming the hippocampal sulcus, the hippocampus proper cornu ammonis (CA), a seahorse-shaped structure containing the hippocampal subfields CA1–4, and the subiculum.[28] The dentate gyrus and hippocampus proper form two C-shaped rings that interlock, with the subiculum connecting them. While the neocortex and hippocampus are both laminar structures, the neocortex is organized horizontally into six neuronal layers whereas the hippocampus is organized into three layers, with its tightly packed large pyramidal neuron cell bodies in the middle layer (Figure 1C). Unlike the somatosensory cortex, for

example, that is also organized vertically into cortical columns of neurons that correspond to the same peripheral receptive field, no such columnar organization occurs in the hippocampus.[29] Large groups of adjacent hippocampal pyramidal neurons (i.e. place cells) are not active all at once such as in cortical brain regions. Thus, the local energy demand in active hippocampus is likely less than in active cortex, and mediators involved in matching neuronal metabolic demand with appropriate increases in local blood flow (e.g. neurovascular coupling; NVC) may be distinct from other more well-studied cortical brain regions.[27, 30]

From a vascular standpoint, vascular density in the hippocampus is a fraction of the vast capillary network in the neocortex. Several studies have exquisitely mapped the microvasculature of the rodent brain and consistently report the hippocampus has less dense vascularization than other brain regions.[31–35] Figure 1D shows a heat map visualization of the vascular volumetric density of a coronal section of mouse brain coded by color scale, with deep blue representing no vascularization.[35] The cortex is highly vascularized with abundant arterioles penetrating the cortex giving rise to a robust microvascular network. In the hippocampus, arterioles penetrate perpendicularly to the coronal plane, and the microvascular network is substantially more sparse, demonstrated by the hippocampus being visually cooler in color than other brain regions (Figure 1D).[35] Further, Ji et al. (2021) showed that the hippocampus is second only to corpus callosum in having the lowest vascular density, with there being fewer microvessels that were more widely spaced, requiring oxygen to diffuse further.[34] Despite lower vascular density, the metabolic demand in the hippocampus was estimated to be matched appropriately, likely due to fewer spatially organized neurons being active at the same time than in cortical brain regions.[34] However, the substantial reduction in capillary density, relatively long distance between microvessels, and tightly packed pyramidal neurons suggests the hippocampus may not be well suited to maintain necessary perfusion under pathological conditions. Diseases that cause even modest reductions in hippocampal blood flow, potentially due to capillary rarefaction, hyperconstriction and/or inward remodeling of HAs, would likely have a tremendous impact on neuronal function, memory and cognition.

The Hippocampal Vasculature is Critical to Neurocognitive Health

Reductions in hippocampal perfusion occur during healthy aging, and also underlie many pathologies that involve hippocampal volume changes (e.g. atrophy) and cognitive decline.[8, 10] In fact, the vascular reserve of the hippocampus is now considered a primary contributing factor to cognitive performance,[36] and understanding hippocampal vascular function is therefore central to protecting neurocognitive health. In older adults (~ 70 years old), greater blood flow to the hippocampus was positively correlated with memory performance, as measured using flow-enhanced signal intensity fMRI during a spatial memory task.[12] Further, older adults that had at least one hippocampus with a mixed vascular supply from both the PCA and AChA had both higher average memory performance and higher learning rate during a memory task than individuals with no mixed vascular supply.[36] Patients with cerebral small vessel disease, most often a result of chronic hypertension and a primary contributor to VCI, performed worse on most cognitive tasks compared to healthy individuals.[36] However, of these patients, those that had

a mixed hippocampal vascular supply performed better on memory tasks than those with a single vascular supply.[36] These findings highlight the importance of hippocampal perfusion in healthy aging and directly implicate the hippocampal vasculature in cognitive health. Further, they suggest that greater hippocampal vascular reserve and improved perfusion may be protective against VCI.

Hippocampal Arterioles are Functionally Unique

The vasculature in the hippocampus forms a rake-like pattern comprised of a series of consistently spaced, alternating arcs of arterioles and venules.[31] The internal transverse hippocampal artery runs in the hippocampal sulcus that sends long arch-like branches of arterioles deep into the hippocampus to perfuse CA1 and CA3 subfields (Figure 1E and 1F).[31, 35] Until relatively recently, functional studies of arterioles perfusing the hippocampus have been limited compared to arterioles perfusing more accessible cortical brain regions. However, pressure myography has now been used to study isolated HAs independently of neuronal and glial influences under physiologically pressurized conditions.[37–39] Figure 2 shows an illustration of the vasculature of the rat hippocampus, and a representative photomicrograph of a HA cannulated and pressurized in an arteriograph chamber for functional pressure myography studies.[37, 40]

The most powerful determinant of hippocampal blood flow is the lumen diameter of its arterioles. This is because resistance to flow is inversely proportional to the radius to the 4th power, such that small decreases in lumen diameter can drastically increase vascular resistance and reduce perfusion, and vice versa.[41] Lumen diameter is a result of a balance between vasoconstrictive and vasodilatory factors, and can rapidly change to control blood flow. In the cerebral circulation, one of the most influential vasoconstrictive stimuli is intravascular pressure. Vascular smooth muscle (VSM) of cerebral arteries and arterioles has the intrinsic ability to constrict or dilate in response to increased or decreased intravascular pressure, respectively.[41, 42] This myogenic response is central to maintaining vascular resistance and cerebral hemodynamics. HAs from healthy male and female rats develop ~ 40 % basal myogenic tone at 40 mmHg intravascular pressure that is similar to penetrating or parenchymal arterioles branching off the MCA to perfuse the striatum and sensorimotor cortex.[38, 43]

In addition to VSM, the endothelium of cerebral arterioles also plays an important role in cerebral hemodynamics by producing vasoactive mediators that influence lumen diameter, vascular resistance and blood flow.[44] In endothelial cells of pial arteries and penetrating arterioles in the cortex, nitric oxide (NO), a potent vasodilator, is basally produced through activity of endothelial NO synthase (eNOS) that counters myogenic tone.[44, 45] NOS inhibition causes robust vasoconstriction of most cerebral arteries and arterioles, demonstrating basal production and release of NO that is important for limiting vasoconstriction due to myogenic and other influences, contributing to regulation of cerebral blood flow.[45–47] In the hippocampus, however, neuronal (n)NOS-derived NO is considered the primary source of basal NO production. Studies show nNOS-containing nerve fibers are located in close proximity to HAs that generate NO and suggest tonic activity of this neuronal network influences lumen diameter of HAs, with little role

for eNOS.[48, 49] In support of this, recent pressure myography studies investigating HA function independently of neuronal influences show that the endothelium does not appear to basally produce NO that is in striking contrast to parenchymal arterioles supplying the sensorimotor cortex.[37, 43, 44] Figure 3 compares the constriction of isolated and pressurized PCAs (upstream of HAs), cortical parenchymal arterioles and HAs in response to NOS inhibition with L-NAME (NG-nitro-L-arginine methyl ester). All vessels had a healthy level of myogenic tone prior to L-NAME treatment. PCA and cortical parenchymal arterioles underwent a 30 – 40 % vasoconstriction when NOS was inhibited, indicating basal NO production in the endothelium of these vascular segments that reduces myogenic tone. However, lumen diameter did not change and there was no constriction of HAs with NOS inhibition (Figure 3A and 3B), supporting that endothelium does not appear to produce basal NO in the hippocampus.[37, 38]

The data presented in Figure 3 were obtained from studies performed in normotensive male rats. However, the lack of response to L-NAME also occurs in HAs from both normotensive and hypertensive male and female rats.[37, 50] The well-established endothelial-dependent and NO-dependent vasodilator acetylcholine also did not elicit a change in HA diameter even at high concentrations known to cause vasodilation of other cerebrovascular segments.[51, 52] It should be noted, however, that the isolated vessel experiments shown in Figure 3 were done under static conditions with no flow through the lumen. It is possible that flow-mediated vasodilation occurs *in vivo* that could involve an eNOS-generated NO component influencing myogenic tone and blood flow in the hippocampus. Whether eNOS is expressed in HAs remains unclear. Regardless, its basal activity is distinct in the hippocampus. Relatively little is known about HA function compared to other, well-studied segments of the cerebrovasculature, including the role, if any, of eNOS in influencing lumen diameter, vascular resistance and hippocampal blood flow.

Additional endothelium-dependent vasodilatory pathways exist that differentially affect vascular resistance depending upon the cerebrovascular segment. Small- and intermediate-conductance calcium-activated potassium (SK_{Ca} and IK_{Ca}) channels are expressed in the endothelium of cortical parenchymal arterioles and contribute to endothelium-derived hyperpolarization.[44] In cortical parenchymal arterioles, but not upstream pial arteries, SK_{Ca} and IK_{Ca} channels are basally active to reduce myogenic tone and regulate resting cerebral blood flow.[43, 44, 53] In HAs, SK_{Ca} and IK_{Ca} channels are expressed and cause robust vasodilation when activated pharmacologically, however, it is not yet clear if these channels are basally active.[37–39] Roles for additional endothelial-dependent vasoactive pathways (e.g. cyclooxygenase) in basal tone remain to be determined.[44] Further, the constellation of ion channels present in VSM cells that contribute to lumen diameter of HAs remains to be investigated. Understanding endothelial and VSM function in the hippocampus is important given that hippocampal perfusion is critical to neurocognitive health and that endothelial and VSM function is compromised in many disease states, including those associated with VCI.

Hippocampal Vascular Function, Perfusion, and Memory in Chronic Hypertension

The risk for dementia is up to 60% higher in those with mid-life hypertension compared to normotensive individuals.[54–57] This is in part due to hypertension increasing the incidence

of ischemic stroke and therefore post-stroke dementia.[1] However, hypertension itself is a substantial contributor to steeper cognitive decline and worse cognitive performance, independently of stroke.[1, 54, 56–58] In fact, elevated mid-life blood pressure correlates with reductions in hippocampal volume that likely contributes to hypertension-induced memory dysfunction, as hippocampal volumetry can be used to grade cognitive decline.[56, 57] Hypoperfusion of the hippocampus is thought to be a primary mechanism by which neuropathological changes occur during chronic hypertension, including hippocampal atrophy, and is a predictor of cognitive decline.[8, 9] Therefore, understanding how chronic hypertension affects hippocampal vascular function and perfusion may allow novel therapeutic targets to be identified in the hopes of slowing memory decline.

A recent pressure myography study investigated myogenic reactivity of HAs in response to changes in intravascular pressure during chronic hypertension using an established genetic model of hypertension, the spontaneously hypertensive rat (SHR).[50] At physiological pressures, HAs from male normotensive rats had ~ 40% myogenic tone. Interestingly, HAs from 6-month-old male SHR were hyperconstricted with smaller lumen diameters compared to arterioles from normotensive Wistar rats and ~ 60 % myogenic tone.[50] Absolute hippocampal blood flow was measured *in vivo* using the hydrogen (H_2) clearance method where the half-life of H_2 clearance was obtained from tissue desaturation measurements and used to calculate absolute blood flow (Figure 4A).[37, 50, 59] Hippocampal perfusion was similar between 4-month-old Wistar rats and SHR; however, at 6 months of age when HAs were hyperconstricted, SHR had a substantial reduction in hippocampal blood flow (Figure 4B). Hippocampal-dependent long-term memory function was investigated using a novel object recognition task in which cognitively intact rats recognize a familiar object and spend the majority of the time investigating a novel object (recognition index > 0.50). Recognition indices were similar between Wistar rats and 4-month-old SHR, indicating similar levels of memory function (Figure 4C). However, memory was impaired in SHR at 6 months of age, with a recognition index of ~ 0.50 indicating no preference for the novel object (Figure 4C). Thus, HA hyperconstriction during hypertension was associated with hippocampal hypoperfusion and memory dysfunction. With a two month age difference in adult rats being equivalent to ~ 8–9 years, these findings demonstrate hemodynamic and cognitive consequences of hypertension-induced HA dysfunction in adulthood that may progress with age.[60]

It is well established that during chronic hypertension, decreased bioavailability of NO causes endothelial dysfunction that increases tone and causes hyperconstriction of pial arteries and cortical parenchymal areterioles.[7, 44, 61, 62] However, as NO does not appear to be similarly produced in endothelium of HAs as in other cerebrovascular segments, the underlying mechanism(s) by which HAs are hyperconstricted in chronic hypertension remain unknown but are likely distinct from hypertension-induced endothelial dysfunction in other brain regions. Also in contrast to other cerebrovascular segments that undergo hypertension-induced inward hypertrophic remodeling (smaller lumen diameter and thicker vascular wall) that reduces vasodilatory capacity and contributes to hypoperfusion, lumen diameters of fully relaxed HAs were similar between groups.[7, 50] Thus, reductions in hippocampal perfusion in 6-month-old SHR was likely due to hyperconstriction of HAs and not inward remodeling, although arteriolar remodeling in the hippocampus may

occur at older ages in SHR. That hyperconstriction rather than remodeling contributes to hippocampal hypoperfusion in mid-life drastically narrows the scope of therapeutic interventions to focus on drugs that cause relaxation and vasodilation of HAs in the hopes to restore perfusion and improve memory function.

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a monogenic form of cerebral small vessel disease and the most frequent genetic cause of VCI.[63] While CADASIL largely shares the clinical and pathological characteristics of hypertension- and age-related sporadic forms of cerebral small vessel disease, it occurs at younger ages and in normotensive patients.[63] In the normotensive *TgNotch3*^{R169C} genetic mouse model of CADASIL that demonstrates impaired learning and memory, VSM depolarization and myogenic tone of HAs were decreased compared to arterioles from wild-type mice.[64] This finding was similar to what occurred in pial arteries and cortical penetrating arterioles from *TgNotch3*^{R169C} mice, with blunted pressure-induced contractility responses due to increased VSM expression of voltage-gated potassium channels that oppose myogenic tone and impair cerebral hemodynamics.[64–66] These studies suggest that any disruption of HA function may contribute to VCI, whether it be hypertension-induced hyperconstriction or hypoconstriction associated with CADASIL, and highlights the therapeutic potential of targeting the hippocampal vasculature to slow cognitive decline and prevent vascular dementia.

NVC in the Hippocampus

NVC is the dynamic communication between neurons, glia and the vasculature to cause local vasodilation in response to neuronal activation to match the metabolic demand of neurons with appropriate blood flow and clear metabolic waste.[7] NVC is a critical component in maintaining neuronal health, and impaired NVC in the cerebral cortex contributes to cognitive decline during healthy aging and in disease states associated with VCI.[1] Many NVC studies in rodents have been performed in the relatively easily accessible somatosensory cortex, primarily measuring relative changes in blood flow in the barrel cortex in response to whisker stimulation or sensory cortex in response to paw pinch. Mechanisms involved in NVC have yet to be fully elucidated, but many signaling molecules, neurotransmitters and metabolites have been shown to be involved in the cortex. However, it is important to consider that these mechanisms may differ based on the brain region being studied, particularly in brain regions with unique vascular and neuronal organization and activity patterns like the hippocampus. Investigating NVC in the hippocampus *in vivo* proves challenging due to its deep location and requiring cognitive tasks to stimulate it physiologically. Although studies are relatively limited, NVC in the hippocampus appears to be distinct from the somatosensory cortex. For example, whisker stimulation causes a rapid local increase in blood flow within a few seconds in the barrel cortex largely through elevated extracellular K^+ activating cortical capillary inward rectifying potassium channels causing hyperpolarization and vasodilation.[67] In the hippocampus, *in vitro* and *in vivo* studies have determined diffusion of nNOS-derived NO to be the critical mediator translating neuronal activity into local increases in hippocampal blood flow that occurs more slowly than in the cortex.[48, 68] A recent study by Shaw et al. (2021) assessed hippocampal NVC *in vivo* by recording neuronal activity and HA diameters in conscious, head-fixed

mice during a virtual spatial navigation task using two-photon microscopy.[33] In response to a similar level of neuronal firing, HAs dilated less than arterioles in the visual cortex that resulted in blunted increase in local blood flow. Given less hippocampal neurons are simultaneously active compared to visual cortex, this lower hyperemic response occurring in the hippocampus was likely sufficient to meet metabolic demand. However, during robust hippocampal neuronal activity (e.g. epileptic seizures), the hippocampus is less capable of maintaining blood flow than regions of the cerebral cortex, resulting in a metabolic crisis that potentiates seizure-induced injury.[69] Together with the ~ 37 % reduction in hippocampal capillary density, these findings suggest the hippocampus has less intrinsic ability to match energy demand with appropriate blood flow that may increase the vulnerability of the hippocampus to hypoxic/ischemic injury under pathological conditions.[32, 33]

Much of what is known about NVC in the hippocampus has been determined in anesthetized rodents using an experimental paradigm that involves measuring NO and O_2 levels and simultaneous changes in blood flow in response to stimulated neuronal activity via a microinjection of glutamate.[68, 70–72] Using this methodology to assess age-related changes in healthy male Fisher 344 rats, Lourenco et al., (2018) determined that hippocampal NVC and spatial memory impairment occurred at ~ 20 months of age.[72] Interestingly, NVC appeared to be impaired due to age-related blunted vascular responses to NO, but not changes in nNOS-derived NO production in response to neuronal activation.[72] These findings suggest impaired hippocampal NVC and HA dysfunction are involved in healthy cognitive aging that may be accelerated during pathologies that promote dementia. A study in the 3xTg-AD triple transgenic mouse model of AD reported NVC was impaired in the hippocampus *in vivo* due to vascular dysfunction rather than changes in NO production or signaling between neurons and the microvasculature.[70, 71] Importantly, this vascular-mediated disruption in NVC preceded cognitive dysfunction, demonstrating hippocampal vascular dysfunction and impaired NVC may have a causal role in memory decline.[71] In a non-obese rat model of type 2 diabetes with impaired hippocampal-dependent spatial memory, reduced NO bioavailability blunted functional hyperemia in the hippocampus in response to activation of glutamatergic neurons, suggesting NVC was impaired due to oxidative stress but not vascular dysfunction.[73] Thus, disease states can have differential effects on critical aspects involved in NVC in the hippocampus. Studies investigating hippocampal NVC *in vivo* are limited at this point in time, however, they are gaining momentum as technology advances to allow simultaneous neuronal activity and perfusion measurements to be made in conscious rodents in this deep brain region.

The ability of isolated and pressurized HAs to vasodilate to mediators of NVC such as NO have been investigated as an indirect assessment of hippocampal NVC, as this is a critical component of increasing local blood flow. Pressure myography studies have revealed that hypertensive disorders may impair NVC via HA dysfunction to contribute to memory dysfunction. Preeclampsia (PE) is a hypertensive disorder of pregnancy that has long-lasting consequences, and is a major risk factor for hypertension, stroke and VCI later in life.[74, 75] In a hypercholesterolemia rat model of PE, HAs demonstrated endothelial dysfunction and impaired vasodilation to NO several months after pregnancy that was associated with impaired long-term memory.[76] Interestingly, memory was intact late in gestation, demonstrating that cognitive decline occurred as a function of time after

PE pregnancy.[77] These findings suggest vascular mechanisms of NVC are impaired in the hippocampus after PE contributing to declining memory function and VCI.

Chronic psychological stress disrupts cognitive function, particularly when it occurs in mid-life, increasing the risk for age-related dementia by 2.5-fold.[78, 79] Chronic stress is associated with reduced hippocampal blood flow and hippocampal atrophy, suggesting the hippocampal vasculature is damaged that could contribute to memory dysfunction and VCI.[80–82] In a rat model of chronic neuroendocrine stress, chronic activation of the hypothalamic-pituitary-adrenal axis caused stress-induced cardiovascular symptoms including hypertension. Long-term memory was impaired that was associated with HA endothelial dysfunction and blunted vasoreactivity to NO.[39] Interestingly, stress-induced memory and HA dysfunction were more robust in male rats than female rats. Further, male rats, regardless of chronic exposure to the neuroendocrine components of the stress response, had lower vascular density and increased distance between capillaries in the hippocampal CA1 region compared to female rats.[39] Thus, impaired vascular responses to mediators of NVC in the hippocampus coupled with sparser vascularization could underlie the sex-dependent increased susceptibility to stress-induced hippocampal dysfunction. These findings suggest chronic stress has deleterious effects on the hippocampus and its vasculature, including potentially impaired NVC that may represent underlying mechanisms by which stress-related disorders contribute to VCI.

A Role for the Hippocampal Vasculature in Post-Stroke Dementia (PSD)

In addition to hypertensive disorders having deleterious effects on the hippocampal vasculature that contribute to memory decline, chronic hypertension is also a leading cause of cerebral ischemic stroke. PSD, defined as dementia occurring within six months after stroke, occurs in up to 80% of ischemic stroke survivors and is a major subtype of vascular dementia, the most severe form of VCI.[1, 83] PSD is increasing in prevalence due to increased life expectancy and decreased stroke-related mortality and involves an array of, and often multiple cognitive domains. Importantly, ~ 70% of stroke patients that achieved successful clinical recovery (e.g. no functional disability 3 months after stroke) had significant impairment in at least one cognitive domain, with memory being one of the most commonly affected domains.[83] Thus, despite easing the physical burden, the remaining cognitive burden can drastically limit the quality of life of stroke survivors. The focus on the cognitive consequences of stroke is increasing, as evidenced by the landmark DISCOVERY (Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on RecoverY) study beginning in 2019 investigating mechanisms of PSD with the goal of developing targets for personalized medicine to improve post-stroke cognition.

The spectrum of cognitive impairment after stroke can often be explained by the location of the infarction; however, that does not seem to be the case with post-stroke memory impairment. Ischemic stroke in brain regions involved in memory (e.g. medial temporal lobe and hippocampus) are rare, yet PSD is associated with impaired memory, decreased hippocampal functionality on fMRI and hippocampal neurodegeneration.[84, 85] While this cognitive consequence of stroke is not well understood, it suggests that brain regions

involved in memory, such as the hippocampus, undergo damage after stroke despite being outside of the primarily affected brain region that may be vascular in nature.

Cerebrovascular dysfunction, including impaired cerebral blood flow autoregulation, is known to occur after ischemic stroke.[86] Vascular dysfunction can occur not only within the ischemic region, but also in the non-ischemic hemisphere, suggesting widespread cerebrovascular dysfunction after focal cerebral ischemia that could impact the hippocampus.[51, 87–89] In rodents, tMCAO results in memory dysfunction by disrupting hippocampal neuroplasticity, the cellular mechanism of learning and memory.[90–92] Importantly, impaired hippocampal neuroplasticity occurs bilaterally.[91, 92] Underlying mechanisms by which hippocampal neuronal network function is disrupted after ischemic stroke remain unclear, but are likely vascular in nature and may involve circulating factors elevated after cerebral ischemia. Such circulating factors include vasoactive peptides, like the potent vasoconstrictor endothelin-1, that increase constriction of otherwise healthy pial arteries.[93–95] Thus, focal cerebral ischemic stroke may indirectly cause HA hyperconstriction and reduce hippocampal perfusion, particularly during chronic hypertension when preexisting HA hyperconstriction and hypoperfusion may be exacerbated and potentiate PSD.[38] Further, circulating levels of proinflammatory cytokines elevated after cerebral ischemia could damage the BBB that could cause hippocampal neuroinflammation well known to contribute to VCI.[96]

The Hippocampal BBB

The BBB is a complex interface between systemically circulating factors and the delicate brain milieu. The BBB plays a critical role in maintaining neuronal homeostasis, and its breakdown is considered an early biomarker of human cognitive dysfunction.[97] Importantly, the BBB in the hippocampus is more susceptible to disruption than other brain regions, thereby increasing the impact on cognition and memory.[97–100] In patients with mild cognitive impairment, increased BBB permeability in the hippocampus occurred earlier and to a greater extent than in cortical brain regions, as measured via dynamic contrast-enhanced MRI.[97, 98] Further, a study in rodents showed that increasing BBB permeability in the hippocampus for less than 48 hours caused impaired spatial memory that persisted for seven days.[101] These findings suggest that even transient disruption of hippocampal BBB function contributes to prolonged memory impairment, and highlights the importance of BBB integrity in the hippocampus in maintaining neurocognition.[101]

The hippocampal BBB may play a central role in PSD. The acute inflammatory response to cerebral ischemic stroke includes activation of peripheral immune cells that produce proinflammatory cytokines such as tumor necrosis factor alpha (TNFα) that is damaging to the BBB.[93] TNFα increases BBB permeability via downregulation and degradation of BBB tight junction proteins.[102] BBB disruption can have long-lasting effects on memory function through activation of microglia, the resident immune cells in the brain, resulting in local neuroinflammation.[101, 103] Activated microglia can become cytotoxic (e.g. M1 microglia) and secrete high levels of TNFα. TNFα then exacerbates neuroinflammation, further potentiating BBB degradation and directly impairing hippocampal neuronal network dynamics causing memory dysfunction.[103–106] This neuroinflammatory cascade in the

hippocampus contributes to cognitive dysfunction in models of AD that may also be an underlying mechanism of PSD.[105, 106] Treatment with the anti-inflammatory agent minocycline decreased neuroinflammation in the hippocampus that improved spatial learning and memory six weeks after tMCAO in healthy rats.[107] In a high-fat diet/low-dose streptozotocin rat model of diabetes, memory was impaired two weeks after tMCAO due to hippocampal neuroinflammation that was associated with increased hippocampal BBB permeability.[108, 109] These studies suggest that the hippocampal BBB may play a central role in post-stroke memory dysfunction, and that protecting the BBB protects from PSD.

In addition to tight junction degradation, TNFα also disrupts the critical biochemical/selective component of the BBB comprised of specific transport proteins known as efflux transporters.[110] Efflux transporters contained within the luminal BBB are powerful ATP-driven pumps that actively efflux ligands (e.g. cytokines, steroids, xenobiotics) back into the circulation, thereby preventing passage in to the brain.[111, 112] Efflux transporters at the hippocampal BBB are implicated in the pathogenesis of AD, and may also have a role in PSD.[113] Importantly, BBB efflux transporters in capillaries in the hippocampus are more susceptible to inhibition than in the cerebral cortex.[99, 100, 111] This not only suggests regional differences in barrier function, but more importantly suggests that such differences selectively increase the susceptibility of the hippocampus to damage in the context of acute efflux transporter failure. In fact, TNFα is one of a few cytokines that directly inhibits p-glycoprotein, the most abundant BBB efflux transporter.[112] Therefore, the BBB in the hippocampus may be selectively disrupted under conditions when circulating TNFα is elevated, such as after cerebral ischemic stroke. Hippocampal BBB components including efflux transporters may represent novel therapeutic targets to mitigate the cognitive consequences associated with focal cerebral ischemic stroke and cognitive impairment associated with inflammatory states including chronic hypertension and diabetes.

Conclusions

Overall, the function of the hippocampal vasculature and hippocampal hemodynamics are critical to neurocognitive health and are compromised under several pathological conditions contributing to VCI. It is possible that treatments that restore arteriole function may protect against age- and disease-related reductions in basal hippocampal blood flow and NVC to improve memory function. Further, evidence suggest that protecting the injury-susceptible hippocampal BBB, specifically efflux transporter function, may represent a novel therapeutic target to minimize the deleterious neuroinflammatory cascade that occurs during systemic inflammation and ameliorate PSD. Figure 5 shows a summary of critical aspects of hippocampal neurovascular function impaired under pathological conditions known to accelerate age-related cognitive decline and contribute to VCI. There is still much to learn about this unique and understudied vascular territory responsible for maintaining basal and activity-dependent perfusion of the injury-prone hippocampus. There are currently no treatments for VCI, only prevention strategies to modify lifestyle risk factors, which have no impact on the healthy aging process. Therefore, it is critical for basic science and clinical studies to further our understanding of pathological mechanisms of age-related dementias to identify potential therapeutic targets. The hippocampal vasculature may be one such target,

including arteriole and BBB function, potentially holding currently untapped therapeutic potential to help alleviate VCI and other dementias.

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Non-standard Abbreviations and Acronyms

AChA	anterior choroidal artery
AD	Alzheimer's disease
BBB	blood-brain barrier
CA	cornu ammonis
CADASIL	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
eNOS	endothelial nitric oxide synthase
HA	hippocampal arteriole
IK_{Ca}	intermediate-conductance calcium-activated potassium channel
L-NAME	NG-nitro-L-arginine methyl ester
MCA	middle cerebral artery
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NOS	nitric oxide synthase
NVC	neurovascular coupling
PCA	posterior cerebral artery
PE	preeclampsia
PSD	post-stroke dementia
SHR	spontaneously hypertensive rat
SK_{Ca}	small-conductance calcium-activated potassium channel
tMCAO	transient middle cerebral artery occlusion
TNFα	tumor necrosis factor alpha
VCI	vascular cognitive impairment

VSM vascular smooth muscle

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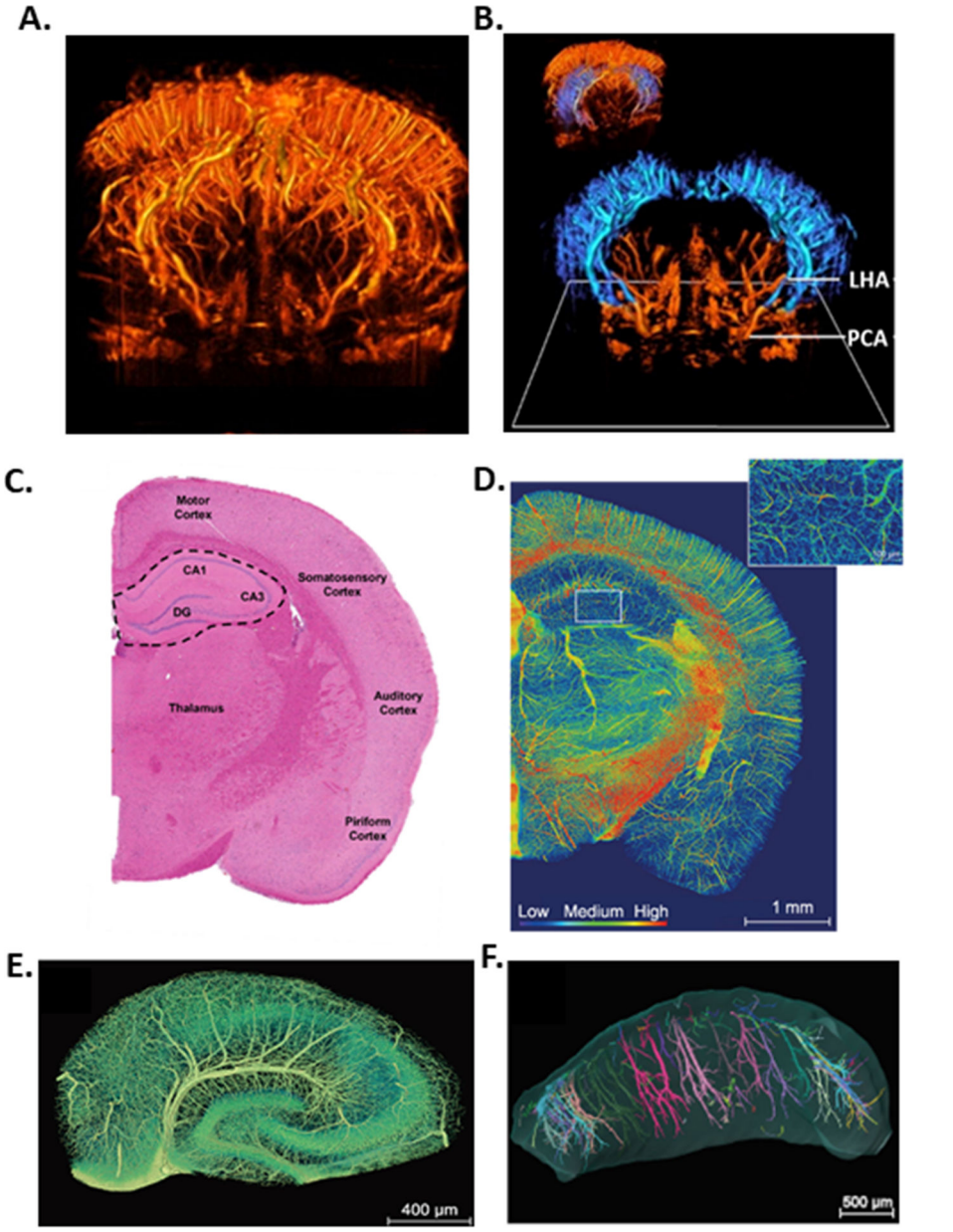

Figure 1.

(A) High-quality 3D reconstruction of the rat brain vasculature. (B) The bilateral hippocampal vasculature (blue) deep within the brain, originating from the posterior cerebral artery (PCA) giving rise to the longitudinal hippocampal artery (LHA) to perfuse the hippocampi. (C) Half of a coronal section of rodent brain stained with H&E (hematoxylin and eosin). The hippocampal formation is outlined and tightly packed pyramidal neurons are visible comprising the hippocampal subfields (DG, dentate gyrus; CA, cornu ammonis). (D) Half of a coronal section of mouse brain with a heat map visualization of the vascular volumetric density coded by color scale. Inset in the hippocampus showing reduced vascular density demonstrated by cooler colors. (E) Coronal section through the hippocampus showing the internal transverse hippocampal artery in the hippocampal sulcus and its

long arch-like arteriole branches that perfuse CA1 and CA3 subfields. (F) Longitudinal view of bilateral hippocampi along the septotemporal axis, with the temporal pole (ventral hippocampus) on the left and septal pole (dorsal hippocampus) on the right. Colors represent individual vessels. Panels A and B contain data and images provided by Iconeus, France and are adapted from *NeuroImage,* 127, Demené et al., 4D microvascular imaging based on ultrafast Doppler tomography, page 481, Copyright © 2016, with permission from Elsevier. Panels D-F are adapted from Zhang et al., 2019 *Nat Sci Rev* doi: 10.1093/nsr/nwz124, an open access journal https://creativecommons.org/licenses/by/4.0/.

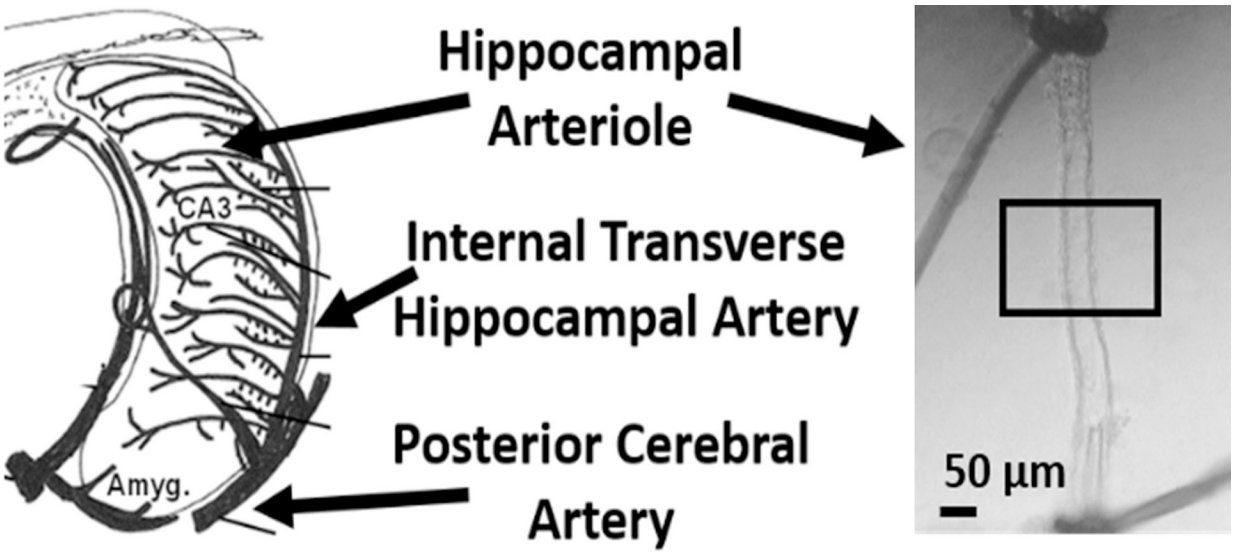

Figure 2.
The arterial blood supply of the rat hippocampus and an isolated and pressurized segment of a hippocampal arteriole cannulated in an arteriograph chamber at 40 mmHg intravascular pressure. Adapted from Johnson & Cipolla, *JCBFM,* Volume 37, Issue 8, Page 2860, Copyright © 2016, with permission of SAGE Publications.

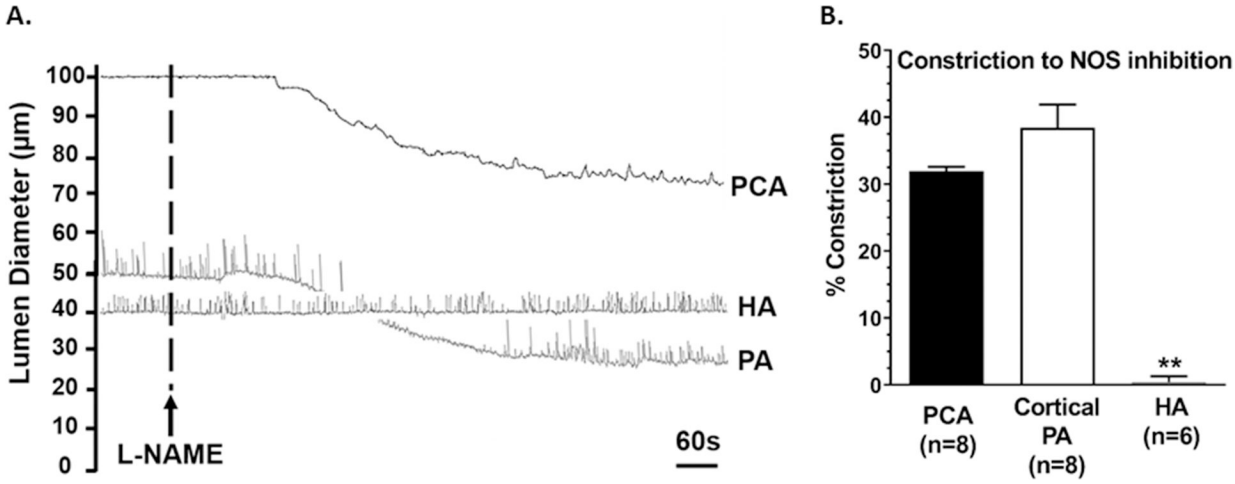

Figure 3.

(A) Representative lumen diameter tracings of an isolated and pressurized posterior cerebral artery (PCA) at 75 mmHg intravascular pressure with ~30% tone, cortical parenchymal arteriole (PA) at 40 mmHg with ~40 % tone and hippocampal arteriole (HA) at 40 mmHg intravascular pressure with ~ 40% tone from male Wistar rats before and after treatment with the nitric oxide synthase (NOS) inhibitor NG-nitro-L-arginine methyl ester (L-NAME, 10^{-3}M). (B) Percent constriction to NOS inhibition. **p<0.01 vs. PCA and PA by one-way ANOVA with post-hoc Bonferroni test.

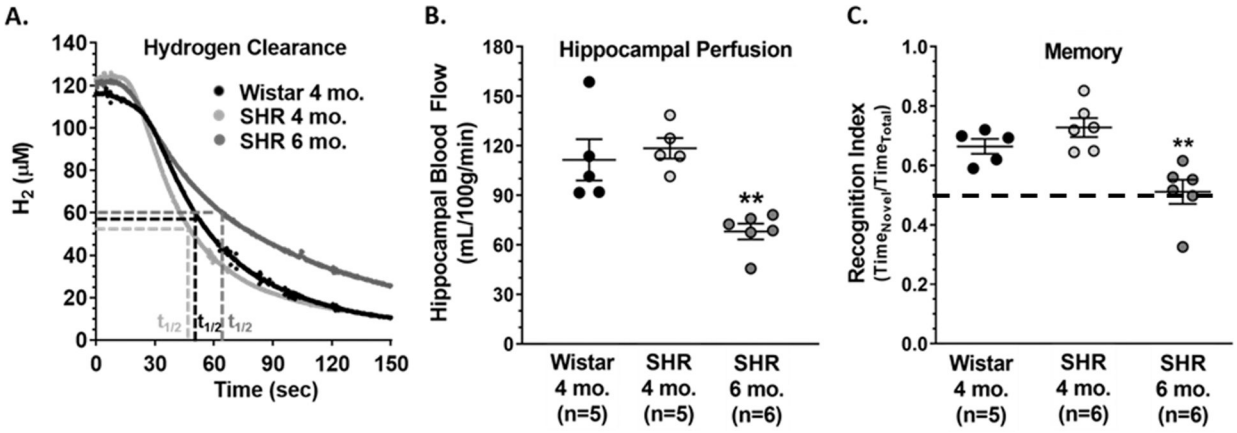

Figure 4.

(A) Representative traces of hydrogen (H_2) clearance used to calculate (B) absolute hippocampal blood flow. (C) Recognition indices of Wistar rats and spontaneously hypertensive rats (SHR) at 4 and 6 months of age. **p<0.01 vs. 4-month-old Wistar and SHR by one-way ANOVA with post-hoc Bonferroni test.

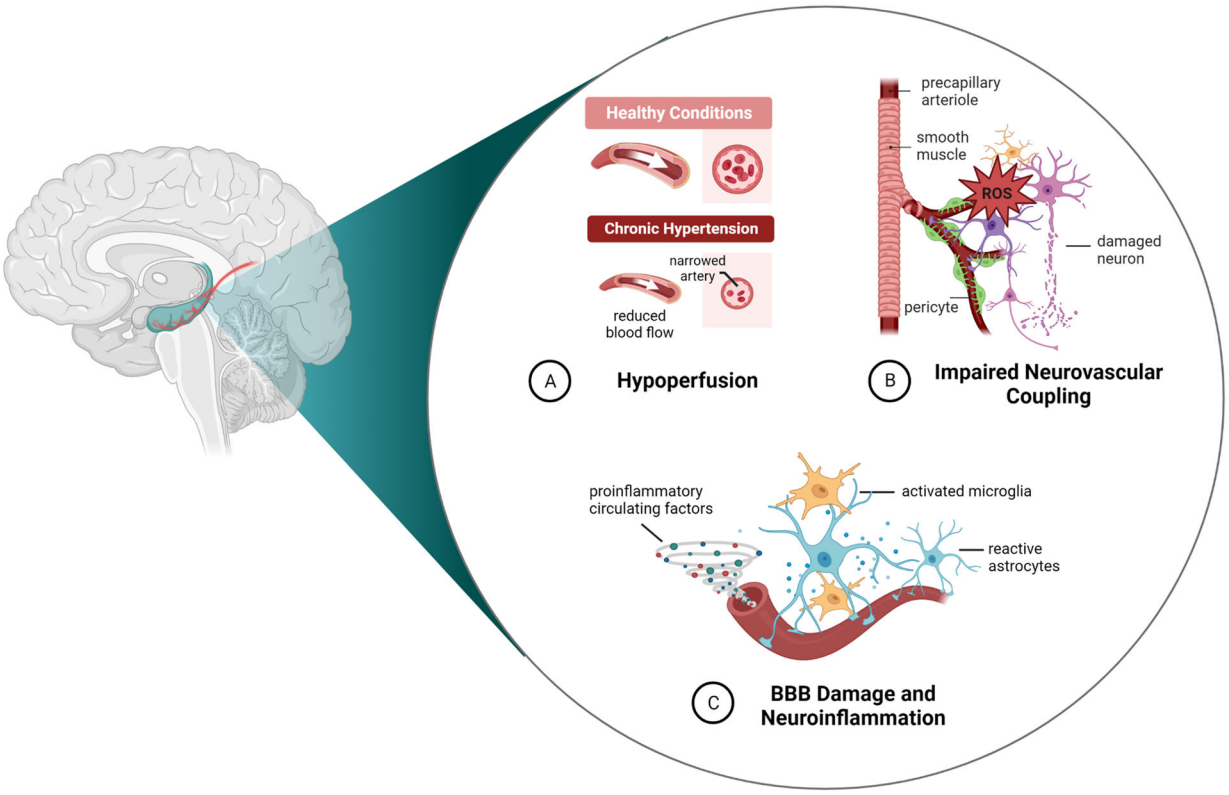

Figure 5.

Summary of how pathological conditions known to accelerate age-related cognitive decline may affect the hippocampal vasculature and neurovascular function to contribute to VCI.