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Microvascular Dysfunction and Cognitive Impairment

T. Michael De Silva^{1,2} and Frank M. Faraci¹

¹Departments of Internal Medicine and Pharmacology, Francois M. Abboud Cardiovascular Center, Carver College of Medicine, University of Iowa, Iowa City Veterans Affairs Healthcare System, Iowa City, IA, USA

²Biomedicine Discovery Institute, Department of Pharmacology, 9 Ancora Imparo Way, Monash University, Clayton, Vic, Australia

Abstract

The impact of vascular risk factors on cognitive function has garnered much interest in recent years. The appropriate distribution of oxygen, glucose and other nutrients by the cerebral vasculature is critical for proper cognitive performance. The cerebral microvasculature is a key site of vascular resistance and a preferential target for small vessel disease. While deleterious effects of vascular risk factors on microvascular function are known, the contribution of this dysfunction to cognitive deficits is less clear. In this review, we summarize current evidence for microvascular dysfunction in brain. We highlight effects of select vascular risk factors (hypertension, diabetes and hyperhomocysteinemia) on the pial and parenchymal circulation. Lastly, we discuss potential links between microvascular disease and cognitive function, highlighting current gaps in our understanding.

Keywords

Endothelium; cerebral circulation; microcirculation; vascular remodeling; hypertension; diabetes

Introduction

Because the brain lacks energy reserves, its normal function depends upon adequate perfusion to constantly supply glucose, oxygen, and other essential nutrients. Multiple mechanisms and a complex interaction between vascular and non-vascular cells provide the integrated control of cerebral blood flow (CBF), predominantly through effects on the diameter of large and small blood vessels. Both large and small blood vessels are major contributors to cerebrovascular resistance and thus regulation of CBF (Faraci, 2011b; Faraci and Heistad, 1990). These two segments of the vasculature are also key sites of disease. Once initiated, vascular disease generally progresses slowly over time, the final consequences of which can be devastating. For example, microvascular or small vessel disease is a key cause of stroke but is also thought to be a major contributor to dementias and other neurological diseases that have a vascular component (Faraci, 2011b; Faraci and

Heistad, 1990; Iadecola, 2013; Joutel and Faraci, 2014; Wardlaw et al., 2013). Our knowledge of molecular and cellular mechanisms that underlie cerebrovascular disease, along with approaches to limit its progression or reverse its effects, are still limited. These issues are particularly true for small vessel disease, which has no specific therapy at this time.

For the purpose of this review, we focus on the microvascular segment of the vasculature. As highlighted in Figure 1, we emphasize the impact of several major cardiovascular risk factors on small vessels. When discussing the microcirculation, we refer to small arteries and arterioles in the pial (or leptomeningeal) circulation, along with penetrating and parenchymal arteries and arterioles, pericytes, capillaries, and venules (Joutel and Faraci, 2014; Pantoni, 2014). A unique feature of the cerebral circulation is the presence of the blood-brain barrier (Dalkara, 2015; Tietz and Engelhardt, 2015). Some aspects of the brain microcirculation, including vasomotor control in the pial circulation and control of blood-brain barrier integrity and transport, have been studied fairly extensively under normal conditions. In contrast, much less is known regarding the parenchymal circulation, particularly in disease. Lastly, the discussion outlines links between cognition and vascular risk factors (Gorelick et al., 2011), along with the impact and potential contribution by the microcirculation.

Cerebral Blood Flow: Control Under Normal Conditions

Regulation of CBF involved numerous cells type and mechanisms. Here we highlight three key areas – endothelium-dependent mechanisms, neurovascular coupling, and autoregulation. For the purpose of this review, we are not discussing what some refer to as chemoregulation of CBF [effects of hypoxia or carbon dioxide (changes in pH)].

Endothelial cells are a major regulator of vasomotor tone, vascular structure and mechanics, fibrinolysis and coagulation, as well as inflammation. Endothelium is also the cellular site of the blood-brain barrier. Through the influence of endothelial nitric oxide synthase (eNOS), endothelial cells in pial and parenchymal arterioles normally exert a dilator influence on vascular tone under control conditions (Cipolla et al., 2009; Faraci, 2011b; Faraci and Heistad, 1998; Katusic and Austin, 2014). Within the parenchyma, these cells also inhibit arteriolar tone via eNOS-independent mechanisms (Cipolla et al., 2009). In addition to effects on resting tone, endothelium mediates vasodilator responses to neurotransmitters, metabolic factors, and shear stress as well as being critical for propagated vasodilation (Chen et al., 2014; Faraci, 2011b; Faraci and Heistad, 1998; Hillman, 2014; Katusic and Austin, 2014; Ku et al., 2015).

Neurovascular coupling (or functional hyperemia) is a term commonly used to describe the physiological process whereby increased activity in neurons activates cellular and molecular pathways that communicate with the vasculature resulting in a increase in CBF. This coupling supports shifting energy demands ensuring adequate delivery of oxygen, glucose, and other nutrients, along with removal of metabolic by-products. Neurovascular coupling has been studied widely in experimental models (mostly in the somatosensory cortex) but also to some degree in human participants (Capone et al., 2010; Capone et al., 2011;

Girouard et al., 2008; Girouard et al., 2006, 2007; Hillman, 2014; Kazama et al., 2004; Liu, 2013; Martin, 2014). In addition to neurons, endothelial cells, astrocytes and perhaps pericytes contribute to this collective response. Signaling ions and molecules that have been proposed to contribute to neurovascular coupling include K^+ , neurotransmitters (acetylcholine, GABA), NO, several prostanoids (eg, PGE_2) and products of cellular metabolism (adenosine) (Bloch et al., 2015; Hillman, 2014; Iadecola, 2013; Jackman and Iadecola, 2014).

Autoregulation reflects the ability of the brain to maintain a relatively constant CBF over a substantial range of perfusion pressures (Cipolla, 2009). Changes in diameter of both arteries and arterioles contribute to autoregulatory responses, with vasodilation when pressure is reduced and vasoconstriction when pressure is increased (Cipolla, 2009; Pires et al., 2013). Changes in myogenic tone (resting tone) and myogenic responses (responses to increases or decreases in pressure) are major contributors to autoregulation (Cipolla, 2009; Hill and Meininger, 2012; Kontos et al., 1978; Pires et al., 2013). Mechanisms that control these responses have been studied widely, although details remain controversial regarding how changes in pressure are sensed and what signaling events, molecules, and pathways are involved (Hill and Meininger, 2012; Walsh and Cole, 2013). Mechanisms that have been implicated include select integrins and G-proteins, ion channels and other regulators of membrane potential, kinase-mediated events, and contractile proteins (Hill and Meininger, 2012). The cellular basis for the myogenic response resides in vascular muscle, but can be modulated by other cell types including endothelium and neurons (Hill and Meininger, 2012).

Sites of Vascular Resistance in Brain

In this section, we summarize several concepts related to vascular resistance, microvascular pressure, as well as their regulation and impact. The distribution of vascular resistance and regulation of microvascular pressure has unique elements in brain (Faraci and Heistad, 1990). Figure 2 summarizes values based on direct measurements of microvascular pressure in pial arterioles perfusing the cerebral cortex. Values obtained were quite consistent across species and laboratories (Baumbach et al., 2006; Baumbach and Heistad, 1983; Baumbach et al., 2003, 2004; Beyer et al., 2008a; Chillon et al., 1997; Faraci et al., 1987; Harper and Bohlen, 1984; Harper et al., 1984; Hurn et al., 1993; Kadel et al., 1990; Mayhan and Faraci, 1990; Shima et al., 1983; Tamaki et al., 1986; Tamaki et al., 1992). These measurements, along with measurements of CBF, illustrate that approximately half of total vascular resistance in brain resides in vessels upstream from this point in the pial circulation. The remaining portion of vascular resistance resides in the parenchyma and is determined by arterioles, capillaries, and small venules. Capillaries are the segment of the circulation with the greatest surface area for oxygen and glucose exchange but are not major contributors to vascular resistance (Burton, 1972; Renkin, 1984). In addition to these baseline features, the relative contribution of resistance of large arteries and small vessels can change acutely and/or chronically. For example, resistance of both segments of the circulation are increased during chronic hypertension, including when these vessels are maximally dilated (Werber and Heistad, 1984). Increases in segmental vascular resistance when maximally dilated can

reflect both loss of vessels within the vascular tree along with other changes in vascular structure (see discussion below).

Evidence suggests that arteriolar pressure is a regulated variable. Under some physiological or pathophysiological conditions, arteriolar pressure can increase or decrease independent of changes in systemic arterial pressure (Baumbach and Heistad, 1983; Faraci and Heistad, 1990). In response to focal cellular activation and increases in CBF (such as during neurovascular coupling), dilation of arterioles and arteries upstream from the site of activation normally occurs (reviewed by Hillman) (Hillman, 2014). Because resistance of large arteries in brain is relatively high, coordinated dilation of upstream vessels is critical to help maintain local arteriolar pressure when CBF increases (Faraci and Heistad, 1990; Fujii et al., 1991). In the absence of flow-mediated vasodilation (also referred to as propagated or conducted vasodilation), local arteriolar pressure would fall resulting in a reduction in local perfusion pressure (Faraci and Heistad, 1990). In this regard, preliminary studies suggest that propagated dilation in parenchymal arterioles is impaired during chronic hypertension (Chan, 2015). Such findings imply that dysregulation of arteriolar pressure (local perfusion pressure) may occur with vascular disease, and represent an additional mechanism that contributes to impaired neurovascular coupling, autoregulation, or other adaptive vasodilator responses.

Hypertension

Many of the most profound changes in the microcirculation occur during chronic hypertension. Effects on this segment of the circulation contribute to fundamental end-organ effects of hypertension in brain. Diverse approaches have been used to study these changes including various genetic, renal, and pharmacological models. Several examples are shown in the Table. Changes in vascular structure and function during hypertension affect each segment of the circulation and cell type (Baumbach and Heistad, 1988; Baumbach et al., 2004; Bloch et al., 2015; Faraci, 2011b; Iadecola, 2013). Overall, the majority of studies in this area have focused on changes in cerebral arteries (large vessels) during hypertension. Within the microcirculation, most of the data on the impact of hypertension (and other vascular risk factors) is derived from studies of the pial circulation rather than vessels within the parenchyma. In the context of this discussion, it is important to recognize that hypertension is extremely common, affecting approximately one out of three adults. The most recent Global Burden of Disease analysis revealed that hypertension is currently the number one risk factor for overall disease burden and health loss worldwide (Lim et al., 2012).

In relation to microvascular structure, three areas will be highlighted - vascular hypertrophy, inward vascular remodeling, and vascular rarefaction. Hypertrophy, or increases in the cross-sectional area of the vessel wall, represents an adaptive response during hypertension that reduces wall stress. The presence of hypertrophy can also potentially encroach on the vessel lumen and thus limit vasodilation. Increases in the cross-sectional area of the arteriolar wall occur in many models of hypertension and descriptions of vascular wall thickening are common in humans with hypertension (Baumbach and Hajdu, 1993; Baumbach and Heistad, 1988; Baumbach et al., 2003, 2004; Chan and Baumbach, 2013a, b). Interestingly, arteriolar

hypertrophy is not unique to hypertension and is seen in other models of vascular disease, including hyperhomocysteinemia, genetic deficiency in superoxide dismutase (*Sod1*), genetic interference with the nuclear receptor peroxisome proliferator-activated receptor- γ (*Ppar γ*) (produced by expressing dominant negative forms of the transcription factor), genetic deficiency in eNOS (or *Nos3*), or chronic inhibition of NOS, among others (Table) (Baumbach et al., 2006; Baumbach et al., 2002; Baumbach et al., 2003, 2004; Beyer et al., 2008a; Chan and Baumbach, 2013a, b; Chillon et al., 1997; Halabi et al., 2008). Of these models, the intervention that produces the greatest relative increase in arteriolar cross-sectional area is genetic deficiency in *Sod1* (Baumbach et al., 2006). This change occurred in the absence of increases in arterial pressure and provides direct evidence that oxidative stress and reactive oxygen species have a major influence on vascular structure. Recent findings in models of hypertension also support a role for oxidative stress in vascular hypertrophy (Baumbach et al., 2004; Chan and Baumbach, 2013a, b).

Inward remodeling represents a three dimensional rearrangement of the vessel wall, resulting in a reduction in lumen diameter that is not due to changes in vasomotor tone or mechanical characteristics. The lumen of the vessel is smaller, even when maximally dilated. In contrast to vascular hypertrophy, inward remodeling occurs more selectively. It has been described in some, but not all forms of hypertension (Figure 3) (Baumbach and Hajdu, 1993; Baumbach et al., 2003). Angiotensin II, a major mediator of vascular effects of the renin-angiotensin system, appears to be a key determinant of inward remodeling in the microcirculation. For example, a reduction in lumen diameter of cerebral arterioles occurs in response to chronic administration of non-pressor or pressor doses of angiotensin II in normal mice, as well as a genetic model with increased expression of renin-angiotensin system components (Figure 3) (Baumbach et al., 2003; Chan and Baumbach, 2013a; Chillon et al., 1997). The renin-angiotensin system plays a key role in inward remodeling in other genetic models of hypertension as well (Chillon and Baumbach, 2001). Considering both hypertrophy and inward vascular remodeling, available evidence suggests that the latter has the greatest impact of vascular resistance and vasodilator reserve during hypertension (Figure 3) (Baumbach and Heistad, 1989; Chillon and Baumbach, 2001). In relation to its physiological consequences, inward vascular remodeling represents a double-edged sword. The reduction in lumen diameter protects capillaries and venules from increases in microvascular pressure, thus protecting the blood-brain barrier from fluctuations in upstream pressure (Baumbach and Heistad, 1988; Mayhan et al., 1987b). However, the increase in minimal resistance (an index of the structure of resistance vessels when maximally dilated) limits vasodilator responses such as autoregulation during reductions in perfusion pressure and collateral-dependent perfusion during ischemia (Baumbach and Heistad, 1988, 1989; Chillon and Baumbach, 2001; Faraci, 2011b).

In relation to mechanisms, vascular hypertrophy and inward remodeling share some features. In response to angiotensin II, reactive oxygen species and NADPH oxidase-dependent processes are involved in both changes (Chan and Baumbach, 2013a, b). There is evidence that elements of the underlying mechanisms may also diverge. For example, angiotensin II transactivates the epidermal growth factor receptor (EGFR), resulting in EGFR phosphorylation in cerebral arterioles (Chillon et al., 1997). Both pharmacological and genetic approaches suggest that EGFR signaling is essential for development of hypertrophy,

but not inward remodeling in the brain microcirculation (Chillon et al., 1997). Other mechanisms, such as activation of calcium-activated chloride channels (TMEM16A) have been implicated in remodeling of cerebral arteries during hypertension (Wang et al., 2012), but their functional role in the microcirculation has not been determined.

A loss of endogenous mechanisms that normally protect against vascular growth and remodeling represents an additional potential cause of vascular changes during hypertension. As noted above, reductions in antioxidant capacity due to decreases in SOD1 expression or activity results in marked vascular hypertrophy (Baumbach et al., 2006). Another example relates to the normal microvascular effects of PPAR γ . Activation of PPAR γ inhibits expression and functional effects of AT1-receptors (Ryan et al., 2004; Sugawara et al., 2001), the receptor that mediates the majority of the detrimental effects of angiotensin II in the vasculature (Faraci, 2011b; Karnik et al., 2015; Modrick et al., 2009a). Conversely, angiotensin II increases activity of Bcr kinase, resulting in phosphorylation and reductions in PPAR γ transcriptional activity (Alexis et al., 2009). It is interesting in this regard that genetic interference with PPAR γ in all cells (using a heterozygous knockin) or in vascular muscle (using a cell-specific promoter) mimic effects of angiotensin II, producing inward remodeling of cerebral arterioles (Beyer et al., 2008a; Halabi et al., 2008). Lastly, the *Notch3* mutation that causes cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), the most common known genetic cause of small vessel disease, also produces inward remodeling in cerebral vessels along with a progressive reduction in capillary density and reduced CBF (Dabertrand et al., 2015; Joutel and Faraci, 2014; Joutel et al., 2010). Overall, these findings support the concept that inward remodeling occurs and may contribute to hypoperfusion in both genetic and non-genetic causes of small vessel disease including some forms of hypertension (Figure 3).

In addition to the systemic renin-angiotensin system, local renin-angiotensin systems exist at the organ level, including in brain (Karnik et al., 2015). Deoxycorticosterone (DOCA)-salt can be used to activate the central renin-angiotensin system while simultaneously suppressing its peripheral counterpart (Grobe et al., 2011). In preliminary studies, we found that DOCA-salt produced modest hypertension, accompanied by impaired endothelial function throughout the brain (cerebral arteries, pial and parenchymal arterioles), while responses in small mesenteric arteries were normal. Local inhibition of AT1 receptors or Rho kinase in pial arterioles in vivo reversed the microvascular dysfunction (De Silva, 2015a). Consistent with the impact of angiotensin II on pial arterioles, inward remodeling was present in parenchymal arterioles following DOCA-salt treatment (unpublished observations)(Figure 3). Others have described reductions in lumen diameter and degeneration of parenchymal arterioles in genetic and renal models of hypertension (Chan et al., 2013; Fan et al., 2015a; Pires et al., 2015; Sabbatini et al., 2001; Ueno et al., 2004). Loss of arteriolar, capillary, and venular wall integrity promotes leakage of proteins from the circulation and local microhemorrhages. Importantly, similar changes are present in small arteries in the parenchyma in the human brain during hypertension, along with reductions in microvessel density and microbleeds (Devlin et al., 2004; Kamath et al., 2006; Plesea et al., 2005).

A third category of structural change is the loss of vessels, also known as rarefaction (Figure 1). Hypertension, along with other select risk factors for vascular disease, is associated with such loss (Moore et al., 2015). Recent studies focused on collateral arterioles in the pial circulation have provided some of the more detailed analyses related to rarefaction (Moore et al., 2015). Collateral vessels are naturally occurring connections between arteries or between arterioles within the microcirculation. Changes in elements of the collateral circulation occur in disease and include inward (or outward) remodeling of the lumen as well as increases or decreases in collateral numbers. The collateral circulation provides an additional mechanism to help maintain CBF in the face of ischemic challenges, reductions in perfusion pressure, or loss of autoregulation. The functional status of collaterals is a predictor of outcomes and the response to therapy in stroke. For example, the integrity of collateral vessels determines the extent of penumbral loss in patients after occlusion of larger arteries upstream (Baumbach et al., 2003). Models of hypertension (renin overexpression or chronic treatment with an NOS inhibitor) and aging exhibit some of the greatest changes in collaterals which include a reduction in both their number and diameter (Faber et al., 2011; Moore et al., 2015). Based on their magnitude, these changes are predicted to substantially increase resistance of collateral vessels (Faber et al., 2011). In relation to mechanisms, several lines of evidence suggest that eNOS-derived NO normally functions to maintain microvascular collaterals (Faber et al., 2011; Moore et al., 2015). As a consequence, loss of this NO-dependent signaling appears to account for rarefaction in the pial circulation during hypertension, aging, and possibly other vascular risk factors (Moore et al., 2015).

Prominent changes in vascular function occur during hypertension. Several areas have received considerable study (mostly in experimental models, but data for some endpoints is available from human participants as well). The term endothelial dysfunction describes endothelial-based abnormalities that increase vascular tone, vascular permeability, and thrombosis. In relation to vascular tone, impaired endothelium-dependent vasodilation in the microcirculation has been described in models in which hypertension has been produced genetically, pharmacologically, and mechanically (using aortic banding) (Table).

Blood-brain barrier changes are common in acute and chronic hypertension (De Silva, 2015b; Ueno et al., 2004). For example, loss of blood-brain barrier integrity occurs in brain regions involved in autonomic control and memory in both genetic and renal models of hypertension (Biancardi et al., 2014; Ueno et al., 2004). These changes are prevented by an inhibitor of AT1-receptors and appear to be due to direct effects of angiotensin II, not effects of increased arterial pressure (Biancardi et al., 2014).

Impaired neurovascular coupling has been described in genetic (SHR) and pharmacologically-induced models (both pressor and slow-pressor doses of Ang II) of hypertension (Table) (Calcinaghi et al., 2013; Capone et al., 2011; Girouard et al., 2008; Kazama et al., 2004). It is worth noting that diminished neurovascular coupling was seen with Ang II- but not phenylephrine-induced hypertension suggesting some forms of hypertension have a greater impact on this key adaptive response (Girouard et al., 2008). Consistent with the findings in the animal models, CBF responses to cognitive tasks are also impaired in hypertensive humans (Jennings et al., 2005).

In relation to mechanisms, a number of common mediators and pathways have been proposed to underlie impaired neurovascular coupling, endothelial dysfunction, and other vascular changes in hypertension. These mediators include AT1-receptors, isoforms of NADPH oxidase (a major source of superoxide that drives oxidative stress), prostanoids, and Rho kinase, among others (Capone et al., 2010; Capone et al., 2011; De Silva, 2015a; Faraci, 2011b; Faraci and Heistad, 1998; Girouard et al., 2006, 2007; Kazama et al., 2004; Mayhan, 1992). As part of the molecular changes that occur as a result of oxidative stress, peroxynitrite (the reaction product of NO and superoxide) activates poly-ADP-ribose polymerase (PARP), a nuclear protein involved with DNA surveillance and repair. Activation of PARP has been implicated in endothelial dysfunction in several disease models (Didion et al., 2006; Girouard et al., 2007; Modrick et al., 2009a; Park et al., 2014). Downstream of PARP, activation of transient receptor potential (TRP) channels with resulting calcium overload may then occur (Didion et al., 2006; Modrick et al., 2009a; Park et al., 2014). In addition to these mediators, other cell types and molecules may be involved. For example, because neurovascular coupling involves neurons, astrocytes, and endothelial cells, abnormalities in one or more of these cells may play a role (Chen et al., 2014; Hillman, 2014). In some cases, the mechanisms that underlie abnormalities in the microcirculation are similar to those described in cerebral arteries, while others may be unique to microvessels (Faraci, 2011b; Faraci and Heistad, 1998; Mayhan, 1992).

In addition to these mechanisms, activation of immune cells and related signaling pathways can occur during microvascular disease. For example, local macrophage accumulation and activation of microglia occurs in cortex and white matter and have been suggested to contribute to brain injury in a genetic model of hypertension (Nakagawa et al., 2013). Immune-related molecular and cellular determinants of atherosclerosis (predominantly a disease of larger arteries) have been studied for many years (Tabas et al., 2015). Recently, there has been emphasis on the role of related mechanisms in hypertension as well (Wenzel et al., 2015). Despite such efforts, the impact of such mechanisms in microvascular disease and to what extent they contribute to reductions in CBF, loss of blood-brain barrier integrity, and so forth, is poorly defined.

Autoregulation is altered during hypertension. Resistance of both large arteries and small vessels are increased during chronic hypertension, both under baseline conditions and when vessels are maximally dilated (Baumbach and Heistad, 1988; Werber and Heistad, 1984). Collectively, these changes in resistance reflect increases in vascular tone as well as structural changes within the vasculature (Baumbach and Heistad, 1988; Cipolla, 2009; Pires et al., 2013). As a consequence, the autoregulatory curve is shifted to the right during hypertension, to a higher range of perfusion pressures (Baumbach and Heistad, 1988; Cipolla, 2009; Pires et al., 2013). The functional impact of this shift includes protection of the downstream vasculature and maintenance of CBF with further, moderate increases in arterial pressure (Baumbach and Heistad, 1988; Cipolla, 2009; Pires et al., 2013). However, the shift also increases the risk for hypoperfusion if pressure falls below the 'reset' range of autoregulation (Cipolla, 2009; Pires et al., 2013).

Diabetes

Diabetes and related metabolic abnormalities are additional risk factors for cerebrovascular disease, stroke, and cognitive impairment (Gorelick et al., 2011; Pantoni, 2014; Wardlaw et al., 2013). In relation to the brain microcirculation, varied models have been studied (Table). They include genetic and pharmacological models of Type 1 diabetes as well as genetic models of Type 2 diabetes and obesity. Much of the attention in this area has been given to models with altered leptin-dependent signaling. Diet-induced obesity is the most common cause of the condition in humans, with high fat feeding now being a very common experimental approach (see(Beyer et al., 2008b; Lynch et al., 2013) for examples).

As with most other risk factors for vascular disease, both structural and functional changes occur in microvessels during diabetes. These changes include impaired endothelial function (endothelium-dependent vasodilation, enhanced thrombosis, and loss of blood-brain barrier integrity), altered myogenic responses, and reduced functional hyperemia (Arrick, 2014; Didion et al., 2005; Didion et al., 2007; Erdos et al., 2004; Ergul et al., 2009; Mayhan et al., 2006; Mayhan et al., 1991; Vetri et al., 2012). At least some of these effects can be mimicked by acute hyperglycemia (Mayhan and Patel, 1995; Nakahata et al., 2008). Structural changes include collagen deposition, thickening of the basement membrane, reductions in microvascular density, and loss of collateral vessels (Ergul et al., 2009). Along with hypertension and aging, some of the greatest effects on the number and diameter of collateral vessels are seen in a model of metabolic syndrome (Faber et al., 2011; Moore et al., 2015). In relation to diabetes, metabolic syndrome is associated with poor collateral status in the pial circulation in patients with acute ischemic stroke (Menon et al., 2013).

Many of these same mechanisms that have been implicated in hypertension appear to contribute to microvascular dysfunction in diabetes. These include a role for AT1-receptors, reactive oxygen species and NADPH oxidase, reductions in eNOS-derived signaling, along with activation of cyclooxygenase, protein kinase C, Rho kinase, and PARP (Abd-Elrahman et al., 2015; Arrick, 2014; Arrick et al., 2008; Didion et al., 2005; Didion et al., 2007; Ergul et al., 2009; Mayhan et al., 2006; Mayhan and Patel, 1995; Mayhan et al., 1991; Moore et al., 2015; Vetri et al., 2012). In addition to effects on vascular tone and microvessel structure, loss of eNOS-derived NO impairs neurogenesis in brain (Chen et al., 2005; Katusic and Austin, 2014). Because neurogenesis is impaired during diabetes (Saravia et al., 2004), it is conceivable that this impairment is due to diabetes-induced endothelial dysfunction and loss of eNOS-mediated signaling. Such a cascade of events has additional implications for long-term cognitive effects and recovery from injury in the presence of diabetes and other metabolism-related abnormalities.

Hyperhomocysteinemia

Hyperhomocysteinemia has been implicated in cerebrovascular disease and stroke, including small vessel disease and changes in cognition (Kamat et al., 2015; Poggesi et al., 2015). Local levels of homocysteine are determined by dietary, genetic, and renal factors. Mouse models genetically deficient in key enzymes within the homocysteine metabolic pathway have been studied including cystathionine β -synthase (*Cbs*), methylenetetrahydrofolate

reductase (*Mthfr*), and methionine synthase (MS, encoded by *Mtr*) (Table). Each of these genetic alterations results in hyperhomocysteinemia. Models using diets containing low folate and/or high methionine to induce hyperhomocysteinemia are also common (Table) (Dayal et al., 2014; Kamat et al., 2015; Kim et al., 2002).

The cerebral microcirculation is very sensitive to local levels of homocysteine. Mild-to-moderate increases in circulating homocysteine are associated with endothelial dysfunction in cerebral arterioles in CBS-, MTHFR-, and MS-deficient mice (Dayal et al., 2004; Dayal et al., 2005; Devlin et al., 2004). The extent of endothelial dysfunction correlates with plasma levels of homocysteine, regardless of the genetic and/or dietary approaches used to alter homocysteine levels. Both dietary and genetic hyperhomocysteinemia was also associated with hypertrophy of cerebral arterioles and increased arteriolar distensibility (Baumbach et al., 2002). Unlike changes that occur in models of hypertension, inward remodeling did not occur of pial arterioles during hyperhomocysteinemia (Baumbach et al., 2002). Other microvascular changes that do occur include increases in oxidative stress and expression of matrix metalloproteinases, basement membrane irregularities, degeneration of pericytes, disruption of the blood-brain barrier, and ultrastructural changes in endothelial mitochondria (Dayal et al., 2004; Kalani et al., 2014; Kamat et al., 2015; Kamath et al., 2006; Kim et al., 2002; Rhodhouse et al., 2013). Collectively, these findings suggest elevated homocysteine (or a closely related metabolite) produces major structural and functional changes in the microcirculation.

Pericytes

Pericytes are an additional cell type in the distal microcirculation, part of what is often referred to as the neurovascular unit (Armulik et al., 2011; Dalkara and Alarcon-Martinez, 2015). These cells are present in relatively high numbers in brain (Armulik et al., 2011; Dalkara and Alarcon-Martinez, 2015). Pericytes are typically described in close proximity to capillaries, extending process longitudinally down the capillary length while occasionally encircling the entire circumference of individual capillaries (Armulik et al., 2011; Hill et al., 2015). Changes in pericytes occur during disease. There is morphological and molecular evidence for pericyte loss, pericyte degeneration, and loss of the spatial association between pericytes and capillaries in models of hypertension, hyperhomocysteinemia, diabetes, and CADASIL (Ghosh et al., 2015; Kim et al., 2002; Price et al., 2012; Suzuki et al., 2003). The functional importance of these changes are not entirely clear at this point. Pericyte loss or dysfunction may contribute to loss of blood-brain barrier integrity and function (Armulik et al., 2011) that has been described with each of these conditions. For example, associations between changes in pericytes, reductions in endothelial adherens-junction proteins, and increases in blood-brain barrier permeability have been described in CADASIL (Ghosh et al., 2015). An effect of pericytes on local capillary perfusion is an additional possible consequence, although direct evidence for such an influence in vivo is very limited. At present, the impact of pericytes on CBF is controversial under control conditions (Armulik et al., 2011; Fernandez-Klett et al., 2010; Hill et al., 2015), making the consequences of changes with disease difficult to predict.

Consequences of Microvascular Disease

What are the consequences of microvascular disease during hypertension or in the presence of other vascular risk factors? Many of the functional and structural changes collectively impact perfusion. In addition, some of the changes promote thrombosis, loss of blood-brain barrier integrity, and in some cases, microhemorrhages. Dysfunction at the level of endothelial cells is likely the key initiating event, and is thought to be a key element of small vessel disease (Faraci, 2011b; Poggesi et al., 2015; Wardlaw et al., 2013). As the endothelial component of microvascular disease progresses (Li et al., 2013; Mayhan et al., 2008; Modrick et al., 2009b; Park et al., 2007; Shi et al., 2014; Walker et al., 2014), the process impacts other cell types in the vessel wall. As summarized in Figure 4, the sequence of events can include endothelial dysfunction, increases in vascular tone and blood-brain barrier permeability, inward vascular remodeling, vascular hypertrophy and rarefaction. As a result, there may be hypoperfusion at rest combined with impairment in the moment-to-moment control of CBF (Figure 4). Loss of adaptive vascular responses occurs including neurovascular coupling and autoregulation. Minimal vascular resistance is elevated so vasodilator reserve is reduced in microvessels including collaterals. The circulation is now predisposed to greater injury in the face of ischemia or other forms of brain injury.

White matter abnormalities are linked to hypertension and other vascular risk factors and are seen very commonly with aging (Rost, 2013). These changes correlate with cognitive dysfunction (Rost, 2013). Reductions in perfusion to white matter is thought to be a common underlying mechanism in this regard as white matter may be sensitive to even modest reductions in local blood flow and PO_2 (Rost, 2013; Wardlaw et al., 2013). Reductions in local PO_2 , and cellular injury occurs in white matter in a genetic model of hypertension (Weaver et al., 2014). Wang et al described reduced blood flow in deep white matter in the early stages of hypertension in humans (Wang et al., 2015). Changes in blood-brain barrier permeability, such as loss of tight junction protein expression and integrity in white matter, occur progressively during hypertension (Fan et al., 2015a; Fan et al., 2015b). The loss of adaptive responses such as neurovascular coupling is thought to also contribute to loss of cognition (Bloch et al., 2015; Iadecola, 2013; Joutel and Faraci, 2014). The relative importance of hypoperfusion (reduced baseline CBF) versus diminished neurovascular coupling per se is not clear however (Figure 4).

Unrelated to the control of vasomotor tone and blood-brain barrier integrity, endothelial cells also affect non-vascular cells. Cerebral endothelium normally promotes neuronal signaling, synaptic function, oligodendrocyte and white matter function, neural progenitor cell function and neurogenesis, while inhibiting activation of microglia and processing of amyloid precursor protein (Faraci, 2011b; Katusic and Austin, 2014; Miyamoto et al., 2014). In addition to effects on perfusion, loss of this collective trophic support in the face of vascular risk factors and endotheliopathy likely contribute to reductions in neuronal and white matter function. Ultimately, cognitive decline and impaired recovery from injury and responses to therapeutics may result.

Potential links between vascular disease and cognition are of great interest. In the absence of ischemia, are alterations or dysfunction in vascular cells (vascular cells only) sufficient to

cause cognitive changes over time? In both animal models and people, links between vascular disease and cognition have been described, but are based very predominantly on associative data, not cause and effect relationships. Associations between vascular disease and cognition are based primarily on the temporal relationship between these endpoints. What have been lacking are experiments that determine whether vascular specific manipulations promote or protect against cognitive decline. Patients with CADASIL may provide proof of concept in this regard. CADASIL is caused by mutations in the *Notch3* receptor, which is expressed predominantly in vascular muscle in adults (Joutel, 2015; Joutel and Faraci, 2014). Thus, a primary vascular cell defect in combination with aging promotes small vessel disease, sequentially resulting in hypoperfusion, dysregulation of CBF, cellular injury, and cognitive decline (Joutel, 2015; Joutel and Faraci, 2014; Joutel et al., 2010). Along these lines, endothelial-specific deficiency in NF- κ B essential modulator impairs endothelium-dependent vasomotor control, produces capillary loss and hypoperfusion, reduces neurovascular coupling and blood-brain barrier integrity, vascular specific alterations which are accompanied by behavioral changes (Ridder et al., 2015).

Vascular disease, including microvascular disease, typically has an aging component (Faraci, 2011a; Toledo et al., 2013). Vascular function progressively declines with age in people and in experimental models and the changes can be accelerated by the presence of hypertension, select genetic alterations, or other vascular risk factors (Figure 4) (Faraci, 2011a; Hatake et al., 1990; Mayhan et al., 2008; Modrick et al., 2009a; Park et al., 2007; Shi et al., 2014; Toledo et al., 2013; Walker et al., 2014). These changes can be modulated (sometimes accelerated) by additional disease modifiers including sex-dependent effects, genetics and epigenetics, metabolism, diet and the environment. This decline in CBF is thought to be a key element of small vessel disease (Joutel, 2015; Poggesi et al., 2015; Wardlaw et al., 2013). Even when small vessel disease arises as the result of other causes (eg, genetic in the case of CADASIL), aging is still a key component of the process (Joutel, 2015; Joutel and Faraci, 2014; Poggesi et al., 2015; Toledo et al., 2013). This impact of aging may in part be explained by age-gene interactions. For example, when combined with aging, partial eNOS deficiency produces endothelial and platelet dysfunction, microthrombosis and infarction, increased permeability of the blood-brain barrier, and cognitive deficits (Tan et al., 2015). A limitation of many experimental models in this area is that they do not incorporate effects of aging into the design.

Cardiovascular risk factors and cognitive impairment

People are living longer and as a result, the relative proportion of older individuals who are also at greatest risk for cognitive abnormalities, is rising. Understanding the reasons for the decline in cognitive performance is of immense interest and importance. The influence of a number of modifiable (e.g. diabetes and hypertension) and non-modifiable (e.g. aging) risk factors on cognition has been investigated extensively. In terms of modifiable risk factors, the link between the existence of cardiovascular risk factors and cognitive abnormalities later in life is best established for hypertension. Hypertension is also a major risk factor for the development of cerebral small vessel disease, which is a major cause of dementia (Gorelick et al., 2011; Joutel and Faraci, 2014; Wardlaw et al., 2013). Most observational studies have concluded that mid-life hypertension increases the risk for dementia later in life

(Launer et al., 1995; Swan et al., 1998). A recent report has provided strong evidence to support effective control of blood pressure in mid life for the preservation of cognitive function later in life. The Atherosclerosis Risk in Communities (ARIC) Study is a prospective epidemiological study of 13,476 individuals from four diverse US communities (Gottesman et al., 2014). While global cognitive function declined in normotensives over the 20-year follow up period, hypertension was associated with an accelerated decline in cognitive function (Gottesman et al., 2014). Anti-hypertensive treatment slowed the cognitive decline, suggesting treatment may need to be started well before the onset of dementia (Gottesman et al., 2014). However, data from interventional studies have been less clear. It is currently uncertain whether blood pressure lowering in the elderly is an effective strategy for reducing the incidence of dementia (Gorelick et al., 2011). More work needs to be done to determine the most effective way to treat cognitive decline due to hypertension in the elderly, however, the answer may lie in the treatment of mid-life hypertension. Diabetes and hyperhomocysteinemia, additional cardiovascular risk factors, are also risk factors for cognitive decline (Kamat et al., 2015; Lu et al., 2009; Maron and Loscalzo, 2009). Whether lowering plasma glucose or homocysteine has beneficial effects on cognition is not entirely clear at present (Cacciapuoti, 2013; Gorelick et al., 2011; Kamat et al., 2015; Maron and Loscalzo, 2009).

Non-modifiable risk factors, such as aging and race, also contribute to the likelihood of cognitive decline (Gorelick et al., 2011). Available evidence suggests that there may not be any sex-dependent difference in the incidence of dementia (Gorelick et al., 2011). Aging is the most important non-modifiable risk factor for cardiovascular diseases. Advancing age is also associated with white matter hyperintensities and increased BBB permeability, both of which are key contributors to cerebral small vessel disease (Prins and Scheltens, 2015; Wardlaw et al., 2013). There is a rapid increase in the incidence of dementia after the seventh decade of life, although incidence rates may slow after 90 years of age (Hall et al., 2005). Importantly, the combination of risk factors such as aging and hypertension dramatically increase the risk of developing dementia (Kivipelto et al., 2006). While the dementia risk attributable to non-modifiable risk factors such as aging cannot be modified, better control of modifiable risk factors from mid-life may well be of immense benefit.

Some Remaining Questions

In this review, we have outlined the impact of select vascular risk factors on aspects of cerebral microvascular structure and function. Because hypertension is the leading risk factor for overall health loss, and mid-life hypertension is associated with late-life cognitive decline, our discussion has focused on its effects to some extent. However, some of the concepts that are presented in relation to hypertension apply to other risk factors as well. Hypertension has numerous effects on the cerebral microcirculation, affecting microvascular structure, endothelial function and neurovascular coupling, along with myogenic responses. Many of these changes result in impaired vasodilator responses. Mechanisms underlying these changes can differ depending on the experimental model, but key contributors include the renin-angiotensin system, oxidative stress, and Rho kinase.

We conclude by presenting some additional questions and areas for study. First, while arterioles within the parenchyma appear to have some unique features compared to large cerebral arteries, it is unclear to what extent parenchymal arterioles are different from small pial arterioles. Second, although some progress has been made in this area, there are still many gaps in our knowledge regarding the contribution of specific cell types to microvascular disease and their impact on CBF, blood-brain barrier integrity, cognition, and other aspects of neurological function. Third, because previous work in this area has generally focused on few brain regions (mainly the parietal and somatosensory cortex), we know relatively little regarding potential microvascular differences between regions, including gray versus white matter. Fourth, the influence of cells other than neurons and astrocytes on the microvasculature, including microglia, oligodendrocytes, perivascular and meningeal macrophages is poorly defined. Fifth, when cell-specific insight has been obtained is often based on studies of normal animal models, not models with cerebrovascular disease or risk factors for stroke and cognitive deficits. Sixth, there has been a growing interest in the role of pericytes in the microcirculation. While progress has been made regarding the influence of this cell type on blood-brain barrier integrity, other areas, such as the impact of pericytes on capillary perfusion are unsettled. Defining the impact of pericytes in vivo has been difficult for several reasons including pericyte heterogeneity and the lack of selective molecular markers (Armulik et al., 2011; Daneman, 2015) or cell-specific promoters. Experiments using truly pericyte-specific manipulations that then define the impact of these cells on microvascular biology in vivo have been lacking. Lastly, studies linking vascular disease to cognitive deficits are based very predominantly on temporal relationships and are therefore associative. Thus, a critical area for future research will be to directly test whether vascular-specific manipulations can prevent or reverse neurological deficits in the face of risk factors for vascular disease.

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Figure 1.
The array of effects, and altered endpoints, that occur in the face of risk factors for vascular disease.

Figure 2.

Levels of arteriolar pressure, expressed as a percent of systemic arterial pressure, in multiple species. Data are redrawn from the following references.(Baumbach et al., 2006; Baumbach and Heistad, 1983; Baumbach et al., 2003, 2004; Beyer et al., 2008a; Chillon et al., 1997; Faraci et al., 1987; Harper and Bohlen, 1984; Harper et al., 1984; Hurn et al., 1993; Kadel et al., 1990; Mayhan and Faraci, 1990; Shima et al., 1983; Tamaki et al., 1986; Tamaki et al., 1992)

Figure 3.

Vascular remodeling expressed as differences in internal diameter of maximally dilated cerebral arterioles (versus controls) in several models of hypertension. Data are shown for hypertensive mice (Baumbach et al., 2003) (R⁺A⁺ and BPH2) and rats (Baumbach and Hajdu, 1993) (SHR and renal hypertension) along with data from mice infused chronically with a pressor dose of angiotensin II (Ang II). (Chan and Baumbach, 2013a) Data from parenchymal arterioles in mice treated with DOCA-salt (De Silva, 2015a) (unpublished observations) are included for comparison.

Figure 4.

Schematic illustration showing the temporal progression of vascular disease and its effect on CBF and cognition with normal aging as well as aging in the presence of vascular risk factors. Both chronic hypoperfusion and loss of acute vasodilator responses [neurovascular coupling (NVC) in this example] are illustrated.

Table

Experimental models used to examine the impact of cardiovascular risk factors and injury on the brain microcirculation.

Model	Vascular Component
Acute hypertension	pial arterioles (Wei et al., 1985)
Aging	cerebral blood flow (Park et al., 2007) pial arterioles (Balbi et al., 2015; Hajdu et al., 1990; Mayhan et al., 2008; Mayhan et al., 1990) parenchymal arterioles (Balbi et al., 2015)
Alcohol	pial arterioles (Sun and Mayhan, 2001; Sun et al., 2006)
Alzheimer's disease	cerebral blood flow (Iadecola et al., 1999; Park et al., 2014), (Park et al., 2008), (Shin et al., 2007) pial arterioles (Han et al., 2015) parenchymal arterioles (Dietrich et al., 2010)
CADASIL	parenchymal arterioles (Dabertrand et al., 2015) cerebral blood flow (Ghosh et al., 2015) pial arterioles (Ghosh et al., 2015)
Cigarette smoke	pial arterioles (Iida et al., 2006; Iida et al., 2008)
Diabetes	
Acute hyperglycemia	pial arterioles (Mayhan and Patel, 1995) parenchymal arterioles (Nakahata et al., 2008; Straub et al., 2009)
streptozotocin (type 1)	pial arterioles (Mayhan et al., 2006; Vetri et al., 2012)
db/db (leptin receptor mutation)	pial arterioles (Rosenblum et al., 1981; Te Riet et al., 2015) parenchymal arterioles (Prakash et al., 2013)
ob/ob (leptin deficient)	pial arterioles (Moore et al., 2015; Rosenblum et al., 1981)
Tally Ho (spontaneous type 2)	pial arterioles (Didion et al., 2007)
Goto-Kakizaki (type 2)	parenchymal arterioles (Prakash et al., 2013)
Akita (type 1)	pial arterioles (Moore et al., 2015)
Diet-induced obesity	pial arterioles (Lynch et al., 2013) cerebral blood flow (Li et al., 2013) parenchymal arterioles (Li et al., 2013)
Hypertension	
Genetic	
R⁺A⁺	pial arterioles (Baumbach et al., 2003)

Model	Vascular Component
BPH2	pial arterioles (Baumbach et al., 2003)
SHR	parenchymal arterioles (Chan et al., 2013; Iddings et al., 2015; Nakahata et al., 2006) pial arterioles (Chan et al., 2008; Mayhan, 1992)
SHRSP	parenchymal arterioles (Chan, 2015; Pires et al., 2015) pial arterioles (Mayhan et al., 1987a, 1988)
Renin transgenic	pial arterioles (Moore et al., 2015)
Mechanical	
Aortic banding	pial arterioles (Chan and Baumbach, 2013b)
Pharmacological	
Ang II (pressor)	cerebral blood flow (Girouard et al., 2008; Kazama et al., 2004)
Ang II (slow-pressor)	cerebral blood flow (Capone et al., 2011)
L-NAME	pial arterioles (Baumbach et al., 2004; Moore et al., 2015)
DOCA-salt	pial arterioles (De Silva, 2015a) parenchymal arterioles (De Silva, 2015a)
Renal	
One-kidney, one-clip	pial arterioles (Baumbach and Hajdu, 1993)
Two-kidney, two-clip	parenchymal arterioles (Fan et al., 2015a)
Hypercholesterolemia	pial arterioles (Kitayama et al., 2007; Moore et al., 2015) cerebral blood flow (Ayata et al., 2013)
Hyperhomocysteinemia	
Mthfr deficient	pial arterioles (Devlin et al., 2004)
Cbs deficient	pial arterioles (Baumbach et al., 2002; Dayal et al., 2004)
Mtr deficient	pial arterioles (Dayal et al., 2005)
Diet-induced	pial arterioles (Baumbach et al., 2002; Dayal et al., 2004; Dayal et al., 2005; Devlin et al., 2004)
Ischemia/reperfusion	pial arterioles (Nelson et al., 1992) parenchymal arterioles (Cipolla and Bullinger, 2008; Cipolla et al., 2014) cerebral blood flow (Kunz et al., 2007)
Nicotine	pial arterioles (Fang et al., 2006)
Obstructive sleep apnea	parenchymal arterioles (Lloyd et al., 2015)
PPARγ interference	

Model	Vascular Component
Systemic (all cells)	pial arterioles (Beyer et al., 2008a)
Vascular muscle	pial arterioles (De Silva et al., 2014; Halabi et al., 2008)
Renal failure	pial arterioles (Bugnicourt et al., 2011)
SOD deficiency	
<i>Sod1</i>	pial arterioles (Baumbach et al., 2006; Didion et al., 2002)
<i>Sod2</i>	pial arterioles (Faraci et al., 2006)
<i>Sod3</i>	pial arterioles (Kitayama et al., 2006)
Stress (chronic)	parenchymal arterioles (Longden et al., 2014)
Subarachnoid hemorrhage	parenchymal arterioles (Koide et al., 2012; Nystoriak et al., 2011; Park et al., 2009; Vollmer et al., 1992) pial arterioles (Yakubu and Leffler, 1997)
Traumatic brain injury	parenchymal arterioles (Golding et al., 1999; Sangiorgi et al., 2013) pial arterioles (Kontos and Wei, 1992)

Abbreviations: SHR, spontaneously hypertensive rat; SHRSP, stroke-prone spontaneously hypertensive rats; R⁺A⁺, transgenic mice expressing human renin and angiotensinogen. Cerebral blood flow based on measurements of local microvascular blood flow, most often using laser-Doppler technology. BPH2, blood pressure high 2; L-NAME, L-N^G-nitroarginine methyl ester. See text for other abbreviations.