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Hypertension impairs neurovascular coupling and promotes microvascular injury: role in exacerbation of Alzheimer's disease

Anna Csiszar · Stefano Tarantini · Gábor A. Fülöp · Tamas Kiss · M. Noa Valcarcel-Ares · Veronica Galvan · Zoltan Ungvari · Andriy Yabluchanskiy

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Abstract Hypertension in the elderly substantially increases both the risk of vascular cognitive impairment (VCI) and Alzheimer's disease (AD); however, the underlying mechanisms are not completely understood. This review discusses the effects of hypertension on structural and functional integrity of cerebral microcirculation, including hypertension-induced alterations in neurovascular coupling responses, cellular and molecular mechanisms involved in microvascular damage (capillary rarefaction, blood-brain barrier disruption), and the genesis of cerebral microhemorrhages and their potential role in exacerbation of cognitive decline associated with AD. Understanding and targeting the hypertension-induced cerebromicrovascular alterations that are involved in the onset and progression of AD and contribute to cognitive impairment are expected to have a major role in preserving brain health in high-risk older individuals.

Keywords Functional hyperemia · Neurovascular coupling · Angiotensin II · High blood pressure · Hypertension · VCID · Endothelial dysfunction · Microcirculation · Alzheimer's disease

A. Csiszar · S. Tarantini · G. A. Fülöp · T. Kiss · M. N. Valcarcel-Ares · Z. Ungvari · A. Yabluchanskiy
Reynolds Oklahoma Center on Aging, Department of Geriatric Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

A. Csiszar · S. Tarantini · G. A. Fülöp · T. Kiss · M. N. Valcarcel-Ares · Z. Ungvari · A. Yabluchanskiy
Translational Geroscience Laboratory, Donald W. Reynolds Department of Geriatric Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

G. A. Fülöp
Division of Clinical Physiology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

V. Galvan
Department of Cellular and Integrative Physiology, Barshop Institute for Longevity and Aging Studies University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
e-mail: Andriy-Yabluchanskiy@ouhsc.edu
e-mail: anna-csiszar@ouhsc.edu

Introduction

Hypertension in the elderly substantially increases the risk of Alzheimer's disease (AD); however, the underlying mechanisms are not completely understood (Forette et al. 1998; Launer et al. 2000; Israeli-Korn et al. 2010; Guo et al. 2001; Marr and Hafez 2014; Petrovitch et al. 2000; van Dijk et al. 2004; Joas et al. 2012). In this review (published as part of the "Translational Geroscience" initiative of the journal (Callisaya et al. 2017; Kane et al. 2017; Kim et al. 2017; Liu et al. 2017; Meschiari et al. 2017; Perrott et al. 2017; Shobin et al. 2017; Ashpole et al. 2017; Bennis et al. 2017; Deepa et al. 2017; Grimmig et al. 2017; Hancock et al. 2017; Konopka et al. 2017; Podlutsky et al. 2017; Sierra and Kohanski 2017; Tenk et al. 2017; Ungvari et al. 2017a; Urfer et al. 2017a, b)), the effects of hypertension on structural and functional integrity of the cerebral microcirculation are considered, with a primary focus on cellular and molecular mechanisms involved in

microvascular damage (capillary rarefaction, BBB disruption), neurovascular uncoupling, and the genesis of cerebral microhemorrhages and their potential role in exacerbation of cognitive decline associated with AD.

Hypertension and the pathogenesis of Alzheimer's disease: microvascular deposition of Aβ and tauopathy

Alzheimer's disease is the most common cause for dementia in the elderly and the sixth leading cause of death in the USA. An estimated 5.5 million Americans are living with AD in 2017, and it is projected that this number will double in the next 20 years. Since the original formulation of the vascular hypothesis of AD in the 1990s, evidence has been fast accumulating which strongly suggests that early stage of AD is indeed primarily a microvascular disorder (Zlokovic 2011). Consistent with this hypothesis, cerebrovascular dysfunction may be the earliest and most abnormal biomarker of AD progression. Large cross-sectional and longitudinal population-based studies consistently showed that a relationship exists between several vascular risk factors and incidence and progression of AD (de la Torre 2010, 2012, 2013, 2017). Among the vascular risk factors for AD, hypertension emerges as a critically important one, as it is known to double the risk for AD in the elderly (Forette et al. 1998; Launer et al. 2000; Israeli-Korn et al. 2010; Guo et al. 2001; Marr and Hafez 2014; Petrovitch et al. 2000; van Dijk et al. 2004; Joas et al. 2012). This observation led to several modifications and expansions of the original vascular hypothesis of AD, invoking hypertension-induced microvascular injury in various pathological manifestations of AD, from cerebral microhemorrhages (Ungvari et al. 2017b) to blood-brain barrier disruption and consequent neuroinflammation (Zlokovic 2011, 2008).

The amyloid cascade hypothesis has been the focus of AD research for two decades, and despite recent challenges, it still remains a frequently invoked hypothesis to explain the molecular cause of AD. The amyloid cascade hypothesis posits that altered production, processing, and deposition of amyloid β-peptide (Aβ) both in the neuropil and around cerebral microvessels plays a central role in the development of AD, a concept that is supported by substantial genetic and biochemical data. Consistent with the deposition of Aβ in the neurovascular unit, there is strong clinical and experimental evidence that increased levels of Aβ in AD associate with progressive, multifaceted cerebromicrovascular impairment, which contributes to both the development of early-stage pre-plaque cognitive dysfunction as well as subsequent progression of the disease (Zlokovic 2011; Gorelick et al. 2011; Iadecola et al. 2009; Niwa et al. 2001, 2002a, b; Park et al. 2005; Girouard and Iadecola 2006; Iadecola 2004; Park et al. 2014, 2013; Fotuhi et al. 2009; Skoog and Gustafson 2006). In agreement with the prediction based on both the vascular hypothesis and the amyloid hypothesis of AD, hypertension exacerbates Aβ-induced cerebromicrovascular impairment in AD, worsening the disease and accelerating its progression. In recent years, a series of important studies have provided critical insights into the pathophysiological mechanistic links among hypertension, Aβ deposition, and the development of AD (Iadecola et al. 2009; Niwa et al. 2002a; Capone et al. 2012; Girouard et al. 2006; Kazama et al. 2004; Faraco et al. 2016; Carnevale and Lembo 2011; Carnevale et al. 2012a, b; Diaz-Ruiz et al. 2009; Farkas et al. 2000; Hsu et al. 2013; Sparks et al. 1995). Using transgenic mouse models and angiotensin II infusion, Faraco and coworkers confirmed the association between hypertension and AD by showing that prolonged hypertension increases microvascular amyloid deposition in Tg2576 mice and enhanced beta-secretase APP cleavage (Faraco et al. 2016). Similar results were reported by other laboratories as well (Diaz-Ruiz et al. 2009). Hypertension induced by transverse aortic coarctation was also reported to exacerbate Aβ deposition in the mouse brain, promoting cognitive decline (Carnevale and Lembo 2011; Carnevale et al. 2012a, b). Further, there are studies extant showing that interaction of hypertension and aging promotes amyloidogenic gene expression in the mouse brain (Csiszar et al. 2013a). Importantly, the effects of high blood pressure on Aβ deposits in the mouse brain are manifested within 4 weeks after induction of hypertension (Carnevale and Lembo 2011; Carnevale et al. 2012a, b), suggesting that early hypertension-induced cerebromicrovascular impairment is sufficient to trigger molecular processes contributing to the pathogenesis of AD. There are studies suggesting that RAGE activation in the cerebral microvessels is a crucial mechanism by which hypertension promotes AD pathologies (Carnevale et al. 2012b). However, it is quite likely that several other mechanisms play equally important roles (Nicolakakis et al. 2008; Tong et al. 2012) and that inhibiting one or more of these molecular targets can limit the onset of microvascular-related AD deficits.

In addition to Aβ pathology, tau pathology is considered an important driver of disease progression in AD

(Raskin et al. 2015). Albeit still not as extensively investigated as Aβ, recent studies have provided critical insights into the mechanistic links between hypertension and tau hyperphosphorylation and misfolding in AD. It has been shown that experimentally induced hypertension aggravates tau-related motor dysfunction in a mouse model of pure tauopathy (Diaz-Ruiz et al. 2009). Lobar microbleeds were independently associated with a higher likelihood of having an abnormal CSF phosphorylated tau 181 protein level ($P = .004$). Studies in a cohort of patients from the Alzheimer's Disease Neuroimaging Initiative showed that, after adjusting for levels of CSF Aβ, lobar microbleeds associated with hypertension were correlated with accelerated longitudinal cognitive decline and with a higher likelihood of having abnormal CSF levels of phosphorylated tau181 (Chiang et al. 2017). Intraneuronal tau hyperphosphorylation preceded by Aβ deposition was demonstrated in a hypertensive rat model, non-transgenic spontaneously hypertensive stroke-prone rats (SHRSP), that displays cerebral small vessel disease (CSVD) as a consequence of hypertension, suggesting that CSVD associated with hypertension leads to increased brain Aβ and subsequent intraneuronal tau hyperphosphorylation (Schreiber et al. 2014). In an independent study, Kurata and collaborators showed that both low- and high-dose telmisartan decreased numbers of Aβ- and phospho-tau-positive neurons and decreased markers of neuroinflammation (Kurata et al. 2014). Interestingly, a potential direct role of hyperphosphorylated and misfolded tau in cerebromicrovascular dysfunction was suggested by a recent report of tau oligomer accumulation in cerebrovasculature of AD and progressive supranuclear palsy (PSP) patients, suggesting that aberrantly misfolded tau may accumulate in cells of cerebromicrovasculature in AD and in "pure" tauopathies (Castillo-Carranza et al. 2017).

Hypertension-induced capillary rarefaction

The brain is the most metabolically active organ in the human body. While it only accounts for 2% of the body mass, it consumes 20–25% of the body's total energy requirements. Since energy stores in the brain are scarce, adequate supply of nutrients is crucial to support normal cerebral function. The brain relies on a dense cerebral microcirculatory network (600 km total length) for continuous supply of nutrients and O_2 and for effective washout of metabolic waste products. It is generally considered that a decline in capillarization in the brain tissue (i.e., cerebromicrovascular rarefaction) contributes to a decline in cerebral blood flow that reduces metabolic support for neural signaling, thereby exacerbating neuronal dysfunction (Khan et al. 2002; Riddle et al. 2003; Sonntag et al. 1997; Troen et al. 2008; Tucsek et al. 2014). In that regard, it is important that increased deposition of Aβ has been shown to profoundly affect brain microvasculature, resulting in degeneration and disappearance of capillaries (Roher et al. 1993) and small vessels (Yamaguchi et al. 1992). Capillary loss ultimately also leads to an impaired clearance of Aβ, which further promotes vascular damage (Faraco and Iadecola 2013). Capillary loss can reach up to 30% in AD aged population when compared to control subjects (Fischer et al. 1990; Buee et al. 1994) and is strongly associated with a reduced cerebral perfusion (Buee et al. 1994). A reduction in cerebral perfusion occurs early in the development of AD before the brain atrophy, and the most severe changes occur in the areas with Aβ and tau pathology (Johnson et al. 2005; Hirao et al. 2005). Patients with mild cognitive impairment also exhibit hypoperfusion in the areas most affected in AD (Johnson et al. 2005; Brown and Thore 2011). Importantly, hypertension per se promotes cerebromicrovascular rarefaction (Feihl et al. 2009; Sokolova et al. 1985; Suzuki et al. 2003; Tarantini et al. 2016a; Toth et al. 2015a) and this effect is significantly exacerbated in old age (Toth et al. 2015a). On the basis of the existing evidence, we posit that the effects of hypertension, AD and old age are highly synergistic, and that hypertension in elderly AD patients results in an exacerbated microvascular structural damage. The mechanisms underlying hypertension-induced microvascular rarefaction are likely multifaceted and may involve endothelial impairment, endothelial apoptosis, decreased NO bioavailiability, oxidative stress, and an imbalance in humoral pro- and anti-angiogenic factors (Tarantini et al. 2016a). The cerebral microcirculation is subject to continuous dynamic structural adaptation, a concept that implies a high plasticity of the cerebral microvascular network (Riddle et al. 2003). Our current understanding is that there is a dynamic balance between capillary regression and growth and that both destruction of capillaries and impaired angiogenesis, due to dysregulated production of autocrine/paracrine regulators of angiogenic processes, is a critical mechanism involved in cerebromicrovascular rarefaction (Tucsek et al. 2014; Ungvari et al. 2010). It is likely that both in AD and in hypertension, capillary regression/

destruction is a primary cause for capillary rarefaction, which is exacerbated by secondary impairment of capillary regrowth. Importantly, comparative analysis of cerebral capillary ultrastructure reveals similar cerebral capillary damage in AD and hypertension (Farkas et al. 2000). Previous studies provide evidence that in AD, capillaries indeed die. The histological footprint of this increased capillary loss is the formation of "string vessels" ("ghost vessels"), which are thin, acellular connective tissue strands, remnants of capillaries, with a lack of endothelial cells (Brown 2010). Capillary regression occurs by endothelial apoptosis, a process initiated by cellular damage, a decline in pro-survival factors, and/or increased presence of pro-apoptotic extracellular signals (including the toxic effects of Aβ) (Fonseca et al. 1832; Lyros et al. 2014; Religa et al. 2013; Wilhelmus et al. 2007). Recent evidence shows that macrophages also play a key role in capillary regression. Further studies are warranted to better understand the synergistic roles for AD, hypertension, and aging processes in regulation of microvascular regression. AD patients are typically old, and there is strong evidence that aging itself is associated with dysregulation of multiple aspects of the angiogenic process, including induction of endothelial cell proliferation, migration, and tube formation (Viana et al. 2015). In experimental mouse models, hypertension also results in dysregulated expression of pro- and anti-angiogenic genes (Tarantini et al. 2016a). Age- (Csiszar et al. 2014; Ungvari et al. 2011a, b) and perhaps AD- (Joshi et al. 2015; Kanninen et al. 2009) related mechanisms responsible for impairment of endothelial angiogenic capacity likely also include dysregulation of Nrf2, a newly discovered regulator of endothelial angiogenic processes (Valcarcel-Ares et al. 2012). There is also strong evidence that a causal link exists among decreased bioavailability of NO, impaired angiogenesis, and microvascular rarefaction (Ungvari et al. 2010). Endothelium-derived NO is both a downstream mediator of pro-angiogenic VEGF and IGF-1 signaling and a critical regulator of microvascular endothelial cell viability. There is ample evidence that AD/microvascular deposition of Aβ (Zlokovic 2011; Girouard and Iadecola 2006; Tong et al. 2012; Austin et al. 2013; Di Marco et al. 2015; Kimbrough et al. 2015), hypertension (Girouard and Iadecola 2006; Girouard et al. 2006; Chrissobolis et al. 2012; Pires et al. 2013; Girouard et al. 2007), and old age (Csiszar et al. 2014; Banki et al. 2015; Csiszar et al. 2002, 2004; Tarantini et al. 2016b; Ungvari et al. 2007; Modrick et al. 2009; Pena Silva et al. 2012) per se promotes microvascular endothelial dysfunction. Thus, it is highly likely that impaired cerebromicrovascular NO production significantly contributes to microvascular rarefaction in old hypertensive AD patients. Several additional mechanisms may also be considered to contribute to structural microvascular rarefaction in hypertensive AD patients, including pericyte damage (Toth et al. 2013a), increased pre-capillary arteriolar constriction and cessation of capillary blood flow, increased susceptibility to microemboli, platelet adhesion, and macrophage activation. Further, the mechanisms underlying the exacerbation of microvascular injury in hypertensive AD patients are also likely to include hemodynamic factors.

There is strong evidence that under normal conditions, pressure-induced myogenic constriction of proximal cerebral arteries, as a critical homeostatic mechanism that assures that increased systemic arterial pressure, cannot penetrate the distal portion of the cerebral microcirculation and cause damage to the thin-walled arteriolar and capillary microvessels (Toth et al. 2013a, 2014a; Kontos et al. 1978; Harper and Bohlen 1984). Young cerebral arteries in the absence of AD exhibit functional and structural adaptation to hypertension, including an augmented myogenic constriction at high pressures and autoregulatory adaptation, which protects the cerebral microcirculation from pressure-induced injury (Toth et al. 2013a, 2014a). In contrast, autoregulatory adaptation to hypertension in compromised both in aging (Toth et al. 2013a, b, 2014a; Springo et al. 2015a) and in AD (Iadecola et al. 2009; Niwa et al. 2002a; Toth et al. 2017; Brickman et al. 2015; den Abeelen et al. 2014; Tarumi et al. 2014; Iadecola 2014). Pathological loss of autoregulatory protection in old hypertensive AD patients likely allows high blood pressure to penetrate the distal, injury-prone portion of the cerebral microcirculation, leading to significant downstream damage (Toth et al. 2017).

Hypertension-induced blood-brain barrier disruption

In recent years, overwhelming evidence has accumulated demonstrating that blood-brain barrier (BBB) breakdown contributes to the onset and progression of the pathological processes associated with AD (Zlokovic 2011, 2008; Carnevale et al. 2012b; Sagare et al. 2013a; Mackic et al. 2002, 1998; Montagne et al. 2015; Sagare et al. 2013b; Winkler et al. 2015; Bell and Zlokovic 2009; Halliday et al.

2016; Nelson et al. 1862; Zlokovic 2013). Hypertension, especially in aging, is known to significantly increase BBB permeability (Toth et al. 2013a, 2014a; Mueller and Heistad 1980; Zhang et al. 2010), which has been linked to the hypertension-induced exacerbation of AD pathologies in mouse models (Carnevale and Lembo 2011; Carnevale et al. 2012a, b). The mechanisms of hypertension-related BBB disruption are likely multifaceted and may involve increased endothelial oxidative stress and endothelial injury, pericyte damage, and changes in tight junctions, which form an essential structural component of the BBB (Toth et al. 2013a; Takemori et al. 2013). Pericytes are important cellular constituents of the BBB (Zlokovic 2008), and recent studies demonstrate that pericyte deficiency in $Pdgfr\beta^{+/-}$ mice leads to significant impairment of BBB function (Bell et al. 2010) and that pericyte loss exacerbates AD-like neurodegeneration in mice (Sagare et al. 2013b). Importantly, hypertension in aging was shown to promote pericyte loss (Toth et al. 2013a), which may contribute to BBB disruption, exacerbating AD pathogenesis. Pericytes have also key roles in preservation of the structural integrity of the cerebral microcirculation (Winkler et al. 2011); thus, loss of pericytes is also likely to contribute to hypertension-induced microvascular rarefaction in brain (Tarantini et al. 2016a; Toth et al. 2013a). Through the damaged BBB, plasma constituents, including IgG, thrombin, and fibrinogen, enter the brain parenchyma (Toth et al. 2013a), which induce of neuroinflammation by activating microglia (Bruce-Keller et al. 2010; Pistell et al. 2010; White et al. 2009; Davalos et al. 2012; Carreno-Muller et al. 2003). There is substantial evidence implicating oxidative stress, microglia activation, and neuroinflammation in the development of AD-like pathologies in hypertensive mice (Carnevale and Lembo 2011; Carnevale et al. 2012a, b).

Hypertension-induced neurovascular uncoupling

Energy and O_2 demand of the brain tissue vary both spatially and temporally with changes in neuronal activity, which require prompt adjustments of blood flow by regulating arteriolar resistance in a highly controlled fashion to maintain cellular homeostasis and function (Mathiesen et al. 1998; Enager et al. 2009). This is accomplished through a process termed neurovascular coupling (or "functional hyperemia"), which is orchestrated by an inter-cellular signaling network comprised of neurons and astrocytes, as well as smooth muscle cells and endothelial cells of cerebral microvessels (Petzold and Murthy 2011; Stobart et al. 2013; Wells et al. 2015; Chen et al. 2014). There is compelling evidence that AD patients exhibit significant impairment of neurovascular coupling responses (Hock et al. 1997; Rombouts et al. 2000). These findings accord with the conclusions of pre-clinical studies demonstrating that in rodent models of AD, functional hyperemia is also significantly impaired (Rancillac et al. 2012; Shin et al. 2007), at least in part, due to increased oxidative stress (Park et al. 2005, 2008; Nicolakakis et al. 2008). Experimental studies support a causal link between impaired neurovascular coupling and cognitive impairment (Tarantini et al. 2015). Indeed, recent evidence suggests that pharmacological interventions that rescue neurovascular coupling responses result in improved cognitive function in mice with AD pathologies (Nicolakakis et al. 2008; Tong et al. 2012). In that regard, it is significant that hypertension also causes marked neurovascular dysfunction (Girouard and Iadecola 2006; Capone et al. 2012; Girouard et al. 2006; Kazama et al. 2004; Faraco et al. 2016; Kazama et al. 2003). Hypertension-induced neurovascular uncoupling superimposed on amyloid pathologies is likely to significantly exacerbate dysregulation of CBF and cognitive decline. Indeed, in $A\beta PP_{swe}/PS1_{dE9}$ mice angiotensin II-induced hypertension was reported to exacerbate impairment of cerebral blood flow regulation (Wiesmann et al. 2016). There is substantial evidence obtained both in pre-clinical and in clinical studies demonstrating that aging per se impairs neurovascular coupling responses (Tong et al. 2012; Balbi et al. 2015; Fabiani et al. 2013; Sorond et al. 2013; Toth et al. 2014b; Zaletel et al. 2005; Park et al. 2007), suggesting that combination of old age, amyloid pathologies, and hypertension likely results in a critical mismatch between supply and demand of oxygen and metabolic substrates in functioning cerebral tissue (Iadecola et al. 2009).

Hypertension-induced cerebral microhemorrhages

Cerebral microhemorrhages (CMHs; also described as microbleeds) are small chronic intracerebral hemorrhages (< 5 to 10 mm in diameter), which develop due to the rupture of small arteries, arterioles, and/or capillaries (Ungvari et al. 2017b). Hypertension (Jeerakathil et al. 2004; Cordonnier et al. 2007; Romero et al. 2014; Roob et al. 1999; Sveinbjornsdottir et al. 2008; Vernooij et al. 2008), advanced age (Jeerakathil et al. 2004; Chai et al. 2016; Caunca et al. 2016), and cerebral amyloid angiopathy and AD (Yates et al. 2011, 2014; Pettersen et al. 2008; Benedictus et al. 2013) are the major risk

factors for CMHs. The prevalence of CMHs reaches 50% in patients at risk (Ungvari et al. 2017b). CMHs are clinically important as they may exacerbate cognitive decline in AD patients. There is strong experimental evidence that aging or vascular AD pathologies exacerbate the effects of hypertension on the pathogenesis of CMHs (Ungvari et al. 2017b; Toth et al. 2015a, 2017; Tarantini et al. 2017), worsening the clinical outcome. The cellular and molecular mechanisms by which hypertension promotes CMHs include induction of oxidative stress and MMP activation in the vascular wall, breakdown of the extracellular matrix, pathological structural adaptation to high blood pressure, and/or impairment of myogenic autoregulatory protection, which allows high blood pressure to penetrate the vulnerable distal portion of the cerebral microcirculation (Toth et al. 2015a, 2017; Tarantini et al. 2017; Wakisaka et al. 2008, 2010). Future studies are needed to identify effective strategies for microvascular protection to prevent the development of CMHs, thereby delaying cognitive decline in AD patients.

Conclusion

Strong epidemiological and experimental evidence indicate that hypertension in the elderly promotes the pathogenesis of AD and/or exacerbates cognitive decline by inducing capillary rarefaction, BBB disruption, and consequential neuroinflammation, by impairing neurovascular coupling responses and promoting the genesis of cerebral microhemorrhages. Because clinical trials with Aβ targeting antibodies (i.e., bapineuzumab and solanezumab) and γ-secretase inhibitors (semagacestat) failed (Laske 2014; Doody et al. 2013), research into treatments that exert microvascular protection and thereby may prevent development/progression of the disease became a high priority. In light of recent pre-clinical and clinical trials showing that anti-hypertensive drugs (including diuretics, angiotensin I receptor blockers, and angiotensin-converting enzyme inhibitors) may have beneficial effects in AD, further studies of the interaction between hypertension and AD pathophysiology are highly warranted. In addition to repurposing existing drugs with microvascular protective effects (Nicolakakis et al. 2008; Papadopoulos et al. 2014, 2016), geroscience research has identified promising novel molecular targets involved in the regulation of cellular aging processes that can be targeted to improve neurovascular health. Among them, the mTOR inhibitor rapamycin (Urfer et al. 2017a) shows great promise in treating AD, as it was shown to rescue cerebromicrovascular function and improve cognition in pre-clinical models of the disease (Lin et al. 2013, 2017; Galvan and Hart 2016; Richardson et al. 2015). Many other geronic factors involved in aging processes, including IGF-1 (Ashpole et al. 2017; Podlutsky et al. 2017), Nrf2 (Ungvari et al. 2011a, b; Valcarcel-Ares et al. 2012; Pearson et al. 2008; Ungvari et al. 2011c; Bailey-Downs et al. 2012), and factors involved in redox regulation (Deepa et al. 2017; Grimmig et al. 2017; Konopka et al.

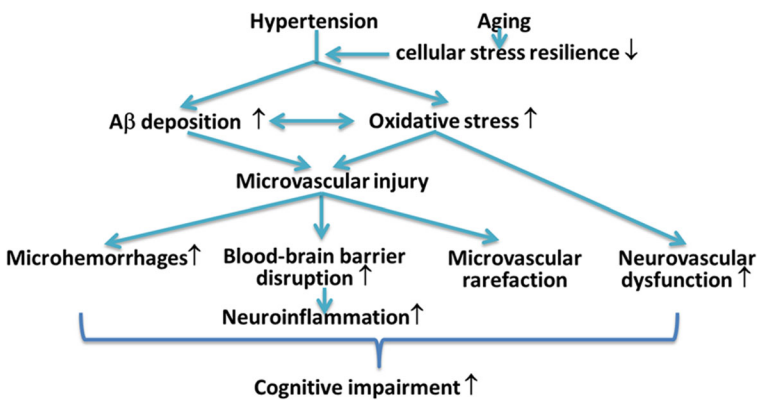

Fig. 1 Cerebromicrovascular alterations by which hypertension promotes the pathogenesis of vascular cognitive impairment and AD. Hypertension promotes microvascular oxidative stress and microvascular injury, which are exacerbated in aging (Girouard et al. 2006; Toth et al. 2015a, 2013a; Springo et al. 2015b). In patients with AD pathologies, hypertension increases the deposition of Aβ and exacerbates cerebromicrovascular dysfunction induced by Aβ. Microvascular injury, aggravated by structural and functional microvascular maladaptation to hypertension, leads to blood-brain barrier disruption promoting neuroinflammation, microhemorrhages, and microvascular rarefaction. Hypertension-induced, oxidative stress-mediated neurovascular uncoupling further compromises the blood supply to the brain. The model predicts that these hypertension-induced structural and functional microvascular alterations critically contribute to cognitive decline in high-risk elderly patients

2017), were shown to influence microvascular health, regulating neurovascular coupling responses (Tarantini et al. 2016b; Toth et al. 2014b, 2015b, c), angiogenesis and capillary rarefaction (Tarantini et al. 2016a; Valcarcel-Ares et al. 2012; Banki et al. 2015; Sonntag et al. 2013; Csiszar et al. 2013b; Ungvari et al. 2013), and the pathogenesis of cerebral microhemorrhages (Ungvari et al. 2017b; Toth et al. 2013a, b, 2014a, 2015a, 2017; Springo et al. 2015a; Tarantini et al. 2017). New developments in our understanding of these microvascular mechanisms and their pathophysiological roles may lead to novel interventions for delaying the progression of AD (Fig. 1).

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