REVIEW | *Advances in Cardiovascular Geroscience*

Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging

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[1]*Department of Geriatric Medicine, Reynolds Oklahoma Center on Aging, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma;* [2]*Department of Neurosurgery and Szentagothai Research Center, University of Pecs, Pecs, Hungary; and* [3]*Department of Medical Physics and Informatics, University of Szeged, Szeged, Hungary*

Toth P, Tarantini S, Csiszar A, Ungvari Z. Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. *Am J Physiol Heart Circ Physiol* 312: H1–H20, 2017. First published October 28, 2016; doi:10.1152/ajpheart.00581.2016.—Increasing evidence from epidemiological, clinical and experimental studies indicate that age-related cerebromicrovascular dysfunction and microcirculatory damage play critical roles in the pathogenesis of many types of dementia in the elderly, including Alzheimer's disease. Understanding and targeting the age-related pathophysiological mechanisms that underlie vascular contributions to cognitive impairment and dementia (VCID) are expected to have a major role in preserving brain health in older individuals. Maintenance of cerebral perfusion, protecting the microcirculation from high pressure-induced damage and moment-to-moment adjustment of regional oxygen and nutrient supply to changes in demand are prerequisites for the prevention of cerebral ischemia and neuronal dysfunction. This overview discusses age-related alterations in three main regulatory paradigms involved in the regulation of cerebral blood flow (CBF): cerebral autoregulation/myogenic constriction, endothelium-dependent vasomotor function, and neurovascular coupling responses responsible for functional hyperemia. The pathophysiological consequences of cerebral microvascular dysregulation in aging are explored, including blood-brain barrier disruption, neuroinflammation, exacerbation of neurodegeneration, development of cerebral microhemorrhages, microvascular rarefaction, and ischemic neuronal dysfunction and damage. Due to the widespread attention that VCID has captured in recent years, the evidence for the causal role of cerebral microvascular dysregulation in cognitive decline is critically examined.

geroscience; senescence; vascular aging; microcirculation; cerebral circulation; cerebrovascular; stroke; functional hyperemia; neurovascular coupling; myogenic constriction; Alzheimer's disease; blood-brain barrier

MAINTENANCE OF ADEQUATE tissue perfusion through a dense cerebromicrovascular network is vital for the preservation of normal brain function (57, 119, 120, 260, 309). The total length of capillaries in the human brain is ~600 km and virtually every neuron is supplied by its own capillary. There is increasing evidence that aging elicits multifaceted functional impairment in the cerebral microcirculation, which plays a critical role in brain aging and the pathogenesis of age-related cognitive impairment (45, 54, 99, 123, 129, 166, 326). To recognize the contribution of cerebromicrovascular mechanisms to cognitive decline the phrase "vascular contributions to cognitive impairment and dementia (VCID)" was coined (46, 97, 237). The VCID concept implies that a spectrum of age-related vascular pathologies (including stroke, microinfarcts, microhemorrhages, leukoaraiosis, and cerebral amyloid angiopathy) can promote cognitive impairment in elderly patients. For the purpose of this review, we focus on the role of age-related dysregulation cerebral blood flow (CBF) in the development of cognitive decline.

Regulation of CBF has to comply with unique requirements, ensuring adequate delivery of nutrients and oxygen at all times, avoiding both hypoperfusion and hyperperfusion of the brain and enabling moment-to-moment adjustment of CBF. First, the

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brain has a very high metabolic demand for oxygen relative to other organs. Second, neurons do not have sufficient energy reserves. Third, metabolic demand rapidly changes with neuronal activation. Fourth, in the closed cranium the space is limited; thus regulation has to maintain normal blood flow and volume and thus intracranial pressure. Fifth, penetration of high pressure to the distal, vulnerable part of the cerebral arterial tree and consequential microvascular damage has to be prevented. To fulfill these requirements, regulation of CBF is exceedingly complex with multiple overlapping regulatory paradigms. There is increasing evidence that even mild impairment of CBF regulation has significant consequences on cerebral function, including impairment of cognition in the elderly. Furthermore, age-related alterations in homeostatic mechanisms also render the aged brain more susceptible to the damaging effects of the comorbid conditions (e.g., hypertension, obesity, neurodegenerative diseases) (50, 281, 287, 288). In this review, the effect of aging on key local vasoregulatory mechanisms acting in the cerebral circulation (myogenic autoregulation, endothelium-dependent pathways, and neurovascular coupling) is considered in terms of potential mechanisms involved in cerebrovascular dysfunction and its pathophysiological consequences.

Aging-Induced Changes in Autoregulation of CBF

Cellular mechanisms underlying autoregulation of CBF. The integrated processes resulting in relatively constant CBF and microvascular pressure in the face of changing central arterial pressure are called autoregulation of CBF (153) (Fig. 1). Dynamic cerebral autoregulation refers to the ability to compensate fast changes in perfusion pressure by adjusting vascular resistance. Static cerebral autoregulation refers to adjustments of vascular resistance in response to larger steady-state changes in perfusion pressure. Dynamic and static cerebral autoregulations are not completely separate mechanistic entities and act on a continuum. The net result is that in healthy individuals CBF does not change in a linear manner with changes in systemic blood pressure and vascular resistance is readily adjusted to changes in perfusion pressure.

The myogenic response, which is intrinsic to the vascular smooth muscle cells, is a key mechanism contributing to autoregulation of CBF (26, 27, 72, 93, 101, 102, 173, 180, 281, 306) (Fig. 1). Accordingly, cerebral arterial vessels actively dilate and constrict in response to decreases and increases in blood pressure, respectively (5, 43, 83, 84, 170, 171, 192). Importantly, in the cerebral circulation large proximal arteries represent a significant part (up to 40%) of total cerebrovascular resistance (73, 104, 147, 171, 258) and their myogenic response is critical for preventing high pressure from reaching the distal part of the cerebral circulation (236, 281). The myogenic reactivity of serially connected cerebral arteries and arterioles effectively protects the microcirculation against the harmful effects of rapid changes in blood pressure, exemplified by the maintenance of steady capillary perfusion pressure during changes in arterial pressure. In addition, a pressure-induced myogenic mechanism maintains intrinsic basal tone of the arterial microvessels, thus enabling optimization of tissue perfusion in the heterogeneous capillary network by neurometabolic and neurovascular/gliovascular coupling mechanisms.

Remarkable progress has been made in the past two decades to elucidate the cellular and molecular mechanisms underlying pressure-induced myogenic constriction of cerebral arterial vessels (96, 142–144, 312). In the search for a soluble mediator and a receptor-mediated signaling pathway previous studies demonstrated that vascular smooth muscle cells located in the wall of cerebral arteries express cytochrome P (CYP)450 4A enzymes that catalyze the formation of the potent vasoconstrictor arachidonic acid metabolite 20-hydroxyeicosatrienoic-acid (20-HETE) and that production of 20-HETE significantly increases in response to elevations in intravascular pressure (71, 92, 93) (Fig. 1). Previous studies showed that 20-HETE lead to activation of protein kinase C, inhibition of Ca^{2+}-activated K^+ channels, and activation of L-type Ca^{2+} (L_{Ca}) and transient receptor potential cation channel 6 (TRPC6) channels, which promote depolarization of vascular smooth muscle cells, increasing intracellular Ca^{2+} levels and promoting vasoconstriction (102). The concept that production of 20-HETE plays a role in myogenic response is supported by the observations that inhibition of 20-HETE formation attenuates pressure-induced arterial myogenic constriction in vitro and impairs the autoregulation of CBF in vivo (102). Moreover, there is evidence that upregulated production of 20-HETE underlies increased myogenic response and autoregulatory adaptation to hypertension (68, 71, 271, 281). In addition to the role of 20-HETE synthesis (158) other pathways, including other stretch-activated TRP channels (TRPM4) (214) and chloride channels (183), integrins, and other cytoskeletal elements (42, 53) and pathways governing smooth muscle cell Ca^{2+} sensitivity (27, 230, 231) also contribute to pressure-induced depolarization and consequent increase in intracellular Ca^{2+} concentration in vascular smooth muscle cells and the development of myogenic constriction of cerebral arteries.

In cerebral arteries pressure-induced myogenic constriction also appears to be augmented by a unique mechanism: flow-induced vasoconstriction. Since the original observations of Schretzenmayr in 1933 (229), there have been hundreds of reports documenting that arteries from virtually all vascular beds in the peripheral circulation (including brachial, femoral, mesenteric, and coronary arteries) dilate in response to increases in blood flow (145). The cerebral circulation is an important exception. While basilar arteries were reported to dilate in response to increases in flow (86) similar to peripheral vessels, isolated middle cerebral arteries of the rat (33, 273), mouse (281) and cat (163) and fronto-temporal small arteries isolated from the human brain (273) exhibit significant constriction in responses to increases of intraluminal flow/shear stress. Flow-induced constriction of both human and rodent cerebral arteries was shown to be mediated by 20-HETE acting via thromboxane/endoperoxide receptors (273). The initial observation that isolated rabbit pial resistance arteries dilate in response to increases in flow when intraluminal pressure is low, but they constrict in response to the same increases in flow when pressure is high (90, 91), led to the formulation of the hypothesis that flow-induced constriction may play a role in autoregulation of CBF (145). Interestingly, like the myogenic response flow-induced constriction is enhanced in hypertension, as well, probably representing another adaptive vasomotor mechanism to high blood pressure (90, 281). In theory, if cerebral arteries dilated to flow, it would reduce the magnitude of myogenic constriction, counteracting myo-
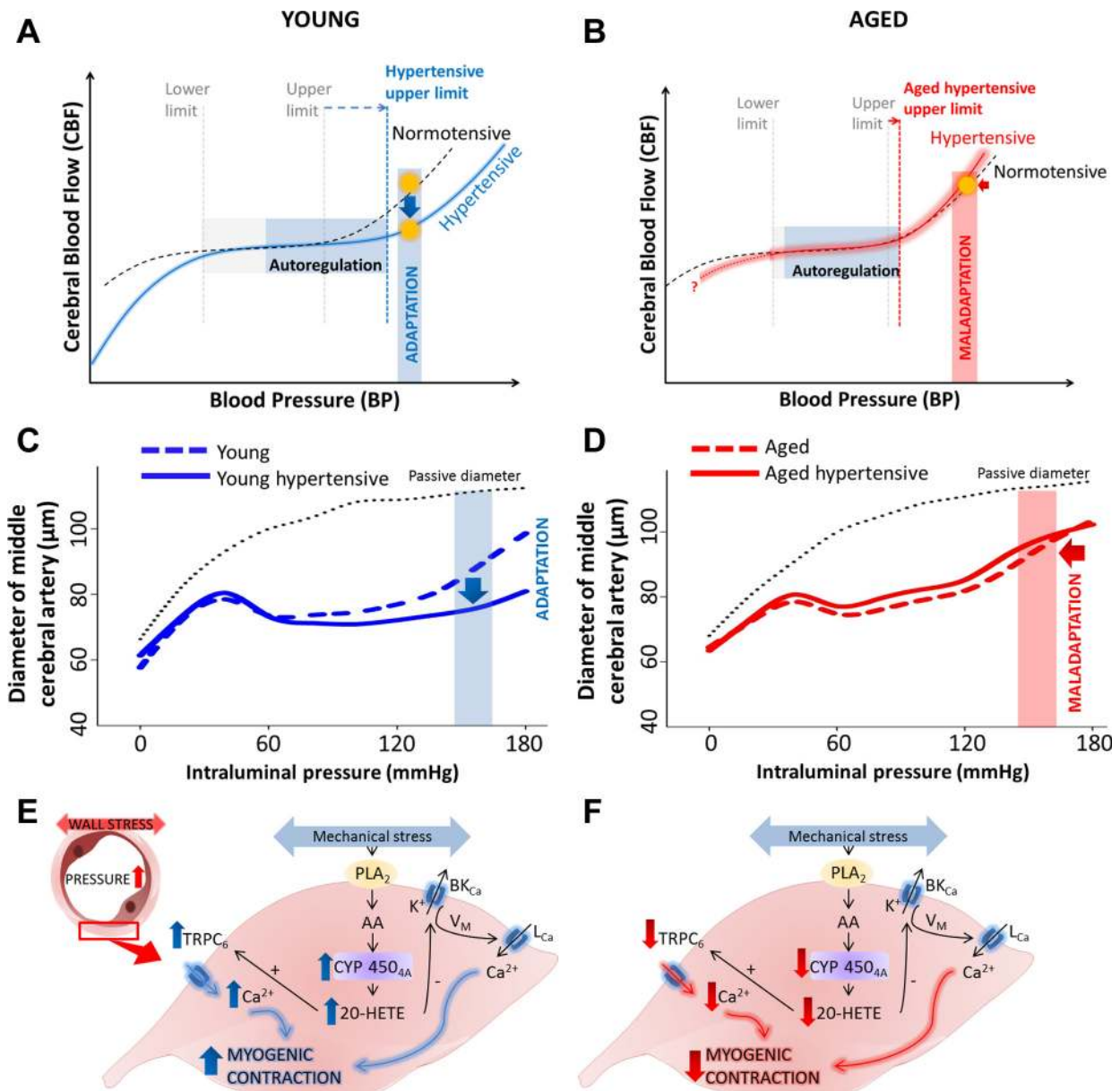
Fig. 1. Aging impairs adaptation of cerebral blood flow (CBF) autoregulation to hypertension. *A*: scheme depicting that under normal conditions autoregulation of CBF maintains a nearly constant blood flow when perfusion pressure changes. This is ensured by pressure-induced myogenic constriction of the cerebral arteries (*C*), a homeostatic mechanism that rapidly adjust vascular resistance to changes in perfusion pressure. The significant increases in the resistance of proximal arteries also assure that increased arterial pressure does not penetrate the distal portion of the microcirculation and cause damage to the thin-walled arteriolar and capillary microvessels in the brain (103, 147). In young organisms in hypertension the myogenic constriction of cerebral arteries is enhanced (*C*) and the range of cerebrovascular autoregulation is extended (*A*), which represent functional adaptation of these vessels to higher systemic blood pressure, optimizing tissue perfusion and protecting the cerebral microcirculation. Aged cerebral arteries do not exhibit a hypertension-induced adaptive increase in myogenic constriction (*D*) and cerebrovascular autoregulatory dysfunction is manifested (*B*) (271, 281). *E* and *F*: proposed scheme showing that in young organisms activation of a 20-hydroxyeicosatrienoic-acid (20-HETE)/transient receptor potential cation channel (TRPC)-dependent pathway underlies functional adaptation of cerebral arteries to hypertension (blue arrows) and that this adaptive response is dysfunctional in aging (red arrows). Accordingly, in smooth muscle cells within the wall of young cerebral arteries (*E*), high pressure-induced mechanical stress leads to the activation of arachidonic acid metabolism (AA) by phospholipase A_2 (PLA_2), and upregulation of the 20-HETE producing CYP450 isoforms. The resulting increased production of the vasoconstrictor eicosanoid 20-HETE activates TRPC6 channels, resulting in increases in vascular smooth muscle Ca^{2+} concentration and subsequent sustained myogenic constriction (281). 20-HETE also blocks the activation of the hyperpolarizing Ca^{2+} activated potassium (BK_{Ca}) channels on vascular smooth muscle cells, which contributes to the increased pressure-induced activation of voltage-dependent L-type Ca^{2+} (L_{Ca}) channels and enhanced myogenic constriction. *F*: in aged cerebral arteries the functional adaptation to hypertension mediated by activation of the 20-HETE/TRPC-dependent pathway is impaired (red arrows).

genic autoregulation of CBF. In contrast, flow-induced constriction is predicted to act as a negative feedback mechanism to autoregulate CBF in concert with pressure-induced myogenic constriction. Further in vivo studies should provide direct experimental evidence to support or reject this hypothesis (308).

Role of autoregulation in cerebromicrovascular protection. The myogenic response of proximal cerebral arteries plays a critical role in neuroprotection, by preventing the penetration of high pressure to the thin-walled distal portion of the microcirculation and protecting the microcirculation from high pressure-induced damage (41, 281, 283). Direct measurements of cerebromicrovascular pressure demonstrate that approximately half of the total vascular resistance in brain depends on changes in the segmental resistance of vessels upstream from the penetrating arteries (for an excellent review see Ref. 57). As a result of the significant resistance of larger proximal arteries, the high central systolic pressure cannot penetrate the microcirculation under steady-state conditions (Fig. 2). In healthy young individuals increases in blood pressure, episodic or sustained, result in proportionate increases in cerebral vascular resistance such that, due to a larger pressure drop along the proximal resistance arteries, the increased pressure does not penetrate the thin-walled microvessels (Fig. 2). Studies in young experimental animals show that during chronic hypertension resistance of both larger and smaller resistance arteries increases (168, 313). Because of these adaptive changes in resistance, capillary pressure is maintained relatively constant (Fig. 2). Thus the thin-walled cerebral microvessels are protected from barotrauma as long as the autoregulatory protective mechanisms are intact and the blood pressure remains within the physiological autoregulatory range. It is believed that alterations in the cerebral autoregulatory capacity in different pathological conditions significantly contribute to cerebromicrovascular damage (281).
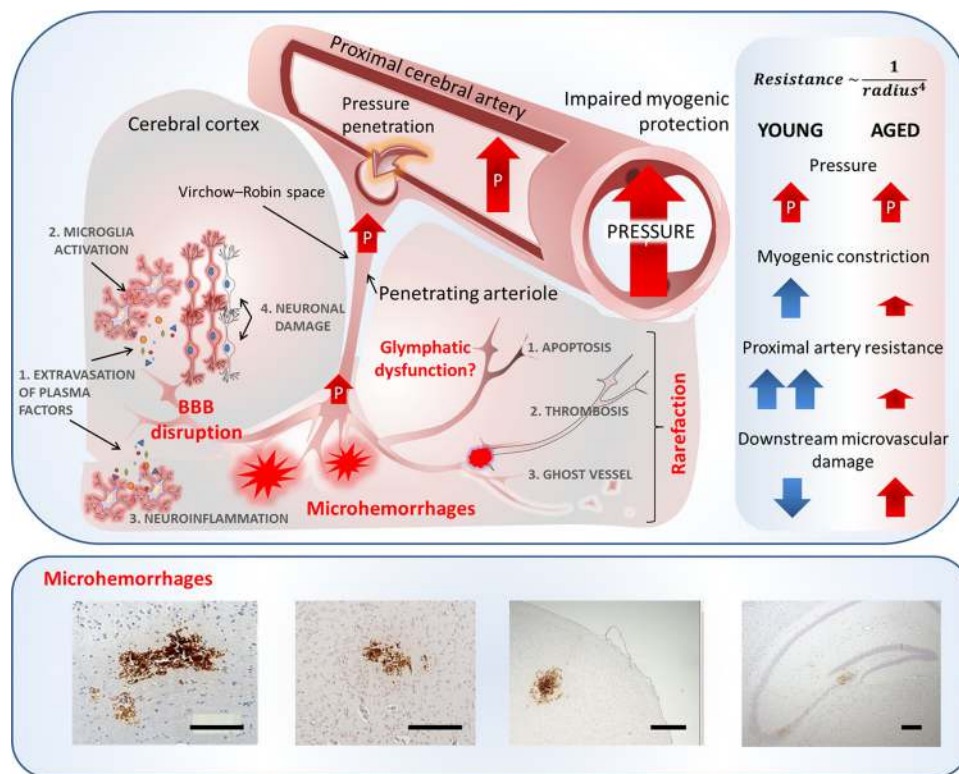

Fig. 2. Age-related autoregulatory dysfunction exacerbates hypertension-induced cerebromicrovascular injury. Shown is a schematic illustration of the likely consequences of autoregulatory dysfunction in the aging brain. The model proposed implies that in healthy young organisms pressure-induced myogenic constriction of the proximal cerebral arteries acts as a critical homeostatic mechanism that assures that increased arterial pressure does not penetrate the distal portion of the microcirculation and cause damage to the thin-walled arteriolar and capillary microvessels in the brain (103, 147). In aging, proximal resistance arteries lose their capability to adapt to hypertension with an enhanced pressure-induced constriction, which leads to a mismatch in perfusion pressure and segmental vascular resistance (resistance is inversely related to the 4th power of vessel radius). Lack of proper autoregulatory protection in aging likely allows high blood pressure to penetrate the vulnerable downstream portion of the cerebral microcirculation. The hemodynamic burden exacerbates age-related disruption of the blood-brain barrier (BBB), leading to extravasation of plasma factors, which promote neuroinflammation (e.g., activation of microglia by IgG via the IgG Fc receptors). Microglia-derived proinflammatory cytokines, chemokines, proteases [i.e., matrix metalloproteinase (MMP)] and reactive oxygen species (ROS) promote neuronal damage (273, 281). In addition, the increased microvascular pressure activates matrix metalloproteinases in the vascular wall in a redox-sensitive manner, contributing to the development of microhemorrhages (276). The age-related autoregulatory dysfunction and its consequences may also contribute to the dysfunction of the glymphatic system (128, 148), and the development of age-related vascular rarefaction (281). We posit that exacerbation of neuroinflammation, cerebral microhemorrhages, glymphatics dysfunction and/or microvascular rarefaction are causally linked to hypertension-induced cognitive impairment in aging (85, 210, 285) and contribute to the increased prevalence of Alzheimer's disease in hypertensive elderly individuals. *Bottom*: representative images showing cerebral microhemorrhages (brown lesions after diaminobenzidine-hematoxylin staining, scale bar = 200 μm) in the brain of aged (24 mo old) hypertensive mice, which associate with autoregulatory dysfunction. Note that most hypertension-induced microhemorrhages are located in the cortical and subcortical region. Hypertension was induced in the mice by treatment with angiotensin II and the nitric oxide synthase inhibitor nitro-L-arginine methyl ester (L-NAME) (279).

Age-related changes in dynamic and static components of cerebral autoregulation. Recent studies suggest that age-related alterations in the cerebral autoregulatory capacity may play an important role in the pathophysiology of brain aging. In mice aging impairs the dynamic component of the myogenic response of isolated cerebral arteries induced by a sudden increase in pressure (281) and impairs myogenic adaptation to pulsatile pressure (250). In contrast, the static component of the myogenic response and static autoregulation of CBF are largely unaffected in the autoregulated range (269, 281). In aged rodents the upper limit of CBF autoregulation appears to be unchanged (281), whereas the lower limit of CBF autoregulation increases by ~20 mmHg (152, 284). The diminished compensatory dilatation of aged cerebral resistance arteries during hypotension likely increases the risk of ischemia of the brain during hypotensive conditions. Analysis of the available human data yielded mixed results (216). In elderly patients Lipsitz et al. (154) found retained dynamic autoregulation by transfer function analysis during standing and sit-to-stand challenges. Other studies also reported retained dynamic autoregulatory function in aged patients challenged by negative pressure release, Valsalva maneuver, thigh cuff test, or sit-to-stand maneuver indicated by normal autoregulatory index and unaffected transfer function in lower frequencies of oscillation in blood pressure (36, 181). Studies of Yam at al. (319) found also no differences between dynamic autoregulatory response of younger and older groups of patients. The findings of studies investigating aging-induced changes in response to sudden hypotension in humans are also controversial. Aging is associated with a higher incidence of postural symptoms (such as syncope), a common condition of sudden blood pressure drop (35), which can cause temporal hypoperfusion in the brain in case of ineffective compensatory decrease in cerebrovascular resistance. Larger postural reduction in cerebral cortical oxygenation (by near-infrared spectroscopy) and in mean blood flow velocity in middle cerebral arteries was found in elderly patients compared with young controls (160, 172). Preliminary studies also show that in the elderly impaired dynamic autoregulation (assessed using gain and phase) predicts development of symptoms during orthostatic tolerance test (226). In contrast, in another study autoregulatory response to hypotension during orthostatic stress was found to be unaffected by aging (140). Wollner et al. (318) investigating aged individuals with postural hypotension demonstrated that patients with clinical signs of cerebral ischemia exhibited autoregulatory failure, meanwhile a similar pressure drop did not cause any symptoms when autoregulatory function was intact. During ergomotor exercise dynamic autoregulation was reported to be intact; however, onset of autoregulatory correction of CBF was found to be delayed in older patients (110). Sorond et al. (244) found regional differences in changes of cerebrovascular resistance: there appears to be a significantly greater decline in blood flow velocity in the area of posterior cerebral artery than in the territory of middle cerebral artery indicating regional differences in dynamic autoregulatory function. Interestingly, the Lipsitz laboratory (232) reported an even more effective autoregulatory response to hypotension and during spontaneous oscillations in blood pressure both in treated and untreated hypertensive elderly patients, which was associated with a disturbed vasoreactivity to changes in CO_2 levels. In summary, studies investigating dynamic autoregulation in elderly patients reported variable results, mostly depending on the measured parameter of dynamic features of autoregulation. Further studies are evidently needed to resolve these controversies. When interpreting the aforementioned data, several limitations should also be considered, including methodological limitations (e.g., lack of direct measurement of cerebrovascular pressure and/or volumetric flow in most studies); potential confounding effects of lifestyle factors and medications, small sample size used in many of the studies relative to the age range of the participants, especially that of older subjects; the substantial interindividual variability in many of the parameters assessed; and the cross-sectional nature of most of the studies. In contrast to findings obtained under steady-state conditions, age-related autoregulatory dysfunction is more evident under conditions of hypertension (281) and increased pressure pulsatility (251) (see below).

Impaired autoregulatory adaptation to hypertension in aging. In industrialized societies, there is a consistent age-related increase in systolic blood pressure (80). In healthy young individuals, the elastic conduit arteries (including the aorta and carotid artery) provide a Windkessel effect to dampen hemodynamic pulsatility and facilitate a continuous blood flow into the cerebral microvessels (23, 267). Due to the age-related stiffening and impaired Windkessel function of conduit arteries, the amplitude of systolic pressure in the aorta significantly increases with age (63, 206). The existing evidence suggests that such an increase in central pulse pressure is transmitted into organs that are characterized by low resistance and high blood flow (108, 175, 311). Arterial wave reflections returning from the peripheral resistance vessels may augment pressure pulsatility in the aged cerebral microcirculation. Hypertension in the elderly is a major risk factor for both large hemorrhagic strokes and microvascular injury (capillary damage, blood-brain barrier disruption, and microhemorrhages) contributing to the development of vascular cognitive impairment (97).

There is increasing evidence in support of the concept that age-related impairment of autoregulatory adaptation to hypertension contributes to the increased susceptibility of the elderly to hypertension-induced microvascular damage and cognitive decline (262, 287). Recently, we demonstrated that in mice aging is associated with impaired myogenic adaptation of cerebral arteries to pulsatile pressure (250). If arteries of elderly hypertensive patients also show impaired myogenic constriction when exposed to pulsatile pressure, this is probably associated with a significant hydrodynamic resistance decrease in the proximal larger resistance arteries, imposing a significantly larger burden on the downstream portion of the cerebral microcirculation. Importantly, a recent study demonstrated that in elderly individuals, higher pulse pressure led to increased CBF pulsatility (262). This finding supports the idea that with aging the cerebral microcirculation lacks protection against increases in pulsatile pressure (250). Recent findings provide important evidence to support the concept that pressure pulsatility and, consequently, CBF pulsatility increase due to age-related increases in central arterial stiffness and wave reflection in elderly patients (265). Cerebromicrovascular damage has long been hypothesized to result from the penetration of increased pulsatile pressure into the vulnerable distal portion of the microcirculation in the elderly (reviewed in Refs. 188, 247). Importantly, in aged individuals increased central arterial stiffness and higher pressure/CBF pulsatility are associated

with increased incidence and volume of white matter damage (287). In the elderly activities that result in significant transient increases in blood pressure also represent a dynamic challenge to the autoregulatory mechanisms of the cerebral circulation. For example, the Valsalva maneuver, which causes a significant transient rise in arterial pressure for a short period of time, inadvertently occurs during daily activities in which straining is present (266). Heavy-weight lifting, defecation straining, playing of wind instruments, nose blowing, heavy coughing, and vomiting are all events that cause a sudden increase in arterial pressure, which simulates the Valsalva maneuver. Anger, startling, sexual intercourse, and vigorous physical exercise, all of which are documented trigger factors for intracerebral hemorrhage, are also characterized by significant transient increases in blood pressure, posing a challenge to the autoregulatory mechanisms of the cerebral circulation. There are also studies showing an association of early morning increases in blood pressure, which is coincident with arousal and arising from overnight sleep (131), with cerebrovascular events in elderly patients.

Previous studies provide evidence that in young organisms cerebral arteries exhibit functional and structural adaptation to hypertension, which protect the injury-prone distal portion of the cerebral microcirculation from pressure overload (179, 203, 222, 223, 254–256, 271, 281). Among these physiological adaptive responses the increased pressure-induced myogenic constriction of cerebral arteries is of great significance (103, 147, 191). Previous studies demonstrated that in young hypertensive animals increased pressure-induced myogenic constriction leads to an increased resistance at the level of the larger pial arteries (269, 281). With the manifestation of this adaptive vascular response, the protective CBF autoregulatory range extends to higher pressure values in hypertensive patients as well as in laboratory animals with pharmacologically induced hypertension (203, 254–256, 281) (Fig. 1). Recently, we provided evidence that cerebral arteries of aged mice do not exhibit a hypertension-induced adaptive increase in myogenic tone observed in young mice and aged-hypertensive animals do not show extension of CBF autoregulation to high pressure values (269, 281). The mechanisms responsible for the age-dependent loss of myogenic protection in hypertension likely involve dysregulation of the pressure-induced activation of the 20-HETE/TRPC6 pathway (271, 281). In theory, dysregulation of potassium channels, including BK_{Ca} channels, may contribute to functional maladaptation of resistance arteries to high pressure (29, 143). 20-HETE inhibits BK_{Ca} channels, which are known to be activated in the high pressure range (200) in the vascular smooth muscle cells in cerebral arteries. Yet, pharmacological inhibition of BK_{Ca} channels does not appear to significantly increase myogenic tone in cerebral arteries isolated from hypertensive aged mice (271). Future studies are warranted to elucidate the role of other mechanisms, including other TRP channels potentially involved in the mediation of myogenic mechanisms (TRPM4 etc.) in age-related functional maladaptation of cerebral arteries to hypertension.

In recent years a growing amount of evidence has provided support to the view that endocrine mechanisms play a crucial role in cerebrovascular alterations associated with advanced aging (241, 294). In particular, the age-related decline in circulating insulin-like growth factor-1 (IGF-1) levels appears to contribute significantly to vascular aging and age-related cerebrovascular alterations (11, 241, 275, 281, 294). Low circulating IGF-1 levels in humans are also associated with an increased risk for hypertension-induced microvascular brain damage (3) and stroke (130, 151), findings that have been also replicated in laboratory animals (240). Using a novel mouse model of endocrine IGF-1 deficiency (adeno-associated viral knockdown of IGF-1 specifically in the mouse liver using Cre-lox technology; $Igf1^{f/f}$ + TBG-iCre-AAV8) (11), we showed that low circulating IGF-1 levels lead to impaired autoregulatory protection in the brain of hypertensive mice, potentially exacerbating cerebromicrovascular injury and neuroinflammation (281). Importantly, in IGF-1-deficient mice hypertension fails to upregulate TRPC6 expression and the TRPC-dependent component of the myogenic constriction (281), mimicking the aging phenotype. Experimental IGF-1 deficiency also mimics other aspects of cerebromicrovascular aging (11, 12, 241, 262, 275). For example, hypertension in rodent models of both aging (281) and IGF-1 deficiency (262) promotes cerebromicrovascular rarefaction. It should be noted that in response to hypertension cerebral arteries also exhibit structural adaptation. Vascular hypertrophy reduces wall stress. Inward remodeling contributes to adaptive increases in segmental vascular resistance, protecting the microcirculation (17–19, 57). Thus it is significant that both aging and IGF-1 deficiency are associated with impaired structural adaptation of cerebral microvessels to hypertension (unpublished observations), which likely exacerbates microvascular injury. There may be a cross talk between IGF-1 and insulin signaling pathways in the smooth muscle cells. There is initial evidence that both insulin resistance (132, 133) and IGF-1 deficiency (48) may impact mitochondrial function and mitochondrial reactive oxygen species (ROS) production in vascular smooth muscle cells, which may affect mechanotransduction of pressure, myogenic constriction, and vasomotor responses. Given the incidence of insulin resistance in aging, further studies are evidently needed to test these possibilities.

In elderly hypertensive patients, the lower limit of autoregulation of CBF is shifted to the right. Previous studies in spontaneously hypertensive rats also demonstrated an age-related shift in the lower limit of autoregulation, which results in significant reduction in CBF in response to experimentally induced hypotension (87, 115). The age- and hypertension-related mechanisms, which impair dilation of cerebral vessel in response to decreases in blood pressure, are presently poorly understood. Arterial morphological changes with aging, including thickening, stiffening, and eccentric remodeling (150), might contribute to the decreased capability of the cerebral vessels to dilate when intraluminal pressure is decreasing. An interesting consideration of the possible mechanisms is the role of endothelium. Recently, Bagher et al. (10) demonstrated that decreasing intraluminal pressure activates TRPV4 channels in endothelial cells of pressurized arterioles leading to increased frequency of spontaneous endothelial calcium events and activation of calcium-activated K^+ channels, which then lead to dilation of the vessel. Age-associated endothelial dysfunction of cerebral vessels (109, 116, 166, 199, 281) might impair these mechanisms. These possibilities should be experimentally tested in the future.

Downstream consequences of cerebrovascular autoregulatory dysfunction. The functional maladaptation of aged cerebral arteries to hypertension is likely responsible for the loss of

autoregulatory protection in the aging brain, which likely allows high blood pressure to penetrate the distal, injury-prone portion of the cerebral microcirculation (Fig. 1). It is likely that when in elderly patients blood pressure exceeds the threshold for vascular injury and the autoregulatory ability of the resistance arteries to protect the cerebral capillaries is breached, microvascular damage also ensues (Fig. 2). Potential downstream consequences of cerebrovascular autoregulatory dysfunction (in the high pressure range) and pressure/volume overload include exacerbated disruption of the blood-brain barrier, neuroinflammation and neurodegeneration, structural damage to capillaries and capillary rarefaction, and increased propensity for intracerebral hemorrhages (Fig. 2). The existing data support this concept showing that in mice aging exacerbates hypertension-induced cerebromicrovascular damage and increases the incidence of cerebral microhemorrhages (276, 281). In aged mice increased blood-brain barrier permeability is exacerbated by hypertension, which associates with increased presence of activated microglia (281). The exacerbation of microvascular damage [including blood-brain barrier disruption (325, 326)] in aged hypertensive subjects is likely causally linked to increased neuroinflammation and cognitive decline (281) and is likely to contribute the known association between hypertension and Alzheimer's disease in aging (50, 56, 59, 60, 64, 75, 77, 94, 97, 114, 118, 122, 124, 125, 138, 169, 178, 205, 215, 218, 235, 238, 239, 248). In that regard it is interesting that a high-impact recent study from the Zlokovic laboratory demonstrates that the level of blood-brain barrier disruption in the aged human hippocampus predicts cognitive impairment in elderly patients (177).

Although a direct cause-and-effect relationship is difficult to prove experimentally, the available clinical evidence strongly support the concept that cerebrovascular autoregulatory dysfunction is causally linked to downstream microcirculatory damage (185, 212, 228, 257, 264). Critical proof of concept was provided recently by the studies of Fan at al. (71) showing that experimental disruption of the myogenic machinery in cerebral arteries (by genetic inhibition of 20-HETE synthesis) results in significant microvascular damage, including blood-brain barrier disruption.

Hypertension in the elderly is often associated with small vessel disease (detected as white matter hyperintensities on MRI images) (reviewed in Ref. 194), which leads to gait disturbances and a decline in cognitive performance, executive function, and processing speed (139, 207, 310). The pathogenesis of with diffuse white matter disease is thought to involve microvascular injury, blood-brain barrier disruption, and consequential demyelination. There is growing evidence suggesting a causal relationship between cerebral autoregulatory dysfunction and brain white matter hyperintensity in older adults (30, 156, 212). The concept that age-related impairment of myogenic autoregulatory protection promotes hypertension-induced downstream microvascular damage and barrier disruption is supported by the observations that in the renal circulation of older hypertensive Faw-Hooded rats impairment of myogenic constriction of the afferent arterioles is associated with increased proteinuria, an indicator of downstream renal microvascular damage (302). The renal circulation features a prominent autoregulatory function similar to the cerebral circulation and previous studies show that in hypertensive hu-

mans renal microvascular injury often associates with clinical markers of cerebral microvascular damage (40, 272).

Aging-induced autoregulatory failure is also likely to contribute to increased prevalence of hypertension-induced intracerebral hemorrhages, especially cerebral microhemorrhages (261) (Fig. 2). Cerebral microhemorrhages are small (<5 mm in humans) vascular lesions associated with rupture of small intracerebral vessels and are considered of emerging importance as a contributing factor to the progressive impairment of neuronal function in aging. Epidemiological studies demonstrate that hypertension in aging is the major risk factor for the development of cerebral microhemorrhages (208). Recent data from animal models extend the clinical findings, showing that impaired functional adaptation of the aged cerebral arteries to hypertension exacerbates the development of cerebral microhemorrhages (279). Importantly, aging not only promotes the penetration of high pressure in the microcirculation but also alters pressure-induced mechanosensitive cellular and molecular pathways in the vascular wall, which render aged cerebral vessels vulnerable to the deleterious effects of hypertension (250, 279). Among other factors, aging was shown to exacerbate pressure-induced oxidative stress and promote activation of matrix metalloproteinases, compromising the structural integrity of cerebral arteries (250, 279).

In addition to prevention of high pressure-induced microcirculatory damage, autoregulation has also to avoid hypoperfusion of cerebral tissue. Due to dysfunction of cerebral autoregulation in hypertensive aged subjects (in whom the lower limit of autoregulation is shifted to higher pressures), inadequate dilation in response to hypotension may cause hypoperfusion and thus ischemic neuronal damage (74).

Aging-Induced Endothelial Dysfunction

The endothelial layer of cerebral vessels is capable of producing a variety of vasoactive substances [nitric oxide (NO), eicosanoid mediators, endothelium-derived hyperpolarizing factors (EDHFs), and endothelins] and it is in direct contact with blood flow making sensitive to changes in hemodynamic forces and various hormones present in the sera. The microvascular endothelium is involved in many aspects of the regulation of CBF. Endothelial NO contributes to setting resting CBF demonstrated by studies showing that acute blockade of NO synthases attenuates basal CBF and leads to hypoperfusion (117). Also, systemic administration of the NO precursor L-arginine increased CBF velocity in humans (88). Aging is associated with endothelial dysfunction in the cerebral circulation, similar to other vascular beds (31, 166, 176). The mechanisms underlying age-related endothelial dysfunction are multifaceted and involve oxidative stress. Accordingly, aging is associated with increased production of ROS in the vasculature of the brain and other organs (52, 195) in part due to an increased activity/expression of NADPH oxidases (195, 279). Aging also leads to increased mitochondrial production of superoxide (250) and impairment of Nrf2-dependent cellular antioxidative pathways (11, 47, 292, 293). Increased levels of superoxide readily react with NO to form peroxynitrite, decreasing the bioavailability of NO and leading to endothelial dysfunction (25, 281). Previous studies suggest that decreased endothelium-dependent vasodilation in aging is a universal phenomenon (89, 149, 198, 220) and may be exacerbated by

upregulation of arginase (24, 134), which decreases cellular L-arginine supply, uncoupling of endothelial nitric oxide synthase, increases in assymetric dimethylarginine (ADMA) levels, endocrine changes (58), and age-related upregulation of angiotensin signaling and chronic vascular inflammation (55, 82, 184). Furthermore, aging-induced endothelial dysfunction is likely exacerbated by comorbid conditions, including metabolic diseases and hypertension (132, 281, 288, 290). Age-related endothelial dysfunction likely contributes to the chronic cerebral hypoperfusion observed in aging and consequent cerebral dysfunction, including cognitive decline (221, 309). Endothelium-dependent NO production also contributes to neurovascular coupling responses (38, 276, 279). Accordingly, recent studies demonstrate that endothelial dysfunction plays a critical role in aging-induced impairment of moment-to-moment adjustment of regional CBF to changes in neuronal activity (195). Endothelium-derived NO is also an important inhibitor of platelet aggregation, smooth muscle cell proliferation, and leukocyte adhesion and exerts potent anti-inflammatory, antiapoptotic, and proangiogenic effects (recently reviewed in Ref. 136). It also modulates cellular metabolism, mitochondrial function, and synaptic transmission (135, 213, 234, 238). Age-related decline in microvascular NO production, therefore, is likely to exert multifaceted detrimental effects on cerebrovascular, neuronal, astrocytic and microglial functions. Age-related impairment of microvascular endothelial cells also impairs angiogenic processes (15, 47, 298, 299), promoting microvascular rarefaction (290). Moreover, there is growing evidence implicating endothelial dysfunction in the pathogenesis of Alzheimer's disease (61). Experimental studies also demonstrate that impaired endothelial NO production increases amyloid precursor protein, Aβ levels, promotes microglial activation, and exacerbates Aβ-induced impairment of cognitive function (6). For further reading on the effects of age-related endothelial dysfunction on the blood-brain barrier and its relation to neurodegenerative diseases (e.g., Alzheimer's disease) we refer to the excellent recent review of Di Marco et al. (61). Aging may also modulate the endothelial production of arachidonic acid metabolites. For example, soluble epoxide-hydrolase [which catalyzes the hydrolysis of the dilator epoxyeicosatrienoic acids (EETs) into their inactive metabolites] was reported to be enhanced in the microvascular endothelium of older patients with cerebral small vessel disease and vascular cognitive impairment (182). There are also studies suggesting that the balance of constrictor and dilator eicosanoid metabolites produced in the microcirculation is altered by aging (16).

Aging-Induced Impairment of Neurovascular Coupling Responses

Cellular and molecular mechanisms of neurovascular coupling. The energetic demand of neurons is very high, but the brain has very little reserve capacity. During neuronal activity there is a requirement for rapid increases in nutrients delivery, as well as washing-out of toxic metabolic by-products. Fulfilling this requirement regional CBF is closely adjusted to neuronal activation in a spatially and temporally well-regulated manner (69, 165). This is ensured by neurovascular coupling responses ("functional hyperemia"; Fig. 3), which maintain the optimal microenvironment for normal neuronal function (4). Neurovascular coupling responses depend on a coordinated interaction of neurons, astrocytes, endothelial cells and smooth muscle cells of cerebral arterioles (4). Recent findings also implicate pericytes and capillary dilation in the initial phase of the CBF response (100). Based on current models of neurovascular coupling, interaction of several parallel processes ensure that neuronal activity is coupled to localized vasodilation and increases in regional CBF. Upon neuronal activation, neuronal nitric oxide synthase-derived NO (34, 162) and/or neuronal prostaglandin release (37) can contribute to dilation of cerebral arterioles both indirectly, through modulating astrocytic mechanisms, and directly, acting on the arteriolar smooth muscle cells. Since astrocytes are positioned between neurons and vascular cells they are in ideal position to transform neuronal activation into blood vessel responses. It appears that the main astrocytic responses that contribute to increases in CBF during neuronal activation are triggered by glutamate released from synapses (209). Glutamate activates metabotropic glutamate receptors (mGluR) and NMDA receptors (253) on astrocytes, leading to increased Ca^{2+} influx, which activates the metabolism of arachidonic acid by cyclooxygenases to prostaglandins (PGE_2) and by epoxygenases to EETs. These mediators can cause dilation of cerebral blood vessels via mechanisms that involve activation of BK_{Ca} channels and TRPV4 channels on vascular smooth muscle cells (79, 187). Under pathological conditions arachidonic acid can be converted into 20-HETE in the neurovascular unit, which elicits constriction of cerebral arterioles counteracting the dilatory stimuli mediated by EETs, prostaglandins, and NO (39, 157). The current view is that the balance between production of dilator and constrictor metabolites of arachidonic acid is influenced by the preceding tone of cerebral vessels, the O_2 level and the availability of NO, among other factors. One of the most important signaling molecules by which astrocytes communicate with each other and with other cells is ATP and its metabolites, adenosine, and ADP. Since ATP is directly linked to astrocytic metabolism, it is logical to assume that purinergic pathways are involved in neurovascular coupling. Indeed, astrocyte-derived ATP, after hydrolyzed to adenosine, contributes to cerebral reactive hyperemia via A2A purinergic receptors on vascular smooth muscle cell. In addition to this pathway, astrocytic ATP released in response to neuronal activation may also act on endothelial P2Y1 receptors triggering the production of endothelial NO and subsequent vasodilation. Indeed, most studies (95, 323) (95, 253, 280), but not all (9), suggest that endothelium-derived NO, released in response to astrocyte-derived signals, contributes importantly to neurovascular coupling. Another hypothesis concerning astrocytic mechanisms of arteriolar dilation during neurovascular coupling centers on the potential dilator role of extracellular K^+. According to the K^+ syphoning theory (202, 317), after neuronal activation astrocytes take up excess extracellular K^+ and transport it to the arterioles where they release it. K^+ in the perivascular space is believed to activate K_{ir} in smooth muscle cells. Since the membrane potential of smooth muscle cells is higher than the reversal potential of K_{ir}, the resulting outward K^+ flux leads to hyperpolarization, decreasing smooth muscle cell intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), and dilating cerebral arterioles (317). The glutamate-induced $[Ca^{2+}]_i$ increase can open BK_{Ca} channels on astrocyte endfeet and release astrocytic K^+ onto blood vessels, as well (81). An
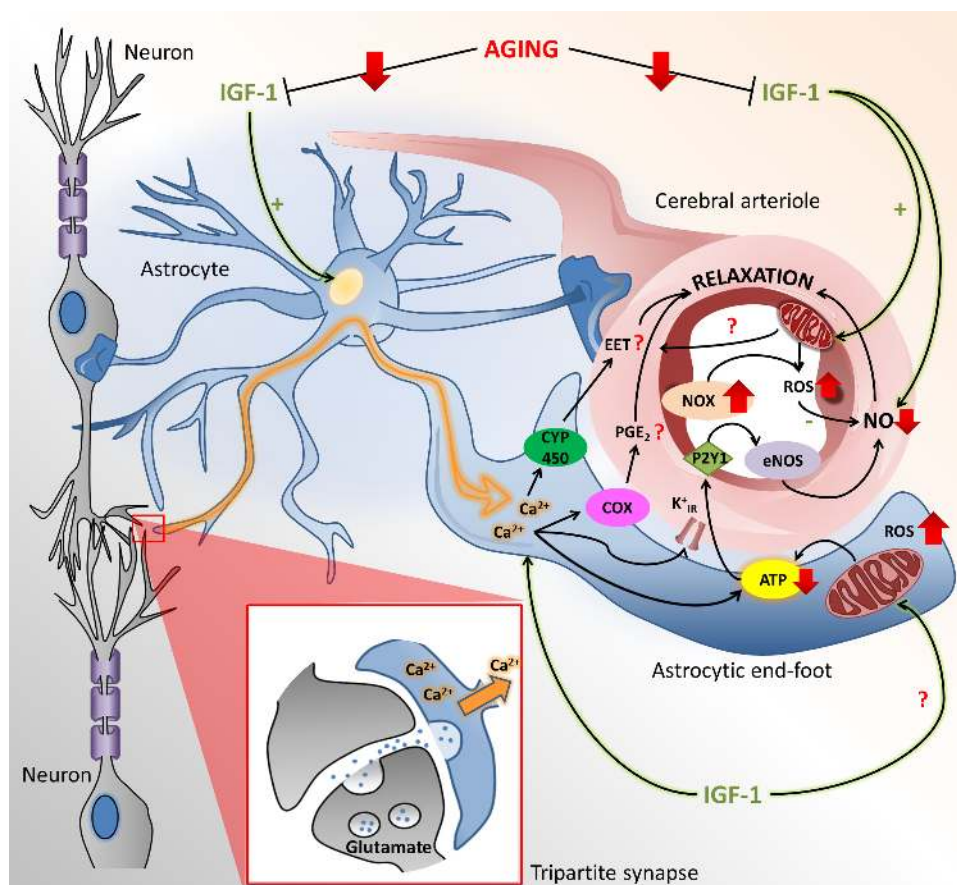
Fig. 3. Aging impairs neurovascular coupling responses: potential role of insulin-like growth factor-1 (IGF-1). Shown is a schematic illustration of age-related alterations in glio-endothelial coupling mechanisms, which are responsible for impaired functional hyperemia in the elderly. Accordingly, under normal conditions astrocytes mediate the interaction between neurons and vascular cells by physically connecting neuronal synapses to cerebrovascular smooth muscle wall. Glutamate released from active excitatory synapses triggers a calcium wave that travels through the astrocyte and reaches the end-feet wrapped around the vessel wall. The glutamate-induced calcium surge activates CYP450- and cyclooxygenase (COX)-mediated production of vasodilator eicosanoids [epoxyeicosatrienoic acids (EETs) and prostaglandins, respectively] and promotes activation of ATP release machinery. Astrocyte-derived ATP promotes endothelial release of vasodilator nitric oxide (NO) via activation of P2Y1 receptors (276). The model predicts that aging impairs all of these mechanisms involved in glio-vascular coupling responses. Of particular importance is the purinergic endothelial NO-mediated pathway, which may be affected by both endothelial oxidative stress [increased ROS production by NOX oxidases (195) and mitochondrial sources] and astrocyte-derived ROS production. The known age-related changes are showed using red arrows. Age-related decreases in levels of circulating IGF-1 is one of the most important endocrine changes accompanying aging. On the basis of evidence obtained in IGF-1-deficient mouse models of aging (275) the model predicts that age-related decline in IGF-1 impairs both astrocyte function and endothelium-mediated mechanisms of functional hyperemia. Note, that the scheme does not include IGF-1 deficiency-induced potential alterations in neuronal release of vasodilator substances and/or the role of IGF-1-related changes in astrocyte-mediated capillary dilation.

important recent study suggested that pericytes may also be involved in activity-evoked increase in CBF by dilating capillaries before arterioles dilate via a PGE_2-dependent pathway, which requires NO to suppress the production of constrictor 20-HETE (100).

Aging-induced alterations in neurovascular coupling. There is increasing evidence that neurovascular coupling is impaired in aging both in humans and laboratory animals (14, 195, 269, 322). Previous studies demonstrate that in healthy aged persons occipital blood flow responses to visual evoked potentials, measured by transcranial Doppler flowmetry, are significantly decreased compared with young ones (269, 322). Although another study using a similar approach did not report an age-related decline in flow response to visual signals, in this study all the participants were under 60 yr of age (219), which makes the interpretation of the findings in the context of aging difficult. Similar to the findings obtained in elderly humans laboratory rodents also exhibit age-related neurovascular un-

coupling (195, 280). There are also studies extant suggesting that aging-induced changes in blood flow response to neuronal activation may show regional differences. For example, Sorond et al. found that aged individuals, unlike young subjects, during word stem completion cognitive task show decreased frontal responses (a brain region supplied by the anterior cerebral artery) as compared with occipital responses (a brain region supplied by posterior cerebral artery) (245).

The mechanisms by which aging impairs neurovascular coupling mechanisms are likely multifaceted (Fig. 3). Although attenuation of the underlying neuronal activity may theoretically contribute to impaired functional hyperemia, age-related neurovascular uncoupling appears to be reversible by interventions that improve cerebrovascular reactivity. The existing evidence suggests that increased production of ROS plays a central role in cerebromicrovascular impairment and neurovascular uncoupling in aging. This concept is supported by experimental findings showing that acute inhibition of

NADPH oxidases is able to rescue neurovascular coupling in aged mice (195). Furthermore, aging is associated with increased ROS production in microvessels both in the brain and other vascular beds (52, 195) due, at least in part, to an increased activity/expression of NADPH oxidases (195). Interestingly, in mouse models of age-related AD-type neurodegeneration, enhanced generation of NADPH-derived ROS was also reported to contribute to neurovascular uncoupling (196, 197). There are multiple pathways through which increased ROS production may impair CBF responses induced by neuronal activation. An increasing body of literature supports the concept that endothelial NO production has an important role in neurovascular coupling (95, 159, 253). In aged rodents increased O_2^- reacts with NO produced by the endothelial cells of cerebral microvessels forming $ONOO^-$. The resulting decreases in bioavailability of NO likely contributes to the impaired neurovascular responses (195). Supporting this concept is the finding that in young rodents inhibition of endothelial NO synthesis using L-NAME significantly attenuates CBF responses to both whisker stimulation and the endothelium-dependent dilator acetylcholine, whereas it does not affect neurovascular responses and endothelium-dependent dilations in aged animals (279). Interestingly, in APP transgenic mice the antioxidants N-acetyl-L-cysteine and tempol also restored neurovascular function (186), suggesting that oxidative stress associated with the pathological processes of Alzheimer's disease plays a causal role in neurovascular uncoupling in this age-related neurodegenerative diseases as well. Age-related endothelial dysfunction is reversible, which offers a potential target for therapeutic interventions for improvement of neurovascular coupling and, consequently, higher brain function in the elderly. Recent studies demonstrate that treatment of aged mice with resveratrol, which decreases cellular ROS production and downregulates NADPH oxidases (49, 204, 291, 295–297), restores microvascular endothelial function and neurovascular coupling in the brain of aged mice (279). It is possible that rescued neurovascular coupling contributes to the beneficial effects of resveratrol treatment on cognitive function reported in aged rodents (155, 190, 324). It is plausible to hypothesize that aging and age-related increased oxidative stress also impair other mechanisms of neurovascular signaling, such as the neuronal production of nitric oxide (321), astrocytic Ca^{2+}-dependent signaling (164), and metabolism of arachidonic acid (137), the K^+-dependent mediation of vascular dilation and the metabolism and action of glutamate (2). Since ischemic injury of pericytes has been causally linked to impaired neurovascular response (100) and the number pericytes and pericyte coverage of microvessels tend to decrease with age (288); it is also possible that age-related alterations of pericytes contribute to neurovascular uncoupling. Future studies are warranted to experimentally test the aforementioned hypotheses.

As discussed above, age-related IGF-1 deficiency was shown to significantly contribute to cerebromicrovascular alterations associated with aging (241, 294). Each cell type involved in neurovascular coupling (i.e., neurons, astrocytes, endothelial cells) abundantly expresses IGF-1 receptors and is a known target of IGF-1 (241). Importantly, we recently found that experimentally induced circulating IGF-1 deficiency impairs neurovascular coupling in the mouse somatosensory cortex via dysregulation of astrocytic glutamate-signaling, impairing production of astrocyte-derived EETs and increasing production of 20-HETE (275). In addition, IGF-1 deficiency also promotes cerebral oxidative stress and endothelial dysfunction, which also contribute to neurovascular uncoupling (273). Future studies are warranted to determine whether IGF-1 deficiency also predicts impaired functional hyperemia in elderly patients and to assess the efficacy of IGF-1 treatment to improve neurovascular coupling responses in animal models of aging.

Potential consequences of neurovascular uncoupling in aging. Because the increased energy consumption has to be fueled by adequate amount of nutrients during neuronal activation (126), the attenuated increase in CBF to neuronal activation most likely disrupts the balance between the metabolic demand of the functioning cerebral tissue and the supply of nutrients (201). Therefore, age-related neurovascular uncoupling is expected to impair neuronal function in the brain. This concept is supported by studies conducted in aged laboratory animals and elderly humans (70, 252, 269, 322) showing that dysfunction of neurovascular coupling is associated with cognitive decline (243). The direct link between neurovascular uncoupling and cognitive decline is supported by recent studies showing that pharmacological treatment of young mice with inhibitors of the mediators of neurovascular coupling impairs functional hyperemia, which is associated with impairment of spatial and recognition memory (260). Importantly, elderly patients living with AD exhibit exacerbated impairment of neurovascular coupling responses (113, 127, 217), which may be contributing to worsening cognitive outcomes over time. Factors impairing neurovascular signaling, such as hypertension and accumulation of Aβ peptide in Alzheimer models (120–122, 141, 186, 268), are also associated with cognitive impairment in laboratory animals, which seem to be reversible by pharmacological treatments that improve neurovascular coupling (186, 268). On the basis of these observations, the neurovascular unit could be considered as a target for pharmacological intervention to reverse/delay cognitive decline associated with both aging and age-related neurodegenerative diseases.

Gait dysfunction of varying severity is present in a significant portion of elderly patients (189, 305) and is a major contributor to falls and predicts increased risk of institutionalization and death (1, 303, 304). Frontal executive functions play an important role in the cortical control of gait and there are studies extant suggesting that an association exists between neurovascular coupling and gait speed (242, 245). Future studies should determine whether pharmacological treatments, which improve neurovascular coupling are also effective in improving gait in the elderly.

Vasomotor responses associated with spreading depolarization highlight additional potential pathophysiological roles for neurovascular coupling responses. Cortical spreading depolarization is an intense depolarization wave that propagates in the cortex, triggering rapid vasoconstriction, followed by a pronounced hyperemic response and then a long-lasting oligemic phase (often called post-spreading depolarization oligemia) (7, 8, 21, 22, 44, 78, 111, 174, 300). There is strong clinical and experimental evidence that cortical spreading depolarizations occur after intracerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, as well as traumatic brain injury (7, 8,

13, 65–67, 105, 107, 112, 161, 193, 225, 227, 307, 316, 318). The clinical significance of these observations lies in the fact that injury-induced depolarizations (e.g., in stroke) propagate along ischemic, but viable, areas adjacent to the damaged core areas, exacerbating the mismatch between blood supply and metabolic demand and thereby worsening the clinical outcome (76, 106). Importantly, age-related alterations in neurovascular coupling pathways significantly increase both the incidence of spreading depolarizations and exacerbate their functional consequences (44, 78, 111, 174).

Perspectives

In the present review we have outlined the current understanding of mechanisms and consequences of age-related impairment of autoregulation of CBF, endothelial dysfunction, and neurovascular uncoupling (Fig. 4). Better understanding the specific age-related cellular and molecular mechanisms that underlie cerebromicrovascular aging is imperative to create usable tools for preventive and therapeutic interventions for age-related cognitive impairment. Future studies should provide answers to a number of critical questions about microvascular dysregulation in VCID. What is the functional role of mitochondrial oxidative stress in microvascular aging? What are the vascular effects of newly discovered mechanisms of aging? How astrocyte phenotype and function are altered in aging? What is the role of dysregulation of glymphatic flow in VCID? What therapeutic interventions are effective to protect the aging glymphatic system? Under what circumstances do perivascular macrophages contribute to cerebromicrovascular dysregulation and the pathogenesis of VCID? In the past

decade significant progress has been made to understand the role of pericyte dysfunction in the pathogenesis of VCID (20, 224, 301, 314, 315). Treatments that target pericytes, preventing/reversing microvascular dysregulation in aging, are needed to be tested. An important area of future research is the link between age-related cerebromicrovascular dysregulation and its role in diffuse white matter disease. The vast majority of previous studies have focused on mainly the somatosensory cortex, whereas age-related microcirculatory alterations in the white matter are less understood. Furthermore, mechanisms involved in autoregulation of CBF and neurovascular coupling are potentially affected by medications used in the elderly. For example, recent studies indicate that widely used, non-steroid anti-inflammatory drugs (NSAIDs), given orally in usual therapeutic doses, inhibit neurovascular coupling in humans (32, 259). A number of drugs (including calcium antagonists) have also the potential to interfere with cerebral autoregulation. Potential cerebrovascular effects of these drugs should be considered in elderly patients, especially in those with advanced atherosclerosis of the arteries supplying the brain, as they may increase the risk of cerebral ischemia. Furthermore, the complex effects of multiple comorbidities and aging (e.g., co-occurrence of hypertension and obesity in geriatric patients with the metabolic syndrome) must be studied simultaneously. Most extant studies investigate the effects of only one disease state in young animal models. To mimic real-life conditions, animal models of aging have to be utilized and interaction of various risk factors has to be elucidated. A critical area for future research will be to develop therapeutic interventions that improve autoregulatory protection of the microcirculation and
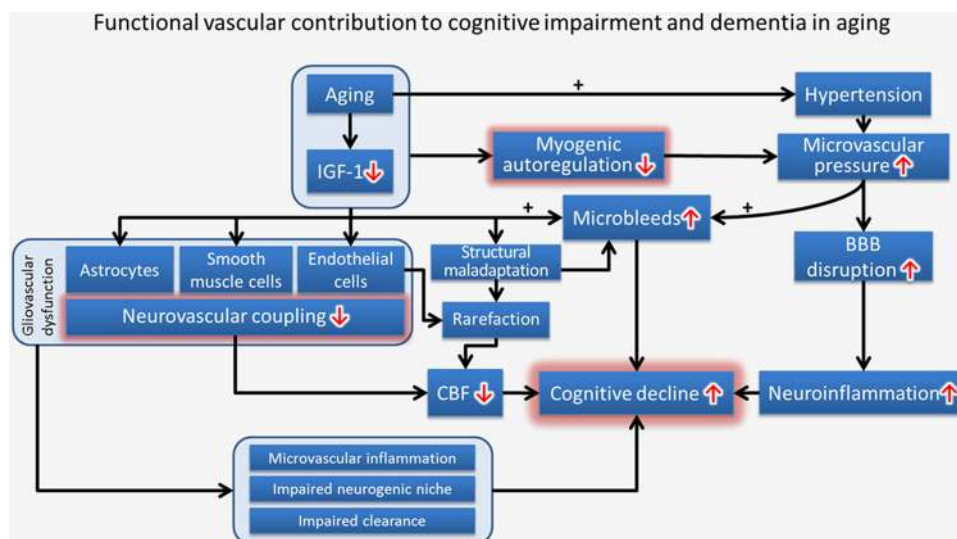

Fig. 4. Functional vascular contributions to cognitive impairment and dementia in aging. The schematic representation illustrates the interrelated microvascular mechanisms that contribute to age-related cognitive decline. The model highlights that age-related IGF-1 deficiency compromises the neurovascular unit, impairing the function of astrocytes, endothelial cells and smooth muscle cells. The resulting endothelial dysfunction and decreased NO bioavailability, increased oxidative stress, and/or dysregulation of astrocytic mediators contribute to neurovascular uncoupling, which impairs cognitive function due to inadequate supply of oxygen and nutrients to active brain regions. Age-related impairment of microvascular homeostasis, including alterations of myogenic autoregulatory mechanisms, renders the aged brain more susceptible to damage induced by comorbid conditions such as hypertension. In particular, the model predicts that impaired myogenic adaptation to hypertension promotes both the pathogenesis of cerebral microhemorrhages and blood-brain-barrier disruption, contributing to neuronal damage and cognitive decline. Aging and age-related IGF-1 deficiency also promote structural remodeling of the cerebral microcirculation, including microvascular rarefaction, contributing to an age-related decline in cerebral blood flow. They also promote structural maladaptation to hypertension, increasing microvascular fragility. Additionally, age-related microvascular proinflammatory alterations, impairment of vascular clearance of toxic waste products (such as Aβ) and metabolic by-products from the brain parenchyma and impaired trophic function of the microvascular endothelium that regulate stem cell self-renewal and differentiation in neurogenic niches could be implicated in impaired cognitive function.

prevent microhemorrhages. Finally, future studies should determine whether interventions that target the microvasculature can prevent and/or reverse cognitive decline associated with aging and age-related pathologies.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

P.T., S.T., A.C., and Z.I.U. conception and design of research; P.T., S.T., A.C., and Z.I.U. prepared figures; P.T., S.T., A.C., and Z.I.U. drafted manuscript; P.T., S.T., A.C., and Z.I.U. edited and revised manuscript; P.T., S.T., A.C., and Z.I.U. approved final version of manuscript.

REFERENCES

1. **Abellan van Kan G, Rolland Y, Andrieu S, Bauer J, Beauchet O, Bonnefoy M, Cesari M, Donini LM, Gillette Guyonnet S, Inzitari M, Nourhashemi F, Onder G, Ritz P, Salva A, Visser M, Vellas B.** Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. *J Nutr Health Aging* 13: 881–889, 2009. doi:10.1007/s12603-009-0246-z.

2. **Adlard PA, Sedjahtera A, Gunawan L, Bray L, Hare D, Lear J, Doble P, Bush AI, Finkelstein DI, Cherny RA.** A novel approach to rapidly prevent age-related cognitive decline. *Aging Cell* 13: 351–359, 2014. doi:10.1111/acel.12178.

3. **Angelini A, Bendini C, Neviani F, Bergamini L, Manni B, Trenti T, Rovati R, Neri M.** Insulin-like growth factor-1 (IGF-1): relation with cognitive functioning and neuroimaging marker of brain damage in a sample of hypertensive elderly subjects. *Arch Gerontol Geriatr* 49, *Suppl* 1: 5–12, 2009. doi:10.1016/j.archger.2009.09.006.

4. **Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA.** Glial and neuronal control of brain blood flow. *Nature* 468: 232–243, 2010. doi:10.1038/nature09613.

5. **Aukes AM, Vitullo L, Zeeman GG, Cipolla MJ.** Pregnancy prevents hypertensive remodeling and decreases myogenic reactivity in posterior cerebral arteries from Dahl salt-sensitive rats: a role in eclampsia? *Am J Physiol Heart Circ Physiol* 292: H1071–H1076, 2007. doi:10.1152/ajpheart.00980.2006.

6. **Austin SA, Santhanam AV, Hinton DJ, Choi DS, Katusic ZS.** Endothelial nitric oxide deficiency promotes Alzheimer's disease pathology. *J Neurochem* 127: 691–700, 2013. doi:10.1111/jnc.12334.

7. **Ayata C.** Spreading depression and neurovascular coupling. *Stroke* 44, *Suppl* 1: S87–S89, 2013. doi:10.1161/STROKEAHA.112.680264.

8. **Ayata C, Lauritzen M.** Spreading depression, spreading depolarizations, and the cerebral vasculature. *Physiol Rev* 95: 953–993, 2015. doi:10.1152/physrev.00027.2014.

9. **Ayata C, Ma J, Meng W, Huang P, Moskowitz MA.** L-NA-sensitive rCBF augmentation during vibrissal stimulation in type III nitric oxide synthase mutant mice. *J Cereb Blood Flow Metab* 16: 539–541, 1996. doi:10.1097/00004647-199607000-00002.

10. **Bagher P, Beleznai T, Kansui Y, Mitchell R, Garland CJ, Dora KA.** Low intravascular pressure activates endothelial cell TRPV4 channels, local Ca^{2+} events, and IKCa channels, reducing arteriolar tone. *Proc Natl Acad Sci USA* 109: 18174–18179, 2012. doi:10.1073/pnas.1211946109.

11. **Bailey-Downs LC, Mitschelen M, Sosnowska D, Toth P, Pinto JT, Ballabh P, Valcarcel-Ares MN, Farley J, Koller A, Henthorn JC, Bass C, Sonntag WE, Ungvari Z, Csiszar A.** Liver-specific knockdown of IGF-1 decreases vascular oxidative stress resistance by impairing the Nrf2-dependent antioxidant response: a novel model of vascular aging. *J Gerontol A Biol Sci Med Sci* 67: 313–329, 2012. doi:10.1093/gerona/glr164.

12. **Bailey-Downs LC, Sosnowska D, Toth P, Mitschelen M, Gautam T, Henthorn JC, Ballabh P, Koller A, Farley JA, Sonntag WE, Csiszar A, Ungvari Z.** Growth hormone and IGF-1 deficiency exacerbate high-fat diet-induced endothelial impairment in obese Lewis dwarf rats: implications for vascular aging. *J Gerontol A Biol Sci Med Sci* 67: 553–564, 2012. doi:10.1093/gerona/glr197.

13. **Balança B, Meiller A, Bezin L, Dreier JP, Marinesco S, Lieutaud T.** Altered hypermetabolic response to cortical spreading depolarizations after traumatic brain injury in rats. *J Cereb Blood Flow Metab* pii: 0271678X16657571, 2016. doi:10.1177/0271678X16657571.

14. **Balbi M, Ghosh M, Longden TA, Jativa Vega M, Gesierich B, Hellal F, Lourbopoulos A, Nelson MT, Plesnila N.** Dysfunction of mouse cerebral arteries during early aging. *J Cereb Blood Flow Metab* 35: 1445–1453, 2015. doi:10.1038/jcbfm.2015.107.

15. **Banki E, Sosnowska D, Tucsek Z, Gautam T, Toth P, Tarantini S, Tamas A, Helyes Z, Reglodi D, Sonntag WE, Csiszar A, Ungvari Z.** Age-related decline of autocrine pituitary adenylate cyclase-activating polypeptide impairs angiogenic capacity of rat cerebromicrovascular endothelial cells. *J Gerontol A Biol Sci Med Sci* 70: 665–674, 2015. doi:10.1093/gerona/glu116.

16. **Barnes JN, Schmidt JE, Nicholson WT, Joyner MJ.** Cyclooxygenase inhibition abolishes age-related differences in cerebral vasodilator responses to hypercapnia. *J Appl Physiol (1985)* 112: 1884–1890, 2012. doi:10.1152/japplphysiol.01270.2011.

17. **Baumbach GL, Dobrin PB, Hart MN, Heistad DD.** Mechanics of cerebral arterioles in hypertensive rats. *Circ Res* 62: 56–64, 1988. doi:10.1161/01.RES.62.1.56.

18. **Baumbach GL, Heistad DD.** Cerebral circulation in chronic arterial hypertension. *Hypertension* 12: 89–95, 1988. doi:10.1161/01.HYP.12.2.89.

19. **Baumbach GL, Heistad DD.** Remodeling of cerebral arterioles in chronic hypertension. *Hypertension* 13: 968–972, 1989. doi:10.1161/01.HYP.13.6.968.

20. **Bell RD, Winkler EA, Sagare AP, Singh I, LaRue B, Deane R, Zlokovic BV.** Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. *Neuron* 68: 409–427, 2010. doi:10.1016/j.neuron.2010.09.043.

21. **Bere Z, Obrenovitch TP, Bari F, Farkas E.** Ischemia-induced depolarizations and associated hemodynamic responses in incomplete global forebrain ischemia in rats. *Neuroscience* 260: 217–226, 2014. doi:10.1016/j.neuroscience.2013.12.032.

22. **Bere Z, Obrenovitch TP, Kozák G, Bari F, Farkas E.** Imaging reveals the focal area of spreading depolarizations and a variety of hemodynamic responses in a rat microembolic stroke model. *J Cereb Blood Flow Metab* 34: 1695–1705, 2014. doi:10.1038/jcbfm.2014.136.

23. **Bergsneider M, Alwan AA, Falkson L, Rubinstein EH.** The relationship of pulsatile cerebrospinal fluid flow to cerebral blood flow and intracranial pressure: a new theoretical model. *Acta Neurochir Suppl* 71: 266–268, 1998.

24. **Berkowitz DE, White R, Li D, Minhas KM, Cernetich A, Kim S, Burke S, Shoukas AA, Nyhan D, Champion HC, Hare JM.** Arginase reciprocally regulates nitric oxide synthase activity and contributes to endothelial dysfunction in aging blood vessels. *Circulation* 108: 2000–2006, 2003. doi:10.1161/01.CIR.0000092948.04444.C7.

25. **Blackwell KA, Sorenson JP, Richardson DM, Smith LA, Suda O, Nath K, Katusic ZS.** Mechanisms of aging-induced impairment of endothelium-dependent relaxation: role of tetrahydrobiopterin. *Am J Physiol Heart Circ Physiol* 287: H2448–H2453, 2004. doi:10.1152/ajpheart.00248.2004.

26. **Bohlen HG, Harper SL.** Evidence of myogenic vascular control in the rat cerebral cortex. *Circ Res* 55: 554–559, 1984. doi:10.1161/01.RES.55.4.554.

27. **Brayden JE, Earley S, Nelson MT, Reading S.** Transient receptor potential (TRP) channels, vascular tone and autoregulation of cerebral blood flow. *Clin Exp Pharmacol Physiol* 35: 1116–1120, 2008. doi:10.1111/j.1440-1681.2007.04855.x.

29. **Brayden JE, Nelson MT.** Regulation of arterial tone by activation of calcium-dependent potassium channels. *Science* 256: 532–535, 1992. doi:10.1126/science.1373909.

30. **Brickman AM, Guzman VA, Gonzalez-Castellon M, Razlighi Q, Gu Y, Narkhede A, Janicki S, Ichise M, Stern Y, Manly JJ, Schupf N, Marshall RS.** Cerebral autoregulation, beta amyloid, and white matter hyperintensities are interrelated. *Neurosci Lett* 592: 54–58, 2015. doi: 10.1016/j.neulet.2015.03.005.

31. **Brown KA, Didion SP, Andresen JJ, Faraci FM.** Effect of aging, MnSOD deficiency, and genetic background on endothelial function: evidence for MnSOD haploinsufficiency. *Arterioscler Thromb Vasc Biol* 27: 1941–1946, 2007. doi:10.1161/ATVBAHA.107.146852.

32. **Bruhn H, Fransson P, Frahm J.** Modulation of cerebral blood oxygenation by indomethacin: MRI at rest and functional brain activation. *J Magn Reson Imaging* 13: 325–334, 2001. doi:10.1002/jmri.1047.

33. **Bryan RM Jr, Marrelli SP, Steenberg ML, Schildmeyer LA, Johnson TD.** Effects of luminal shear stress on cerebral arteries and arterioles. *Am J Physiol Heart Circ Physiol* 280: H2011–H2022, 2001.

34. **Busija DW, Bari F, Domoki F, Louis T.** Mechanisms involved in the cerebrovascular dilator effects of N-methyl-d-aspartate in cerebral cortex. *Brain Res Brain Res Rev* 56: 89–100, 2007. doi:10.1016/j.brainresrev.2007.05.011.

35. **Campbell AJ, Spears GF, Borrie MJ.** Examination by logistic regression modelling of the variables which increase the relative risk of elderly women falling compared to elderly men. *J Clin Epidemiol* 43: 1415–1420, 1990. doi:10.1016/0895-4356(90)90110-B.

36. **Carey BJ, Eames PJ, Blake MJ, Panerai RB, Potter JF.** Dynamic cerebral autoregulation is unaffected by aging. *Stroke* 31: 2895–2900, 2000. doi:10.1161/01.STR.31.12.2895.

37. **Cauli B, Hamel E.** Revisiting the role of neurons in neurovascular coupling. *Front Neuroenergetics* 2: 9, 2010. doi:10.3389/fnene.2010.00009.

38. **Chen BR, Kozberg MG, Bouchard MB, Shaik MA, Hillman EM.** A critical role for the vascular endothelium in functional neurovascular coupling in the brain. *J Am Heart Assoc* 3: e000787, 2014. doi:10.1161/JAHA.114.000787.

39. **Cheng J, Wu CC, Gotlinger KH, Zhang F, Falck JR, Narsimhaswamy D, Schwartzman ML.** 20-Hydroxy-5,8,11,14-eicosatetraenoic acid mediates endothelial dysfunction via IkappaB kinase-dependent endothelial nitric-oxide synthase uncoupling. *J Pharmacol Exp Ther* 332: 57–65, 2010. doi:10.1124/jpet.109.159863.

40. **Cho EB, Shin HY, Park SE, Chun P, Jang HR, Yang JJ, Kim HJ, Kim YJ, Jung NY, Lee JS, Lee J, Jang YK, Jang EY, Kang M, Lee JM, Kim C, Min JH, Ryu S, Na DL, Seo SW.** Albuminuria, cerebrovascular disease and cortical atrophy: among cognitively normal elderly individuals. *Sci Rep* 6: 20692, 2016. doi:10.1038/srep20692.

41. **Cipolla MJ.** *The Cerebral Circulation*. San Rafael, CA: Morgan & Claypool Life Sciences, 2009. 21452434

42. **Cipolla MJ, Gokina NI, Osol G.** Pressure-induced actin polymerization in vascular smooth muscle as a mechanism underlying myogenic behavior. *FASEB J* 16: 72–76, 2002. doi:10.1096/cj.01-0104hyp.

43. **Cipolla MJ, Sweet J, Chan SL, Tavares MJ, Gokina N, Brayden JE.** Increased pressure-induced tone in rat parenchymal arterioles vs. middle cerebral arteries: role of ion channels and calcium sensitivity. *J Appl Physiol (1985)* 117: 53–59, 2014. doi:10.1152/japplphysiol.00253.2014.

44. **Clark D, Institoris A, Kozák G, Bere Z, Tuor U, Farkas E, Bari F.** Impact of aging on spreading depolarizations induced by focal brain ischemia in rats. *Neurobiol Aging* 35: 2803–2811, 2014. doi:10.1016/j.neurobiolaging.2014.06.013.

45. **Cooper LL, Woodard T, Sigurdsson S, van Buchem MA, Torjesen AA, Inker LA, Aspelund T, Eiriksdottir G, Harris TB, Gudnason V, Launer LJ, Mitchell GF.** Cerebrovascular damage mediates relations between aortic stiffness and memory. *Hypertension* 67: 176–182, 2016. doi:10.1161/HYPERTENSIONAHA.115.06398.

46. **Corriveau RA, Bosetti F, Emr M, Gladman JT, Koenig JI, Moy CS, Pahigiannis K, Waddy SP, Koroshetz W.** The science of vascular contributions to cognitive impairment and dementia (VCID): a framework for advancing research priorities in the cerebrovascular biology of cognitive decline. *Cell Mol Neurobiol* 36: 281–288, 2016. doi:10.1007/s10571-016-0334-7.

47. **Csiszar A, Gautam T, Sosnowska D, Tarantini S, Banki E, Tucsek Z, Toth P, Losonczy G, Koller A, Reglodi D, Giles CB, Wren JD, Sonntag WE, Ungvari Z.** Caloric restriction confers persistent antioxidative, pro-angiogenic, and anti-inflammatory effects and promotes anti-aging miRNA expression profile in cerebromicrovascular endothelial cells of aged rats. *Am J Physiol Heart Circ Physiol* 307: H292–H306, 2014. doi:10.1152/ajpheart.00307.2014.

48. **Csiszar A, Labinskyy N, Perez V, Recchia FA, Podlutsky A, Mukhopadhyay P, Losonczy G, Pacher P, Austad SN, Bartke A, Ungvari Z.** Endothelial function and vascular oxidative stress in long-lived GH/IGF-deficient Ames dwarf mice. *Am J Physiol Heart Circ Physiol* 295: H1882–H1894, 2008. doi:10.1152/ajpheart.412.2008.

49. **Csiszar A, Sosnowska D, Wang M, Lakatta EG, Sonntag WE, Ungvari Z.** Age-associated proinflammatory secretory phenotype in vascular smooth muscle cells from the non-human primate Macaca mulatta: reversal by resveratrol treatment. *J Gerontol A Biol Sci Med Sci* 67: 811–820, 2012. doi:10.1093/gerona/glr228.

50. **Csiszar A, Tucsek Z, Toth P, Sosnowska D, Gautam T, Koller A, Deak F, Sonntag WE, Ungvari Z.** Synergistic effects of hypertension and aging on cognitive function and hippocampal expression of genes involved in β-amyloid generation and Alzheimer's disease. *Am J Physiol Heart Circ Physiol* 305: H1120–H1130, 2013. doi:10.1152/ajpheart.00288.2013.

52. **Csiszar A, Ungvari Z, Edwards JG, Kaminski P, Wolin MS, Koller A, Kaley G.** Aging-induced phenotypic changes and oxidative stress impair coronary arteriolar function. *Circ Res* 90: 1159–1166, 2002. doi:10.1161/01.RES.0000020401.61826.EA.

53. **D'Angelo G, Mogford JE, Davis GE, Davis MJ, Meininger GA.** Integrin-mediated reduction in vascular smooth muscle $[Ca^{2+}]_i$ induced by RGD-containing peptide. *Am J Physiol Heart Circ Physiol* 272: H2065–H2070, 1997.

54. **Daulatzai MA.** Cerebral hypoperfusion and glucose hypometabolism: key pathophysiological modulators promote neurodegeneration, cognitive impairment, and Alzheimer's disease. *J Neurosci Res*. 2016. doi:10.1002/jnr.23777.

55. **de Cavanagh EM, Inserra F, Ferder L.** Angiotensin II blockade: how its molecular targets may signal to mitochondria and slow aging. Coincidences with calorie restriction and mTOR inhibition. *Am J Physiol Heart Circ Physiol* 309: H15–H44, 2015. doi:10.1152/ajpheart.00459.2014.

56. **De Reuck JL, Deramecourt V, Auger F, Durieux N, Cordonnier C, Devos D, Defebvre L, Moreau C, Capparos-Lefebvre D, Pasquier F, Leys D, Maurage CA, Bordet R.** The significance of cortical cerebellar microbleeds and microinfarcts in neurodegenerative and cerebrovascular diseases. A post-mortem 7.0-tesla magnetic resonance study with neuropathological correlates. *Cerebrovasc Dis* 39: 138–143, 2015. doi:10.1159/000371488.

57. **De Silva TM, Faraci FM.** Microvascular dysfunction and cognitive impairment. *Cell Mol Neurobiol* 36: 241–258, 2016. doi:10.1007/s10571-015-0308-1.

58. **Deer RR, Stallone JN.** Effects of estrogen on cerebrovascular function: age-dependent shifts from beneficial to detrimental in small cerebral arteries of the rat. *Am J Physiol Heart Circ Physiol* 310: H1285–H1294, 2016. doi:10.1152/ajpheart.00645.2015.

59. **den Abeelen AS, Lagro J, van Beek AH, Claassen JA.** Impaired cerebral autoregulation and vasomotor reactivity in sporadic Alzheimer's disease. *Curr Alzheimer Res* 11: 11–17, 2014. doi:10.2174/1567205010666131119234845.

60. **den Heijer T, Launer LJ, Prins ND, van Dijk EJ, Vermeer SE, Hofman A, Koudstaal PJ, Breteler MM.** Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* 64: 263–267, 2005. doi:10.1212/01.WNL.0000149641.55751.2E.

61. **Di Marco LY, Venneri A, Farkas E, Evans PC, Marzo A, Frangi AF.** Vascular dysfunction in the pathogenesis of Alzheimer's disease—a review of endothelium-mediated mechanisms and ensuing vicious circles. *Neurobiol Dis* 82: 593–606, 2015. doi:10.1016/j.nbd.2015.08.014.

63. **Diaz-Otero JM, Garver H, Fink GD, Jackson WF, Dorrance AM.** Aging is associated with changes to the biomechanical properties of the posterior cerebral artery and parenchymal arterioles. *Am J Physiol Heart Circ Physiol* 310: H365–H375, 2016. doi:10.1152/ajpheart.00562.2015.

64. **Díaz-Ruiz C, Wang J, Ksiezak-Reding H, Ho L, Qian X, Humala N, Thomas S, Martínez-Martín P, Pasinetti GM.** Role of hypertension in aggravating Abeta neuropathology of AD type and tau-mediated motor impairment. *Cardiovasc Psychiatry Neurol* 2009: 107286, 2009. doi:10.1155/2009/107286.

65. **Dreier JP.** The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. *Nat Med* 17: 439–447, 2011. doi:10.1038/nm.2333.

66. **Dreier JP, Drenckhahn C, Woitzik J, Major S, Offenhauser N, Weber-Carstens S, Wolf S, Strong AJ, Vajkoczy P, Hartings JA;**

COSBID Study Group. Spreading ischemia after aneurysmal subarachnoid hemorrhage. *Acta Neurochir Suppl* 115: 125–129, 2013.

67. **Dreier JP, Fabricius M, Ayata C, Sakowitz OW, William Shuttleworth C, Dohmen C, Graf R, Vajkoczy P, Helbok R, Suzuki M, Schiefecker AJ, Major S, Winkler MK, Kang EJ, Milakara D, Oliveira-Ferreira AI, Reiffurth C, Revankar GS, Sugimoto K, Dengler NF, Hecht N, Foreman B, Feyen B, Kondziella D, Friberg CK, Piilgaard H, Rosenthal ES, Westover MB, Maslarova A, Santos E, Hertle D, Sánchez-Porras R, Jewell SL, Balança B, Platz J, Hinzman JM, Lückl J, Schoknecht K, Schöll M, Drenckhahn C, Feuerstein D, Eriksen N, Horst V, Bretz JS, Jahnke P, Scheel M, Bohner G, Rostrup E, Pakkenberg B, Heinemann U, Claassen J, Carlson AP, Kowoll CM, Lublinsky S, Chassidim Y, Shelef I, Friedman A, Brinker G, Reiner M, Kirov SA, Andrew RD, Farkas E, Güresir E, Vatter H, Chung LS, Brennan KC, Lieutaud T, Marinesco S, Maas AI, Sahuquillo J, Dahlem MA, Richter F, Herreras O, Boutelle MG, Okonkwo DO, Bullock MR, Witte OW, Martus P, van den Maagdenberg AM, Ferrari MD, Dijkhuizen RM, Shutter LA, Andaluz N, Schulte AP, MacVicar B, Watanabe T, Woitzik J, Lauritzen M, Strong AJ, Hartings JA.** Recording, analysis, and interpretation of spreading depolarizations in neurointensive care: review and recommendations of the COSBID research group. *J Cereb Blood Flow Metab* pii: 0271678X16654496, 2016. doi:10.1177/0271678X16654496.

68. **Dunn KM, Renic M, Flasch AK, Harder DR, Falck J, Roman RJ.** Elevated production of 20-HETE in the cerebral vasculature contributes to severity of ischemic stroke and oxidative stress in spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol* 295: H2455–H2465, 2008. doi:10.1152/ajpheart.00512.2008.

69. **Enager P, Piilgaard H, Offenhauser N, Kocharyan A, Fernandes P, Hamel E, Lauritzen M.** Pathway-specific variations in neurovascular and neurometabolic coupling in rat primary somatosensory cortex. *J Cereb Blood Flow Metab* 29: 976–986, 2009. doi:10.1038/jcbfm.2009.23.

70. **Fabiani M, Gordon BA, Maclin EL, Pearson MA, Brumback-Peltz CR, Low KA, McAuley E, Sutton BP, Kramer AF, Gratton G.** Neurovascular coupling in normal aging: a combined optical, ERP and fMRI study. *Neuroimage* 85: 592–607, 2014.

71. **Fan F, Geurts AM, Murphy SR, Pabbidi MR, Jacob HJ, Roman RJ.** Impaired myogenic response and autoregulation of cerebral blood flow is rescued in CYP4A1 transgenic Dahl salt-sensitive rat. *Am J Physiol Regul Integr Comp Physiol* 308: R379–R390, 2015. doi:10.1152/ajpregu.00256.2014.

72. **Faraci FM, Baumbach GL, Heistad DD.** Myogenic mechanisms in the cerebral circulation. *J Hypertens Suppl* 7: S61–S64; discussion S65, 1989.

73. **Faraci FM, Heistad DD.** Regulation of large cerebral arteries and cerebral microvascular pressure. *Circ Res* 66: 8–17, 1990. doi:10.1161/01.RES.66.1.8.

74. **Faraco G, Iadecola C.** Hypertension: a harbinger of stroke and dementia. *Hypertension* 62: 810–817, 2013. doi:10.1161/HYPERTENSIONAHA.113.01063.

75. **Faraco G, Park L, Zhou P, Luo W, Paul SM, Anrather J, Iadecola C.** Hypertension enhances Aβ-induced neurovascular dysfunction, promotes β-secretase activity, and leads to amyloidogenic processing of APP. *J Cereb Blood Flow Metab* 36: 241–252, 2016. doi:10.1038/jcbfm.2015.79.

76. **Farkas E, Bari F.** Spreading depolarization in the ischemic brain: does aging have an impact? *J Gerontol A Biol Sci Med Sci* 69: 1363–1370, 2014. doi:10.1093/gerona/glu066.

77. **Farkas E, De Jong GI, Apró E, De Vos RA, Steur EN, Luiten PG.** Similar ultrastructural breakdown of cerebrocortical capillaries in Alzheimer's disease, Parkinson's disease, and experimental hypertension. What is the functional link? *Ann N Y Acad Sci* 903: 72–82, 2000. doi:10.1111/j.1749-6632.2000.tb06352.x.

78. **Farkas E, Obrenovitch TP, Institóris Á, Bari F.** Effects of early aging and cerebral hypoperfusion on spreading depression in rats. *Neurobiol Aging* 32: 1707–1715, 2011. doi:10.1016/j.neurobiolaging.2009.10.002.

79. **Fernandes J, Lorenzo IM, Andrade YN, Garcia-Elias A, Serra SA, Fernández-Fernández JM, Valverde MA.** IP3 sensitizes TRPV4 channel to the mechano- and osmotransducing messenger 5′-6′-epoxyeicosatrienoic acid. *J Cell Biol* 181: 143–155, 2008. doi:10.1083/jcb.200712058.

80. **Fields LE, Burt VL, Cutler JA, Hughes J, Roccella EJ, Sorlie P.** The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension* 44: 398–404, 2004. doi:10.1161/01.HYP.0000142248.54761.56.

81. **Filosa JA, Bonev AD, Straub SV, Meredith AL, Wilkerson MK, Aldrich RW, Nelson MT.** Local potassium signaling couples neuronal activity to vasodilation in the brain. *Nat Neurosci* 9: 1397–1403, 2006. doi:10.1038/nn1779.

82. **Flavahan S, Chang F, Flavahan NA.** Local renin-angiotensin system mediates endothelial dilator dysfunction in aging arteries. *Am J Physiol Heart Circ Physiol* 311: H849–H854, 2016. doi:10.1152/ajpheart.00422.2016.

83. **Fog M.** The relationship between the blood pressure and the tonic regulation of the pial arteries. *J Neurol Psychiatry* 1: 187–197, 1938. doi:10.1136/jnnp.1.3.187.

84. **Forbes HS.** Regulation of the cerebral vessels; new aspects. *AMA Arch Neurol Psychiatry* 80: 689–695, 1958. doi:10.1001/archneurpsyc.1958.02340120025004.

85. **Forette F, Seux ML, Staessen JA, Thijs L, Birkenhäger WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R.** Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 352: 1347–1351, 1998. doi:10.1016/S0140-6736(98)03086-4.

86. **Fujii K, Heistad DD, Faraci FM.** Effect of diabetes mellitus on flow-mediated and endothelium-dependent dilatation of the rat basilar artery. *Stroke* 23: 1494–1498, 1992. doi:10.1161/01.STR.23.10.1494.

87. **Fujishima M, Sadoshima S, Ogata J, Yoshida F, Shiokawa O, Ibayashi S, Omae T.** Autoregulation of cerebral blood flow in young and aged spontaneously hypertensive rats (SHR). *Gerontology* 30: 30–36, 1984. doi:10.1159/000212604.

88. **Furchgott RF, Vanhoutte PM.** Endothelium-derived relaxing and contracting factors. *FASEB J* 3: 2007–2018, 1989.

89. **Gano LB, Donato AJ, Pasha HM, Hearon CM Jr, Sindler AL, Seals DR.** The SIRT1 activator SRT1720 reverses vascular endothelial dysfunction, excessive superoxide production, and inflammation with aging in mice. *Am J Physiol Heart Circ Physiol* 307: H1754–H1763, 2014. doi:10.1152/ajpheart.00377.2014.

90. **Garcia-Roldan JL, Bevan JA.** Augmentation of endothelium-independent flow constriction in pial arteries at high intravascular pressures. *Hypertension* 17: 870–874, 1991. doi:10.1161/01.HYP.17.6.870.

91. **Garcia-Roldan JL, Bevan JA.** Flow-induced constriction and dilation of cerebral resistance arteries. *Circ Res* 66: 1445–1448, 1990. doi:10.1161/01.RES.66.5.1445.

92. **Ge Y, Murphy SR, Fan F, Williams JM, Falck JR, Liu R, Roman RJ.** Role of 20-HETE in the impaired myogenic and TGF responses of the Af-Art of Dahl salt-sensitive rats. *Am J Physiol Renal Physiol* 307: F509–F515, 2014. doi:10.1152/ajprenal.00273.2014.

93. **Gebremedhin D, Lange AR, Lowry TF, Taheri MR, Birks EK, Hudetz AG, Narayanan J, Falck JR, Okamoto H, Roman RJ, Nithipatikom K, Campbell WB, Harder DR.** Production of 20-HETE and its role in autoregulation of cerebral blood flow. *Circ Res* 87: 60–65, 2000. doi:10.1161/01.RES.87.1.60.

94. **Gelber RP, Launer LJ, White LR.** The Honolulu-Asia Aging Study: epidemiologic and neuropathologic research on cognitive impairment. *Curr Alzheimer Res* 9: 664–672, 2012. doi:10.2174/156720512801322618.

95. **Girouard H, Park L, Anrather J, Zhou P, Iadecola C.** Cerebrovascular nitrosative stress mediates neurovascular and endothelial dysfunction induced by angiotensin II. *Arterioscler Thromb Vasc Biol* 27: 303–309, 2007. doi:10.1161/01.ATV.0000253885.41509.25.

96. **Gokina NI, Knot HJ, Nelson MT, Osol G.** Increased Ca^{2+} sensitivity as a key mechanism of PKC-induced constriction in pressurized cerebral arteries. *Am J Physiol Heart Circ Physiol* 277: H1178–H1188, 1999.

97. **Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S; American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia.** Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke* 42: 2672–2713, 2011. doi:10.1161/STR.0b013e3182299496.

99. **Hajdu MA, Heistad DD, Siems JE, Baumbach GL.** Effects of aging on mechanics and composition of cerebral arterioles in rats. *Circ Res* 66: 1747–1754, 1990. doi:10.1161/01.RES.66.6.1747.

100. **Hall CN, Reynell C, Gesslein B, Hamilton NB, Mishra A, Sutherland BA, O'Farrell FM, Buchan AM, Lauritzen M, Attwell D.** Capillary pericytes regulate cerebral blood flow in health and disease. *Nature* 508: 55–60, 2014. doi:10.1038/nature13165.

101. **Halpern W, Osol G.** Influence of transmural pressure of myogenic responses of isolated cerebral arteries of the rat. *Ann Biomed Eng* 13: 287–293, 1985. doi:10.1007/BF02584246.

102. **Harder DR, Narayanan J, Gebremedhin D.** Pressure-induced myogenic tone and role of 20-HETE in mediating autoregulation of cerebral blood flow. *Am J Physiol Heart Circ Physiol* 300: H1557–H1565, 2011. doi:10.1152/ajpheart.01097.2010.

103. **Harper SL, Bohlen HG.** Microvascular adaptation in the cerebral cortex of adult spontaneously hypertensive rats. *Hypertension* 6: 408–419, 1984. doi:10.1161/01.HYP.6.3.408.

104. **Harper SL, Bohlen HG, Rubin MJ.** Arterial and microvascular contributions to cerebral cortical autoregulation in rats. *Am J Physiol Heart Circ Physiol* 246: H17–H24, 1984.

105. **Hartings JA, Bullock MR, Okonkwo DO, Murray LS, Murray GD, Fabricius M, Maas AI, Woitzik J, Sakowitz O, Mathern B, Roozenbeek B, Lingsma H, Dreier JP, Puccio AM, Shutter LA, Pahl C, Strong AJ; Co-Operative Study on Brain Injury Depolarisations.** Spreading depolarisations and outcome after traumatic brain injury: a prospective observational study. *Lancet Neurol* 10: 1058–1064, 2011. doi:10.1016/S1474-4422(11)70243-5.

106. **Hartings JA, Shuttleworth CW, Kirov SA, Ayata C, Hinzman JM, Foreman B, Andrew RD, Boutelle MG, Brennan KC, Carlson AP, Dahlem MA, Drenckhahn C, Dohmen C, Fabricius M, Farkas E, Feuerstein D, Graf R, Helbok R, Lauritzen M, Major S, Oliveira-Ferreira AI, Richter F, Rosenthal ES, Sakowitz OW, Sánchez-Porras R, Santos E, Schöll M, Strong AJ, Urbach A, Westover MB, Winkler MK, Witte OW, Woitzik J, Dreier JP.** The continuum of spreading depolarizations in acute cortical lesion development: examining Leão's legacy. *J Cereb Blood Flow Metab* pii: 0271678X16654495, 2016. doi:10.1177/0271678X16654495.

107. **Hartings JA, Wilson JA, Hinzman JM, Pollandt S, Dreier JP, DiNapoli V, Ficker DM, Shutter LA, Andaluz N.** Spreading depression in continuous electroencephalography of brain trauma. *Ann Neurol* 76: 681–694, 2014. doi:10.1002/ana.24256.

108. **Hashimoto J, Ito S.** Central pulse pressure and aortic stiffness determine renal hemodynamics: pathophysiological implication for microalbuminuria in hypertension. *Hypertension* 58: 839–846, 2011. doi:10.1161/HYPERTENSIONAHA.111.177469.

109. **Hatake K, Kakishita E, Wakabayashi I, Sakiyama N, Hishida S.** Effect of aging on endothelium-dependent vascular relaxation of isolated human basilar artery to thrombin and bradykinin. *Stroke* 21: 1039–1043, 1990. doi:10.1161/01.STR.21.7.1039.

110. **Heckmann JG, Brown CM, Cheregi M, Hilz MJ, Neundörfer B.** Delayed cerebrovascular autoregulatory response to ergometer exercise in normotensive elderly humans. *Cerebrovasc Dis* 16: 423–429, 2003. doi:10.1159/000072567.

111. **Hertelendy P, Menyhárt Á, Makra P, Süle Z, Kiss T, Tóth G, Ivánkovits-Kiss O, Bari F, Farkas E.** Advancing age and ischemia elevate the electric threshold to elicit spreading depolarization in the cerebral cortex of young adult rats. *J Cereb Blood Flow* pii: 0271678X16643735, 2016.

112. **Hinzman JM, Andaluz N, Shutter LA, Okonkwo DO, Pahl C, Strong AJ, Dreier JP, Hartings JA.** Inverse neurovascular coupling to cortical spreading depolarizations in severe brain trauma. *Brain* 137: 2960–2972, 2014. doi:10.1093/brain/awu241.

113. **Hock C, Villringer K, Müller-Spahn F, Wenzel R, Heekeren H, Schuh-Hofer S, Hofmann M, Minoshima S, Schwaiger M, Dirnagl U, Villringer A.** Decrease in parietal cerebral hemoglobin oxygenation during performance of a verbal fluency task in patients with Alzheimer's disease monitored by means of near-infrared spectroscopy (NIRS)--correlation with simultaneous rCBF-PET measurements. *Brain Res* 755: 293–303, 1997. doi:10.1016/S0006-8993(97)00122-4.

114. **Hoffman LB, Schmeidler J, Lesser GT, Beeri MS, Purohit DP, Grossman HT, Haroutunian V.** Less Alzheimer disease neuropathology in medicated hypertensive than nonhypertensive persons. *Neurology* 72: 1720–1726, 2009. doi:10.1212/01.wnl.0000345881.82856.d5.

115. **Hoffman WE, Albrecht RF, Miletich DJ.** The influence of aging and hypertension on cerebral autoregulation. *Brain Res* 214: 196–199, 1981. doi:10.1016/0006-8993(81)90454-6.

116. **Hongo K, Nakagomi T, Kassell NF, Sasaki T, Lehman M, Vollmer DG, Tsukahara T, Ogawa H, Torner J.** Effects of aging and hypertension on endothelium-dependent vascular relaxation in rat carotid artery. *Stroke* 19: 892–897, 1988. doi:10.1161/01.STR.19.7.892.

117. **Hortobágyi L, Kis B, Hrabák A, Horváth B, Huszty G, Schweer H, Benyó B, Sándor P, Busija DW, Benyó Z.** Adaptation of the hypothalamic blood flow to chronic nitric oxide deficiency is independent of vasodilator prostanoids. *Brain Res* 1131: 129–137, 2007. doi:10.1016/j.brainres.2006.11.009.

118. **Iadecola C.** Hypertension and dementia. *Hypertension* 64: 3–5, 2014. doi:10.1161/HYPERTENSIONAHA.114.03040.

119. **Iadecola C.** The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. *Acta Neuropathol* 120: 287–296, 2010. doi:10.1007/s00401-010-0718-6.

120. **Iadecola C.** The pathobiology of vascular dementia. *Neuron* 80: 844–866, 2013. doi:10.1016/j.neuron.2013.10.008.

121. **Iadecola C, Davisson RL.** Hypertension and cerebrovascular dysfunction. *Cell Metab* 7: 476–484, 2008. doi:10.1016/j.cmet.2008.03.010.

122. **Iadecola C, Park L, Capone C.** Threats to the mind: aging, amyloid, and hypertension. *Stroke* 40, *Suppl*: S40–S44, 2009. doi:10.1161/STROKEAHA.108.533638.

123. **Ighodaro ET, Abner EL, Fardo DW, Lin AL, Katsumata Y, Schmitt FA, Kryscio RJ, Jicha GA, Neltner JH, Monsell SE, Kukull WA, Moser DK, Appiah F, Bachstetter AD, Van Eldik LJ, Alzheimer's Disease Neuroimaging Initiative (ADNI), Nelson PT.** Risk factors and global cognitive status related to brain arteriolosclerosis in elderly individuals. *J Cereb Blood Flow Metab* pii: 0271678X16643735, 2016. 10.1177/0271678X15621574.

124. **Inaba M, White L, Bell C, Chen R, Petrovitch H, Launer L, Abbott RD, Ross GW, Masaki K.** White matter lesions on brain magnetic resonance imaging scan and 5-year cognitive decline: the Honolulu-Asia aging study. *J Am Geriatr Soc* 59: 1484–1489, 2011. doi:10.1111/j.1532-5415.2011.03490.x.

125. **Israeli-Korn SD, Masarwa M, Schechtman E, Abuful A, Strugatsky R, Avni S, Farrer LA, Friedland RP, Inzelberg R.** Hypertension increases the probability of Alzheimer's disease and of mild cognitive impairment in an Arab community in northern Israel. *Neuroepidemiology* 34: 99–105, 2010. doi:10.1159/000264828.

126. **Ivanov AI, Malkov AE, Waseem T, Mukhtarov M, Buldakova S, Gubkina O, Zilberter M, Zilberter Y.** Glycolysis and oxidative phosphorylation in neurons and astrocytes during network activity in hippocampal slices. *J Cereb Blood Flow Metab* 34: 397–407, 2014. doi:10.1038/jcbfm.2013.222.

127. **Janik R, Thomason LA, Chaudhary S, Dorr A, Scouten A, Schwindt G, Masellis M, Stanisz GJ, Black SE, Stefanovic B.** Attenuation of functional hyperemia to visual stimulation in mild Alzheimer's disease and its sensitivity to cholinesterase inhibition. *Biochim Biophys Acta* 1862: 957–965, 2016. doi:10.1016/j.bbadis.2015.10.023.

128. **Jessen NA, Munk AS, Lundgaard I, Nedergaard M.** The glymphatic system: a beginner's guide. *Neurochem Res* 40: 2583–2599, 2015. doi:10.1007/s11064-015-1581-6.

129. **Jessen SB, Mathiesen C, Lind BL, Lauritzen M.** Interneuron deficit associates attenuated network synchronization to mismatch of energy supply and demand in aging mouse brains. *Cereb Cortex* pii: bhv261, 2015.

130. **Johnsen SP, Hundborg HH, Sørensen HT, Orskov H, Tjønneland A, Overvad K, Jørgensen JO.** Insulin-like growth factor (IGF) I, -II, and IGF binding protein-3 and risk of ischemic stroke. *J Clin Endocrinol Metab* 90: 5937–5941, 2005. doi:10.1210/jc.2004-2088.

131. **Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K.** Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation* 107: 1401–1406, 2003. doi:10.1161/01.CIR.0000056521.67546.AA.

132. **Katakam PV, Gordon AO, Sure VN, Rutkai I, Busija DW.** Diversity of mitochondria-dependent dilator mechanisms in vascular smooth muscle of cerebral arteries from normal and insulin-resistant rats. *Am J Physiol Heart Circ Physiol* 307: H493–H503, 2014. doi:10.1152/ajpheart.00091.2014.

133. **Katakam PV, Snipes JA, Steed MM, Busija DW.** Insulin-induced generation of reactive oxygen species and uncoupling of nitric oxide

synthase underlie the cerebrovascular insulin resistance in obese rats. *J Cereb Blood Flow Metab* 32: 792–804, 2012. doi:10.1038/jcbfm.2011.181.

134. **Katusic ZS.** Mechanisms of endothelial dysfunction induced by aging: role of arginase I. *Circ Res* 101: 640–641, 2007. doi:10.1161/CIRCRESAHA.107.162701.

135. **Katusic ZS, Austin SA.** Endothelial nitric oxide: protector of a healthy mind. *Eur Heart J* 35: 888–894, 2014. doi:10.1093/eurheartj/eht544.

136. **Katusic ZS, Austin SA.** Neurovascular protective function of endothelial nitric oxide–recent advances. *Circ J* 80: 1499–1503, 2016. doi:10.1253/circj.CJ-16-0423.

137. **Keleshian VL, Modi HR, Rapoport SI, Rao JS.** Aging is associated with altered inflammatory, arachidonic acid cascade, and synaptic markers, influenced by epigenetic modifications, in the human frontal cortex. *J Neurochem* 125: 63–73, 2013. doi:10.1111/jnc.12153.

138. **Kemper TL, Blatt GJ, Killiany RJ, Moss MB.** Neuropathology of progressive cognitive decline in chronically hypertensive rhesus monkeys. *Acta Neuropathol* 101: 145–153, 2001.

139. **Kim YJ, Kwon HK, Lee JM, Cho H, Kim HJ, Park HK, Jung NY, San Lee J, Lee J, Jang YK, Kim ST, Lee KH, Choe YS, Kim YJ, Na DL, Seo SW.** Gray and white matter changes linking cerebral small vessel disease to gait disturbances. *Neurology* 86: 1199–1207, 2016. doi:10.1212/WNL.0000000000002516.

140. **Kim YS, Bogert LW, Immink RV, Harms MP, Colier WN, van Lieshout JJ.** Effects of aging on the cerebrovascular orthostatic response. *Neurobiol Aging* 32: 344–353, 2011. doi:10.1016/j.neurobiolaging.2009.02.019.

141. **Kimbrough IF, Robel S, Roberson ED, Sontheimer H.** Vascular amyloidosis impairs the gliovascular unit in a mouse model of Alzheimer's disease. *Brain* 138: 3716–3733, 2015. doi:10.1093/brain/awv327.

142. **Knot HJ, Nelson MT.** Regulation of arterial diameter and wall $[Ca^{2+}]$ in cerebral arteries of rat by membrane potential and intravascular pressure. *J Physiol* 508: 199–209, 1998. doi:10.1111/j.1469-7793.1998.199br.x.

143. **Knot HJ, Nelson MT.** Regulation of membrane potential and diameter by voltage-dependent K^+ channels in rabbit myogenic cerebral arteries. *Am J Physiol Heart Circ Physiol* 269: H348–H355, 1995.

144. **Knot HJ, Standen NB, Nelson MT.** Ryanodine receptors regulate arterial diameter and wall $[Ca^{2+}]$ in cerebral arteries of rat via Ca^{2+}-dependent K^+ channels. *J Physiol* 508: 211–221, 1998. doi:10.1111/j.1469-7793.1998.211br.x.

145. **Koller A, Toth P.** Contribution of flow-dependent vasomotor mechanisms to the autoregulation of cerebral blood flow. *J Vasc Res* 49: 375–389, 2012. doi:10.1159/000338747.

147. **Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL Jr.** Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *Am J Physiol Heart Circ Physiol* 234: H371–H383, 1978.

148. **Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, Xie L, Kang H, Xu Q, Liew JA, Plog BA, Ding F, Deane R, Nedergaard M.** Impairment of paravascular clearance pathways in the aging brain. *Ann Neurol* 76: 845–861, 2014. doi:10.1002/ana.24271.

149. **La Favor JD, Kraus RM, Carrithers JA, Roseno SL, Gavin TP, Hickner RC.** Sex differences with aging in nutritive skeletal muscle blood flow: impact of exercise training, nitric oxide, and α-adrenergic-mediated mechanisms. *Am J Physiol Heart Circ Physiol* 307: H524–H532, 2014. doi:10.1152/ajpheart.00247.2014.

150. **Lakatta EG, Levy D.** Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation* 107: 139–146, 2003. doi:10.1161/01.CIR.0000048892.83521.58.

151. **Laron Z, Klinger B, Silbergeld A.** Patients with Laron syndrome have osteopenia/osteoporosis. *J Bone Miner Res* 14: 156–157, 1999. doi:10.1359/jbmr.1999.14.1.156.

152. **Lartaud I, Bray-des-Boscs L, Chillon JM, Atkinson J, Capdeville-Atkinson C.** In vivo cerebrovascular reactivity in Wistar and Fischer 344 rat strains during aging. *Am J PhysiolHeart Circ Physiol* 264: H851–H858, 1993.

153. **Lassen NA.** Autoregulation of cerebral blood flow. *Circ Res* 15, *Suppl*: 201–204, 1964.

154. **Lipsitz LA, Mukai S, Hamner J, Gagnon M, Babikian V.** Dynamic regulation of middle cerebral artery blood flow velocity in aging and hypertension. *Stroke* 31: 1897–1903, 2000. doi:10.1161/01.STR.31.8.1897.

155. **Liu GS, Zhang ZS, Yang B, He W.** Resveratrol attenuates oxidative damage and ameliorates cognitive impairment in the brain of senescence-accelerated mice. *Life Sci* 91: 872–877, 2012. doi:10.1016/j.lfs.2012.08.033.

156. **Liu J, Tseng BY, Khan MA, Tarumi T, Hill C, Mirshams N, Hodics TM, Hynan LS, Zhang R.** Individual variability of cerebral autoregulation, posterior cerebral circulation and white matter hyperintensity. *J Physiol* 594: 3141–3155, 2016. doi:10.1113/JP271068.

157. **Liu X, Li C, Falck JR, Roman RJ, Harder DR, Koehler RC.** Interaction of nitric oxide, 20-HETE, and EETs during functional hyperemia in whisker barrel cortex. *Am J Physiol Heart Circ Physiol* 295: H619–H631, 2008. doi:10.1152/ajpheart.01211.2007.

158. **Liu X, Li C, Gebremedhin D, Hwang SH, Hammock BD, Falck JR, Roman RJ, Harder DR, Koehler RC.** Epoxyeicosatrienoic acid-dependent cerebral vasodilation evoked by metabotropic glutamate receptor activation in vivo. *Am J Physiol Heart Circ Physiol* 301: H373–H381, 2011. doi:10.1152/ajpheart.00745.2010.

159. **Longden T, Nelson M.** Recruitment of the vascular endothelium into neurovascular coupling. *Proc Br Pharmacol Soc* 9: 062P, 2011.

160. **Lucas RA, Cotter JD, Morrison S, Ainslie PN.** The effects of ageing and passive heating on cardiorespiratory and cerebrovascular responses to orthostatic stress in humans. *Exp Physiol* 93: 1104–1117, 2008. doi:10.1113/expphysiol.2008.042580.

161. **Lückl J, Dreier JP, Szabados T, Wiesenthal D, Bari F, Greenberg JH.** Peri-infarct flow transients predict outcome in rat focal brain ischemia. *Neuroscience* 226: 197–207, 2012. doi:10.1016/j.neuroscience.2012.08.049.

162. **Ma J, Ayata C, Huang PL, Fishman MC, Moskowitz MA.** Regional cerebral blood flow response to vibrissal stimulation in mice lacking type I NOS gene expression. *Am J Physiol Heart Circ Physiol* 270: H1085–H1090, 1996.

163. **Madden JA, Christman NJ.** Integrin signaling, free radicals, and tyrosine kinase mediate flow constriction in isolated cerebral arteries. *Am J Physiol Heart Circ Physiol* 277: H2264–H2271, 1999.

164. **Mathiesen C, Brazhe A, Thomsen K, Lauritzen M.** Spontaneous calcium waves in Bergman glia increase with age and hypoxia and may reduce tissue oxygen. *J Cereb Blood Flow Metab* 33: 161–169, 2013. doi:10.1038/jcbfm.2012.175.

165. **Mathiesen C, Caesar K, Akgören N, Lauritzen M.** Modification of activity-dependent increases of cerebral blood flow by excitatory synaptic activity and spikes in rat cerebellar cortex. *J Physiol* 512: 555–566, 1998. doi:10.1111/j.1469-7793.1998.555be.x.

166. **Mayhan WG, Faraci FM, Baumbach GL, Heistad DD.** Effects of aging on responses of cerebral arterioles. *Am J Physiol Heart Circ Physiol* 258: H1138–H1143, 1990.

168. **Mayhan WG, Werber AH, Heistad DD.** Protection of cerebral vessels by sympathetic nerves and vascular hypertrophy. *Circulation* 75: I107–I112, 1987.

169. **McGuinness B, Todd S, Passmore P, Bullock R.** Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev* 4: CD004034, 2009. doi:10.1002/14651858.CD004034.pub3.

170. **Mchedlishvili G.** Physiological mechanisms controlling cerebral blood flow. *Stroke* 11: 240–248, 1980. doi:10.1161/01.STR.11.3.240.

171. **Mchedlishvili GI, Mitagvaria NP, Ormotsadze LG.** Vascular mechanisms controlling a constant blood supply to the brain ("autoregulation"). *Stroke* 4: 742–750, 1973. doi:10.1161/01.STR.4.5.742.

172. **Mehagnoul-Schipper DJ, Vloet LC, Colier WN, Hoefnagels WH, Jansen RW.** Cerebral oxygenation declines in healthy elderly subjects in response to assuming the upright position. *Stroke* 31: 1615–1620, 2000. doi:10.1161/01.STR.31.7.1615.

173. **Mellander S.** Functional aspects of myogenic vascular control. *J Hypertens Suppl* 7: S21–S30; discussion S31, 1989.

174. **Menyhárt Á, Makra P, Szepes BE, Tóth OM, Hertelendy P, Bari F, Farkas E.** High incidence of adverse cerebral blood flow responses to spreading depolarization in the aged ischemic rat brain. *Neurobiol Aging* 36: 3269–3277, 2015. doi:10.1016/j.neurobiolaging.2015.08.014.

175. **Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ.** Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. *Brain* 134: 3398–3407, 2011. doi:10.1093/brain/awr253.

176. **Modrick ML, Didion SP, Sigmund CD, Faraci FM.** Role of oxidative stress and AT$_1$ receptors in cerebral vascular dysfunction with aging. *Am*

J Physiol Heart Circ Physiol 296: H1914–H1919, 2009. doi:10.1152/ajpheart.00300.2009.

177. **Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, Toga AW, Jacobs RE, Liu CY, Amezcua L, Harrington MG, Chui HC, Law M, Zlokovic BV.** Blood-brain barrier breakdown in the aging human hippocampus. *Neuron* 85: 296–302, 2015. doi:10.1016/j.neuron.2014.12.032.

178. **Moss MB, Jonak E.** Cerebrovascular disease and dementia: a primate model of hypertension and cognition. *Alzheimers Dement* 3, *Suppl*: S6–S15, 2007. doi:10.1016/j.jalz.2007.01.002.

179. **Mueller SM, Heistad DD.** Effect of chronic hypertension on the blood-brain barrier. *Hypertension* 2: 809–812, 1980. doi:10.1161/01.HYP.2.6.809.

180. **Mueller SM, Heistad DD, Marcus ML.** Total and regional cerebral blood flow during hypotension, hypertension, and hypocapnia. Effect of sympathetic denervation in dogs. *Circ Res* 41: 350–356, 1977. doi:10.1161/01.RES.41.3.350.

181. **Narayanan K, Collins JJ, Hamner J, Mukai S, Lipsitz LA.** Predicting cerebral blood flow response to orthostatic stress from resting dynamics: effects of healthy aging. *Am J Physiol Regul Integr Comp Physiol* 281: R716–R722, 2001.

182. **Nelson JW, Young JM, Borkar RN, Woltjer RL, Quinn JF, Silbert LC, Grafe MR, Alkayed NJ.** Role of soluble epoxide hydrolase in age-related vascular cognitive decline. *Prostaglandins Other Lipid Mediat* 113-115: 30–37, 2014. doi:10.1016/j.prostaglandins.2014.09.003.

183. **Nelson MT, Conway MA, Knot HJ, Brayden JE.** Chloride channel blockers inhibit myogenic tone in rat cerebral arteries. *J Physiol* 502: 259–264, 1997. doi:10.1111/j.1469-7793.1997.259bk.x.

184. **Nevitt C, McKenzie G, Christian K, Austin J, Hencke S, Hoying J, LeBlanc A.** Physiological levels of thrombospondin-1 decrease NO-dependent vasodilation in coronary microvessels from aged rats. *Am J Physiol Heart Circ Physiol* 310: H1842–H1850, 2016. doi:10.1152/ajpheart.00086.2016.

185. **New DI, Chesser AM, Thuraisingham RC, Yaqoob MM.** Cerebral artery responses to pressure and flow in uremic hypertensive and spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol* 284: H1212–H1216, 2003. doi:10.1152/ajpheart.00644.2002.

186. **Nicolakakis N, Aboulkassim T, Ongali B, Lecrux C, Fernandes P, Rosa-Neto P, Tong XK, Hamel E.** Complete rescue of cerebrovascular function in aged Alzheimer's disease transgenic mice by antioxidants and pioglitazone, a peroxisome proliferator-activated receptor gamma agonist. *J Neurosci* 28: 9287–9296, 2008. doi:10.1523/JNEUROSCI.3348-08.2008.

187. **Nilius B, Watanabe H, Vriens J.** The TRPV4 channel: structure-function relationship and promiscuous gating behaviour. *Pflugers Arch* 446: 298–303, 2003. doi:10.1007/s00424-003-1028-9.

188. **O'Rourke MF, Safar ME.** Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension* 46: 200–204, 2005. doi:10.1161/01.HYP.0000168052.00426.65.

189. **Oh-Park M, Holtzer R, Xue X, Verghese J.** Conventional and robust quantitative gait norms in community-dwelling older adults. *J Am Geriatr Soc* 58: 1512–1518, 2010. doi:10.1111/j.1532-5415.2010.02962.x.

190. **Oomen CA, Farkas E, Roman V, van der Beek EM, Luiten PG, Meerlo P.** Resveratrol preserves cerebrovascular density and cognitive function in aging mice. *Front Aging Neurosci* 1: 4, 2009. doi:10.3389/neuro.24.004.2009.

191. **Osol G, Halpern W.** Myogenic properties of cerebral blood vessels from normotensive and hypertensive rats. *Am J Physiol Heart Circ Physiol* 249: H914–H921, 1985.

192. **Osol G, Laher I, Cipolla M.** Protein kinase C modulates basal myogenic tone in resistance arteries from the cerebral circulation. *Circ Res* 68: 359–367, 1991. doi:10.1161/01.RES.68.2.359.

193. **Østergaard L, Dreier JP, Hadjikhani N, Jespersen SN, Dirnagl U, Dalkara T.** Neurovascular coupling during cortical spreading depolarization and -depression. *Stroke* 46: 1392–1401, 2015. doi:10.1161/STROKEAHA.114.008077.

194. **Østergaard L, Engedal TS, Moreton F, Hansen MB, Wardlaw JM, Dalkara T, Markus HS, Muir KW.** Cerebral small vessel disease: capillary pathways to stroke and cognitive decline. *J Cereb Blood Flow Metab* 36: 302–325, 2016. doi:10.1177/0271678X15606723.

195. **Park L, Anrather J, Girouard H, Zhou P, Iadecola C.** Nox2-derived reactive oxygen species mediate neurovascular dysregulation in the aging mouse brain. *J Cereb Blood Flow Metab* 27: 1908–1918, 2007. doi:10.1038/sj.jcbfm.9600491.

196. **Park L, Anrather J, Zhou P, Frys K, Pitstick R, Younkin S, Carlson GA, Iadecola C.** NADPH-oxidase-derived reactive oxygen species mediate the cerebrovascular dysfunction induced by the amyloid beta peptide. *J Neurosci* 25: 1769–1777, 2005. doi:10.1523/JNEUROSCI.5207-04.2005.

197. **Park L, Zhou P, Pitstick R, Capone C, Anrather J, Norris EH, Younkin L, Younkin S, Carlson G, McEwen BS, Iadecola C.** Nox2-derived radicals contribute to neurovascular and behavioral dysfunction in mice overexpressing the amyloid precursor protein. *Proc Natl Acad Sci USA* 105: 1347–1352, 2008. doi:10.1073/pnas.0711568105.

198. **Park SY, Ives SJ, Gifford JR, Andtbacka RH, Hyngstrom JR, Reese V, Layec G, Bharath LP, Symons JD, Richardson RS.** Impact of age on the vasodilatory function of human skeletal muscle feed arteries. *Am J Physiol Heart Circ Physiol* 310: H217–H225, 2016. doi:10.1152/ajpheart.00716.2015.

199. **Paterno R, Faraci FM, Heistad DD.** Age-related changes in release of endothelium-derived relaxing factor from the carotid artery. *Stroke* 25: 2457–2460; discussion 2461–2452, 1994.

200. **Paternò R, Heistad DD, Faraci FM.** Potassium channels modulate cerebral autoregulation during acute hypertension. *Am J Physiol Heart Circ Physiol* 278: H2003–H2007, 2000.

201. **Paulson OB, Hasselbalch SG, Rostrup E, Knudsen GM, Pelligrino D.** Cerebral blood flow response to functional activation. *J Cereb Blood Flow Metab* 30: 2–14, 2010. doi:10.1038/jcbfm.2009.188.

202. **Paulson OB, Newman EA.** Does the release of potassium from astrocyte endfeet regulate cerebral blood flow? *Science* 237: 896–898, 1987. doi:10.1126/science.3616619.

203. **Paulson OB, Strandgaard S, Edvinsson L.** Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 2: 161–192, 1990.

204. **Pearson KJ, Baur JA, Lewis KN, Peshkin L, Price NL, Labinskyy N, Swindell WR, Kamara D, Minor RK, Perez E, Jamieson HA, Zhang Y, Dunn SR, Sharma K, Pleshko N, Woollett LA, Csiszar A, Ikeno Y, Le Couteur D, Elliott PJ, Becker KG, Navas P, Ingram DK, Wolf NS, Ungvari Z, Sinclair DA, de Cabo R.** Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metab* 8: 157–168, 2008. doi:10.1016/j.cmet.2008.06.011.

205. **Petrovitch H, White LR, Izmirilian G, Ross GW, Havlik RJ, Markesbery W, Nelson J, Davis DG, Hardman J, Foley DJ, Launer LJ.** Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. *Neurobiol Aging* 21: 57–62, 2000. doi:10.1016/S0197-4580(00)00106-8.

206. **Phan TS, Li JK, Segers P, Chirinos JA.** Misinterpretation of the determinants of elevated forward wave amplitude inflates the role of the proximal aorta. *J Am Heart Assoc* 5: e003069, 2016. doi:10.1161/JAHA.115.003069.

207. **Pinter D, Enzinger C, Fazekas F.** Cerebral small vessel disease, cognitive reserve and cognitive dysfunction. *J Neurol* 262: 2411–2419, 2015. doi:10.1007/s00415-015-7776-6.

208. **Poels MM, Ikram MA, van der Lugt A, Hofman A, Krestin GP, Breteler MM, Vernooij MW.** Incidence of cerebral microbleeds in the general population: the Rotterdam Scan Study. *Stroke* 42: 656–661, 2011. doi:10.1161/STROKEAHA.110.607184.

209. **Porter JT, McCarthy KD.** Hippocampal astrocytes in situ respond to glutamate released from synaptic terminals. *J Neurosci* 16: 5073–5081, 1996.

210. **PROGRESS Collaborative Group.** Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 358: 1033–1041, 2001. doi:10.1016/S0140-6736(01)06178-5.

212. **Purkayastha S, Fadar O, Mehregan A, Salat DH, Moscufo N, Meier DS, Guttmann CR, Fisher ND, Lipsitz LA, Sorond FA.** Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. *J Cereb Blood Flow Metab* 34: 228–234, 2014. doi:10.1038/jcbfm.2013.180.

213. **Raju K, Doulias PT, Evans P, Krizman EN, Jackson JG, Horyn O, Daikhin Y, Nissim I, Yudkoff M, Nissim I, Sharp KA, Robinson MB, Ischiropoulos H.** Regulation of brain glutamate metabolism by nitric oxide and S-nitrosylation. *Sci Signal* 8: ra68, 2015. doi:10.1126/scisignal.aaa4312.

214. **Reading SA, Brayden JE.** Central role of TRPM4 channels in cerebral blood flow regulation. *Stroke* 38: 2322–2328, 2007. doi:10.1161/STROKEAHA.107.483404.

215. **Reitz C, Tang MX, Manly J, Mayeux R, Luchsinger JA.** Hypertension and the risk of mild cognitive impairment. *Arch Neurol* 64: 1734–1740, 2007. doi:10.1001/archneur.64.12.1734.

216. **Robertson AD, Edgell H, Hughson RL.** Assessing cerebrovascular autoregulation from critical closing pressure and resistance area product during upright posture in aging and hypertension. *Am J Physiol Heart Circ Physiol* 307: H124–H133, 2014. doi:10.1152/ajpheart.00086.2014.

217. **Rombouts SA, Barkhof F, Veltman DJ, Machielsen WC, Witter MP, Bierlaagh MA, Lazeron RH, Valk J, Scheltens P.** Functional MR imaging in Alzheimer's disease during memory encoding. *AJNR Am J Neuroradiol* 21: 1869–1875, 2000.

218. **Rosendorff C, Beeri MS, Silverman JM.** Cardiovascular risk factors for Alzheimer's disease. *Am J Geriatr Cardiol* 16: 143–149, 2007. doi:10.1111/j.1076-7460.2007.06696.x.

219. **Rosengarten B, Aldinger C, Spiller A, Kaps M.** Neurovascular coupling remains unaffected during normal aging. *J Neuroimaging* 13: 43–47, 2003. doi:10.1111/j.1552-6569.2003.tb00155.x.

220. **Ross AJ, Gao Z, Pollock JP, Leuenberger UA, Sinoway LI, Muller MD.** β-Adrenergic receptor blockade impairs coronary exercise hyperemia in young men but not older men. *Am J Physiol Heart Circ Physiol* 307: H1497–H1503, 2014. doi:10.1152/ajpheart.00584.2014.

221. **Sabayan B, Westendorp RG, Grond J, Stott DJ, Sattar N, van Osch MJ, van Buchem MA, de Craen AJ.** Markers of endothelial dysfunction and cerebral blood flow in older adults. *Neurobiol Aging* 35: 373–377, 2014. doi:10.1016/j.neurobiolaging.2013.08.020.

222. **Sadoshima S, Fujishima M, Yoshida F, Ibayashi S, Shiokawa O, Omae T.** Cerebral autoregulation in young spontaneously hypertensive rats. Effect of sympathetic denervation. *Hypertension* 7: 392–397, 1985.

223. **Sadoshima S, Yoshida F, Ibayashi S, Shiokawa O, Fujishima M.** Upper limit of cerebral autoregulation during development of hypertension in spontaneously hypertensive rats–effect of sympathetic denervation. *Stroke* 16: 477–481, 1985. doi:10.1161/01.STR.16.3.477.

224. **Sagare AP, Bell RD, Zhao Z, Ma Q, Winkler EA, Ramanathan A, Zlokovic BV.** Pericyte loss influences Alzheimer-like neurodegeneration in mice. *Nat Commun* 4: 2932, 2013. doi:10.1038/ncomms3932.

225. **Sakowitz OW, Santos E, Nagel A, Krajewski KL, Hertle DN, Vajkoczy P, Dreier JP, Unterberg AW, Sarrafzadeh AS.** Clusters of spreading depolarizations are associated with disturbed cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. *Stroke* 44: 220–223, 2013. doi:10.1161/STROKEAHA.112.672352.

226. **Sanders M, Meel – van den Abeelen A, Slump C, Lagro J, Claassen J.** Reduced cerebral autoregulation as the genesis of symptoms in orthostatic intolerance in elderly. *FASEB J* 28, *Suppl*: 1069.3, 2014.

227. **Sarrafzadeh A, Santos E, Wiesenthal D, Martus P, Vajkoczy P, Oehmchen M, Unterberg A, Dreier JP, Sakowitz O.** Cerebral glucose and spreading depolarization in patients with aneurysmal subarachnoid hemorrhage. *Acta Neurochir Suppl* 115: 143–147, 2013.

228. **Schaafsma A, Veen L, Vos JP.** Three cases of hyperperfusion syndrome identified by daily transcranial Doppler investigation after carotid surgery. *Eur J Vasc Endovasc Surg* 23: 17–22, 2002. doi:10.1053/ejvs.2001.1545.

229. **Schretzenmayr A.** Über Kreislaufregulatorische Vorgange an den grossen Arterien bei der Muskelarbeit. *Pflugers Arch* 232: 743–748, 1933. doi:10.1007/BF01754829.

230. **Schubert R, Lidington D, Bolz SS.** The emerging role of Ca^{2+} sensitivity regulation in promoting myogenic vasoconstriction. *Cardiovasc Res* 77: 8–18, 2008.

231. **Schubert R, Mulvany MJ.** The myogenic response: established facts and attractive hypotheses. *Clin Sci (Lond)* 96: 313–326, 1999. doi:10.1042/cs0960313.

232. **Serrador JM, Sorond FA, Vyas M, Gagnon M, Iloputaife ID, Lipsitz LA.** Cerebral pressure-flow relations in hypertensive elderly humans: transfer gain in different frequency domains. *J Appl Physiol (1985)* 98: 151–159, 2005. doi:10.1152/japplphysiol.00471.2004.

233. **Sinclair LI, Tayler HM, Love S.** Synaptic protein levels altered in vascular dementia. *Neuropathol Appl Neurobiol* 41: 533–543, 2015. doi:10.1111/nan.12215.

234. **Skoog I, Gustafson D.** Update on hypertension and Alzheimer's disease. *Neurol Res* 28: 605–611, 2006. doi:10.1179/016164106X130506.

235. **Smeda JS, VanVliet BN, King SR.** Stroke-prone spontaneously hypertensive rats lose their ability to auto-regulate cerebral blood flow prior to stroke. *J Hypertens* 17: 1697–1705, 1999. doi:10.1097/00004872-199917120-00006.

236. **Snyder HM, Corriveau RA, Craft S, Faber JE, Greenberg SM, Knopman D, Lamb BT, Montine TJ, Nedergaard M, Schaffer CB, Schneider JA, Wellington C, Wilcock DM, Zipfel GJ, Zlokovic B, Bain LJ, Bosetti F, Galis ZS, Koroshetz W, Carrillo MC.** Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. *Alzheimers Dement* 11: 710–717, 2015. doi:10.1016/j.jalz.2014.10.008.

237. **Solano Fonseca R, Mahesula S, Apple DM, Raghunathan R, Dugan A, Cardona A, O'Connor J, Kokovay E.** Neurogenic niche microglia undergo positional remodeling and progressive activation contributing to age-associated reductions in neurogenesis. *Stem Cells Dev* 25: 542–555, 2016. doi:10.1089/scd.2015.0319.

238. **Solfrizzi V, Panza F, Colacicco AM, D'Introno A, Capurso C, Torres F, Grigoletto F, Maggi S, Del Parigi A, Reiman EM, Caselli RJ, Scafato E, Farchi G, Capurso A; Italian Longitudinal Study on Aging Working Group.** Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology* 63: 1882–1891, 2004. doi:10.1212/01.WNL.0000144281.38555.E3.

239. **Sonntag WE, Carter CS, Ikeno Y, Ekenstedt K, Carlson CS, Loeser RF, Chakrabarty S, Lee S, Bennett C, Ingram R, Moore T, Ramsey M.** Adult-onset growth hormone and insulin-like growth factor I deficiency reduces neoplastic disease, modifies age-related pathology, and increases life span. *Endocrinology* 146: 2920–2932, 2005. doi:10.1210/en.2005-0058.

240. **Sonntag WE, Deak F, Ashpole N, Toth P, Csiszar A, Freeman W, Ungvari Z.** Insulin-like growth factor-1 in CNS and cerebrovascular aging. *Front Aging Neurosci* 5: 27, 2013. doi:10.3389/fnagi.2013.00027.

241. **Sorond FA, Galica A, Serrador JM, Kiely DK, Iloputaife I, Cupples LA, Lipsitz LA.** Cerebrovascular hemodynamics, gait, and falls in an elderly population: MOBILIZE Boston Study. *Neurology* 74: 1627–1633, 2010. doi:10.1212/WNL.0b013e3181df0982.

242. **Sorond FA, Hurwitz S, Salat DH, Greve DN, Fisher ND.** Neurovascular coupling, cerebral white matter integrity, and response to cocoa in older people. *Neurology* 81: 904–909, 2013. doi:10.1212/WNL.0b013e3182a351aa.

243. **Sorond FA, Khavari R, Serrador JM, Lipsitz LA.** Regional cerebral autoregulation during orthostatic stress: age-related differences. *J Gerontol A Biol Sci Med Sci* 60: 1484–1487, 2005. doi:10.1093/gerona/60.11.1484.

244. **Sorond FA, Kiely DK, Galica A, Moscufo N, Serrador JM, Iloputaife I, Egorova S, Dell'Oglio E, Meier DS, Newton E, Milberg WP, Guttmann CR, Lipsitz LA.** Neurovascular coupling is impaired in slow walkers: the MOBILIZE Boston Study. *Ann Neurol* 70: 213–220, 2011. doi:10.1002/ana.22433.

245. **Sorond FA, Schnyer DM, Serrador JM, Milberg WP, Lipsitz LA.** Cerebral blood flow regulation during cognitive tasks: effects of healthy aging. *Cortex* 44: 179–184, 2008. doi:10.1016/j.cortex.2006.01.003.

246. **Sörös P, Whitehead S, Spence JD, Hachinski V.** Antihypertensive treatment can prevent stroke and cognitive decline. *Nat Rev Neurol* 9: 174–178, 2013. doi:10.1038/nrneurol.2012.255.

247. **Sparks DL, Scheff SW, Liu H, Landers TM, Coyne CM, Hunsaker JC III.** Increased incidence of neurofibrillary tangles (NFT) in nondemented individuals with hypertension. *J Neurol Sci* 131: 162–169, 1995. doi:10.1016/0022-510X(95)00105-B.

248. **Springo Z, Tarantini S, Toth P, Tucsek Z, Koller A, Sonntag WE, Csiszar A, Ungvari Z.** Aging exacerbates pressure-induced mitochondrial oxidative stress in mouse cerebral arteries. *J Gerontol A Biol Sci Med Sci* 70: 1355–1359, 2015. doi:10.1093/gerona/glu244.

249. **Springo Z, Toth P, Tarantini S, Ashpole NM, Tucsek Z, Sonntag WE, Csiszar A, Koller A, Ungvari ZI.** Aging impairs myogenic adaptation to pulsatile pressure in mouse cerebral arteries. *J Cereb Blood Flow Metab* 35: 527–530, 2015. doi:10.1038/jcbfm.2014.256.

250. **Springo Z, Toth P, Tarantini S, Ashpole NM, Tucsek Z, Sonntag WE, Csiszar A, Koller A, Ungvari ZI.** Aging impairs myogenic adaptation to pulsatile pressure in mouse cerebral arteries. *J Cereb Blood Flow Metab* 35: 527–530, 2015. doi:10.1038/jcbfm.2014.256.

251. **Stefanova I, Stephan T, Becker-Bense S, Dera T, Brandt T, Dieterich M.** Age-related changes of blood-oxygen-level-dependent signal dynamics during optokinetic stimulation. *Neurobiol Aging* 34: 2277–2286, 2013. doi:10.1016/j.neurobiolaging.2013.03.031.

252. **Stobart JL, Lu L, Anderson HD, Mori H, Anderson CM.** Astrocyte-induced cortical vasodilation is mediated by D-serine and endothelial nitric oxide synthase. *Proc Natl Acad Sci USA* 110: 3149–3154, 2013. doi:10.1073/pnas.1215929110.

253. **Strandgaard S.** Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. *Circulation* 53: 720–727, 1976. doi:10.1161/01.CIR.53.4.720.

254. **Strandgaard S, Jones JV, MacKenzie ET, Harper AM.** Upper limit of cerebral blood flow autoregulation in experimental renovascular hypertension in the baboon. *Circ Res* 37: 164–167, 1975. doi:10.1161/01.RES.37.2.164.

255. **Strandgaard S, Olesen J, Skinhoj E, Lassen NA.** Autoregulation of brain circulation in severe arterial hypertension. *BMJ* 1: 507–510, 1973. doi:10.1136/bmj.1.5852.507.

256. **Strandgaard S, Paulson OB.** Cerebral blood flow and its pathophysiology in hypertension. *Am J Hypertens* 2: 486–492, 1989.

257. **Stromberg DD, Fox JR.** Pressures in the pial arterial microcirculation of the cat during changes in systemic arterial blood pressure. *Circ Res* 31: 229–239, 1972. doi:10.1161/01.RES.31.2.229.

258. **Szabo K, Rosengarten B, Juhasz T, Lako E, Csiba L, Olah L.** Effect of non-steroid anti-inflammatory drugs on neurovascular coupling in humans. *J Neurol Sci* 336: 227–231, 2014. doi:10.1016/j.jns.2013.10.048.

259. **Tarantini S, Hertelendy P, Tucsek Z, Valcarcel-Ares MN, Smith N, Menyhart A, Farkas E, Hodges EL, Towner R, Deak F, Sonntag WE, Csiszar A, Ungvari Z, Toth P.** Pharmacologically-induced neurovascular uncoupling is associated with cognitive impairment in mice. *J Cereb Blood Flow Metab* 35: 1871–1881, 2015. doi:10.1038/jcbfm.2015.162.

260. **Tarantini S, Toth P, Sosnowska D, Gautam T, Tucsek Z, Koller A, Sonntag WE, Csiszar A, Ungvari Z.** Aging exacerbates hypertension-induced intracerebral microbleeds in mice. *Aging Cell* 28, *Suppl*: 1079.1076, 2014.

261. **Tarantini S, Tucsek Z, Valcarcel-Ares MN, Toth P, Gautam T, Giles CB, Ballabh P, Wei JY, Wren JD, Ashpole NM, Sonntag WE, Ungvari Z, Csiszar A.** Circulating IGF-1 deficiency exacerbates hypertension-induced microvascular rarefaction in the mouse hippocampus and retrosplenial cortex: implications for cerebromicrovascular and brain aging. *Age (Dordr)* 38: 273–289, 2016. doi:10.1007/s11357-016-9931-0.

262. **Tarumi T, Ayaz Khan M, Liu J, Tseng BY, Parker R, Riley J, Tinajero C, Zhang R.** Cerebral hemodynamics in normal aging: central artery stiffness, wave reflection, and pressure pulsatility. *J Cereb Blood Flow Metab* 34: 971–978, 2014. doi:10.1038/jcbfm.2014.44.

265. **Tiecks FP, Lam AM, Matta BF, Strebel S, Douville C, Newell DW.** Effects of the valsalva maneuver on cerebral circulation in healthy adults. A transcranial Doppler study. *Stroke* 26: 1386–1392, 1995. doi:10.1161/01.STR.26.8.1386.

266. **Tomoto T, Sugawara J, Nogami Y, Aonuma K, Maeda S.** The influence of central arterial compliance on cerebrovascular hemodynamics: insights from endurance training intervention. *J Appl Physiol (1985)* 119: 445–451, 2015. doi:10.1152/japplphysiol.00129.2015.

267. **Tong XK, Lecrux C, Rosa-Neto P, Hamel E.** Age-dependent rescue by simvastatin of Alzheimer's disease cerebrovascular and memory deficits. *J Neurosci* 32: 4705–4715, 2012. doi:10.1523/JNEUROSCI.0169-12.2012.

268. **Topcuoglu MA, Aydin H, Saka E.** Occipital cortex activation studied with simultaneous recordings of functional transcranial Doppler ultrasound (fTCD) and visual evoked potential (VEP) in cognitively normal human subjects: effect of healthy aging. *Neurosci Lett* 452: 17–22, 2009. doi:10.1016/j.neulet.2009.01.030.

269. **Toth P, Csiszar A, Tucsek Z, Sosnowska D, Gautam T, Koller A, Laniado Schwartzman M, Sonntag WE, Ungvari ZI.** Role of 20-HETE, TRP channels, and BK$_{Ca}$ in dysregulation of pressure-induced Ca^{2+} signaling and myogenic constriction of cerebral arteries in aged hypertensive mice. *Am J Physiol Heart Circ Physiol* 305: H1698–H1708, 2013. doi:10.1152/ajpheart.00377.2013.

271. **Toth P, Koller A, Pusch G, Bosnyak E, Szapary L, Komoly S, Marko L, Nagy J, Wittmann I.** Microalbuminuria, indicated by total versus immunoreactive urinary albumins, in acute ischemic stroke patients. *J Stroke Cerebrovasc Dis* 20: 510–516, 2011. doi:10.1016/j.jstrokecerebrovasdis.2010.03.002.

272. **Toth P, Rozsa B, Springo Z, Doczi T, Koller A.** Isolated human and rat cerebral arteries constrict to increases in flow: role of 20-HETE and TP receptors. *J Cereb Blood Flow Metab* 31: 2096–2105, 2011. doi:10.1038/jcbfm.2011.74.

273. **Toth P, Tarantini S, Ashpole NM, Tucsek Z, Milne GL, Valcarcel-Ares NM, Menyhart A, Farkas E, Sonntag WE, Csiszar A, Ungvari Z.** IGF-1 deficiency impairs neurovascular coupling in mice: implications for cerebromicrovascular aging. *Aging Cell* 14: 1034–1044, 2015. doi:10.1111/acel.12372.

275. **Toth P, Tarantini S, Davila A, Valcarcel-Ares MN, Tucsek Z, Varamini B, Ballabh P, Sonntag WE, Baur JA, Csiszar A, Ungvari Z.**

276. **Toth P, Tarantini S, Springo Z, Tucsek Z, Gautam T, Giles CB, Wren JD, Koller A, Sonntag WE, Csiszar A, Ungvari Z.** Aging exacerbates hypertension-induced cerebral microhemorrhages in mice: role of resveratrol treatment in vasoprotection. *Aging Cell* 14: 400–408, 2015. doi:10.1111/acel.12315.

279. **Toth P, Tarantini S, Tucsek Z, Ashpole NM, Sosnowska D, Gautam T, Ballabh P, Koller A, Sonntag WE, Csiszar A, Ungvari Z.** Resveratrol treatment rescues neurovascular coupling in aged mice: role of improved cerebromicrovascular endothelial function and downregulation of NADPH oxidase. *Am J Physiol Heart Circ Physiol* 306: H299–H308, 2014. doi:10.1152/ajpheart.00744.2013.

280. **Toth P, Tucsek Z, Sosnowska D, Gautam T, Mitschelen M, Tarantini S, Deak F, Koller A, Sonntag WE, Csiszar A, Ungvari Z.** Age-related autoregulatory dysfunction and cerebromicrovascular injury in mice with angiotensin II-induced hypertension. *J Cereb Blood Flow Metab* 33: 1732–1742, 2013. doi:10.1038/jcbfm.2013.143.

281. **Toth P, Tucsek Z, Tarantini S, Sosnowska D, Gautam T, Mitschelen M, Koller A, Sonntag WE, Csiszar A, Ungvari Z.** IGF-1 deficiency impairs cerebral myogenic autoregulation in hypertensive mice. *J Cereb Blood Flow Metab* 34: 1887–1897, 2014. doi:10.1038/jcbfm.2014.156.

283. **Toyoda K, Fujii K, Takata Y, Ibayashi S, Fujikawa M, Fujishima M.** Effect of aging on regulation of brain stem circulation during hypotension. *J Cereb Blood Flow Metab* 17: 680–685, 1997. doi:10.1097/00004647-199706000-00009.

284. **Trenkwalder P.** The Study on COgnition and Prognosis in the Elderly (SCOPE)–recent analyses. *J Hypertens Suppl* 24, *Suppl* 1: S107–S114, 2006. doi:10.1097/01.hjh.0000220415.99610.22.

285. **Tsao CW, Seshadri S, Beiser AS, Westwood AJ, Decarli C, Au R, Himali JJ, Hamburg NM, Vita JA, Levy D, Larson MG, Benjamin EJ, Wolf PA, Vasan RS, Mitchell GF.** Relations of arterial stiffness and endothelial function to brain aging in the community. *Neurology* 81: 984–991, 2013. doi:10.1212/WNL.0b013e3182a43e1c.

287. **Tucsek Z, Toth P, Sosnowska D, Gautam T, Mitschelen M, Koller A, Szalai G, Sonntag WE, Ungvari Z, Csiszar A.** Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. *J Gerontol A Biol Sci Med Sci* 69: 1212–1226, 2014. doi:10.1093/gerona/glt177.

288. **Tucsek Z, Toth P, Tarantini S, Sosnowska D, Gautam T, Warrington JP, Giles CB, Wren JD, Koller A, Ballabh P, Sonntag WE, Ungvari Z, Csiszar A.** Aging exacerbates obesity-induced cerebromicrovascular rarefaction, neurovascular uncoupling, and cognitive decline in mice. *J Gerontol A Biol Sci Med Sci* 69: 1339–1352, 2014. doi:10.1093/gerona/glu080.

290. **Ungvari Z, Bagi Z, Feher A, Recchia FA, Sonntag WE, Pearson K, de Cabo R, Csiszar A.** Resveratrol confers endothelial protection via activation of the antioxidant transcription factor Nrf2. *Am J Physiol Heart Circ Physiol* 299: H18–H24, 2010. doi:10.1152/ajpheart.00260.2010.

291. **Ungvari Z, Bailey-Downs L, Gautam T, Sosnowska D, Wang M, Monticone RE, Telljohann R, Pinto JT, de Cabo R, Sonntag WE, Lakatta EG, Csiszar A.** Age-associated vascular oxidative stress, Nrf2 dysfunction, and NF-kappaB activation in the nonhuman primate Macaca mulatta. *J Gerontol A Biol Sci Med Sci* 66: 866–875, 2011. doi:10.1093/gerona/glr092.

292. **Ungvari Z, Bailey-Downs L, Sosnowska D, Gautam T, Koncz P, Losonczy G, Ballabh P, de Cabo R, Sonntag WE, Csiszar A.** Vascular oxidative stress in aging: a homeostatic failure due to dysregulation of NRF2-mediated antioxidant response. *Am J Physiol Heart Circ Physiol* 301: H363–H372, 2011. doi:10.1152/ajpheart.01134.2010.

293. **Ungvari Z, Csiszar A.** The emerging role of IGF-1 deficiency in cardiovascular aging: recent advances. *J Gerontol A Biol Sci Med Sci* 67: 599–610, 2012. doi:10.1093/gerona/gls072.

294. **Ungvari Z, Labinskyy N, Mukhopadhyay P, Pinto JT, Bagi Z, Ballabh P, Zhang C, Pacher P, Csiszar A.** Resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells. *Am J Physiol Heart Circ Physiol* 297: H1876–H1881, 2009. doi:10.1152/ajpheart.00375.2009.

295. **Ungvari Z, Orosz Z, Labinskyy N, Rivera A, Xiangmin Z, Smith K, Csiszar A.** Increased mitochondrial H$_2$O$_2$ production promotes endothe-

Purinergic glio-endothelial coupling during neuronal activity: role of P2Y1 receptors and eNOS in functional hyperemia in the mouse somatosensory cortex. *Am J Physiol Heart Circ Physiol* 309: H1837–H1845, 2015. doi:10.1152/ajpheart.00463.2015.

lial NF-κB activation in aged rat arteries. *Am J Physiol Heart Circ Physiol* 293: H37–H47, 2007. doi:10.1152/ajpheart.01346.2006.

296. **Ungvari Z, Orosz Z, Rivera A, Labinskyy N, Xiangmin Z, Olson S, Podlutsky A, Csiszar A.** Resveratrol increases vascular oxidative stress resistance. *Am J Physiol Heart Circ Physiol* 292: H2417–H2424, 2007. doi:10.1152/ajpheart.01258.2006.

297. **Ungvari Z, Tucsek Z, Sosnowska D, Toth P, Gautam T, Podlutsky A, Csiszar A, Losonczy G, Valcarcel-Ares MN, Sonntag WE, Csiszar A.** Aging-induced dysregulation of dicer1-dependent microRNA expression impairs angiogenic capacity of rat cerebromicrovascular endothelial cells. *J Gerontol A Biol Sci Med Sci* 68: 877–891, 2013. doi:10.1093/gerona/gls242.

298. **Valcarcel-Ares MN, Gautam T, Warrington JP, Bailey-Downs L, Sosnowska D, de Cabo R, Losonczy G, Sonntag WE, Ungvari Z, Csiszar A.** Disruption of Nrf2 signaling impairs angiogenic capacity of endothelial cells: implications for microvascular aging. *J Gerontol A Biol Sci Med Sci* 67: 821–829, 2012. doi:10.1093/gerona/glr229.

299. **Varga DP, Puskás T, Menyhárt Á, Hertelendy P, Zölei-Szénási D, Tóth R, Ivánkovits-Kiss O, Bari F, Farkas E.** Contribution of prostanoid signaling to the evolution of spreading depolarization and the associated cerebral blood flow response. *Sci Rep* 6: 31402, 2016. doi:10.1038/srep31402.

300. **Vates GE, Takano T, Zlokovic B, Nedergaard M.** Pericyte constriction after stroke: the jury is still out. *Nat Med* 16: 959, 2010. doi:10.1038/nm0910-959.

301. **Vavrinec P, Henning RH, Goris M, Landheer SW, Buikema H, van Dokkum RP.** Renal myogenic constriction protects the kidney from age-related hypertensive renal damage in the Fawn-Hooded rat. *J Hypertens* 31: 1637–1645, 2013. doi:10.1097/HJH.0b013e328361d506.

302. **Verghese J, Ambrose AF, Lipton RB, Wang C.** Neurological gait abnormalities and risk of falls in older adults. *J Neurol* 257: 392–398, 2010. doi:10.1007/s00415-009-5332-y.

303. **Verghese J, Holtzer R, Lipton RB, Wang C.** Quantitative gait markers and incident fall risk in older adults. *J Gerontol A Biol Sci Med Sci* 64: 896–901, 2009. doi:10.1093/gerona/glp033.

304. **Verghese J, LeValley A, Hall CB, Katz MJ, Ambrose AF, Lipton RB.** Epidemiology of gait disorders in community-residing older adults. *J Am Geriatr Soc* 54: 255–261, 2006. doi:10.1111/j.1532-5415.2005.00580.x.

305. **Vinall PE, Simeone FA.** Cerebral autoregulation: an in vitro study. *Stroke* 12: 640–642, 1981. doi:10.1161/01.STR.12.5.640.

306. **von Bornstädt D, Houben T, Seidel JL, Zheng Y, Dilekoz E, Qin T, Sandow N, Kura S, Eikermann-Haerter K, Endres M, Boas DA, Moskowitz MA, Lo EH, Dreier JP, Woitzik J, Sakadžić S, Ayata C.** Supply-demand mismatch transients in susceptible peri-infarct hot zones explain the origins of spreading injury depolarizations. *Neuron* 85: 1117–1131, 2015. doi:10.1016/j.neuron.2015.02.007.

307. **Wagerle LC, Busija DW.** Effect of thromboxane A2/endoperoxide antagonist SQ29548 on the contractile response to acetylcholine in newborn piglet cerebral arteries. *Circ Res* 66: 824–831, 1990. doi:10.1161/01.RES.66.3.824.

308. **Wang L, Du Y, Wang K, Xu G, Luo S, He G.** Chronic cerebral hypoperfusion induces memory deficits and facilitates Aβ generation in C57BL/6J mice. *Exp Neurol* 283, Pt A: 353–364, 2016. doi:10.1016/j.expneurol.2016.07.006.

309. **Wang N, Allali G, Kesavadas C, Noone ML, Pradeep VG, Blumen HM, Verghese J.** Cerebral small vessel disease and motoric cognitive risk syndrome: results from the Kerala-Einstein Study. *J Alzheimers Dis* 50: 699–707, 2015. doi:10.3233/JAD-150523.

310. **Webb AJ, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM.** Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. *Stroke* 43: 2631–2636, 2012. doi:10.1161/STROKEAHA.112.655837.

311. **Welsh DG, Morielli AD, Nelson MT, Brayden JE.** Transient receptor potential channels regulate myogenic tone of resistance arteries. *Circ Res* 90: 248–250, 2002. doi:10.1161/hh0302.105662.

312. **Werber AH, Heistad DD.** Effects of chronic hypertension and sympathetic nerves on the cerebral microvasculature of stroke-prone spontaneously hypertensive rats. *Circ Res* 55: 286–294, 1984. doi:10.1161/01.RES.55.3.286.

313. **Winkler EA, Bell RD, Zlokovic BV.** Central nervous system pericytes in health and disease. *Nat Neurosci* 14: 1398–1405, 2011. doi:10.1038/nn.2946.

314. **Winkler EA, Bell RD, Zlokovic BV.** Pericyte-specific expression of PDGF beta receptor in mouse models with normal and deficient PDGF beta receptor signaling. *Mol Neurodegener* 5: 32, 2010. doi:10.1186/1750-1326-5-32.

315. **Winkler MK, Dengler N, Hecht N, Hartings JA, Kang EJ, Major S, Martus P, Vajkoczy P, Woitzik J, Dreier JP.** Oxygen availability and spreading depolarizations provide complementary prognostic information in neuromonitoring of aneurysmal subarachnoid hemorrhage patients. *J Cereb Blood Flow Metab* pii: 0271678X16641424, 2016. doi:10.1177/0271678X16641424.

316. **Witthoft A, Filosa JA, Karniadakis GE.** Potassium buffering in the neurovascular unit: models and sensitivity analysis. *Biophys J* 105: 2046–2054, 2013. doi:10.1016/j.bpj.2013.09.012.

317. **Woitzik J, Hecht N, Pinczolits A, Sandow N, Major S, Winkler MK, Weber-Carstens S, Dohmen C, Graf R, Strong AJ, Dreier JP, Vajkoczy P; COSBID Study Group.** Propagation of cortical spreading depolarization in the human cortex after malignant stroke. *Neurology* 80: 1095–1102, 2013. doi:10.1212/WNL.0b013e3182886932.

318. **Wollner L, McCarthy ST, Soper ND, Macy DJ.** Failure of cerebral autoregulation as a cause of brain dysfunction in the elderly. *BMJ* 1: 1117–1118, 1979. doi:10.1136/bmj.1.6171.1117.

319. **Yam AT, Lang EW, Lagopoulos J, Yip K, Griffith J, Mudaliar Y, Dorsch NW.** Cerebral autoregulation and ageing. *J Clin Neurosci* 12: 643–646, 2005. doi:10.1016/j.jocn.2004.08.017.

320. **Yu W, Juang S, Lee J, Liu T, Cheng J.** Decrease of neuronal nitric oxide synthase in the cerebellum of aged rats. *Neurosci Lett* 291: 37–40, 2000. doi:10.1016/S0304-3940(00)01377-X.

321. **Zaletel M, Strucl M, Pretnar-Oblak J, Zvan B.** Age-related changes in the relationship between visual evoked potentials and visually evoked cerebral blood flow velocity response. *Funct Neurol* 20: 115–120, 2005.

322. **Zhang F, Xu S, Iadecola C.** Role of nitric oxide and acetylcholine in neocortical hyperemia elicited by basal forebrain stimulation: evidence for an involvement of endothelial nitric oxide. *Neuroscience* 69: 1195–1204, 1995. doi:10.1016/0306-4522(95)00302-Y.

323. **Zhao YN, Li WF, Li F, Zhang Z, Dai YD, Xu AL, Qi C, Gao JM, Gao J.** Resveratrol improves learning and memory in normally aged mice through microRNA-CREB pathway. *Biochem Biophys Res Commun* 435: 597–602, 2013. doi:10.1016/j.bbrc.2013.05.025.

324. **Zlokovic BV.** The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron* 57: 178–201, 2008. doi:10.1016/j.neuron.2008.01.003.

325. **Zlokovic BV.** Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci* 12: 723–738, 2011. doi:10.1038/nrn3114.

326. **Zou AP, Fleming JT, Falck JR, Jacobs ER, Gebremedhin D, Harder DR, Roman RJ.** 20-HETE is an endogenous inhibitor of the large-conductance Ca^{2+}-activated K^+ channel in renal arterioles. *Am J Physiol Regul Integr Comp Physiol* 270: R228–R237, 1996.