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OPINION PAPER

The role of exercise in the reversal of IGF-1 deficiencies in microvascular rarefaction and hypertension

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Abstract Hypertension has been linked with peripheral and central reductions in vascular density, and with devastating effects on brain function. However, the underlying mechanisms in the relationship between blood pressure and cognitive impairment have yet to be fully elucidated. Here, we review compelling evidence from two lines of inquiry: one that links microvascular rarefaction with insulin-like growth factor 1 (IGF-1) deficiencies, and another which posits that vascular dysfunction precedes hypertension. Based on the findings from experimental and clinical studies, we propose that these lines of evidence converge, and suggest that age-related declines in IGF-1 concentrations precede microvascular rarefaction, initiate an increase in vascular resistance, and therefore are causally linked to onset of hypertension. Physical exercise provides a relevant model for supporting our premise, given the well-established effects of exercise in attenuating vascular dysfunction, hypertension, IGF-1 deficiency, and cognitive decline. We highlight here the role of exercise-induced increases in blood flow in improving vascular integrity and enhancing angiogenesis via the actions of IGF-1, resulting in reversal of rarefaction and hypertension, and enhancement of cerebral blood flow and cognition.

Keywords Hypertension · IGF-1 · Growth factor · Exercise · Rarefaction · Cognition · Brain

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Introduction

Hypertension is a major public healthcare crisis in the USA, with the American Heart Association (AHA) estimating prevalence at more than 103 million adults ≥ 20 years of age (Muntner et al. 2018). The risk of becoming hypertensive increases with age—75% of adults 65 to 74 years old and 82% of those 75 years and older have high blood pressure. Further, nearly 24% of hypertensive adults are between 20 and 44 years of age (Muntner et al. 2018). Even more troubling is the fact that 16% of the nearly 41 million men and 45 million women with hypertension are unaware of their condition (Benjamin et al. 2018). Given the high prevalence of hypertension and its deleterious effects on the brain (Gorelick et al. 2011; Kilander et al. 1998), identifying underlying causal mechanisms to attenuate hypertension-induced pathology is of critical importance.

There is strong evidence that increasing age is highly correlated with pathophysiological and functional alterations in the cardiovascular and cerebrovascular systems (AHA et al. 2016), and that decreased cerebral blood

flow (CBF) (Ainslie et al. 2008; Chen et al. 2011) and vascular disease are important contributing factors to aging-related cognitive decline (Gorelick et al. 2011; Kilander et al. 1998; Raz et al. 2003). Vascular dysfunction and a weakened vasomotor capacity to respond to fluctuations in intravascular pressure during the cardiac cycle have been linked with compromised cardiovascular function and increased risk of hypertension, stroke, myocardial infarction, and congestive heart failure (AHA et al. 2016).

Here, we propose a causal link between insulin-like growth factor-1 (IGF-1) deficits and hypertension, wherein IGF-1 deficiencies induce microvascular rarefaction (MVR), which increases vascular resistance and blood pressure. We also propose that exercise counteracts the deleterious effects of age-related growth factor reductions, moderates vascular resistance and rarefaction, and improves cerebral blood flow (CBF) in the setting of essential hypertension. We begin with a discussion of the systemic and central effects of untreated hypertension, and present evidence linking growth factor deficiencies with MVR and development of hypertension. Last, we discuss exercise as a potential mechanism by which the deleterious effects of growth factor deficiencies might be reversed.

Essential hypertension: cause and consequence

A large percentage of individuals diagnosed with elevated blood pressure have primary or essential hypertension (Berglund et al. 1976; Carretero and Oparil 2000), wherein secondary causes such as renovascular diseases are absent (Carretero and Oparil 2000). Elevations in both systolic and diastolic blood pressure are highly correlated with ischemic and hemorrhagic strokes, with systolic pressure conferring the greatest cardiovascular risk (Cutler 1996). In fact, hypertensive patients have a sevenfold higher likelihood of developing atherothrombotic brain infarcts than normotensive patients (Kannel et al. 1976).

Cardiovascular risk factors engender endothelial dysfunction and induce ischemic diseases (Hill et al. 2003), leading to systemic increases in vascular resistance, which are triggered by a thickening of the walls of the resistance vessels, a reduction in lumen diameters, and hypertension (Phillips and Whisnant 1992). Importantly, the microcirculation, specifically, vasoconstriction in small arteries, ultimately impact peripheral resistance. The resulting wall remodeling via reductions in vessel diameter has prompted some researchers to speculate that endothelial dysfunctions may precede the development of a hypertensive state (Brandes 2014; Humar et al. 2009).

Chronic hypertension is also associated with impairment in cerebral autoregulation that leads to further escalations in blood pressure. Autoregulation is the intrinsic capacity of the brain to maintain blood flow to sustain neuronal metabolism despite perfusion pressure changes. Hyperperfusion can occur when arterial pressure exceeds the autoregulatory threshold, leading to disruption in vascular, endothelial, and blood-brain barrier integrity (Paulson et al. 1990). To protect the brain from higher arterial pressures, the autoregulatory curve shifts to the right (Paulson et al. 1990; Pavy-Le Traon et al. 2002; Strandgaard 1976; Strandgaard et al. 1973), indicating progressively greater blood vessel constriction, which has been linked to cerebral white matter hyperintensities (Purkayastha et al. 2014). While this adaptive autoregulatory mechanism protects the brain from excessive pressure, if perfusion pressure is normalized with antihypertensives, the adaptive shift toward lower blood pressure may predispose the brain to hypoperfusion and depressed neuronal function (Feldstein 2012; Klabunde 2005). Chronic hypoperfusion in rodents has been linked to reduced CBF, hippocampal reactive astrogliosis, neuronal cell death, and enduring cognitive deficits (Cechetti et al. 2012). In older adults, the capacity of cerebral autoregulation to protect the brain from chronic states of hypoperfusion is diminished, a limitation that often results in devastating consequences, with disruptions of the neurovascular unit contributing to beta-amyloid buildup (ElAli et al. 2013).

Chronic hypertension exerts insidious consequences on brain structure, resulting in cognitive changes (Birns and Kalra 2009). The deleterious effects of chronic elevations in blood pressure on the brain include decreased cerebral blood flow (CBF) (Beason-Held et al. 2007) and loss of cerebral white matter integrity (O'sullivan et al. 2002; Verhaaren et al. 2013). Elevated blood pressure is also associated with increased risk of vascular dementia (Lis and Gaviria 1997), Alzheimer's disease (Feldstein 2012) and vascular cognitive impairment (Kilander et al. 1998) with more pronounced cognitive effects seen in individuals with uncontrolled hypertension (Brady et al. 2005). Prospective studies have shown an association between chronicity of hypertension and cognitive deficits in later life (Elias et al. 1993;

Qiu et al. 2005; Yaffe et al. 2014). The late-life decrease in cognitive performance was particularly striking when blood pressure remained untreated in middle-age (Kilander et al. 1998; Launer et al. 1995; Qiu et al. 2005). The Systolic Blood Pressure Intervention Trial - Memory and Cognition in Decreased Hypertension (SPRINT-MIND) study showed that compared to standard treatment (< 140 mmHg), intensive management of systolic blood pressure (< 120 mmHg) was effective in reducing the risk of developing mild cognitive impairment (SPRINT MIND 2019).

Microvascular rarefaction and its effects

Vascular rarefaction, the reduction of the number of perfused vessels, is mainly found in arteriolar and capillary networks (Prewitt et al. 1982), which are responsible for a significant proportion of total network resistance in cerebral cortical vascular beds (Gould et al. 2017). Rarefaction can be functional or structural. Functional rarefaction of microvessels results from vasoconstriction, and in the setting of hypertension, the loss of perfusion precedes structural rarefaction of the microvasculature (Prewitt 1990), is considered reversible and can result from decreased availability of nitric oxide, increased presence of endogenous vasoconstrictors (e.g., endothelin, prostaglandins) or sympathetic tone, as well as reduced availability of growth factors (Lip and Hall 2007). In contrast, structural rarefaction of the resistance vessels, arterioles and capillaries, entails a loss of vessels in a vascular network. This effect can occur in response to vasoconstriction and loss of perfusion, or to a decrease in the availability of endogenous vascular growth factors (Lip and Hall 2007) that are responsible for cellular functions, including survival, migration and differentiation of neuronal and glial cells (Friedman 2012).

MVR may also occur from deficient “angiogenesis” (le Noble et al. 1998), here used as a generalized term describing vascular development. Vascular development can be separated into three physiologically distinct stages: vasculogenesis, angiogenesis, and vascular remodeling. Vasculogenesis is the early developmental process of blood vessel formation that arises from differentiating endothelial cells and occurs primarily during embryogenesis. In contrast, angiogenesis can occur across the lifespan of the individual and is the means by which new capillaries emanate from existing vessels (Risau 1997). Last, vascular remodeling involves the pruning and restructuring of existing vasculature into a vascular network (Risau 1997).

Dysregulated vascular development appears to underlie the manifestation of a number of diseases and conditions, including rheumatoid arthritis, malignant tumors (Folkman 1995), and hypertension (le Noble et al. 1998; Noon et al. 1997; Struijker et al. 1992). Early research advanced the notion that vessel rarefaction is partly the result of increased total peripheral resistance, ultimately leading to hypertension (Greene et al. 1989), and observations from both experimental and clinical studies reported MVR in hypertension. Structural rarefaction of capillaries and arterioles was detected in young spontaneously hypertensive rats prior to elevations in blood pressure (le Noble et al. 1990). Similarly, studies show that changes in vascular structure and capillary rarefaction may precede clinical manifestations of essential hypertension in humans (Antonios et al. 1999), and that diffuse systemic MVR could be the dominant defect in essential hypertension (Levy et al. 2001).

Reduced microvascular density has been reported in patients with established hypertension (Prewitt 1990; Struijker et al. 1992), and in those with borderline or early essential hypertension (Struijker et al. 1992; Sullivan et al. 1983). Compared to healthy controls, for example, patients (52 ± 9 years of age) with untreated mild-moderate hypertension had reduced retinal microvascular density (Bosch et al. 2017). In addition, functional impairment of pericytes, the contractile cells responsible for capillary dilation, has been shown to result in impaired vasodilation in the cerebral circulation (Hall et al. 2014; Peppiatt et al. 2006). Impaired vasodilation at the level of the capillaries and rarefaction of microvessels have been associated with a familial predisposition to primary hypertension (Noon et al. 1997), with evidence suggesting that impaired angiogenesis in early development interrupts microvascular network formation (Noon et al. 1997; Poston 2007) predisposing normotensive offspring of hypertensive individuals to develop hypertension (Noon et al. 1997).

Microcirculatory rarefaction and increased vascular resistance result in significant modifications in tissue hemodynamics and oxygen delivery. In an extension of their earlier work, Greene et al. applied a mathematical model of tissue oxygen transport to analyze the effects of MVR on tissue oxygen distribution (Greene et al. 1992). The results indicated that as metabolic rate

increased, a 65% decrease in total available oxygen was observed in rarefied tissues in hypertensive rats. The authors concluded that changes in oxygen levels may impact not only hemodynamics in the microcirculation, but potentially the entire body (Greene et al. 1992). Given that rarefaction impacts blood flow resistance at the tissue level to a similar extent as vasoconstriction, a reduction in the number of microvessels with the corresponding decrease in available surface areas for gas exchange and increased diffusion distances may ultimately overwhelm the network's capacity to regulate blood flow. MVR in hypertension is characterized by a decreased efficiency of tissue to regulate its own oxygen delivery (Greene et al. 1992) and is a causal factor in the formation of cerebral white matter lesions (Joutel et al. 2010)—a common finding in hypertensive individuals (Iadecola and Davisson 2008). Thus, cerebral rarefaction exerts profound deleterious effects on cognitive function in individuals with hypertension (de La Torre 2012; Toth et al. 2016).

Microvascular rarefaction and altered cerebral hemodynamics

The overall regulation of CBF is thought to be mediated primarily by the cerebral vascular network of arteries, arterioles, and capillaries (Cipolla 2009; Filosa et al. 2016). Studies have shown age-related decreases in CBF (Ainslie et al. 2008; Lynch et al. 1999), with evidence that reductions in CBF are more pronounced in those over than under 60 years of age (Ainslie et al. 2008; Kawamura et al. 1993), and that older women have higher CBF than age-matched men (Lu et al. 2010). Vascular loss in persons with essential hypertension leads to significant consequences for cerebral autoregulation and blood flow (Beason-Held et al. 2007; Li et al. 2015).

The relationship between resting cerebral blood flow (rCBF) and blood pressure was assessed in older hypertensive individuals over a 7-year period (Beason-Held et al. 2007). Compared with controls, those with hypertension showed decreased regional rCBF across cortical areas, including the prefrontal cortex, anterior cingulate cortex, and occipital regions. Changes in rCBF were associated with chronicity of hypertension, suggesting that the deleterious effects of elevated blood pressure may be additive. A similar study examined the association between blood pressure, antihypertensive medications, and changes in parenchymal CBF (pCBF). Results of this longitudinal (mean = 3.9 years) study showed that poorly controlled and untreated hypertension were associated with decreased pCBF (Muller et al. 2012).

Collectively, data strongly suggest that vascular pathologies (Gorelick et al. 2011), including those associated with chronic hypertension (Novak and Hajjar 2010), are major contributors to loss of microvascular density and vessel wall remodeling and suggest a potential mechanism by which hypertension contributes to the pathogenesis of vascular cognitive impairments and dementia (Gorelick et al. 2011; O'Brien et al. 2003) in elderly patients with hypertension. Increased cerebrovascular resistance has been shown to be related to decreased cognition and AD pathology (Yew and Nation 2017), while increased CBF and decreased arterial stiffness have been correlated with better overall cognitive function (Tarumi et al. 2013).

Microvascular density: physiology and pathophysiology

Reduction in the availability of certain hormones and growth factors including growth hormone (GH), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) may result in MVR. IGF-1 is a known cerebral angiogenic factor with insulin-sensitizing effects (Lopez-Lopez et al. 2004), facilitated via endocrine and exercise-induced paracrine (local release) mechanisms (Velloso 2008) (see Fig. 1). Endocrine release of IGF-1 is mediated by pituitary growth hormone (GH), which acts as the primary driver of hepatic IGF-1 synthesis, whereas exercise studies confirm the anabolic effects of IGF-1 on skeletal muscles via paracrine mechanisms (Velloso 2008). VEGF is an equally important angiogenic factor involved in the GH/IGF cascade. The release of VEGF is induced by IGF-1-stimulated release of hypoxia-inducible factor (HIF-1α) (Fukuda et al. 2002; Krock et al. 2011). In the central nervous system (CNS), VEGF regulates microvascular density and offers protection against CNS pathologies (Lange et al. 2016), whereas its inhibition is implicated in capillary rarefaction (Robinson et al. 2010). Evidence from both animal and human studies shows that chronic VEGF inhibition results in decreased endothelial cell survival, reduced blood flow, and vascular loss (Inai et al. 2004; Robinson et al. 2010; Steeghs et al. 2008).

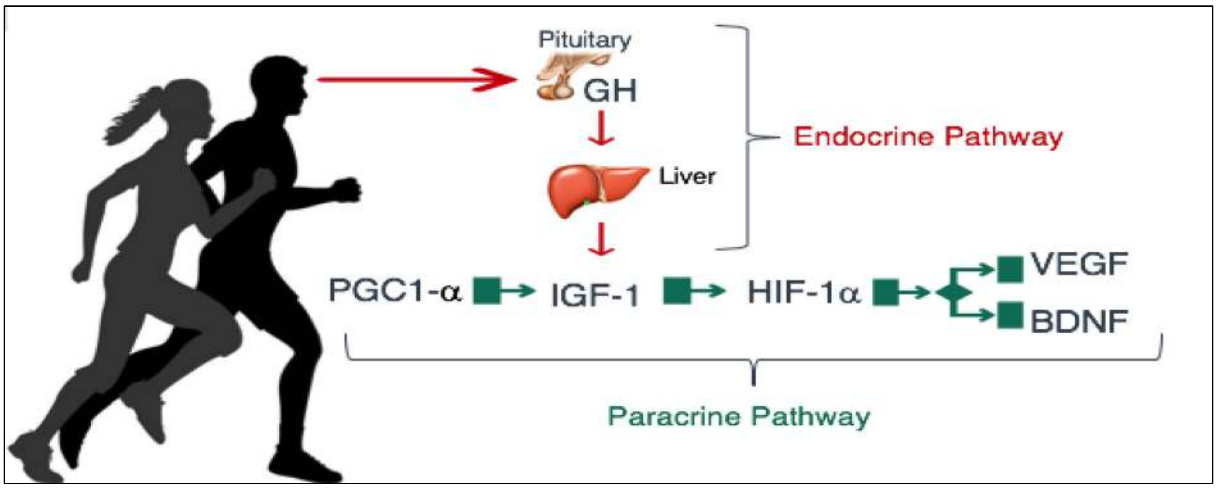

Fig. 1 Endocrine and paracrine release of IGF-1. GH growth hormone, IGF-1 insulin-like growth hormone, PGC1-α peroxisome gamma coactivator 1α, HIF-1α hypoxia-inducible factor 1α, VEGF vascular endothelial growth factor, BDNF brain-derived neurotrophic factor (Organ images created with BioRender.com)

In the absence of VEGF, the vasodilator nitric oxide is reduced, resulting in vasoconstriction, increased resistance, and hypertension (Kamba and McDonald 2007; Small et al. 2014).

Animal studies suggest that reductions in circulating IGF-1 concentrations and hypertension parallel age-related microvascular changes, including loss of myogenic tone, impaired neurovascular coupling (Csiszar et al. 2017), and cerebromicrovascular autoregulation (Toth et al. 2014). IGF-1 deficiencies induce pathological vessel wall remodeling that result in a weakening of the cerebral arteries and are associated with functional maladaptation to hypertension and increased risk for microhemorrhages (Fulop et al. 2018). Microhemorrhages weaken the vessels predisposing them to high-pressure induced rupture resulting in loss of immune privilege across the blood-brain barrier, neuroinflammation (Sweeney et al. 2018; Toth et al. 2014), neuronal dysfunction (Sonntag et al. 1997), and cognitive decline and AD onset in elderly populations (reviewed in Csiszar et al. (2017)).

Animal models support findings from human studies that showed increased incidence of microhemorrhages in hypertensive adults (Romero et al. 2014). Experimental hypertension in IGF-1-deficient mice led to more cerebral microhemorrhages and contributed to earlier onset of neurological dysfunction (Tarantini et al. 2017). In a later study, endocrine IGF-1 deficiencies promoted a worsening of hypertension-induced loss of microvascular density in the hippocampus and neocortex, and IGF-1-deficient mice had decreased gene expression of proangiogenic factors in these brain regions, while antiangiogenic factors were upregulated (Tarantini et al. 2016)).

Pleiotropic effects of IGF-1 on longevity, DNA repair, and malignancies

IGF-1 concentrations increase incrementally from birth, reaching a peak during adolescence. Thereafter, a progressive decrease in IGF-1 begins in the 2nd and 3rd decades of life, and continues throughout the lifespan (Brabant et al. 2003). In early life, IGF-1 levels drive growth during critical developmental periods (Sonntag et al. 2012). However, in later life, elevated IGF-1 levels contribute to development of age-related pathologies, including cancer and diabetes (Ashpole et al. 2017), whereas IGF-1 deficiencies promote apoptosis of damaged cells, protect against DNA damage, and reduce cancer risk (Guevara-Aguirre et al. 2011). These paradoxical functions suggest that IGF-1 effects differ depending on the age and sex of the organism (Ashpole et al. 2017). Mouse models of IGF-1 deficiencies in later life had no impact on lifespan (Ashpole et al. 2017; Ikeno et al. 2003). However, deficiencies in early development resulted in increased lifespan and resistance to malignant neoplasms in females, whereas a shortened lifespan was reported in males (Ashpole et al. 2017). Conversely, elevated levels of IGF-1 in early life

impacted an individual's predisposition to malignancies in adulthood (reviewed in Podlutsky et al. (2017)).

Moreover, new evidence highlights a possible synergistic effect of nutrition and IGF-1 on inflammation and life-span regulation. For example, early-life caloric restriction increased gene expression of transforming growth factor-β (TGF-β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) in normal mice, whereas caloric restriction reduced gene expression of these factors and reduced lifespan of GH knockout mice (IGF-1 deficient) in females (Fang et al. 2017). Relevant to this discussion, TGF-β is an anti-inflammatory cytokine mainly expressed in skeletal muscle and implicated in development, tissue homeostasis, immune functions, and control of disease pathogenesis (Guo and Wang 2009). TGF-β has bifunctional properties; elevated levels are associated with various forms of cancer while low levels are associated with cardiovascular diseases (reviewed in Gordon and Blobe (2008). Therefore, the decrease of TGF-β in female IGF-1-deficient mice (Fang et al. 2017) emphasizes the role of IGF-1 signaling in aging, disease development, and lifespan. The disparities between early and later life GH/IGF-1 deficiencies and their downstream effects have led some investigators to infer that longevity and neoplasms in animal models may be attributable to low GH rather than reductions in IGF-1 levels (Aguiar-Oliveira and Bartke 2018; Aguiar-Oliveira et al. 2010; Brown-Borg 1996; Brown-Borg and Bartke 2012).

The role of IGF-1 in rarefaction

Evidence from animal (Breese et al. 1991; Juul 2003) and human (Goodman-Gruen and Barrett-Connor 1997; Juul et al. 1994; Zhu et al. 2017) models demonstrate a significant age-related decrease in the GH/IGF-1 cascade. The temporal pattern of this decline has suggested that age-related reductions in IGF-1 may be causally linked to vascular pathologies in aging (Sonntag et al. 2000). This hypothesis is consistent with evidence from human studies indicating that, unlike rodent models in which a deficiency in the GH/ IGF-1 is proposed as a conserved mechanism of aging and increased lifespan (Ashpole et al. 2017; Brown-Borg 1996), a decline in these factors in humans is accompanied by increased risk for hypertension (Hunt et al. 2006; Juul et al. 2002), loss of microvascular density (Antonios et al. 2003; Antonios et al. 1999), and other adverse cardiometabolic manifestations with no evidence of increased longevity (Sonntag et al. 2012).

IGF-1 enhances endothelial cell function and vascular smooth muscle cell survival (Conti et al. 2004). In addition, the transformation from stable to unstable atherosclerotic plaque is, in part, attributable to low IGF-1 levels (Bayes-Genis et al. 2000; Okura et al. 2001). Given its vasodilatory properties (Sowers 1997), IGF-1 lowers blood pressure (Hunt et al. 2006). Thus, low circulating IGF-1 concentrations are associated with increased vasoconstriction, leading to a rise in blood pressure in middle-aged adults (Hunt et al. 2006), and increased cardiovascular risk (Schutte et al. 2010; Sonntag et al. 2012; Sowers 1997).

Inhibition of IGF-1 results in endothelial dysfunction, increased vascular resistance and elevation in systolic blood pressure in rodents (Tivesten et al. 2002). In humans, the relationship between IGF-1 levels and risk of hypertension was examined in a follow-up study of 2046 nonhypertensive and nondiabetic women 48–61 years of age (Zhang et al. 2011). Age was inversely correlated with IGF-1 levels and compared with those with low IGF-1 levels at baseline, individuals with elevated levels of IGF-1 had a 38% reduced risk of developing hypertension at the 4-year follow-up examination. These findings corroborate other studies that showed a reduced level of IGF-1 to be a strong predictor of cardiovascular disease (Juul et al. 2002; Laughlin et al. 2004). Further, a meta-analytic study with nearly 15,000 participants showed a curvilinear relationship between IGF-1 levels and all-cause mortality (Burgers et al. 2011).

In the CNS, IGF-1 release (Hughes et al. 1999) indicates that IGF-1 appears to serve angiogenic and neurotrophic functions and is implicated in stem cell proliferation (Arsenijevic et al. 2001), in brain plasticity via modification of synaptic formation (Torres-Aleman 1999), and in neuroprotection (Carro et al. 2000; Hughes et al. 1999; Lopez-Lopez et al. 2004). Further, age-related reductions in IGF-1 levels may reduce resistance to stress and restrict injury repair in the CNS (Carlson et al. 2014; Wine et al. 2009). However, the presence of IGF-1 receptors in the brain even in older animals suggests that despite reductions in local release of IGF-1, peripherally released IGF-1 plays a role in brain function across the lifespan (Fernandez and Torres-Alemán 2012), and supports the role of exercise-induced IGF-1 release.

Given the inverse relationship between IGF-1 and systemic cardiovascular disease (Juul 2003; Juul et al. 2002), it is not surprising that low IGF-1 levels have been linked with increased stroke risk. A comparison of IGF-1 levels in 254 stroke patients with age-matched controls found a negative correlation between circulating IGF-1 and IGFBP-3 (an IGF-binding protein) concentrations, and risk of ischemic stroke (Johnsen et al. 2005), with later confirmation of IGF-1/IGFBP-3's neuroprotective role in poststroke neurological outcome at 90 days (De Smedt et al. 2011; Denti et al. 2004). Further, several animal studies showed that delivery of exogenous GH/IGF enhances cortical capillarization (Sonntag et al. 1997), postsynaptic density in the hippocampus (Shi et al. 2004), and helps restore cognitive function (Lichtenwalner et al. 2001; Lopez-Lopez et al. 2004). Further evidence supporting the role of IGF-1 in cerebrovascular density comes from studies demonstrating that biological aging is associated with decreased IGF-1 levels (Breese et al. 1991; Sonntag et al. 1999). Low circulating levels of IGF-1 were associated with decreased capillary density in the hippocampus (Sonntag et al. 2000; Sonntag et al. 1997; Tarantini et al. 2016), which was reversible with IGF-1 infusion (Sonntag et al. 1997).

In humans, IGF-1 levels are positively related to hippocampal volume and memory (Maass et al. 2016). Higher IGF-1 levels in elderly subjects are associated with better cognitive function, whereas low IGF-1 levels are associated with cognitive impairment (Doi et al. 2015; Frater et al. 2018; Landi et al. 2007; Rollero et al. 1998), Alzheimer's disease, and vascular dementia (Quinlan et al. 2017; Watanabe et al. 2005).

IGF-1 deficiencies precede vascular rarefaction and hypertension

Racial/genetic differences

The prevalence of hypertension in the African American black population is nearly 45% higher than any other race (Benjamin et al. 2018). A comparison between 171 white and black men (40–80 years) showed that black men had lower IGF-1 levels than their white counterparts under 70 years old (McGreevy et al. 2005). More recently, a comparison of 409 South African black and white men showed that black men had higher blood pressure and lower IGF-1 levels (Koegelenberg et al. 2016).

Studies show that prior to the age of 40, white and black adults have comparable IGF-1 levels, but when older, accelerated declines in IGF-1 levels are observed in blacks, coincident with the increased incidence of hypertension in this population (Schutte et al. 2010). Similar observations linking hypertension and IGF-1 levels were recorded in middle-aged African American males (Platz et al. 1999). Conversely, a large sample (N = 6061) from the US National Health and Nutrition Examination Survey III (NHANES III) reported higher IGF-1 levels in adult males than females. White females had lower IGF-1 levels than black women, whereas no differences in IGF-1 levels emerged between black and white males (Berrigan et al. 2009).

Differences in IGF-1 levels could be the result of genetic differences in IGF-1 in different racial groups. For example, black neonates (Rohrmann et al. 2009) and black prepubertal children (Higgins et al. 2005) showed lower concentrations of IGF-1 compared to their white counterparts. Both studies attributed IGF-1 differences to genetic factors (Rohrmann et al. 2009), and support an earlier study in adult twin pairs between 44 and 77 years of age that attributed 38% of the racial variance between IGF-1 levels in whites and blacks to genetic variation (Harrela et al. 1996). More recent studies, however, argue that obesity and anthropometric variables contribute to IGF-1 racial variances rather than genetic or ethnic differences. A recent study concluded that maternal obesity contributed to IGF-1 discrepancies between black and white neonates (Vidal et al. 2013). This conclusion is supported by a study that showed an inverse relationship between body mass indices (BMIs) and IGF-1 levels (Faupel-Badger et al. 2009). BMIs > 24 have been shown to increase GH sensitivity and to stimulate IGF-1 synthesis, whereas in obese individuals (BMI > 37), GH in conjunction with IGF-1 result in a decrease and contribute to insulin resistance, onset of metabolic syndrome, and increased cardiovascular disease (reviewed in Clemmons (2012)).

The role of sex steroids

On average, men under 60 years of age have higher blood pressure than age-matched women (Benjamin et al. 2018). After the sixth decade of life, however,

blood pressure in women increases and becomes equally prevalent in both sexes (Benjamin et al. 2018; Dubey et al. 2002). Interestingly, blood pressure elevations in women do not coincide with early phases of perimenopause but is instead observed an average of 5–20 years after menopause onset (Luoto et al. 2000). This delay after menopause on blood pressure suggests that loss of estrogen itself may not be the sole factor responsible for elevations in blood pressure, but rather offers the possibility that loss of estrogen may be a catalyst for a biochemical cascade that ultimately causes structural vascular changes, and in time, hypertension. Evidence for this notion is provided by studies that emphasize the role of sex steroids in modulating the GH/IGF-1 cascade (Leung et al. 2004) and vascular function (Khalil 2005). Specifically, research indicates that premenopausal women have 20% more IGF-1 than men (Díez 1999); in the sixth decade of life, however, the IGF-1 levels of women drop below those of men of the same age (Goodman-Gruen and Barrett-Connor 1997). This relationship was further illustrated in a follow-up study of middle-aged premenopausal women showing that those who experienced menopause at the 6-year follow-up had a greater decline in IGF-1 levels and greater increases in blood pressure compared to women who remained premenopausal (Poehlman et al. 1997).

In summary, age-related decreases in growth factors result in decreased angiogenesis and loss of microvascular density. The resultant increase in peripheral and central vascular resistance predisposes individuals to increased cardiovascular risk, including increased hypertension, a condition strongly linked with decreased cerebral blood flow and cognitive impairment (see Fig. 2).

Exercise effects

Hypertension

The effects of exercise on cardiovascular health, specifically, resting heart rate and blood pressure modulation, have been established as an effective antihypertensive therapeutic modality (AHA et al. 2016; Pescatello et al. 2004). Indeed, studies highlight a consistent inverse relationship between blood pressure and exercise (Brown et al. 2010; Pialoux et al. 2009). Endurance aerobic exercise (mean = 16 weeks) in adults with hypertension (mean = 45 years of age), for instance, elicited a 5–7 mmHg reduction in blood pressure (Pescatello et al. 2004). Further, compared to moderate intensity exercise, a 12-week high-intensity exercise intervention in older (mean = 52 years of age) hypertensive adults resulted in 12 mmHg versus 4.5 mmHg reductions in systolic blood pressure, and 8 mmHg versus 3.5 mmHg reductions in diastolic blood pressure (Molmen-Hansen et al. 2012).

A meta-analysis of randomized controlled trials that included > 2400 participants with at least 1 additional coronary heart disease risk factor (e.g., myocardial infarction or stroke, type 2 diabetes, current cigarette smoking, or other atherosclerotic cardiovascular disease) showed that exercise was inversely related with

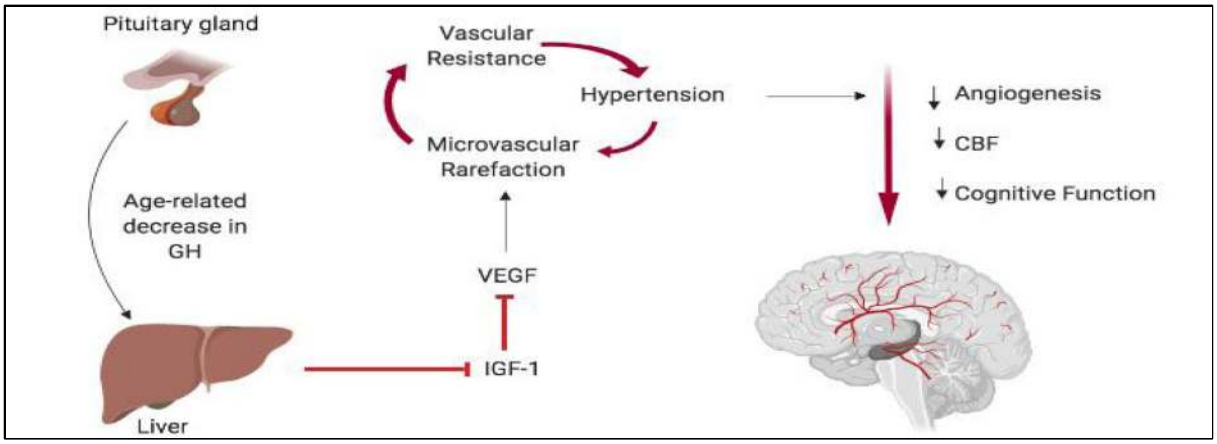

Fig. 2 GH/IGF-1 deficiency cascade leading to microvascular rarefaction. GH growth hormone, IGF-1 insulin-like growth hormone, VEGF vascular endothelial growth factor, CBF cerebral blood flow (Created with BioRender.com)

reductions in mean systolic and diastolic blood pressure, with the blood pressure-lowering effects of exercise simulating those achieved by pharmaceutical antihypertensive treatments (ALLHAT 2002).

Microvascular rarefaction

A decrease in microvascular density has been implicated in onset of hypertension (Antonios et al. 1999), in which lower skin capillary density serves a pathogenic role in increased peripheral resistance and hypertension (Ciuffetti et al. 2002; Lee 2002). This effect was illustrated in a study that examined cardiovascular reactivity and capillary density during exercise in 61 untreated newly diagnosed hypertensive men (27–48 years old), and in 26 age-matched normotensive healthy controls. Significantly higher blood pressure and heart rate were recorded in hypertensive subjects (Ciuffetti et al. 2003). Compared to healthy controls, those with hypertension showed marked decreases in capillary density, abnormal cardiovascular reactivity to exercise stress, a reduction in total peripheral resistance and increased vasoconstriction (Ciuffetti et al. 2003). A recent study reported in the Journal of the American College of Cardiology (JACC) reported similar results in 50 untreated, newly diagnosed hypertensive adults (25–40 years of age). After 12 weeks of moderate intensity exercise, blood pressure decreased significantly along with corresponding increases in retinal capillary density (Liang et al. 2019a). In addition, moderate intensity exercise enhanced endothelial function leading to decreased MVR (Liang et al. 2019b).

Exercise-induced IGF-1 increase in blood flow and cognition

The systemic effects of fitness initiate cellular and molecular events in the CNS that trigger improvements in structure, cognition, and memory (Bherer et al. 2013; Erickson et al. 2013; Erickson et al. 2011; Floel et al. 2010; Lucas et al. 2012; Ruscheweyh et al. 2011; Tsai et al. 2015; Vaughan et al. 2014), and mitigate the effects of age-related decline (Bherer et al. 2013). Moreover, exercise is neuroprotective (Coelho et al. 2013; Coelho et al. 2014; Currie et al. 2009; de Melo Coelho et al. 2013; Neeper et al. 1995; Neeper et al. 1996; Stein et al. 2018; Voss et al. 2016; Wrann et al. 2013; Zhao et al. 2016; Zoladz et al. 2008) and enhances poststroke recovery (Oberlin et al. 2017).

Compelling evidence indicates that improvements in the brain are linked to a biochemical cascade stimulated by exercise-induced increases in blood flow. Exercise has been shown to alter cerebrovascular function by increasing reactivity to CO_2 thus increasing cerebral perfusion (Braz and Fisher 2016), enhancing CBF (Ainslie et al. 2008; Bailey et al. 2013; Lucas et al. 2015), and hippocampal blood volume (Pereira et al. 2007) in older individuals. Exercise-induced increase in shear stress in blood vessels initiate the formation of reactive oxygen species (ROS) (Radak et al. 2013b) and vascular inflammation (Gleeson et al. 2011). Both ROS and inflammation have damaging effects on endothelial function (Thomas et al. 2008). However, chronic exercise may function as a preparatory mechanism that decreases oxidative damage on the vasculature via release of peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1-α), a transcriptional coactivator, that induces mitochondrial biogenesis and modulates ROS (Austin and St-Pierre 2012; Radak et al. 2001; Radak et al. 2013a; Yokokawa et al. 2018). Further, exercise has been shown to reduce the effects of ischemic injuries by increasing vascular integrin expression (membrane receptor adhesion molecules involved in growth factor regulation during angiogenesis) and microvascular density in the brain (Ding et al. 2006b; Eliceiri and Cheresh 2000).

Additionally, evidence from both animal and human research indicates that exercise stimulates the synthesis and release of growth factors (Cassilhas et al. 2007b; Cotman et al. 2007; Fabel et al. 2003). Interactions between IGF-1, VEGF, and BDNF facilitate the effects of chronic exercise on cerebrovascular function (Cotman et al. 2007; Fabel et al. 2003) and promote and protect axonal and dendritic outgrowths, and neuronal cell differentiation.

IGF-1 signaling is considered a causal mediator of exercise-induced structural and functional brain changes with a similar downstream cascade to BDNF, such that inhibition of IGF-1 abolished the effects of exercise on BDNF and memory functions in animals (Carro et al. 2000; Ding et al. 2006a). Moreover, exercise has been shown to increase uptake of hepatically released IGF-1 into the hippocampus (Trejo et al. 2007). PGC1-α, a VEGF stimulator (Arany et al. 2008), is released by skeletal muscles and functions as a master regulator of mitochondrial biogenesis (Yokokawa et al. 2018) by

reducing insulin's inhibitory effects on GH and IGF-1 (Ji and Kang 2015). Reducing the impact of insulin on GH and IGF release was highlighted in a study in which therapeutic introduction of IGF-1 contributed to reversal of mitochondrial dysfunctions, including apoptosis and tissue damage, hypertension, and neurological deficits (Sádaba et al. 2016).

Specifically, exercise-induced elevations in IGF-1 levels have been linked with perfusion changes (Maass et al. 2016; Schwarz et al. 1996; Stein et al. 2018). Exercise has been shown to elicit a 40% increase in IGF-1 leading to an increase in cerebral microvascular density, whereas suppression of IGF-1 prevented angiogenesis in adult mice (Lopez-Lopez et al. 2004). Similar results were reported by Fernandes et al. (2012), wherein capillary rarefaction and decreased levels of VEGF were observed in an untreated animal model of hypertension (Fernandes et al. 2012), and an exercise intervention re-established VEGF levels with parallel attenuation of capillary rarefaction in skeletal muscles (Fernandes et al. 2012).

Animal studies have illuminated the role of exercise-induced growth factor release and their role in enhanced cognition (Lazarov et al. 2010; van Praag 2008; van Praag et al. 1999a; van Praag et al. 2005). IGF-1-stimulated BDNF and VEGF release have been implicated in neurogenesis, synaptogenesis, angiogenesis (Ding et al. 2006a; Lopez-Lopez et al. 2004), and capillarization (Cassilhas et al. 2007b). IGF-1 activates a molecular cascade associated with neuronal differentiation from stem cells (neurogenesis) (van Praag et al. 1999b; van Praag et al. 2005) and enhances neurite outgrowth and synaptogenesis via the BDNF pathway (Chao et al. 2006; Eadie et al. 2005). IGF-1 signaling is considered a causal mediator of exercise-induced structural and functional brain changes, and inhibition of this pathway appears to abolish the effects of exercise on BDNF and memory functions in animals (Carro et al. 2000; Ding et al. 2006a). Moreover, a recent study in brain-specific IGF-1 overexpressing mice highlights the generalized benefits of IGF-1 (Farias Quipildor et al. 2019). Compared to younger control mice, chronic exposure to IGF-1 in aged mice enhanced hippocampal and white matter volumes, increased myelin densities and exercise tolerance (preferentially in male mice) but did not prevent age-related cognitive decline. Follow-up delivery of intranasal IGF-1 in the same aged mice, however, restored learning and memory and enhanced neurogenesis (Farias Quipildor et al. 2019).

Similarly, results from human studies have implicated a role for exercise-induced growth factor release in cognition. A 1-year exercise intervention in healthy young men showed elevations in serum IGF-1 levels (Schwarz et al. 1996). The relationship between cognitive function and IGF-1 was investigated in a study of 75 of elderly (65 years of age) hypertensive patients. Serum IGF-1 was significantly correlated with cognition, such that those with cognitive impairment had lower IGF-1 levels and more pronounced temporal lobe and hippocampal atrophy than those with normal cognitive scores (Angelini et al. 2009). In a later study, IGF-1 levels were measured in 3582 older adults (mean age = 79 years) free of dementia at baseline, and another group of participants (N = 2053) free of dementia or stroke who underwent brain MRI. After a mean follow-up period of 7.4 years, participants with the lowest IGF-1 levels had a 51% greater risk of Alzheimer's dementia, and those with higher levels of IGF-1 had greater brain volumes (Westwood et al. 2014). Similar results have been observed with resistance training. A 12-week resistance training intervention in older (mean age > 60 years old) sedentary women resulted in an increase in IGF-1 levels (Vale et al. 2017), and increased IGF-1 was positively related with cognitive function in older adults after a 52-week intervention (Tsai et al. 2015), and after a 24-week intervention in 62 sedentary elderly (Cassilhas et al. 2007a).

Conclusions

We have summarized data from diverse lines of investigation that demonstrate age-related decreases in GH/IGF-1 and their physiological and clinical effects. Based on this evidence, we propose that essential hypertension is partly mediated by IGF-1 deficits that result in MVR and increased vascular resistance, which precede a reduction in CBF, and may be causally related to increased blood pressure and cognitive impairment. A convergence of findings from exercise studies are consistent with our premise and provide further support for this hypothesis. Given the evidence that exercise increases endocrine and paracrine release of IGF-1, thereby stimulating systemic and central angiogenesis, reversing vascular resistance, decreased CBF, and

cognitive dysfunctions, we suggest that exercise-mediated release of growth factors may be necessary and sufficient for reversal of age-related reductions in IGF-1, MVR, and hypertension. For instance, exercise in animal models has been shown to elicit a 40% increase in IGF-1 leading to an increase in cerebral microvascular density, whereas suppression of IGF-1 prevented angiogenesis (Lopez-Lopez et al. 2004). Overall, our conclusion highlights previous work that linked MVR with decreased IGF-1 levels (Sonntag et al. 2000; Sonntag et al. 1997), and others that posited that loss of microvascular density may be a primary hypertensinogenic factor (Antonios et al. 1999; Brandes 2014; Feihl et al. 2006; Greene et al. 1989; Humar et al. 2009; le Noble et al. 1998; Levy et al. 2001).

Whether IGF-1 deficiencies and MVR in hypertension are causally related remains an open question. Future studies will be needed to ascertain the extent to which growth factors might provide an explanation for the association between exercise and reversal of systemic MVR, hypertension, and cognitive changes via IGF-1 release. If our hypothesis is confirmed, the ability for exercise to prevent or reverse MVR and hypertension, via activations of the endocrine and paracrine growth factor pathways, would have implications for age-related cognitive decline. This is especially meaningful given that onset of essential hypertension often occurs in the fourth decade of life, with nearly 44% of those becoming hypertensive before 44, and another 47% developing hypertension between 45 and 54 years of age (Muntner et al. 2018). Since chronic hypertension increases the risk for cardiovascular diseases and target-organ damage (Cutler 1996), and chronic untreated hypertension in middle age has harmful effects on late-life cognitive function, prevention of early hypertensive states is of critical importance.

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