Exercise and Vascular Insulin Sensitivity in the Skeletal Muscle and Brain

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OLVER, T.D., M.H. LAUGHLIN, and J. PADILLA. Exercise and vascular insulin sensitivity in the skeletal muscle and brain. *Exerc. Sport Sci. Rev.*, Vol. 47, No. 2, pp. 66–74, 2019. *We present the hypothesis that exercise-induced hyperemia, perhaps through vascular shear stress, represents an important factor responsible for the effects of physical activity (PA) on vascular insulin sensitivity. Specifically, we postulate PA involving the greatest amount of skeletal muscle mass and the greatest central neural recruitment maximizes perfusion and consequently enhances vascular insulin sensitivity in the skeletal muscle and brain.* **Key Words:** vascular insulin signaling, skeletal muscle, brain, physical activity, exercise, blood flow, shear stress

Key Points

- Insulin resistance in the skeletal muscle and brain vasculatures represents a unifying pathology linking metabolic, neuro-, and vascular diseases.
- Routine physical activity (PA) is an effective therapeutic approach to optimize vascular insulin signaling in the skeletal muscle and brain.
- PA that involves a large skeletal muscle mass and modulates intensity to recruit more muscle fibers within each muscle, as well as requires a significant central neural recruitment, will maximize vascular adaptations that promote vascular insulin sensitivity in the skeletal muscle and brain.
- Future research should focus on whether vasometabolic and vasoneural treatment outcomes in preclinical and clinical populations with insulin resistance are improved when such mechanistic concepts are integrated into prescriptive-based PA interventions.

INTRODUCTION

In 1939, Abramson *et al.* (1) examined the vascular actions of insulin shock therapy and reported that insulin-induced hypoglycemia resulted in increased peripheral limb blood flow in patients with schizophrenia. Shortly thereafter, Ferris *et al.* (2) and later Porta *et al.* (3) demonstrated that insulin-induced hypoglycemia either had no effect or a small vasodilatory effect on intracranial/cerebral blood flow in patients with schizophrenia. Granted these initial observations do not reflect nonpathological conditions, these findings highlight the earliest direct evidence of insulin-stimulated vasodilation in the peripheral vasculature.

Since then, researchers have validated and extended upon earlier findings by demonstrating that physiological and pharmacological doses of exogenous insulin stimulate peripheral vasodilation during euglycemia (4–8) and by providing evidence that endogenous insulin also stimulates vasodilation (9–12). Notably, the magnitude of insulin-stimulated peripheral vasodilation appears blunted in the setting of various insulin-resistant states in humans (*i.e.*, obesity and type 2 diabetes (T2D)) (9,11,13–15) and in experimental animal models (diet-induced and genetic models of T2D as well as insulin-treated T1D) (16–24). There is growing consensus that insulin-stimulated vasodilation is a physiologically relevant phenomenon and depressed insulin-stimulated vasodilation serves as a hallmark of vascular dysfunction (21,25–28). Being physically active or participating in structured exercise training can improve insulin-stimulated vasodilation in the setting of health and disease, with such improvements occurring most readily in tissue regions that undergo a relative increase in activity during the transition from rest to exercise (21,28). Herein, we address the hypothesis that exercise-induced improvements in vascular insulin sensitivity occur in a region-specific manner within the skeletal muscle and cerebral vasculatures and in relation to local increases in blood flow during exercise (Fig. 1).

Brief Overview of Endothelial Insulin Signaling

Available evidence indicates the peripheral hemodynamic effects of insulin are mediated by a combination of neurohumoral (6,8,29–33) and endothelial vasodilator and vasoconstrictor signals (19,21,25,27,28,34–36). This review will focus primarily on the effects of insulin on the vascular endothelium and endothelial mechanisms through which exercise training exerts therapeutic benefits on vascular insulin sensitivity.

At the molecular level, insulin binds to endothelial insulin receptor substrate-1 (IRS-1), which activates two primary signaling cascades, the phosphatidylinositol-4,5-bisphosphate 3-kinase

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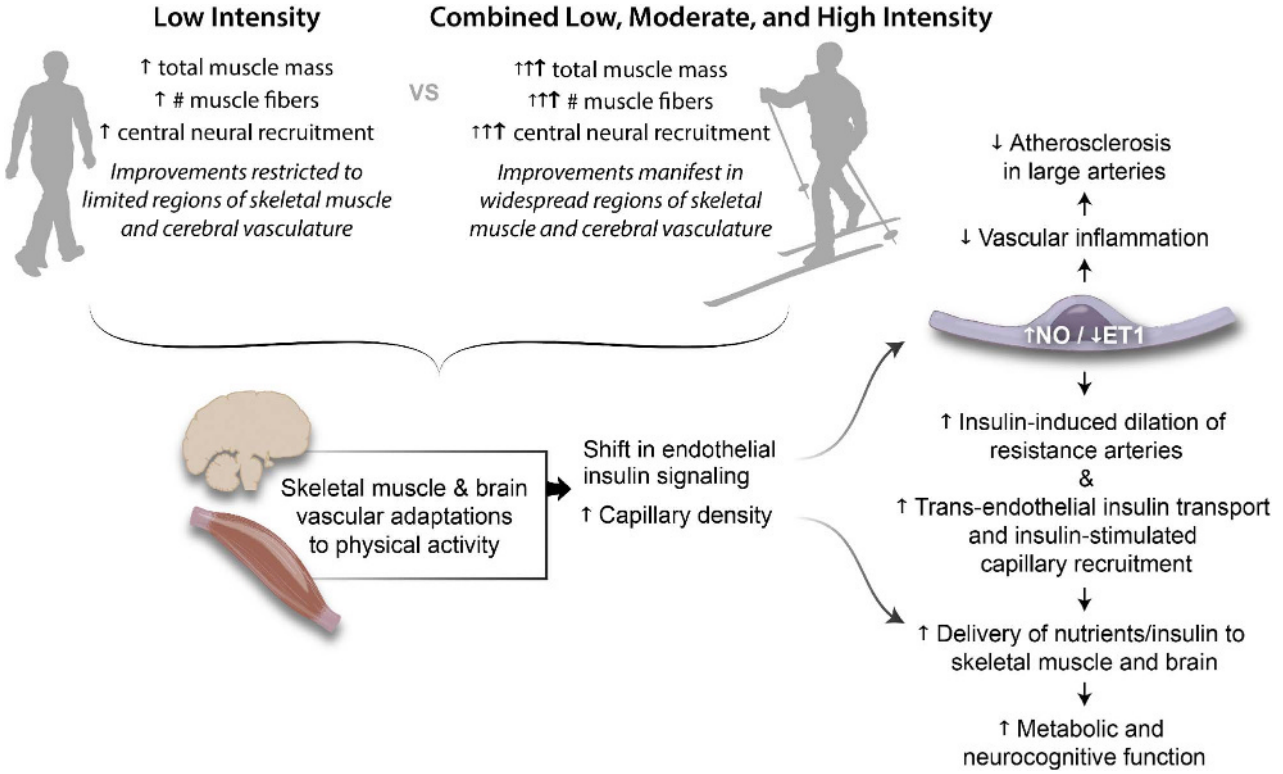

Figure 1. Skeletal muscle and brain vascular adaptations to physical activity include enhanced endothelial insulin sensitivity and capillary density. Adaptations occur primarily in arteries that supply tissue regions that undergo a relative increase in activity during exercise. Whereas low-intensity walking involves recruitment of a small amount of total muscle mass, few muscle fibers within each muscle and a small population of neurons in a small number of brain regions; combined low-, moderate-, and high-intensity cross-country skiing involves recruitment of a large amount of total muscle mass, many muscle fibers within each muscle, and requires activation of a larger population of neurons from a greater number of brain regions. Therefore, we speculate that compared with low-intensity walking (or any similar exercise that only involves a small amount of skeletal muscle and neural recruitment), cross-country skiing (or any similar whole-body exercise where intensity and duration can be manipulated to modulate the total number of skeletal muscle fibers and brain regions involved) confers more widespread improvements in vascular insulin sensitivity and capillary density. Enhanced endothelial insulin sensitivity corresponds with greater production of nitric oxide (NO) relative to endothelin-1 (ET-1). This shift is associated with reduced vascular inflammation and attenuated progression of atherosclerosis in conduit arteries, improved insulin-induced dilation in resistance arteries, increased insulin-stimulated capillary recruitment, enhanced nutrient delivery, and potentially augmented transendothelial insulin transport in the skeletal muscle and the brain. Improvements in nutrient delivery are further enhanced by physical activity–induced increases in microvascular volume/capillary density. The cumulative effect of enhanced vascular insulin sensitivity and capillary density may include improved metabolic and neurocognitive function in the skeletal muscle and brain, respectively.

(PI3K)/protein kinase B (Akt)/nitric oxide (NO) pathway and the Ras/mitogen-activated protein kinase (MAPK)/endothelin-1 (ET-1) pathway (25,36) (Fig. 2). Activation of the former pathway induces anti-atherogenic and vasodilator signaling, whereas activation of the latter pathway induces pro-atherogenic and vasoconstrictor signaling. Under healthy circumstances (in many vascular beds/arteries), the net effect of insulin administration is a NO-dependent vasodilation suggesting activation of the PI3K/Akt/NO pathway predominates (25,27,36).

Selective vascular insulin resistance refers to a shift in endothelial insulin signaling reflected by decreased IRS-1–induced activation of PI3K/Akt/NO with no change or increased activation of MAPK/ET-1 (25,36). Thus, the imbalance promotes pro-atherogenic and ET-1–dependent vasoconstrictor signaling (16,17). Current evidence suggests that selective vascular insulin resistance may occur early in the development of metabolic derangement (11,18) and is implicated in decreased elasticity and progression of atherosclerosis in conduit arteries, impaired blood flow control, reduced capillary perfusion and nutrient delivery, and limited transendothelial nutrient/insulin transport within specified tissues/organs (21,25–28). The underlying causes of vascular insulin resistance are likely multifactorial. In the setting of insulin deficiency or insulin resistance, lipotoxicity, glucotoxicity, inflammation, and oxidative stress may all serve a role in directly and indirectly impairing insulin signaling (25,36,37). For example, the aforementioned metabolic perturbations are implicated in elevating endothelial cell diacylglycerol that activates protein kinase C isoforms and subsequently reduces tyrosine phosphorylation of IRS-1, decreasing the downstream activation of the Akt and NO pathway. Furthermore, hyperinsulinemia also may enhance MAPK activation directly, which can inhibit subsequent IRS-1 activation and downstream signaling (25,36). Indeed, published animal work shows obesity/T2D or palmitic acid-induced deficits in insulin-stimulated vasodilation in isolated arterioles can be reversed acutely with inhibition of protein kinase C beta (18) or theta (38) as well as ET-1A receptor inhibition (19).

Routine exercise consistently enhances vascular insulin sensitivity (for review, see (21,28)). Initial cross-sectional data reveal insulin-stimulated vasodilation in the lower limb is greater in endurance-trained athletes compared with otherwise healthy sedentary controls (39). In healthy control rodents and rodents with insulin-treated type 1 diabetes, improvements in insulin-stimulated vasodilation after endurance training are associated with increases in endothelial NO synthase protein (20). Of note, in the latter study, insulin treatment was adjusted biweekly to equalize hyperglycemia/blood glucose concentrations for all rats

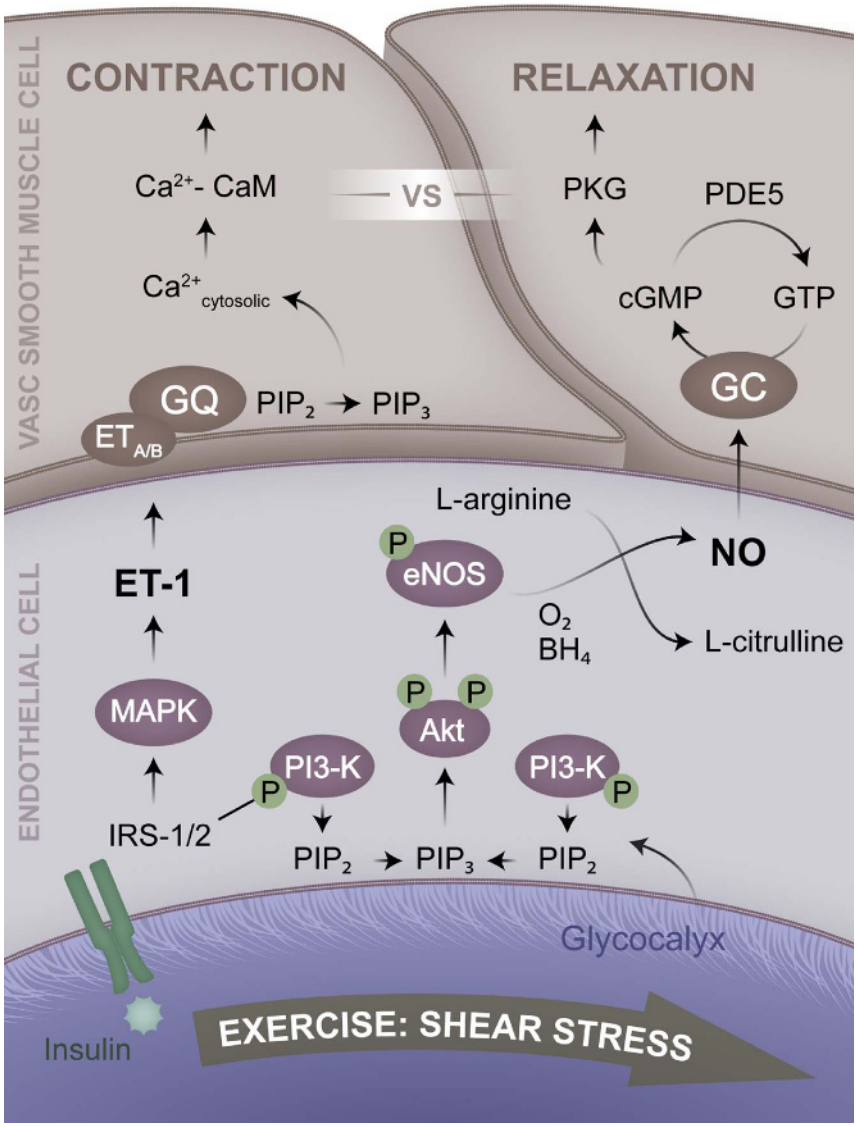

Figure 2. Schematic depicting the dependence of both vascular shear stress and endothelial insulin signaling on the PI3K/Akt/NO pathway signaling cascade. Briefly, vascular shear stress causes the deformation of luminal endothelial mechanoreceptors/glycocalyx that stimulates intracellular activation of the PI3K/Akt/NO pathway and insulin stimulates activation of both the endothelial PI3K/Akt/NO and the MAPK/ET-1 pathway. The vascular actions of insulin are influenced by the balance between the two pathways. The dependence of both vascular shear stress and endothelial insulin signaling on the PI3K/Akt/NO pathway raises the possibility that vascular shear stress enhances vascular insulin sensitivity by promoting activation of the PI3K/Akt/NO pathway. VASC, vascular; IRS1/2, insulin receptor substrate 1/2; $ET_{A/B}$, endothelin receptor; CaM, calcium calmodulin complex; cyt, cytosolic; PIP, phosphatidylinositol 4,5-phosphate; GC, guanylate cyclase; PDE5, phosphodiesterase 5; eNOS, endothelial NO synthase; O_2, oxygen; BH_4, tetrahydrobiopterin; P, phosphorylated.

with type 1 diabetes, highlighting that the therapeutic effect of endurance training occurred independent of chronic improvements in hyperglycemia. Furthermore, when comparing wheel-running with metformin or food restriction in obese/T2D rodents, although all treatments exerted similar beneficial effects on body composition and HbA1c, only wheel-running improved insulin-induced dilation in isolated skeletal muscle arterioles (22,40,41). Collectively, these data suggest that the beneficial effect of regular exercise is conferred independent of fat loss and enhanced glycemic control and may be related to local or systemic signals subjected to the vasculature during exercise (Fig. 1). To better understand the mechanisms responsible for the therapeutic benefits of acute and chronic exercise, we now discuss some of the signals experienced by the vasculature in response to exercise as well as some key chronic vascular adaptations to exercise training.

EXERCISE AND VASCULAR SHEAR STRESS — SKELETAL MUSCLE

Generally, the skeletal muscle is grouped into three fiber types classified according to both their contractile and metabolic properties (42): slow-twitch oxidative (SO); fast-twitch, glycolytic (FG); and fast-twitch, oxidative, glycolytic (FOG). Skeletal muscle blood flow increases with exercise intensity and is distributed heterogeneously within and among skeletal muscles in relation to fiber-type composition and recruitment during exercise (43–52). During the transition from rest to maximal exercise, skeletal muscle blood flow may increase up to a 10-fold and can reach up to 300–400 $mL \cdot 100\ g^{-1} \cdot min^{-1}$ (45,53,54). Of interest, the vasculature supplying skeletal muscle fibers that undergo a relative increase in activity during exercise may experience increased vascular shear stress (*i.e.*, the frictional force of blood acting against the lumen wall) during exercise (45,53).

Vascular shear stress causes the deformation of a population of mechanoreceptors that appear to be coupled to glycocalyx, located on the apical surface of endothelial cells. This in turn activates the mechanosensitive PI3K/Akt/NO signaling pathway (53,55) (Fig. 2). It is currently believed that acute or repeated exposure to exercise-induced increases in vascular shear stress, and by extension acute or repeated exposure to enhanced endothelial PI3K/Akt/NO signaling, is involved in changes in vasomotor control (*i.e.*, improved endothelial-dependent vasodilation) (23,56,57) and vascular remodeling (reflected by an increase in the number, diameter, and density of arterioles and capillaries) in active skeletal muscle (45,49,53,58–71). It is important to note that available evidence, predominantly from animals, suggests that exercise training modulates vascular function and structure of arteries/arterioles in spatially distinct (45,61,71–84), intensity-dependent manner (23,45,58–62,69) and adaptations tend to be concentrated in the muscle tissue that experiences the greatest relative increase in activity during training sessions (58–60,70,85–91). For example, both moderate-intensity continuous endurance and high-intensity interval training increase capillary density in animals (69) and humans (21,63,64); however, work in animals suggests that such increases in capillary density after training occur predominantly in SO versus FOG/FG muscle fibers, respectively (21,49,69,89,90). This phenomenon is perhaps not as clear in humans, as recent work from Cocks *et al.* (63) shows that although the increase in capillary density in the vastus lateralis of obese men tends to be greater after moderate-intensity continuous (40–60 min·d^{-1} at 65% $\dot{V}O_{2peak}$, 5 d·wk^{-1}, for 4 wk) than high-intensity interval sprint (4–6× repeat Wingate tests, interspersed with 4.5 min rest, 5 d·wk^{-1}, for 4 wk) cycling training (19% vs 6%, respectively), training-induced increases in capillary-to-fiber ratio or capillary contacts per fiber were similar between training regimens and not fiber-type specific. Of note, these results may be influenced by the skeletal muscle examined and muscle fibers sampled between groups as well as pre-/posttraining, as the vastus lateralis contains SO, FOG, and FG fibers and the depth and fiber composition of the muscle biopsy may impact the results (92,93).

Acute and Chronic Exercise — Vascular Insulin Signaling

In hallmark studies, Dela *et al.* (94,95) examined the effect of either one-legged cycling (30 min·d^{-1} at 70% $\dot{V}O_{2peak}$, 6 d·wk^{-1}, for 10 wk) (94) or resistance exercise training (leg press, knee extension, and hamstring curls; 3–4 sets of 8–12 repetitions at ~70%–80% 1 repetition-max, performed 3 d·wk^{-1}, for 6 wk) (95) on lower limb blood flow responses during a euglycemic hyperinsulinemic clamp in patients with T2D. They found that insulin-mediated vasodilation and glucose clearance were greater in the trained limb, but not in the untrained limb, from pre- to posttraining. They reported similar findings in young and old men after the same one-legged cycling program (96), and more recently, similar findings were documented after a single bout of one-legged cycling exercise (~50% peak workload for 60 min, with 3 × 5 min intervals at 100% peak workload) (97). Eskelinen *et al.* (98) examined insulin-stimulated glucose uptake in the upper and lower limbs after either moderate-intensity endurance (40–60 min·d^{-1} at 60% $\dot{V}O_{2peak}$, 3 d·wk^{-1}, for 2 wk) or high-intensity interval sprint (4–6× repeat Wingate tests, 3 d·wk^{-1}, for 2 wk) cycling training and reported that training-induced improvements in skeletal muscle glucose uptake were restricted to the lower limbs (*i.e.*, active skeletal muscle). Furthermore, although both training programs improved glucose uptake in the vastus lateralis, intermedius, and medialis, only interval sprint training increased glucose uptake in the rectus femoris (98). The authors speculated that the latter observation related to different muscle activation patterns during exercise and the inability of moderate-intensity endurance exercise to activate the rectus femoris (see Table). The relation between skeletal muscle fiber recruitment during exercise and vascular insulin sensitivity is further exemplified by work in obese rats with T2D that shows that training-induced improvements in insulin-mediated vasodilation of resistance arteries after moderate-intensity continuous and high-intensity interval training are most robust in red and white portions of the gastrocnemius muscle, respectively (23,41). Taken together, these findings highlight the following important concepts: 1) the beneficial effects of exercise training on insulin sensitivity are related to improved insulin-stimulated vasodilation; 2) improvements in insulin-mediated vasodilation occur in relation to skeletal muscle activation and skeletal muscle fiber recruitment within each muscle during exercise (*i.e.*, in relation to the exercise hyperemic response); and 3) such improvements can be conferred with acute and chronic exercise as well as independently of long-term improvements in body composition or metabolic status.

Shear Stress and Insulin Signaling — Crossing Paths

Vascular shear stress and insulin-stimulated vasodilation are both reliant on activation of the PI3K/Akt/NO pathway (36,55) (Fig. 2). Of note, the vascular insulin-sensitizing effect of exercise seems to be restricted to portions of the vasculature that undergo a relative increase in blood flow during exercise (23,41,94,97,99). Furthermore, recent human work reveals that improvements in insulin-stimulated lower limb microvascular perfusion and leg glucose uptake 4 h after one-legged cycling exercise are blunted (to nonexercised levels) with NO inhibition administered during the insulin clamp (97). Given that exercise-related improvements in insulin signaling can occur independent of longstanding changes in metabolic status, are localized to active skeletal muscle, and blunted by NO inhibition, this raises the possibility that vascular shear stress primes endothelial cells to become more insulin sensitive and enhance insulin-stimulated NO signaling. In support of this view, recently published work established that the insulin-sensitizing effects of vascular shear stress are independent of skeletal muscle contraction (100). First, it was demonstrated in cultured human aortic endothelial cells that compared with cells exposed to low shear conditions (3 dynes·cm^{-2}), those exposed to 1 h of increased shear stress (20 dynes·cm^{-2}) subsequently exhibited a shift in insulin signaling characterized by an increased activation of endothelial NO synthase relative to MAPK. Second, it was demonstrated in isolated porcine skeletal muscle resistance arteries that compared with arteries kept under no-flow conditions, those exposed to 1 h of increased shear stress (20 dynes·cm^{-2}) subsequently displayed enhanced insulin-stimulated vasodilation. Previous shear stress only augmented insulin-stimulated vasodilation and not endothelium-independent vasodilation, suggesting that the effect is conferred through an endothelial-dependent mechanism. Lastly, the translational relevance of these *in vitro* findings was validated by demonstrating that compared with

TABLE. Human studies examining the effect of exercise on vascular insulin signaling

Study Type/Authors	Population	Physical Activity	Main Findings
		Cross-sectional observations	
Ebeling *et al.* (1993) (116)	Healthy men (28 ± 2 yr)	Bandy players vs sedentary control	Insulin did not induce significant vasodilation, but Brandy players displayed increased blood flow and insulin-stimulated glucose uptake in the forearm
Hardin *et al.* (1995) (39)	Healthy men (25 ± 1 yr)	Endurance athletes vs sedentary control	Runners displayed greater insulin-stimulated vasodilation and glucose uptake in the lower limb
		Acute exercise intervention	
Richter *et al.* (1989) (5)	Healthy men (21–24 yr)	Single leg cycle ergometer exercise (75% of max work capacity for 60 min)	Exercise improved insulin-stimulated glucose uptake but not lower limb vasodilation
Bisquolo *et al.* (2005) (117)	Healthy men (32 ± 2 yr)	Cycle ergometer exercise (50% peak O_2 uptake for 45 min)	Exercise improved insulin-stimulated vasodilation in the forearm
Sjøberg *et al.* (2017) (97)	Healthy men (25 ± 1 yr)	Single leg cycle ergometer exercise (50% peak workload for 60 min, with 3 × 5 min intervals at 100% peak workload	Exercise improved insulin-stimulated glucose uptake and vasodilation in the lower limb
		Exercise training intervention	
Dela *et al.* (1995) (94)	Healthy men and men with T2D (58 ± 3 yr)	Single leg cycle ergometer exercise (30 min per d at 70% $\dot{V}O_{2peak}$, 6 d per wk, for 10 wk)	Training improved insulin-stimulated glucose uptake and insulin-stimulated vasodilation in the trained limb
Dela *et al.* (1996) (96)	Healthy young (23 ± 1 yr) and old men (59 ± 1 yr)	Single leg cycle ergometer exercise (30 min per d at 70% $\dot{V}O_{2peak}$, 6 d per wk, for 10 wk)	Training improved insulin-stimulated glucose uptake and insulin-stimulated vasodilation in the trained limb
Holten *et al.* (2004) (95)	Healthy men and men with T2D (62 ± 2 yr)	Single leg strength training exercise (leg press, knee extensions, ham string curls, 3–4 sets for 8–12 reps at 70%–80% 1 RM, 3 d per wk, for 6 wk)	Training improved insulin-stimulated glucose uptake and insulin-stimulated vasodilation in the trained limb
Vinet *et al.* (2015) (118)	Healthy men and women and men and women with metabolic syndrome (59 ± 1 yr)	Lifestyle intervention: diet education program with monitored walking or aqua gym and resistance training (8 exercises, 3 sets of 10 repetitions, 4–5 d per wk for 6 months)	Lifestyle intervention improved insulin-stimulated cutaneous perfusion response
Eskelinen *et al.* (2015) (98)	Healthy men (40–55 yr)	Moderate continuous endurance cycling (60% $\dot{V}O_{2max}$ for 40–60 min, 3 d per wk for 2 wk) or high-intensity interval sprint cycling (4–6 repeated Wingate tests, interspersed with 4.5 min recovery, 3 d per wk for 2 wk)	Training improved insulin-stimulated glucose uptake in lower vs upper limbs, with high-intensity training affecting a greater amount of quadriceps muscle tissue
Honkala *et al.* (2017) (115)	Insulin resistant men and women (44–54 yr)	Moderate continuous endurance cycling (60% $\dot{V}O_{2max}$ for 40–60 min, 3 d per wk for 2 wk) or high-intensity interval sprint cycling (4–6 repeated Wingate tests, interspersed with 4.5 min recovery, 3 d per wk for 2 wk)	Only high-intensity sprint training increased aerobic capacity and reduced insulin-stimulated glucose uptake in the brain
Russel *et al.* (2017) (119)	Men and women with T2D (52 ± 2 yr)	Whole-body resistance training (leg press, pull down, chest press, lunges, seated row, back fly, bicep curl, incline chest press, dumbbell shoulder press, leg extension, leg curl, dips, lateral raise, triceps extensions, dumbbell deadlift and push-ups, 1 set of 6–15 reps at 65%–85% 1 RM, 3 d per wk for 6 wk)	Training improved forearm skeletal muscle, but not skin, microvascular blood flow response to an oral glucose challenge

RM, repetition maximum.

the control leg, single leg heating resulting in increased blood flow, and likely attendant increase in shear stress, caused a subsequent augment in popliteal artery blood flow and calf microvascular perfusion in response to a systemic infusion of insulin. Collectively, these findings support the hypothesis that vascular shear stress may be a primary mechanism through which exercise enhances vascular insulin sensitivity.

Other vascular adaptations likely responsible for the effects of exercise training on insulin-stimulated glucose/insulin delivery and transendothelial insulin transport are increases in microvascular perfusion/capillary recruitment (97,101) and increased capillary volume or density (63,102–104). In this regard, an increased capillary density after moderate continuous aerobic training (45 min·d^{-1} at 75% $\dot{V}O_{2max}$, 3 d·wk^{-1}, for 6 months) independently increases insulin sensitivity in older adults (102). Indeed, enhanced vascular density and volume after aerobic training (21) provide greater potential for delivery of nutrients and insulin to the target organ (Fig. 1).

FUTURE PERSPECTIVES

Exercise and Endothelial Insulin Signaling in the Brain

In contrast to the skeletal muscle, global brain blood flow increases only modestly (~0%–20%) during incremental exercise until ~60% $\dot{V}O_{2max}$ and may remain unchanged or decrease at higher intensities (likely the result of decreasing $PaCO_2$ values). However, evidence from miniature swine, dogs, ponies, and humans reveals that exercise increases regional brain blood flow in a structurally specific and intensity-dependent manner (up to ~70% above basal values within the most active structures (45,53,105)). Furthermore, recent human data indicate cerebral blood flow may increase in the recovery period immediately after high-intensity exercise (106). Brain regions recruited at the onset and during sustained exercise include those involved in central command, motor execution, equilibrium, cardiorespiration, auditory, olfactory, and visual regions (45,53). Although much less established, work in humans and animals indicates cerebrovascular adaptations to exercise training may be both structurally and intensity-dependent (53,107,108). With regards to the effects of exercise on vascular insulin signaling in the cerebrovasculature, recent work in obese rats with T2D reveals that increased physical activity (wheel-running) improves insulin-mediated cranial/cerebral vasodilation and maintains cerebellum blood flow during insulin stimulation *in vivo*. Furthermore, improvements in insulin-stimulated posterior cerebral artery vasodilation after wheel running were associated with an increased contribution of insulin-induced NO and decreased contribution of insulin-induced MAPK/ET-1 signaling (19). Of note, branches

of the posterior cerebral artery supply the cerebellum and the cerebellum is believed to be active during exercise, highlighting (similar to the skeletal muscle) exercise training-induced improvements in insulin-stimulated vasodilation may occur in relation to regional brain activation and corresponding blood flow responses during exercise (109–111).

Recent work in obese/T2D swine reveals impaired insulin-induced pial artery vasodilation coincides with depressed insulin-stimulated Akt signaling in the prefrontal cortex (18). The significance of insulin modulation of brain blood flow control and the role of insulin in central nervous system (CNS) function remain to be elucidated fully. However, it has become clearer that insulin signaling is critical to normal CNS function (*e.g.*, insulin action in the brain is involved in improving memory and mood, inhibiting food intake, reducing bodyweight, increasing peripheral insulin sensitivity, reducing gluconeogenesis and lipolysis in the fasting state, and increasing postprandial thermogenesis) and CNS insulin resistance is implicated in the abnormal regulation of behavior and neurocognitive impairment/pathologies (26). The brain relies predominantly on insulin-independent glucose uptake, and insulin stimulation has little effect on brain glucose metabolism in healthy individuals. However, insulin stimulation increases brain glucose uptake in individuals with impaired glucose tolerance (*i.e.*, insulin-stimulated glucose uptake is maximal in the fasting state under healthy but not insulin resistance conditions) (112). In stark contrast to the skeletal muscle, reduced insulin-stimulated brain glucose uptake may reflect improved metabolic/insulin sensitivity. Improvements in insulin sensitivity in the brain may be attributed to enhanced insulin transport across the blood brain barrier. Briefly, one mechanism through which transendothelial insulin transport is achieved is by binding to insulin receptors located on the luminal membrane of brain endothelial cells, becoming internalized through an endocytotic process and being shuttled across the endothelial cell. Insulin is then released and can interact with vascular smooth muscle cells, pericytes, and astrocytes or enter into the brain interstitial fluid and interact directly with neurons (23). Recent work in mice highlights that receptor-mediated transendothelial insulin transport in the microvasculature is NO-dependent (113) and represents a primary mechanism through which insulin uptake is achieved in the brain. Furthermore, diet-induced obesity in mice impairs transendothelial insulin transport in the brain (114). Whether exercise improves transendothelial insulin transport in the brain and whether such improvements are related to exercise-induced vascular shear stress have not been examined.

Recently, it was demonstrated that high-intensity interval sprint cycling training (4–6× repeat Wingate tests, 3 $d \cdot wk^{-1}$, for 2 wk), but not moderate-intensity endurance cycling training (40–60 $min \cdot d^{-1}$ at 60% $\dot{V}O_{2peak}$, 3 $d \cdot wk^{-1}$, for 2 wk), reduced glucose uptake during insulin stimulation in the cerebellum, superior frontal gyrus, medial frontal gyrus, temporal cortex, thalamus, cingulate gyrus, and occipital cortex (115). The authors speculated the superior effect of high-intensity interval sprint training may be the result of greater exercise-related neural recruitment, exercise-related changes in brain metabolism, and possibly improvements in insulin transport across the blood brain barrier. Sprint exercise lasting 30 s (performed on a cycle ergometer similar to the repeat Wingate protocol mentioned previously) is associated with a transient increase in the index of cerebral blood flow during the sprint, followed by a gradual decline to near or below baseline values by the end of the sprint and then a significant hyperemic response during the post-sprint recovery (lasting at least 60 s after the sprint) (106). Thus, it is conceivable that the hemodynamic effects of high-intensity interval exercise contribute to cerebrovascular adaptations to training that improve cerebrovascular insulin sensitivity (*i.e.*, improved insulin-stimulated NO signaling, enhanced vascular density/volume after training, and possibly improvements in transendothelial insulin transport). Indeed, mounting evidence from humans and animal models indicates regular exercise enhances cerebrovascular NO signaling, vascular volume, and capillary density in a region-specific and intensity-dependent manner within the brain (53,107,108). Furthermore, it is speculated that these adaptations are related to regional brain activation and vascular shear stress experienced during the exercise bout (53,107,108). Whether these exercise-induced signals or training-induced adaptations confer a benefit to CNS insulin signaling is an area for further study.

Vascular Training

Aerobic and resistance exercise training improve vascular insulin sensitivity with improvements occurring in the vascular supply of the skeletal muscles and possibly brain regions that undergo a relative increase in activity/blood flow during exercise (see Table). We contend that the added benefit of including different exercise modalities and incorporating low-, moderate-, and high-intensity exercise is not simply "more is better." Consider that different exercise modes and intensities require activation of different skeletal muscles, different fiber recruitment patterns, and different brain regions or populations of neurons within the same brain region. Therefore, using different modes and intensities of exercise will modulate the spatial distribution of functional and structural vascular adaptations to exercise training in both the skeletal muscle and the brain. As such, we postulate that providing the duration of the stimulus is sufficient (*i.e.*, one that exceeds a minimum threshold to induce adaptation); exercise programs designed to activate the most skeletal muscle and the most muscle fibers within each skeletal muscle (*i.e.*, the greatest relative increase in fiber recruitment during exercise) and require global, diverse, and integrated neural output (*i.e.*, learning and using complex and coordinated motor/sensorimotor activation use elements of strategy, consist of repetitive and novel stimuli, and engage multiple senses) will promote the most direct and widespread vascular adaptations. For this reason, we recommend modulating mode and intensity of exercise to maximize skeletal muscle fiber and CNS neural recruitment with the goal of generating the greatest enhancement in vascular insulin signaling in the most amount of vascular tissue (Fig. 1).

Participation in recreational physical activity or structured exercise training is widely accepted to be beneficial for metabolic and neurocognitive function. Likewise, they are essential in maintaining or improving vascular insulin sensitivity; however, the underlying mechanisms remain unresolved. We speculate that exercise-induced improvements in vascular insulin signaling are conferred, at least in part, through exercise-induced vascular shear stress. Accordingly, going forward, it is important that future research experimentally tests if indeed exercise-induced shear stress enhances vascular insulin sensitivity, as well as determines the molecular mechanisms by which this occurs. Additional unanswered questions are as follows:

- to what extent the skeletal muscle and brain microvasculature is subjected to increased shear stress during exercise?
- are the molecular mechanisms by which exercise enhances micro- and macrovascular insulin sensitivity the same?
- do exercise-induced improvements in vascular insulin signaling contribute to improvements in metabolic and neurocognitive function?
- do the effects of exercise-induced vascular shear stress extend beyond the vasculature (*i.e.*, does vascular NO production impart benefits in surrounding tissues?)?

These and other questions are critical in elucidating the underlying mechanisms responsible for the insulin-sensitizing effects of exercise on the vasculature and essential for the development of prescriptive-based personalized exercise medicine.

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