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Chapter 1

Insulin Resistance and Endothelial Dysfunction: Macro and Microangiopathy

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Additional information is available at the end of the chapter

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1. Introduction

Insulin has classically been considered a hormone that acts primarily on skeletal muscle, adipose tissue and the liver in the control of glucose homeostasis. However, recent evidence indicates that insulin is also a vascular hormone that has an essential role in both regulating glucose homeostasis through influencing blood flow (e.g. glucose uptake in skeletal muscle and adipose tissue) and in maintaining vascular health.

Among the most important cardiovascular actions of insulin is to stimulate production of the potent vasodilator nitric oxide (NO) from vascular endothelium, increasing blood flow to skeletal muscle and other target tissues. These actions take place not only on conduit arteries (i.e. macrovasculature), but also on resistance and terminal arterioles (i.e. microvasculature). Abnormally high insulin concentrations (i.e. early stage of type 2 diabetes) and/or insulin resistance (i.e. tissues do not respond to insulin normally) have a profound impact on vascular homeostasis that manifests as impaired endothelial function, vasodilation, microvessel disease (i.e. retinopathy and nephropathy), and enhanced vascular inflammation and atherosclerotic lesion formation.

Approximately 90-95% of patients with diabetes mellitus have type 2 diabetes, which is characterized by insulin resistance or the inability of insulin to exert its metabolic actions. Indeed, early in the disease the pancreas produces more and more insulin to compensate for insulin resistance in target tissues. Eventually the pancreas may 'wear out' and the patient may no longer be able to produce insulin. Furthermore, there is good support for the notion that insulin resistance is itself an important risk factor for cardiovascular disease.

Thus, this chapter is intended to summarize the current available literature describing the physiologic and pathophysiologic role of insulin in the vasculature, and the mechanisms underlying the development of vascular insulin resistance from three standpoints. First, the role of insulin in the vasculature will be discussed with a specific focus on the interactions between the vascular and metabolic effects of insulin. Second, the role that vascular insulin resistance may play in the pathogenesis of vascular disease will be explored. Finally, this chapter will present evidence for the beneficial effects of exercise and physical activity in managing insulin resistance (i.e. improved insulin sensitivity) and improving endothelial function.

2. Physiological role of insulin in the vasculature

2.1. Signaling pathways

It has been more than 90 years since the role of insulin in glucose homeostasis was first discovered. Since that time, it has been established that insulin receptors are expressed on nearly every cell surface in the body, and great strides have been made in understanding insulin signal transduction pathways. In the endothelium, insulin simultaneously stimulates the production of the vasodilator NO and the vasoconstrictor endothelin-1 (ET-1) through signaling pathways that closely parallel the insulin signaling pathways which regulate glucose uptake and cell growth and differentiation in skeletal muscle, adipose, and other tissues.

Typically, the net result of insulin stimulation in the vasculature is vasodilation, which serves to distribute blood flow to target tissues for glucose uptake. The hemodynamic effects of insulin typically account for up to 40% of insulin-stimulated skeletal muscle glucose uptake [1-10]. However, in insulin resistant states, the balance between the production of vasodilator and vasoconstrictor substances shifts, impairing insulin-stimulated vasodilation and contributing to reductions in insulin-stimulated glucose uptake [1, 2, 11-14].

2.1.1. Insulin signaling in the endothelium — Vasodilation

The insulin receptor is a cell-surface heterotetrameric protein comprised of two extracellular α subunits and two transmembrane β subunits joined by disulfide bonds. The binding of insulin to the extracellular α subunits initiates conformational changes that activate intrinsic tyrosine kinase activity on the intracellular portion of the transmembrane β subunits. Activation of the receptor tyrosine kinase promotes trans-autophosphorylation of the β subunits as well as the tyrosine phosphorylation of multiple docking proteins, including insulin receptor substrates 1 (IRS-1) and 2 (IRS-2). IRS-1 is necessary for insulin-stimulated production of NO in the endothelium [15], whereas IRS-2 is primarily implicated in delivery of insulin to the skeletal muscle interstitium [16] but may also contribute to NO production [17].

The src homology 2 (SH2) domain of the p85 regulatory subunit of phosphoinosiditde 3-kinase (PI-3K) binds to the tyrosine phosphorylated IRS-1, activating catalytic p110 subunit of PI-3K. PI-3K then converts the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2)

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to phosphatidylinositol 3,4,5-trisphosphate (PIP_3), which recruits 3-phosphoinositide-dependent protein kinase-1 (PDK1) and protein kinase B (PKB) to the plasma membrane where PDK1 activates PKB, also known as Akt. Finally, Akt directly phosphorylates endothelial nitric oxide synthase (eNOS) at Ser1177, catalyzing the conversion of L-arginine to L-citrulline and NO. Insulin may also stimulate the production of the vasodilator prostacyclin (PGI_2) from the vascular endothelium [18, 19]. Although the signaling mechanism appears to be independent of insulin-stimulated NO production, it has yet to be elucidated.

2.1.2. Insulin signaling in the endothelium — Vasoconstriction

In addition to stimulating the production of NO through the PI-3K/Akt pathway, insulin also stimulates the production of the potent vasoconstrictor ET-1 through a separate mitogen-activated protein kinase (MAPK) pathway [20-22]. The divergence of the two pathways originates at IRS-1 where the binding of PI3-K differentiates the NO pathway and the binding of growth factor receptor bound protein 2 (Grb2) initiates the ET-1 pathway.

As described above, the binding of insulin to the insulin receptor initiates a cascade of autophosphorylation events including the activation of the docking proteins IRS-1 and IRS-2. Concurrently, the Src homology containing (Shc) protein is also activated by the insulin receptor. Binding of the SH2 domain of Grb2 to the phosphorylated tyrosine residues of IRS-1 or Shc activates the preassociated guanosine triphosphate (GTP) exchange factor Sos (son of sevenless). Sos activates Ras (rat sarcoma), a small GTP binding protein, that subsequently binds and activates the serine-threonine protein kinase Raf (rapidly growing fibrosarcoma). Raf activates MAPK/extra-cellular signal-regulated kinase (MEK) which then activates ERK1/2, also known as p44/42 mitogen-activated protein kinase (MAPK). Activation of MAPK ultimately leads to insulin-stimulated production of ET-1 [20]. However, the specific cell signaling events linking the activation of MAPK and ET-1 production are poorly understood.

2.1.3. Insulin signaling in the endothelium — Opposing pahways

The branches of the insulin signaling pathway yielding NO and ET-1 are widely viewed as distinct. However, inhibition of the MAPK pathway augments activation of eNOS, and, conversely, blockade of the PI3K pathway enhances expression of vascular adhesion molecules downstream of MAPK [23], indicating that there is likely some interaction between the two branches of the insulin signaling cascade.

2.1.4. Anti-inflammatory and atheroprotective effects of insulin

The primary atheroprotective effects of insulin are exerted through the production of NO. In addition to being a vasodilator, NO also exhibits antithrombic, antifibrinolytic, and antiatherogenic properties, including mitigation of cell growth and proliferation and inhibition of platelet and leukocyte adhesion. NO also stimulates arteriogenesis (reviewed [24]) and mitochondrial biogenesis [25] and positively modulates mitochondrial function [26].

Additionally, insulin prevents tumor necrosis factor (TNF) α-induced apoptosis of endothelial cells by inhibiting caspase-9 activity [27] and increases the expression of antioxidant enzymes, including heme oxygenase-1 (HO-1) through the PI-3K/Akt pathway [28].

Activation of the insulin receptor creates a 'burst' of intracellular reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2). At normal physiological concentrations, H_2O_2 transiently inactivates negative regulators of insulin signaling, including protein tyrosine phosphatase 1B (PTP1B), protein phosphatase 2A (PP2A), and phosphatase and tensin homolog (PTEN). Thus, when the insulin receptor is activated, the resulting burst of H_2O_2, in effect, removes inhibition of signal transduction through the insulin signaling cascade.

In summary, insulin stimulates two pathways in the endothelium. One leads to the production of the vasodilator NO through PI3K and Akt, whereas the other mediates production of the vasoconstrictor ET-1 through MAPK (Figure 1).

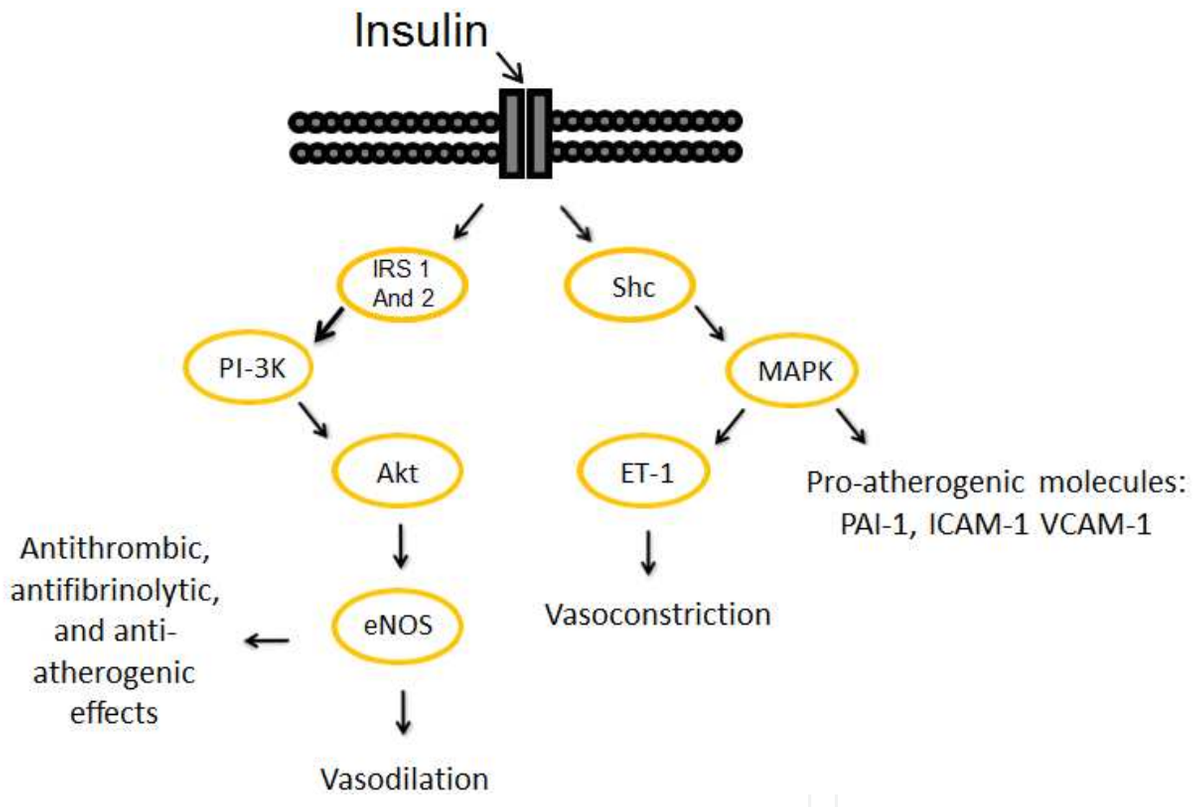

Figure 1. Insulin, vasodilation and vasoconstriction, pathways in the endothelium. IRS-1 and 2, insulin receptor substrate-1 and -2; PI-3K, phosphoinosiditde 3-kinase; Akt or PKB, protein kinase B; eNOS, endothelial nitric oxide synthase; Shc, Src homology containing; MAPK, mitogen-activated protein kinase pathway; PAI-1, plasminogen activator inhibitor type-1; ICAM-1, intracellular adhesion molecule; VCAM-1, vascular cell adhesion molecule; ET-1, endothelin-1.

2.2. Vascular effects

Insulin-stimulated production of NO from endothelium leads to capillary recruitment, vasodilation, increased blood flow to target tissues (e.g., skeletal muscle), and subsequent

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augmentation of glucose disposal. Removal of the endothelium or inhibition of NOS ablates insulin-stimulated vasodilation *in vitro* [29-34], and insulin-mediated blood flow is abolished by co-administration of the NOS inhibitor L-N^G-monomethyl-L-arginine (L-NMMA) *in vivo* [35, 36], establishing the critical role of NO in insulin-stimulated vasodilation.

Increases in circulating insulin that accompany ingestion of a mixed meal or a glucose challenge increase limb blood flow and decrease vascular resistance [9, 37]. Insulin-stimulated production of NO from the vascular endothelium leads to increases in skeletal muscle blood flow *in vivo*, and these increases have been proposed to occur in two phases [8]. The first occurs within five minutes of insulin stimulation and involves the dilation of terminal arterioles that increase the number of perfused capillaries (i.e., capillary recruitment) without concomitant changes in total limb blood flow [38]. Subsequently, there is a relaxation of larger resistance vessels, which increases overall limb blood flow; this effect can be observed within 30 minutes of insulin stimulation, while peak flow is reached after two hours [39].

As previously described, PI-3K-dependent insulin-signaling pathways regulate vasodilator actions of insulin, while the MAPK-dependent insulin-signaling pathways promote vasoconstrictor actions of insulin. Nevertheless, in the absence of disease, the opposing cardiovascular actions of insulin exist in a balance that support cardiovascular and metabolic homeostasis.

Baron [40] was the first to theorize that the ability of insulin to increase limb/muscle blood flow might be a critical component of insulin-stimulated glucose uptake. Indeed, a number of studies have demonstrated a strong correlation between limb blood flow and glucose uptake across a broad range of insulin infusion rates [1, 2, 12-14, 41, 42]. Intravenous infusion of insulin is reported to increase total limb blood flow in the majority [2, 5, 40, 43-46] but not all [47-50] human studies. There are a number of theories to explain why an insulin-stimulated increase in blood flow is not always observed. Discrepancies among studies could be the result of differences in subject selection as well as differences in physical fitness, muscularity, endothelial function, and capillary density of study subjects. Technical limitations or differences in sensitivity of various experimental approaches for estimating limb blood flow (e.g., plethysmography, thermodilution, dye dilution, Doppler ultrasound) may also contribute to contradictory reports. It has been suggested that while an increase in total blood flow is not always observed, insulin can re-distribute blood flow by influencing which vessels are perfused without affecting total blood flow [51, 52].

Insulin modulates microvascular perfusion through the relaxation of terminal arteries and through capillary recruitment [38, 40, 44, 46, 53-55]. Strong correlations between measures of insulin-mediated capillary recruitment and skeletal muscle glucose uptake [14, 54] have been viewed by some as evidence of insulin regulating 'nutritive' blood flow[5, 52-54]. In other words, insulin may promote the dilation of specific terminal arterioles to increase perfusion of capillary beds that experience little or no perfusion under basal conditions [52]. Support for this notion comes from a number of studies demonstrating that increases in capillary recruitment and microvascular blood flow precede increases in glucose uptake in response to insulin, whereas changes in bulk limb blood flow are typically observed after the onset of changes in glucose disposal [44]. Together, these data suggest that changes in bulk flow may be secondary to changes in capillary recruitment.

In addition to stimulating vasodilation, insulin promotes opposing mechanisms which lead to vasoconstriction, including activation of the sympathetic nervous system and secretion of the vasoconstrictor ET-1 from the endothelium [56, 57]. Increases in sympathetic nerve activity and circulating catecholamines are observed following insulin infusion or meal ingestion [58-60]. The sympatho-excitatory effects of insulin are thought to function primarily to maintain blood pressure by offsetting peripheral vasodilation [58]. In support of this theory, insulin decreases blood pressure in persons with autonomic failure [61], and, in patients who have undergone regional sympathectomy, increases in blood flow in the denervated limb precede changes in blood flow in the innervated limb [62]. Although there is evidence of cholinergic involvement in hemodynamic responses to insulin in rats [63], neither cholinergic nor β-adrenergic systems appear to be involved in humans [64].

3. Insulin resistance and endothelial dysfunction

3.1. Signaling pathways

3.1.1. Changes in insulin signaling in the endothelium in insulin resistance

Lipotoxicity, glucotoxicity, and inflammation disrupt insulin signaling in the endothelium and lead to reduced insulin-stimulated blood flow in obesity and type 2 diabetes.

3.1.2. Reactive oxygen species

In type 2 diabetes, glucotoxicity and lipotoxicity, stimulate the production of ROS. Elevations in ROS contribute to the development and progression of vascular complications associated with type 2 diabetes by directly interfering with insulin signaling and limiting NO bioavailability.

Hyperglycemia activates the polyol pathway, converting excess glucose to sorbitol and finally fructose [65]. When fructose reacts with proteins, lipids, and nucleic acids, advanced glycation end products (AGE) are formed, which, in turn, stimulate ROS production [66]. Hyperglycemia further contributes to ROS by inducing peroxidation of circulating glucose and lipoproteins and interfering with auto-oxidation processes [67]. Neurohormonal over-activation and inflammation also contribute to ROS (superoxide) formation via stimulation of NADPH oxidase activity and expression [68]. ROS generation is further compounded by reductions in superoxide dismutase, catalase, and glutathione peroxidase, which impair antioxidant capacity in type 2 diabetes [69].

When generated in excess, ROS impairs insulin signaling by impairing insulin-stimulated activation of Akt and eNOS [70, 71] and limiting NO bioavailability [72]. Typically, the production of NO occurs in a sequence of tightly coupled reactions involving eNOS, tetrahydrobiopterin (BH_4), and several other co-factors [73]. ROS limits BH_4 availability, resulting in eNOS uncoupling and superoxide production [73]. Additionally, ROS may interact directly with NO to form the powerful oxidant peroxynitrite (ONOO-), which may contribute to further

uncoupling of eNOS. In other words, excess oxidative stress diverts NO to inactivate free radicals, thereby limiting the amount of NO available for vasoregulatory processes. Finally, eNOS expression is reduced in type 2 diabetes, putatively as a result of reduced or altered shear stress patterns.

3.1.3. Alternative mechanisms by which lipotoxicity and glucotoxicity interfere with insulin signaling in the endothelium

Lipotoxicity (dyslipidemia) contributes to endothelial insulin resistance by impairing the PI3K/Akt/eNOS branch of the insulin signaling pathway while augmenting the MAPK/ET-1 branch [6]. Elevated free fatty acids (FFAs) and lipid metabolites (diacylglycerols, ceramides, acyl coenzyme As) activate protein kinase C (PKC), IkB kinase β (IKKB), and nuclear factor-κB (NF-κB), which serine phosphorylate IRS-1 [23, 74, 75]. Unlike tyrosine phosphorylation, which activates IRS-1, serine phosphorylation deactivates IRS-1 and effectively blunts insulin-stimulated production of NO.

Glucotoxicity activates the hexosamine biosynthetic pathway, promoting the production of *O*-linked β-N-acetylglucosamine (*O*-GlcNAc). Insulin signaling is impaired when O-linked glycosylation obstructs key phosphorylation sites on IRS-1 and eNOS [70, 76]. AGEs generated as a result of hyperglycemia activate PKC, which inhibits activation of PI-3K/Akt via serine phosphorylation of IRS-1/2 [77], as well as NF-κB, which increases the expression of ET-1 [78]. AGEs also accelerate the degradation of eNOS mRNA [79].

3.1.4. Cytokines, hormones, and other proteins

Elevated cytokines are associated with insulin resistance and contribute to endothelial dysfunction. Increases in cytokines, including TNF-α, C-reactive protein (CRP), and interleukin-6 (IL-6), inhibit insulin-stimulated NO production by decreasing eNOS expression and by activating serine kinases which serine phosphorylate and inactivate IRS-1/2, thereby inhibiting the PI3K/Akt/eNOS pathway [8, 31, 80, 81]. Moreover, TNF-α and CRP enhance ET-1 production [82, 83].

Obesity and type 2 diabetes are associated with elevations in leptin and resistin, which contribute to increases in TNF-α, IL-6, ROS, and ET-1 [84-87]. Leptin also enhances serine phosphorylation of IRS-1, thereby impairing insulin signaling through the PI-3K/Akt pathway [88]. Resistin, on the other hand, reduces eNOS expression [89]. Conversely, although adiponectin and ghrelin stimulate NO production through PI-3K/Akt signaling pathways and enhance NO bioavailability [90-92], both are reduced in individuals who are obese or have type 2 diabetes.

3.1.5. Proatherogenic effects of insulin

Insulin also stimulates the expression of pro-atherogenic molecules in the endothelium through MAPK-dependent pathways [93], including, plasminogen activator inhibitor type-1 (PAI-1) [94], intracellular adhesion molecule (ICAM-1) [95], vascular cell adhesion molecule (VCAM-1) [95], and E-selectin [95]. Inhibition of PI-3K or Akt results in increased expression

of these pro-atherogenic molecules, indicating that the PI-3K/Akt pathway may inhibit the expression of atherothrombic factors in addition to stimulating the production of protective molecules, including NO [95].

3.2. Vascular effects

The vascular actions of insulin are altered in insulin resistant states owing to impairments in the PI3K/Akt/eNOS pathway, over-activation of the MAPK/ET-1 pathway, and/or altered bioavailability of or sensitivity to NO and/or ET-1. Furthermore, impairments in vascular responses to insulin are proportional to the degree of metabolic insulin resistance [43, 96]. Shared causal factors such as glucotoxicity, lipotoxicity, inflammation, and oxidative stress interact at multiple levels to create reciprocal relationships between insulin resistance and endothelial dysfunction that may help explain the frequent clustering of metabolic and cardiovascular disorders [8].

There is a strong association between insulin resistance and endothelial dysfunction, measured in terms of impaired endothelium-dependent vasodilatation [97, 98]. For instance, in healthy volunteers there is a close correlation between insulin sensitivity and basal NO production [99]. In addition, insulin-resistant humans have impaired endothelium-dependent vasodilator responses, measured using a variety of techniques [97, 100]. Endothelial dysfunction is also detectable in healthy first-degree relatives of patients with type 2 diabetes, who are themselves at increased risk of developing diabetes [101].

Furthermore, reduced efficacy of insulin to stimulate blood flow has been demonstrated in obesity, type 2 diabetes, and polycystic ovarian syndrome [45, 102]. The relationship between insulin resistance and endothelial dysfunction is independent of traditional cardiovascular risk factors (including blood pressure, plasma cholesterol, and triglycerides), yet a potential contribution of other confounding factors cannot be ruled out. Animal studies have also described similar findings [103-105]. Winters et al. reported impaired endothelium-dependent vasodilatation in mice with obesity and insulin resistance secondary to a naturally occurring gene mutation [103]. Transgenic mice with perturbations of the insulin-signaling pathway causing insulin resistance exhibit impairment of endothelium-dependent vasodilatation, whilst the response to exogenous NO donors remains intact [105].

Insulin resistance results in a selective impairment of the vasodilating and anti-atherogenic PI3-K/Akt pathway, whereas MAPK pathway remains unaffected [6, 106]. As a result, the compensatory hyperinsulinaemia occurring in insulin resistant states overactivates the MAPK pathway, favoring vasoconstriction. Insulin resistance and hyperinsulinemia transpire concurrently, rendering the deleterious consequences on endothelial function more severe than the sum of each alone.

Clinical studies have shown that high free fatty acid concentrations are associated with impairment of endothelium-dependent vasodilation and increased blood pressure [4, 107], putatively as a consequence of decreased NO availability. As previously mentioned, one of the characteristics of insulin resistance is the presence of chronic low grade inflammation along with increased circulating levels of cytokines and of inflammatory markers, including TNF-

α[108, 109]. Interestingly, TNF-α concentrations are negatively associated with capillary recruitment, perhaps explaining, at least in part, its relationship with insulin resistance [110]. ET-1 plays a pivotal role in insulin resistance and vascular dysfunction [111], as shown by experiments carried out both *in vitro* and *in vivo. In vitro*, sustained exposure of insulin-responsive cells to ET-1 impairs insulin sensitivity [112, 113]. Similarly, ET-1 causes insulin resistance *in vivo*, which may be prevented by administration of drugs which interfere with the ET-1 receptor type A [114].

The loss of skeletal muscle capillary density is observed in insulin resistance and type 2 diabetes, and insulin action is positively correlated with capillary density [115]. Furthermore, vasodilation in skeletal muscle in response to insulin infusion is reduced in obese subjects in comparison with lean controls [43]. Insulin-mediated capillary recruitment is blunted in cases of insulin resistance and obesity and is tightly linked to impairments in glucose uptake [52, 116]. Under conditions of insulin resistance, the balance of insulin action shifts toward vasoconstriction. This further exacerbates insulin resistance by limiting the delivery of insulin and nutrients to myocytes by decreasing nutritive flow and available capillary surface area.

4. Vascular insulin resistance and the role of exercise

Physical activity may be beneficial in slowing the initiation and progression of insulin resistance and cardiovascular disease through favorable effects on body weight, insulin sensitivity, glycemic control, blood pressure, lipid profiles, fibrinolysis, inflammatory defense systems, and endothelial function [117]. For instance, exercise exerts many of the same effects in the muscle vasculature as insulin [118]. Exercise efficiently increases muscle capillary recruitment, as well as total muscle blood flow [119]. Furthermore, exercise effects are thought to be mediated by intermittent shear stress (tangential force of blood flowing on the endothelial surface), an established physiological stimulus for NO [120]. Extensive comprehensive reviews regarding the global beneficial effects and/or recommendations of exercise/physical activity in patients with insulin resistance have been previously published elsewhere [117, 121-123]. The following section is intended to present the available evidence of the beneficial effects of exercise/physical activity on endothelial function.

4.1. Acute effects of exercise

Studies examining the acute effects of aerobic exercise training on endothelial function in insulin resistance subjects with few or no other major comorbidities are limited. One study examined blood ET-1 (a powerful endogenous vasoconstrictor) levels and leg blood flow during insulin infusions in healthy older subjects (non-diabetic and physically active, ~70 years of age) that were assigned into exercise training and control groups. The exercise training group treadmill exercised for 45-min at 70% of maximum heart rate. Only in the exercise training group did leg blood flow at baseline tend to increase while ET-1 blood plasma levels declined [124].

Other studies demonstrating declines in insulin sensitivity in response to acute physical inactivity in healthy populations [125-127] are corroborated by evidence that reducing sedentary time in order to improve metabolic health is equally if not more important than the benefits associated with a physically active lifestyle [128, 129]. Importantly, unfavorable changes in insulin sensitivity with the bed rest [125] were associated with decreases in forearm and calf flow-mediated dilation (FMD), an index of vascular endothelial function. Basal arterial tone also increased with bed rest as evidenced by decreased brachial artery diameter and increased systolic blood pressure.

4.2. Chronic effects of exercise training

Although studies examining the chronic effects of aerobic exercise training on endothelial function in persons with insulin resistance or type 2 diabetes range widely in their experimental design, the results of these studies indicate that exercise training improves endothelial function. For instance, in obese insulin resistant males and females, exercising three times per week (30-min each time using an unspecified modality) at 60- 80% of maximal heart rate under supervision and at home for at least 150-min/week for 6 months improved brachial FMD [130]. Conversely, microvascular reactivity did not improve following the exercise program in the same subjects. Furthermore, in hemodialysis patients, a 3-month aerobic exercise training program improved arterial stiffness (assessed using artery pressure waveform analysis) [131].

Exercise training also improves/maintains endothelial function in the obese Zucker rats (OZ), a model of insulin resistance and obesity, relative to non-exercising OZ. A treadmill exercise program (24 m/min, 30-min/day, 5 days/wk for 4-6wks) was shown to improve functional hyperemia and endothelial-dependent vasodilation in the spinotrapezius microvasculature when measured using intravital microscopy [132]. The same exercise program improved microvascular endothelial function in OZ due to decreased thromboxane receptor-mediated vasoconstriction [133], and not due to increased blood pressure [132]. It should be noted that these OZ studies were conducted at single time-points while the rats were developing and/or had already developed insulin resistance. See the "OLETF" studies described below for a summary of the effects of exercise on endothelial function during insulin resistance time-course studies.

Similar to the effects of acute physical inactivity, chronic physical inactivity (~6 years) led to the development of insulin resistance and reduced FMD in lean adult male rhesus monkeys [127]. Furthermore, insulin-mediated changes in capillary blood volume were inversely correlated with the degree of insulin resistance and directly with physical activity levels.

Studies using the Otsuka Long-Evans Tokushima Fatty (OLETF) rat model of insulin resistance and obesity have revealed that chronic aerobic physical activity alone (i.e. free access to running wheels from 12-40 weeks of age) maintains/improves endothelial function in conduit [134] and resistance arteries [34, 135-137]. These studies established that the maintained/improved endothelial function in the OLETFs was mediated by improvements in NO signaling and/or attenuated ET-1 sensitivity and/or production. Additionally, insulin resistance manifested prior to significant progressive declines (20-35%) in endothelial function [134]. Other OLETF studies demonstrating the positive effect of exercise training (i.e. a training program

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on a treadmill) as an interventional measure for endothelial function were conducted at single time-points while the rats were developing and/or had developed insulin resistance [138, 139].

It deserves mention that the experimental design of the OZ [132, 133] and several OLETF [34, 134-137] studies that were described above were such that the chronic aerobic exercise training/physical activity served as a *preventative* measure for endothelial dysfunction associated with insulin resistance. Additionally, all human (for both acute and chronic studies) and some of the OLETF studies [138, 139] discussed above the exercise training also served as an interventional measure for endothelial dysfunction associated with insulin resistance.

Although there is evidence that resistance training improves insulin-stimulated glucose uptake, there have been few studies specifically examining the effects of resistance training on insulin-mediated blood flow. Juel *et al*. [140] compared the effects of six weeks of progressive single-leg strength training (3 days/wk, 3 sets of 10 repetitions at 70-80% of one repetition maximum; leg press, knee extension, and hamstring curl) on leg flow determined by thermodilution during a two-stage hyperinsulinemic-euglycemic clamp in the trained and untrained legs of ten patients with type 2 diabetes and seven male controls. Prior to the intervention, insulin-stimulated leg blood flow was greater in controls. Following the intervention, basal blood flow was similar between the trained and untrained legs in both groups, and leg blood flow was higher in the trained leg during the second stage of insulin infusion in healthy controls and during both stages in patients with type 2 diabetes. These findings seem to suggest that resistance training may enhance insulin-mediated blood flow in healthy individuals as well as those with type 2 diabetes. However, it is unclear whether changes in capillarity may contribute to this response.

Chronic exercise training produces increases in the expression and activity of proteins involved in insulin signaling and glucose uptake as well as increases in mitochondrial biogenesis and fatty acid oxidation [141, 142]. Chronic exercise training also increases eNOS expression in vessels experiencing increases in blood flow during exercise [143] and up-regulates antioxidant enzymes including, superoxide dismutase and glutathione peroxidase [144]. Finally, chronic exercise also reverses factors known to stimulate ROS formation, including, inflammation, glucotoxicity, and lipotoxicity [144]. Together, these adaptations likely contribute to improvements in endothelial function associated with exercise training.

5. Final conclusions

In summary, insulin stimulates two pathways in the endothelium. One pathway leads to the production of the vasodilator NO through PI3K and Akt, while the other mediates production of the vasoconstrictor ET-1 through MAPK [6, 31, 145]. Insulin-mediated glucose disposal is largely dependent upon the vasodilatory effects of insulin, which enhance blood flow and, thus, delivery of glucose and insulin to target tissues. Typically, insulin-stimulated vasodilation is responsible for up to 40% of insulin-stimulated glucose disposal following a meal [8].

The glucotoxicity, lipotoxicity, and inflammation associated with insulin resistance work in concert to alter insulin signaling, leading to an imbalance in the production of vasodilator and vasoconstrictor substances in response to insulin. Resulting impairments in the PI3K/Akt/

eNOS pathway concomitant with enhanced stimulation of the MAPK/ET-1 pathway precipitate hypertension, reduced blood flow, and impaired delivery of glucose and insulin to target tissues [7, 8, 52, 146]. Similar perturbations are observed in skeletal muscle insulin signaling in obesity and type 2 diabetes [8, 52], indicating that the metabolic and vascular insulin resistance associated with obesity and type 2 diabetes may develop in tandem.

Alterations in vascular NO bioavailability and/or attenuated ET-1 or attenuated thromboxane sensitivity/production appear to contribute to endothelial dysfunction associated with insulin resistance. These studies also collectively suggest that endothelial dysfunction can be improved/maintained with acute or chronic aerobic exercise training/physical activity when used either thru interventional or preventative measures. The beneficial effect of exercise on vascular insulin action was consistent across studies of conduit artery blood flow *in vivo* and microvascular reactivity to insulin *in vitro*, in both humans and rodents, and in response to both short-term and chronic exercise training. Clearly, even in cases of prolonged disease progression, exercise training might be able to remedy some of the effects of insulin resistance on the vasculature.

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