The Union of Vascular and Metabolic Actions of Insulin in Sickness and in Health

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Disorders of metabolic homeostasis including type 2 diabetes, obesity, and dyslipidemias are characterized by both insulin resistance and endothelial dysfunction. Insulin resistance and endothelial dysfunction are also prominent features of important cardiovascular disorders including hypertension, coronary artery disease, and atherosclerosis. Indeed, insulin resistance is thought to be the tie that binds metabolic and cardiovascular disorders together in an unhappy union called the metabolic syndrome (aka the insulin resistance syndrome). Although these associations are well established, molecular mechanisms explaining the underlying pathophysiology are not completely understood. Interestingly, inflammation mediated by innate immune signaling pathways has been implicated in both metabolic insulin resistance and vascular endothelial dysfunction. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Kim et al demonstrate that treatment of vascular endothelial cells with the free fatty acid (FFA) palmitate activates IKKβ (a proinflammatory signaling molecule), impairs insulin signaling, and decreases insulin-stimulated production of nitric oxide (NO). Importantly, inhibitory effects of FFA treatment on insulin signaling and NO production are blocked by overexpression of a dominant inhibitory mutant of IKKβ. Moreover, deleterious effects of FFA treatment are recapitulated by overexpression of wild-type IKKβ. Thus, Kim et al have uncovered an additional link between metabolic and vascular pathophysiology that helps to explain mechanisms underlying the metabolic syndrome and related cardiovascular diseases. To understand the importance of these findings it is useful to review the mechanisms coupling vascular and metabolic physiology, the role of inflammation in insulin resistance, and the role of insulin resistance to couple vascular and metabolic pathophysiology (Figure).

Coupling of Hemodynamic and Metabolic Physiology Through Insulin Action
Regulation of hemodynamic and metabolic homeostasis may be coupled by physiological actions of insulin in the vascular endothelium to stimulate production of NO. The metabolic action of insulin to promote glucose uptake in skeletal muscle and adipose tissue is initiated by activation of the insulin receptor tyrosine kinase, subsequent phosphorylation of IRS-1, binding and activation of PI 3-kinase, activation of the serine kinase PDK-1, and Akt and PKC-ζ, leading to recruitment of GLUT4 glucose transporters to the cell surface. A similar pathway exists in vascular endothelium involving the insulin receptor, IRS-1, PI 3-kinase, PDK-1, and Akt that leads to phosphorylation and activation of eNOS by Akt with a resultant increase in production of NO. Insulin-stimulated production of NO leads to capillary recruitment, vasodilation, and increased blood flow to skeletal muscle that improves delivery of glucose and insulin to skeletal muscle. Indeed, insulin-stimulated increases in capillary recruitment and total limb blood flow per se may account for up to 40% of insulin-mediated glucose disposal. Thus, insulin signaling pathways that are shared in common in distinct tissues with vascular or metabolic functions may help to tightly couple regulation of vascular function with glucose metabolism.

Insulin Resistance, Endothelial Dysfunction, and Inflammation
Metabolic insulin resistance has both genetic and acquired causes. The causes for acquired insulin resistance related to diabetes and obesity include glucotoxicity and lipotoxicity resulting from hyperglycemia and elevated FFA levels. Elevated levels of glucose and lipids increase oxidative stress, advanced glycation end products, flux through the hexosamine biosynthetic pathway, activation of PKC, and activation of proinflammatory pathways in skeletal muscle and adipose tissue leading to insulin resistance. Of note, these same mechanisms also participate in endothelial dysfunction. With respect to inflammation, elevations in FFA associated with obesity and diabetes are linked to activation of IKKβ. This leads to cross-talk between inflammatory signaling and insulin signaling that impairs IRS-1/PI 3-kinase function and causes metabolic insulin resistance. It is known that elevations in FFA also lead to endothelial dysfunction. The study by Kim et al suggests that IKKβ may be mediating insulin resistance in endothelium in response to FFA resulting in endothelial dysfunction using a mechanism similar to that in metabolic targets of insulin. Thus IKKβ may play an important role in both metabolic insulin resistance and vascular endothelial dysfunction.

Coupling of Vascular and Metabolic Pathophysiology Through Insulin Resistance
A variety of rodent models support the idea that insulin resistance may couple vascular and metabolic pathophysiol-
ogy. For example, mice that are homozygous null for the eNOS gene have an expected hemodynamic phenotype of increased basal blood pressure.21 Interestingly, these eNOS knockout mice also have metabolic insulin resistance and markedly diminished insulin-stimulated increases in hindlimb muscle blood flow.22,23 Similarly, IRS-1 knock-out mice that have an expected metabolic phenotype of insulin resistance24 are also hypertensive with impaired endothelium-dependent vasodilation.25 Finally, transgenic mice with endothelium-specific ablation of the insulin receptor have a metabolic phenotype of insulin resistance on either a low salt or high salt diet suggesting that insulin signaling in vascular endothelium contributes to insulin-mediated glucose disposal in certain contexts.26 Interestingly, infusing intra-lipid into rats to raise circulating FFA levels causes a significant 65% impairment in insulin-mediated skeletal muscle capillary recruitment with a concomitant 40% decrease in glucose disposal during a glucose clamp.27 The finding by Kim et al that FFA-mediated activation of IKKβ in vascular endothelium leads to impaired insulin signaling and decreased insulin-stimulated production of NO provides further support for the idea that parallel signaling mechanisms in skeletal muscle and vascular endothelium serve to couple metabolic and vascular pathophysiology.

**Future Prospects**

Inflammatory mechanisms appear to be important for mediating both metabolic insulin resistance and impaired insulin action in vascular endothelium that contribute to the relationship between metabolic and cardiovascular disorders. This has implications for novel therapeutic strategies because drugs that reduce inflammation would be predicted to improve both metabolic and endothelial function. Indeed, recent clinical studies have demonstrated additive beneficial endothelial and metabolic effects of combining statins (that have antiinflammatory properties) with angiotensin II type 1 receptor blockers, fenofibrate, or angiotensin converting enzyme inhibitors in the treatment of patients with hypertension, hyperlipidemia, or type 2 diabetes, respectively.28–30

The union of vascular and metabolic actions of insulin in sickness and in health. Insulin-stimulated production of NO in vascular endothelium is mediated by the insulin receptor (IR) tyrosine kinase that phosphorylates IRS-1, leading to binding and activation of PI 3-kinase and activation of PDK-1, which in turn phosphorylates and activates Akt and finally phosphatidylserine-dependent eNOS. The resulting increase in production of NO mediates vasodilation and increased blood flow. Insulin-stimulated glucose uptake in skeletal muscle and adipose tissue involves a similar signaling pathway culminating in translocation of GLUT4 glucose transporters to the cell surface. Under healthy conditions, vasodilator actions of insulin augment direct effects of insulin on glucose transport in skeletal muscle and adipose tissue to increase glucose uptake. In metabolic and cardiovascular diseases including diabetes, obesity, dyslipidemias, hypertension, coronary artery disease, and atherosclerosis, inflammatory signaling through IKKβ in response to cytokines and elevated FFA levels causes insulin resistance in both vascular endothelium and metabolic targets of insulin. Thus, inflammatory mechanisms of insulin resistance are shared in vascular endothelium and metabolic targets of insulin, and this contributes to both metabolic and cardiovascular diseases.

**References**

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