Distinct Mechanisms for Globular Adiponectin That Integrate Vascular and Metabolic Actions of Insulin to Help Maintain Coordinated Cardiovascular and Glucose Homeostasis

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In the current issue of *Circulation Research*, Zhao et al. present interesting and important studies describing mechanisms by which insulin and adiponectin interact to integrate cardiovascular and metabolic physiology. The mechanism revealed by these studies uses both parallel and distinct pathways that may have important implications for the pathophysiology of diabetes mellitus, obesity, and their cardiovascular complications, as well as for the development of novel effective therapies in the future.

**Integration of Metabolic and Vascular Actions of Insulin to Promote Metabolic Homeostasis**

The molecular signaling pathways in skeletal muscle and adipose tissue responsible for direct actions of insulin to enhance glucose uptake and disposal involve activation of the insulin receptor, which then initiates a signaling cascade, involving IRS-1/PI3K/PDK-1/Akt and PKC-ζ, that culminates further downstream in the translocation of insulin response glucose transporters (GLUT4) from intracellular compartments to the cell surface, where GLUT4 acts as a facilitative transporter to drive glucose down its concentration gradient.2,3 Strikingly similar insulin signaling pathways in vascular endothelium involving insulin receptor/IRS-1/PI3K/PDK-1/Akt/eNOS promote increased production of the potent vasodilator nitric oxide that increases blood flow and capillary recruitment leading to increased delivery of the substrate (glucose) and the hormone (insulin) to metabolic targets, including skeletal muscle.4,5 These vascular actions of insulin represent a secondary mechanism for insulin to promote glucose uptake and disposal. Indeed, ~40% of insulin-stimulated glucose uptake in skeletal muscle may be attributed to vascular actions of insulin in conduit arteries and recruitment of nutritive capillaries.4,7 In addition, the transendothelial transport of insulin has recently been identified as a potential rate-limiting step in metabolic actions of insulin.8-10 Taken together, it is apparent that reciprocal relationships between insulin resistance and endothelial dysfunction help tie together metabolic diseases with their cardiovascular complications and also present novel therapeutic targets.5

**Adiponectin Signaling and Action**

Adiponectin is a 30-kDa protein secreted predominantly by adipocytes that regulates metabolic and cardiovascular homeostasis through both central and peripheral biological actions, which mimic many important metabolic, vascular, and anti-inflammatory actions of insulin. Adiponectin is unique among adipocytokines in that its circulating levels are inversely related to obesity and insulin resistance. The molecular cloning of adiponectin,11 its functional receptors adipor1 and R2,12 and the first signaling protein that interacts with the adiponectin receptors (APPL1)13 have allowed for rapid dissection of molecular mechanisms of adiponectin action that explain its ability to mimic both metabolic and vascular actions of insulin through activation of adenosine monophosphate–activated protein kinase and Akt.14-16 Thus, like insulin, adiponectin has direct actions to promote GLUT4 translocation13 in metabolic targets and to promote activation of endothelial nitric oxide synthase and NO production in vascular endothelial cells.14 Other insulin-sensitizing or insulin-mimetic actions of adiponectin include enhancing insulin sensitivity and fatty acid oxidation, improving β-cell function and survival17 and decreasing inflammation, atherosclerosis,18 and hepatic glucose production.19 It is also becoming increasingly clear that adiponectin plays a role in cardiovascular physiology and integrating vascular and metabolic homeostasis.20-23

**Interplay of Adiponectin and Insulin Actions in Coordinating Metabolic and Vascular Homeostasis**

The study in this month’s issue by Zhao et al.1 provides new mechanistic insights linking adiponectin-mediated glucose uptake in skeletal muscle and its effects on increasing NO-mediated vasodilation in small nutritive capillaries, thereby showing a beneficial coupling of metabolic and cardiovascular activity similar to insulin. Overnight fasted Sprague-Dawley rats received intraperitoneal injection of globular adiponectin (gAd) that raised circulating adiponectin levels. This resulted in increased capillary recruitment reflected by a larger microvascular blood volume with an overall increase in microvascular blood flow. This effect was NO mediated as L-NAME pretreatment abolished the increase in microvascular blood flow. As a result, there was an increase in skeletal muscle insulin uptake and an increase in whole body glucose disposal (both effects also abolished by L-NAME). gAd also augmented
Thus, this study provides an important link to tie metabolic Akt and adenosine monophosphate–activated protein kinase.

Inactivation of endothelial nitric oxide synthase activation. In downstream physiological actions that contribute to the pathophysiology of diabetes mellitus, obesity, and their cardiovascular complications, as well as for developing novel therapeutic approaches. For example, adiponectin, oxidoreductase-like protein in mice shows beneficial effects on insulin resistance.29 Some investigators have proposed that the in vivo effects of gAd are unimportant because of its very low circulating concentrations.17 However, in the current study, gAd has no effect on endothelial uptake of $^{125}$I-insulin.1 Thus, this represents an important distinction between adiponectin and insulin action in the coupling of vascular and metabolic actions. That is, the primary role of adiponectin is to augment microvascular endothelial exchange surface area. Therapeutic interventions to increase adiponectin levels are one potential option for safely treating cardiometabolic pathophysiology. Lifestyle modifications, renin–angiotensin system blockade, fenofibrate, thiazolidinediones, statins, and nebulol have all been shown to increase plasma levels of adiponectin.20 Adiponectin exists as trimers, hexamers, and as higher molecular weight forms in the circulation.24 Because of extremely high circulating levels of the hormone, some have proposed that altering the ratio of circulating adiponectin to higher molecular weight forms would be a more advantageous therapeutic approach than increasing its total levels. The disulfide bond A oxidoreductase–like protein promotes adiponectin multimerization, and overexpression of disulfide bond A oxidoreductase–like protein in mice shows beneficial effects on insulin resistance.29 Some investigators have proposed that the in vivo effects of gAd are unimportant because of its very low circulating concentrations.17 However, in the current study, gAd has greater bioactivity than full length adiponectin. Methods to enhance proteolytic cleavage of full length adiponectin to gAd may serve as a potential therapeutic approach for enhancing adiponectin bioactivity.28 Additional research on the role of adiponectin as a therapeutic agent may lead to the development of an additional safe intervention to help curtail the epidemic of metabolic and cardiovascular diseases.

**Disclosures**

None.

**References**


Key Words: Editorials ■ adiponectin ■ endothelium ■ glucose ■ insulin ■ protein kinases
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Circ Res. 2013;112:1205-1207
doi: 10.1161/CIRCRESAHA.113.301316

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/112/9/1205

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