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[1] 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.

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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.[6,7] 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 adenoisne monophosphate–activated protein kinase and Akt.[14–16] Thus, like insulin, adiponectin has direct actions to promote GLUT4 translocation[13] 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 survival[17] 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

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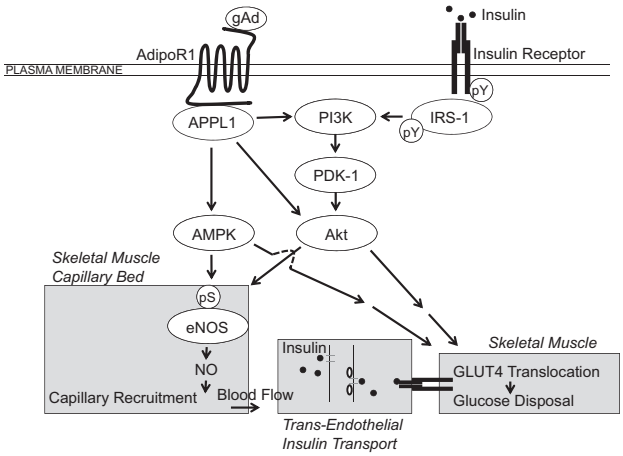

Figure. Overlapping mechanisms of globular adiponectin and insulin actions that integrate skeletal muscle capillary recruitment and glucose disposal. Insulin promotes glucose uptake and disposal directly in skeletal muscle by activating insulin receptor (IR) signaling pathways involving IR/IRS-1/PI3K/PDK-1/Akt and other signaling events that culminate in the translocation of the insulin-responsive glucose transporter GLUT4 from the intracellular compartment to the cell surface, where GLUT4 acts as a facilitative glucose transporter to drive glucose down its concentration gradient. In the vascular endothelium, the activation of IR/IRS-1/PI3K/PDK-1/Akt/eNOS generates nitric oxide, a potent vasodilator, which increases blood flow and capillary recruitment to increase the delivery of substrates (glucose) and hormones (insulin) to metabolic target tissues. This provides an important mechanism for the vascular actions of insulin to contribute to direct metabolic actions of insulin in skeletal muscle. Indeed, the NO-dependent vasodilator actions of insulin may account for up to 40% of the metabolic effects of insulin in promoting glucose uptake and disposal in skeletal muscle. Another important vascular action of insulin that contributes to its metabolic effects is the rate-limiting transendothelial transport of insulin across the endothelial barrier allowing insulin direct access to its metabolic targets. Adiponectin is an important hormone secreted predominantly by adipose cells, which regulates both metabolic and vascular homeostasis. Many metabolic and vascular actions of adiponectin mimic those of insulin and this serves to both augment insulin actions and sensitize tissues to the effects of insulin. However, the action of insulin and adiponectin differ in both upstream signaling pathways and in downstream physiological actions that contribute to the overall integration of the physiological effects of adiponectin and insulin. These subtleties are important for understanding the pathophysiology of diabetes mellitus, obesity, and their cardiovascular complications, as well as for developing novel and effective therapeutic approaches. For example, adiponectin, through proximal signaling molecules, adipoR1 and APPL1, activates both adenoisne monophosphate–activated protein kinase (AMPK) and Akt, which are both upstream kinases for endothelial nitric oxide synthase activation. In downstream actions, transendothelial transport of insulin is important for integrating vascular and metabolic actions of insulin, whereas adiponectin does not have significant effects on transendothelial transport of insulin. Thus, both the adiponectin and the insulin pathway could be independently targeted to elicit optimal and nonoverlapping effects.

the effects of insulin in increasing capillary blood volume and microvascular blood flow, as opposed to insulin that involved only Akt, gAd-mediated vascular signaling resulting in activation of endothelial nitric oxide synthase involved both Akt and adenoisne monophosphate–activated protein kinase. Thus, this study provides an important link to tie metabolic actions of adiponectin to its vasodilator effects. In fact, the effects of adiponectin on metabolic pathways seem to be, in large part, a result of its action on microvascular recruitment and dilation, expanding the microvascular exchange surface area. Adiponectin's effects on NO-mediated vasodilation of large conduit vessels have been previously described.[24,25] However, this is the first study to show the important role of adiponectin in recruiting smaller, nutritive vessels that are likely to play a more important role in coupling metabolic and vascular physiology (Figure).

Another important aspect of the study by Zhao et al[1] is the concept that insulin action in skeletal muscle is dependent not only on insulin delivery to muscle microcirculation but also on transendothelial transport of insulin into the skeletal muscle interstitium.[26,27] Importantly, in the current study, gAd had 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 nebivolol 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.[28] 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.

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