Adipocyte-derived adiponectin is cardioprotective: fat cells can be our friends

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The combination of high-fat diet and sedentary lifestyle common in industrialized countries has led to an epidemic of obesity with associated increases in cardiovascular diseases, such as diabetes and atherosclerosis. Although investigators have made great progress in the last 10 years elucidating the molecular basis of the associations between excess adipose tissue and diabetes and cardiovascular disease, much is yet to be learned. It is axiomatic that adipose tissue serves as a storage depot for excess triglycerides and releases free fatty acids to meet increasing energy demands. Recent studies demonstrate that adipose tissue also secretes a number of proteins into the circulation that regulate glucose and lipid metabolism throughout the body. These so-called “adipokines” include, among others, TNF-\(\alpha\), plasminogen-activator inhibitor type 1, resistin, leptin, and adiponectin. Dysregulation of adipokine synthesis plays a critical role in linking insulin resistance to obesity (2, 4). Insulin resistance, diabetes, obesity, and dyslipidemia are characterized by lower plasma levels of adiponectin (hypoadiponectinemia) (1, 11, 15) and elevated plasma levels of TNF-\(\alpha\) (8). Hypoadiponectinemia, like that observed in adiponectin knockout mice (10, 15) and humans with mutations in the adiponectin gene (6, 9), is correlated with insulin resistance, diabetes, and atherosclerosis. Strategies to normalize specific adipokines show promise at reversing symptoms of metabolic disease (8, 12, 15). For instance, in an experimental model of murine hyperlipidemia, adiponectin treatment both mimics and enhances the metabolic role of insulin in skeletal muscle by increasing free fatty acid and glucose uptake and oxidation and decreasing triglyceride content (4, 14). In a rodent model of obesity, neutralization of TNF-\(\alpha\) reverses insulin resistance (8). There is at least one animal study showing that adiponectin administration results in weight loss in the absence of a reduction in calorie intake, (4). Thus the potential for adiponectin therapy to reverse symptoms of metabolic syndrome as well as to slow or reverse weight gain seems promising.

In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Takano et al. (13) narrow their focus to adiponectin effects in the coronary circulation of normal patients and patients with coronary spastic angina and microvascular angina. Like Furuhashi et al. (5), they report a transcardiac gradient of plasma adiponectin in nondiabetic control subjects and attribute the lower venous levels of adiponectin to uptake within the coronary vasculature. Their most significant findings include positive correlations between the arterial-to-venous adiponectin gradient and epicardial coronary diameter and coronary blood flow in response to the endothelium-dependent dilator acetylcholine. The transcardiac gradient was not correlated with coronary vasomotor responses to endothelium-independent vasodilators, sodium nitroprusside, and isosorbide dinitrate. The dependency of vasomotor responses to acetylcholine on the transcardiac adiponectin gradient suggests that the synthesis or release of endogenous nitric oxide or other endothelium-dependent vasodilators within a segment of the coronary circulation normally regulates, at least in part, on adiponectin signaling.

When compared with control subjects, patients with coronary spastic angina or microvascular angina exhibit significantly lower plasma levels of adiponectin as well as no transcardiac gradient of adiponectin. In fact, most of the patients with coronary spastic angina constricted in response to acetylcholine, and the coronary blood flow responses of patients with microvascular angina were significantly diminished compared with those in control arteries. Furuhashi et al. (5) also showed an absence of a transcardiac gradient of adiponectin in patients with Type 2 diabetes. Insulin resistance can be involved in the pathogenesis of coronary spastic angina or microvascular angina (3, 7). In the Takano et al. (13) study, patients with coronary spastic angina, but not those with microvascular angina, were insulin resistant, as determined by the homeostasis model assessment of insulin resistance. The authors speculate that insulin resistance likely accounts for the low levels of adiponectin in angina patients and that the lower transcardiac uptake of adiponectin by the coronary circulation plays a role in the pathogenesis of coronary spastic angina and microvascular angina.

These results raise interesting and potentially novel new thoughts regarding the regulation of coronary flow in humans. This study clearly demonstrated increased transcardiac gradients in normal individuals and both reduced levels and the absence of a gradient in either vasospastic or microvascular angina patients. Venous levels of adiponectin are dependent on the basal aorta (arterial) levels, potential increases from production by the heart, and decreases by uptake from the heart (vasculature). It is possible that that adiponectin basal level correlates with the health of endothelium in the entire body and that production and/or uptake of adiponectin from endothelium or surrounding tissue is necessary for normal endothelium-dependent responses. The most interesting question is what is first–adiponectin uptake failure resulting in endothelium dysfunction or endothelium dysfunction resulting in failure of the endothelium to take up adiponectin. Further studies are needed to accurately measure cardiac production and uptake of adiponectin in vivo to help answer this interesting question. In addition, further studies are needed to evaluate whether endothelium-dependent release of other important mediators, such as endothelium-derived hyperpolarizing factor, is adiponectin dependent.

Regardless of the failure mode, adiponectin may be a promising therapeutic target to improve vasomotor responses and endothelium health in the coronary macro- and microcircula-

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tion. Further studies are needed to describe the effects of this hormone before large-scale clinical trials are performed.

REFERENCES


