Adiponectin and Cardiovascular Disease

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Obesity is strongly associated with metabolic and cardiovascular disorders. Adiponectin is an adipose-derived plasma protein that is downregulated in subjects with obesity-related disorders. Low levels of adiponectin are associated with the increased prevalence of obesity-linked cardiovascular diseases, including ischemic heart disease and peripheral artery disease. Experimental findings have shown that adiponectin has beneficial effects in the cardiovascular system by directly acting on the component cells of the heart and blood vessels. Adiponectin protects cardiovascular tissues under conditions of stress through a number of mechanisms: inhibition of pro-inflammatory and hypertrophic responses, and stimulation of endothelial cell responses. These effects of adiponectin are mainly attributed to the modulation of signaling molecules, including AMP-activated protein kinase. Thus, adiponectin could be a promising therapeutic target for cardiovascular diseases. (Circ J 2009; 73: 608–614)

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Adiponectin: an Adipose Tissue-Derived Adipocytokine

In the industrial countries, obesity is closely associated with the development of metabolic syndrome, hypertension, atherosclerosis and heart disease.1,2 However, despite the prevalence of obesity, the links between it and the development of cardiovascular disease are poorly understood at the molecular level. It is now recognized that adipose tissue functions as an endocrine organ by secreting adipocytokines, such as leptin, tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor type 1, interleukin (IL)-1β, IL-10, retinol binding protein-4, and adiponectin, that are directly involved in obesity-linked disorders.3,4

Adiponectin, also referred to as ACRP30 and AdipoQ,5–7 is an adipose tissue-derived adipokine abundantly present in human plasma, ranging between 3 and 30 μg/ml.8 It exists in human and mouse plasma as different oligomers: trimer, hexamer and high-molecular-weight (HMW) forms.9,10 Adiponectin contains a collagen-repeat domain at the N terminus and a globular domain at the C terminus with a sequence homology to complement factor C1q. Adiponectin is also processed by proteolysis, and fragments including the globular domain have been detected in both human and mouse plasma, although they are negligible.11 Adiponectin transcript is exclusively expressed in adipose tissue in mice5,6,12 Many adipocytokines are positively regulated by adiposity, but adiponectin levels in plasma are negatively regulated by accumulation of body fat, visceral fat in particular.13 In this regard, plasma adiponectin levels are low in obese individuals.8,14 Clinical studies implicate hypo-adiponectinemia in the pathogenesis of type 2 diabetes,15–17 coronary artery disease (CAD),18–21 and hypertension.22 Increasing evidence from experimental studies indicates that adiponectin plays a protective role in the development of insulin resistance, hypertension and cardiovascular disease. Thus, adiponectin could be a key molecule for clarifying the pathogenesis of obesity-linked disorders.

Adiponectin Level and Cardiovascular Disease: Epidemiological Studies

Ischemic Heart Disease

Several clinical studies show that adiponectin levels are lower in patients with clinical manifestations of CAD than in age- and BMI-adjusted control subjects.18,19 High levels of adiponectin are associated with a decreased risk of CAD in male diabetic patients and with cardiovascular outcomes in patients with end-stage renal failure.24 However, the association between plasma adiponectin level and CAD is controversial: 2 prospective studies found no significant association in either American Indians25 or British women,26 but a more recent large prospective and meta-analysis study found a weak association.27 The differences in the results may relate to underlying differences in the study populations or gender differences, so future population studies will be required to clarify whether hypo-adiponectinemia is a dependable indicator of CAD.

With respect to acute myocardial infarction (AMI), low plasma adiponectin levels are observed in patients with acute coronary syndrome.28 A prospective study has shown that high plasma adiponectin levels are associated with a lower risk of myocardial infarction (MI) in healthy men, independent of the level of C-reactive protein or glycemic status.29 Furthermore, a rapid decline in the adiponectin level following MI30 and a persistently low level could be predictive of future adverse cardiac events in men following AMI.31 More recently, our group investigated the association between plasma adiponectin level, and myocardial damage and function after successful reperfusion therapy in patients with AMI, as estimated by scintigraphy, and found that the plasma adiponectin level measured after coronary artery intervention could be an independent predictor of...
improvement of cardiac damage and function. Adiponectin promotes ischemia-mediated revascularization. Adiponectin supplementation has also been shown to stimulate blood vessel growth in animal models of corneal angiogenesis and Matrigel plug implantation. Adiponectin stimulates endothelial cell migration and differentiation into capillary-like structures, and prevents endothelial apoptosis in vitro. Circulating endothelial progenitor cells (EPCs) are believed to contribute to the modulation of the vascular response. The number of EPCs derived from APN-KO mice are significantly reduced compared with wild-type (WT) mice under conditions of hindlimb ischemia. Conversely, adenosivirus-mediated delivery of adiponectin promotes EPC mobilization in both WT and APN-KO mice. Incubation of human peripheral blood mononuclear cells with adiponectin leads to an increase in the number of EPCs, and adiponectin induces EPC differentiation into network structures and serves as a chemoattractant in EPC migration. Consistent with these findings, it has been shown that adiponectin stimulates nitric oxide production in endothelial cells through AMP-activated protein kinase (AMPK)-dependent and AMPK-independent phosphorylation of endothelial nitric oxide synthase (eNOS). APN-KO mice on high-salt diets exhibit high blood pressure accompanied by reduced eNOS expression in the aorta and they also develop increased brain infarction after ischemia–reperfusion (IR) compared with WT mice, accompanied by reduced eNOS activation in the ischemic cerebral tissue. Thus, the adiponectin–eNOS regulatory axis protects against the development of vascular insufficiency and endothelial dysfunction.

Atherosclerosis
Administration of adenosivirus-mediated adiponectin reduces atherosclerotic lesion size in apolipoprotein E knockout (ApoE-KO) mice, accompanied by reductions in the expression of class A scavenger receptor, TNF-α, and vascular cell adhesion molecule-1. Adiponectin stimulates nitric oxide production in endothelial cells through AMPK-dependent and AMPK-independent pathways. In humans, adiponectin inhibits the transformation of macrophages to foam cells thorough suppression of class A scavenger receptor expression. Adiponectin also reduces lipopolysaccharide (LPS)-stimulated TNF-α production and increases anti-inflammatory cytokine IL-10 in human macrophages. In recent studies, it was reported that adiponectin facilitates the removal of apoptotic cells by macrophages and modulates the processes of inflammation. Adiponectin may suppress inflammatory cytokines, such as TNF-α, in part through its ability to promote the clearance of apoptotic cells. Thus, adiponectin has anti-inflammatory properties, and adiponectin supplementation could be beneficial for the treatment or prevention of atherosclerotic diseases.

Myocardial IR Injury
Obesity-linked disorders have been implicated in the progression, severity, and outcomes of ischemic heart disease. Recently, it was shown that APN-KO mice develop larger infarcts following IR injury. IR in APN-KO mice resulted in an increase in myocardial apoptotic activity and TNF-α expression, and administration of adiponectin protein to WT mice led to reduced infarct size and improved cardiac function. Recently, Tao et al reported that adiponectin promotes ischemia-mediated revascularization. Adiponectin supplementation has also been shown to stimulate blood vessel growth in animal models of corneal angiogenesis and Matrigel plug implantation. Adiponectin stimulates endothelial cell migration and differentiation into capillary-like structures, and prevents endothelial apoptosis in vitro. Circulating endothelial progenitor cells (EPCs) are believed to contribute to the modulation of the vascular response. The number of EPCs derived from APN-KO mice are significantly reduced compared with wild-type (WT) mice under conditions of hindlimb ischemia. Conversely, adenosivirus-mediated delivery of adiponectin promotes EPC mobilization in both WT and APN-KO mice. Incubation of human peripheral blood mononuclear cells with adiponectin leads to an increase in the number of EPCs, and adiponectin induces EPC differentiation into network structures and serves as a chemoattractant in EPC migration. Consistent with these findings, it has been shown that adiponectin stimulates nitric oxide production in endothelial cells through AMP-activated protein kinase (AMPK)-dependent and AMPK-independent phosphorylation of endothelial nitric oxide synthase (eNOS). APN-KO mice on high-salt diets exhibit high blood pressure accompanied by reduced eNOS expression in the aorta and they also develop increased brain infarction after ischemia–reperfusion (IR) compared with WT mice, accompanied by reduced eNOS activation in the ischemic cerebral tissue. Thus, the adiponectin–eNOS regulatory axis protects against the development of vascular insufficiency and endothelial dysfunction.

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ponectin-mediated protection from IR injury is linked to inhibition of excess peroxynitrite-induced oxidative and nitrative stress. Adiponectin suppresses excess reactive oxygen species (ROS) production in various cell types, including endothelial cells, and this reduction in both ROS and reactive nitrogen species may contribute to the protective action of adiponectin in MI. Furthermore, increased adiponectin production by caloric restriction (CR) confers resistance to myocardial IR injury. These findings have led to the proposal that adiponectin treatment may have clinical utility in the treatment of patients suffering from AMI. It has been also shown that myocardial IR injury leads to a transient drop in adiponectin concentration. Adiponectin was detected in injured but not sham-operated hearts, accompanied by a negligible increase in adiponectin transcript in the myocardium. Systemic delivery of adiponectin to APN-KO mice led to the accumulation of adiponectin in IR-injured hearts but not in the uninjured hearts. These findings suggest that adipose-derived adiponectin might protect the heart from injury by accumulating in tissues subjected to ischemic damage through leakage from the vascular compartment. Recently, a number of studies have shown that the adiponectin transcript is upregulated in damaged heart tissue. Adiponectin transcripts are synthesized by cardiomyocytes and are upregulated in mouse models of myocardial injury. In addition, adiponectin transcripts are downregulated in dilated cardiomyopathy. These findings suggest that the endogenous production of adiponectin may contribute to cardioprotective effects, although it has never been directly demonstrated.

In cultured cardiac myocytes, adiponectin suppresses apoptosis under conditions of hypoxia–reoxygenation, and pro-survival actions are mediated by the ability of adiponectin to promote AMPK signaling. Adiponectin also inhibits LPS-induced TNF-α production, an anti-inflammatory action that is partly mediated by its ability to activate cyclooxygenase-2 (COX-2) dependent synthesis of prostaglandin E2. A recent study show that adiponectin-induced COX-2 expression is reduced by a sphingosine kinase-1 (SphK-1) inhibitor or knockdown of SphK-1, and that treatment with a sphingosine-1-phosphate (S1P) receptor antagonist also diminished COX-2 expression in response to adiponectin. Thus, adiponectin stimulates COX-2 expression in cardiac myocytes partly through the Shpk-1-S1P receptor-dependent pathway. Consistent with these in vitro findings, APN-KO hearts show reduced COX-2 induction by IR compared with WT hearts, and COX-2 inhibition partially reverses the inhibitory actions of adiponectin on infarct size and TNF-α production. These findings suggest that adiponectin protects the heart from acute ischemia through activation of independent pathways involving both AMPK-mediated anti-apoptotic effects and COX-2-mediated anti-inflammatory effects.

**Cardiac Hypertrophy**

Obesity-related diseases are associated with pathological cardiac remodeling, characterized by myocardial hypertrophy and experimental studies have shown that adiponectin is protective against its development. APN-KO mice develop severe concentric cardiac hypertrophy and exhibit increased mortality after pressure-overload caused by aortic constriction in comparison with WT mice. Conversely, adenovirus-mediated overexpression of adiponectin attenuates cardiac hypertrophy following pressure overload in APN-KO, WT, and diabetic db/db mice. Supplementation of adiponectin also attenuates cardiac hypertrophy caused by angiotensin II infusion in APN-KO and WT mice; severe cardiac fibrosis is observed in angiotensin-II-infused APN-KO mice compared with WT mice. Overexpression of adiponectin improved angiotensin-II-induced cardiac fibrosis in APN-KO mice, whereas this effect was not observed in peroxisome proliferator-activated receptor (PPAR)-α KO mice.

A series of in vitro experiments were performed to assess the mechanisms of these cardioprotective effects. In cultured cardiac myocytes, adiponectin stimulates the phosphoryla-
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The thiazolidinediones (TZDs), commonly referred to as glitazones, are a relatively new class of oral agent for treating type 2 diabetes. It is reported that TZDs increase secretion of adiponectin by activating the PPAR-γ in adipocytes.86–87 Pioglitazone-induced amelioration of insulin resistance and diabetes is mediated, at least in part, through adiponectin-dependent pathway.88 Experimental and clinical studies have demonstrated that pioglitazone has beneficial effects on cardiovascular disease, including cardiac hypertrophy.89–92 Chronic administration of pioglitazone to rats with salt-sensitive hypertension attenuates the development of LVH and fibrosis, which is likely to be attributable to stimulation of adiponectin secretion.93 Therefore, adiponectin may play an essential role in the cardioprotective effects of pioglitazone, but detailed biochemical and genetic studies are required to better understand these effects.

CR has been shown to extend the life span of many species by retarding the aging process.94 Recently, it was reported that CR confers resistance to myocardial IR injury by increasing adiponectin levels.95 CR improves both survival and myocardial damage in obese mice with viral myocarditis, which is accompanied by increased adiponectin levels in plasma and the myocardium.95 CR also enhances recovery of blood flow in response to limb ischemia in WT mice, accompanied by increased levels of eNOS phosphorylation and plasma adiponectin.95 The stimulatory actions of CR on revascularization and eNOS phosphorylation of ischemic limbs are abolished in APN-KO mice, and, furthermore, CR does not improve blood flow recovery in the ischemic limbs of eNOS-KO mice96 Thus, CR promotes revascularization in response to tissue ischemia via an AMPK-eNOS-dependent mechanism that is mediated by adiponectin. Collectively, nutritional approaches aimed at increasing adiponectin production could be useful in the treatment of cardiovascular diseases.

Finally, the biologically active forms of adiponectin need to be identified through additional epidemiological and experimental studies of treating cardiovascular disease. The HMW form is reported to activate AMPK signaling in hepatocytes, whereas the trimer form activates AMPK in skeletal muscle.97 The HMW form of adiponectin also stimulates AMPK phosphorylation in endothelial cells, but AMPK is activated by the trimer in cardiac myocytes.98 Thus, the different oligomers of adiponectin stimulate distinct signal transduction cascades in different cell types, resulting in diverse biological activities.

Conclusion

Hypo-adiponectinemia contributes to the development of obesity-related disorders. In general, low levels of adiponectin are associated with increased prevalence of obesity-linked cardiovascular disorders, including ischemic heart disease and PAD. However, it remains controversial whether adiponectin is a promising predictor or risk factor for certain cardiovascular disorders, so future studies are necessary to elucidate the causal link between adiponectin level and the development of cardiovascular diseases. Experimental studies show adiponectin deficiency contributes to exacerbated remodeling, increased damage and enhanced inflammatory responses in the cardiovascular system under pathological conditions. Conversely, adiponectin protects against the development of atherosclerosis, ischemic injury and tissue remodeling by directly affecting the heart and blood vessels. The favorable effects of adiponectin are associated with an anti-inflammatory reaction, anti-apoptotic effect, anti-hypertrophic response, and inhibition of interstitial fibrosis, so adiponectin could be a promising therapeutic molecule.

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References


