

Adiponectin, obesity, and cardiovascular disease

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Abstract

Several adipocyte-secreted factors have been demonstrated to potentially link obesity, insulin resistance, and cardiovascular disease. Among those, adiponectin is an insulin-sensitizing and anti-inflammatory adipokine, concentrations of which are decreased in obesity-associated metabolic and vascular disorders. Recently, two adiponectin receptors (AdipoR) have been isolated and adenosine monophosphate kinase (AMPK), as well as acetyl coenzyme A carboxylase (ACC), appear to be critical downstream mediators for various effects of this adipokine. In addition to beneficial metabolic effects, adiponectin seems to be vasoprotective by interfering with various atherogenic processes. Of clinical interest, thiazolidinediones (TZDs) which are used in the treatment of type 2 diabetes stimulate adiponectin expression and secretion whereas several hormones dysregulated in insulin resistance and obesity downregulate this adipokine. The current knowledge on regulation and function of adiponectin in obesity, insulin resistance, and cardiovascular disease is summarized in this review and its clinical implications are discussed.

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1. Adiponectin a novel adipokine dysregulated in insulin resistance, obesity, and cardiovascular disease

Type 2 diabetes which is frequently characterized by insulin resistance of peripheral tissues such as liver, muscle, and fat which cannot be overcome by hypersecretion of pancreatic β -cells is one of the most common chronic diseases and affects about 150 million people worldwide [1,2]. Insulin resistance is often associated with increased body weight and cardiovascular dysfunction and several adipocyte-secreted proteins such as adiponectin, tumor necrosis factor (TNF) α , resistin, and interleukin (IL)-6 have been described which might provide a link between these pathological states [3].

Among those, adiponectin was originally identified by four independent groups using different experimental approaches and is, therefore, also called Acrp30, GBP28, apM1, and AdipoQ [4–7]. Expression and plasma levels of adiponectin are decreased in insulin resistance and obesity [6] and synthesis

of this adipokine increases when insulin sensitivity is improved and weight is lost [8,9]. Interestingly, low adiponectin serum levels at baseline independently predict future risk to develop type 2 diabetes mellitus in humans [10]. Furthermore, several studies indicate that adiponectin levels are significantly decreased in patients with coronary artery disease as compared to matched controls [11,12] and high plasma adiponectin predicts a lower risk of future myocardial infarction [13]. Moreover, hypoadiponectinemia is a marker for predisposition to hypertension in men [14]. Adiponectin synthesis and secretion are increased by insulin-sensitizing thiazolidinediones (TZDs) in vitro and in vivo (Fig. 1) [15–19]. Interestingly, even treatment of insulin-sensitive subjects with the TZD rosiglitazone for 2 weeks results in a 130% increase in adiponectin plasma levels [20]. In contrast, various hormones inducing insulin resistance and dysregulated in obesity downregulate adiponectin expression (Fig. 1). For example, β -adrenergic activation inhibits adiponectin mRNA expression in mouse and human fat cells in vitro (Fig. 1) [21,22]. Glucocorticoids decrease adiponectin mRNA synthesis and secretion in 3T3-L1 cells, as well as in human adipocytes (Fig. 1) [23–25]. In accordance with these findings, removal of the adrenal gland in ob/ob mice leading to decreased levels of glucocorticoids increases adiponectin

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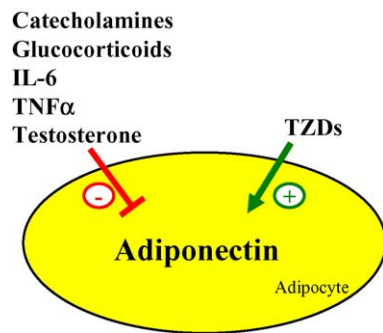


Fig. 1. Regulation of adiponectin in adipocytes.

[26]. Conversely, transgenic overexpression of 11β -hydroxysteroid dehydrogenase type 1 in fat tissue leading to increased local glucocorticoid levels decreases expression of the adipokine in vivo [27]. Furthermore, adiponectin mRNA expression and protein secretion are decreased in mouse 3T3-L1 adipocytes and human primary adipocytes by $\text{TNF}\alpha$ and IL-6 (Fig. 1) [15,23,24,28]. Moreover, a sexual dimorphism exists with plasma adiponectin concentrations being significantly lower in men as compared to women and testosterone inhibiting adiponectin secretion in 3T3-L1 adipocytes (Fig. 1) [29,30].

Taken together, these studies indicate that adiponectin is upregulated by insulin-sensitizing TZDs and suppressed by insulin resistance-inducing hormones. However, these studies do not rule out the possibility that adiponectin is simply a factor passively regulated by insulin resistance, obesity, and cardiovascular disease. In the next two paragraphs, therefore, the accumulating evidence of adiponectin actively influencing insulin sensitivity and vascular function is summarized and its implications are then discussed.

2. Influence of adiponectin on insulin sensitivity

In 2001 the first study has been published indicating that adiponectin actively influences insulin sensitivity [31]. A C-terminal globular adiponectin fragment is able to reduce plasma glucose concentrations via increased fatty acid oxidation in muscle (Fig. 2) [31]. These observations are confirmed and extended by two other studies [18,32]. The authors demonstrate that a globular fragment increases fatty acid combustion in muscle cells much more potently as compared to full length adiponectin thereby reducing plasma glucose levels (Fig. 2) [18]. In contrast to muscle, in liver cells only full length but not globular adiponectin potently augments insulin-induced inhibition of glucose output in vivo and in vitro (Fig. 2) [32,33]. Furthermore, adiponectin also alters insulin sensitivity and metabolism of adipocytes in a paracrine manner (Fig. 2) [34]. Thus, globular adiponectin further enhances insulin-stimulated glucose uptake at sub-maximal insulin concentrations and reverses the inhibitory effect of $\text{TNF}\alpha$ on insulin-stimulated glucose uptake in fat

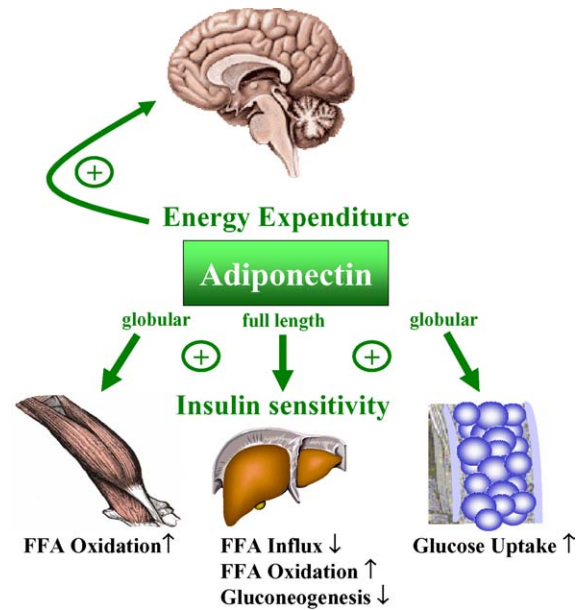


Fig. 2. Hypothetical model for the actions of adiponectin on insulin sensitivity and energy expenditure.

cells in vitro (Fig. 2) [34]. Knockout (KO) studies further support adiponectin's role as an endogenous insulin sensitizer. Thus, two out of three studies show impaired insulin sensitivity in adiponectin KO mice as compared to wild type (WT) controls [35–37]. Furthermore, it has recently been suggested that adiponectin also acts in the brain to increase energy expenditure and cause weight loss (Fig. 2) [38].

The signaling pathways mediating adiponectin's insulin-sensitizing effects have been better understood in recent years. Thus, two adiponectin receptors (AdipoR) have been identified [39]. Both proteins are predicted to contain seven transmembrane domains, which are structurally and functionally distinct from G-protein-coupled receptors [39]. AdipoR1 is preferentially expressed in muscle as high-affinity receptor for globular adiponectin and low-affinity receptor for full-length adiponectin, whereas AdipoR2 is abundantly found in liver and serves as intermediate-affinity receptor for both forms of adiponectin [39]. Both receptors are also expressed in 3T3-L1 fat cells [40]. Downstream of AdipoR, activation of adenosine monophosphate kinase (AMPK) followed by inhibition of acetyl coenzyme A carboxylase (ACC), as well as stimulation of peroxisome proliferator-activated receptor (PPAR) α appears essential for adiponectin action [32,41]. Thus, in liver stimulation of AMPK leads to decreased levels of gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (Fig. 2) [18,32]. In muscle, adiponectin stimulates proteins involved in fatty acid transport and oxidation such as CD36, acyl-coenzyme A oxidase, uncoupling protein-2, and PPAR α resulting in enhanced fat combustion and energy dissipation (Fig. 2) [18,32]. Activation of AMPK followed by inhibition of ACC by globular adiponectin has also been demonstrated in rat adipocytes [34].

3. Influence of adiponectin on endothelial and vascular function

Besides its profound insulin-sensitizing effects, recent studies support adiponectin's role as an anti-inflammatory vasoprotective adipokine. First, major steps in the pathogenesis of atherosclerosis are summarized and then the influence of adiponectin on cardiovascular disease is described.

Early in atherosclerosis, various lipoproteins such as low density lipoproteins (LDL) and lipoprotein (LP) are deposited in the intima of the vascular wall (Fig. 3). These intima-associated LPs are oxidized and induce various adhesion molecules in endothelial cells such as vascular cell adhesion molecule (VCAM)-1, intracellular adhesion molecule (ICAM)-1, and E-selectin (Fig. 3). Mononuclear cells attach to endothelial cells via these adhesion molecules and migrate into the subendothelial space (Fig. 3). This process is induced by various bioreactive mediators among which monocyte chemoattractant protein (MCP)-1 plays a prominent role. Once resident in the vessel wall, monocytes develop into macrophages and as they take up oxidized LDL through scavenger receptors (SR) differentiate into foam cells. This process is supported by acyl-coenzyme A:cholesterol acyltransferase-1 (ACAT-1) in macrophages, which catalyzes the formation of cholesteryl esters. As a secondary event, synthesis of vasodilating NO by endothelial NO synthase (eNOS) is impaired (Fig. 3) [42,43].

Adiponectin influences various aspects of endothelial function. Thus, this adipokine inhibits TNF α -induced expression of VCAM-1, ICAM-1, and E-selectin in human aortic endothelial cells in vitro (Fig. 3) [12]. Moreover, TNF α -stimulated adhesion of monocytes on endothelial cells is inhibited by adiponectin (Fig. 3) [12]. Signaling studies suggest that adiponectin suppresses TNF α -induced I κ B α phosphorylation and subsequent nuclear factor (NF) κ B activation in human endothelial cells without affecting other

TNF α -mediated phosphorylation signals including Jun N-terminal kinase (JNK), p38 mitogen-activated protein (MAP) kinase, and Akt [44]. Furthermore, globular adiponectin inhibits cell proliferation and superoxide release induced by oxidized LDL in bovine endothelial cells [45]. Importantly, adiponectin directly stimulates NO production in human and bovine aortic endothelial cells [46,47]. This adipokine also ameliorates the suppression of eNOS activity after treatment of endothelial cells with oxidized LDL [45]. Apoptosis of human endothelial cells is suppressed by a high-molecular-weight form of adiponectin [48]. Ouchi et al. [49] demonstrate that adiponectin stimulates differentiation of human endothelial cells into capillary-like structures in vitro. Besides these well-defined effects on endothelial cell function, adiponectin suppresses human aortic smooth muscle cell proliferation and migration through direct binding with platelet-derived growth factor and inhibition of growth factor-induced MAP kinase signaling in vitro [50,51]. Moreover, foam cell transformation of human monocyte-derived macrophages is suppressed by reducing the expression of macrophage class A SR and inhibiting ACAT-1 expression and activity (Fig. 3) [52,53].

In vivo studies using adiponectin KO mice support the view of this adipokine as an endogenous vasoprotector. Thus, KO mice as compared to WT controls show neointimal thickening and increased proliferation of vascular smooth muscle cells after mechanical injury of arteries [36,51]. Interestingly, adenovirus-mediated re-expression of adiponectin attenuates neointimal proliferation in adiponectin KO mice [51]. In accordance with these results, treatment of apolipoprotein E (apoE)-deficient mice which develop early atherosclerosis with adiponectin-expressing adenoviruses results in a 30% decrease in lesion formation as compared to control mice expressing β -galactosidase [54]. Immunohistochemical analyses show that adenovirus-synthesized adiponectin migrates to foam cells in the fatty streak lesions [54]. In a

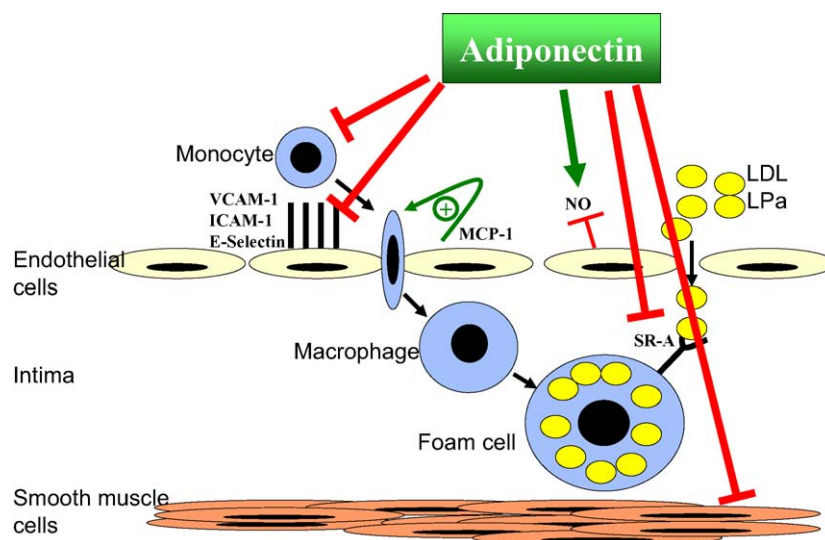


Fig. 3. Major steps in the pathogenesis of atherosclerosis which are further detailed in the text. Adiponectin inhibits upregulation of adhesion molecules, attachment of monocytes to endothelial cells, transformation from macrophages to foam cells, as well as proliferation and migration of vascular smooth muscle cells. Moreover, NO production of endothelial cells is stimulated by this adipokine.

similar experimental setting, apoE KO mice overexpressing globular adiponectin show amelioration of atherosclerosis despite similar plasma glucose and lipid levels [55]. In accordance with *in vitro* studies, a downregulation of VCAM-1, class A SR, and TNF α is demonstrated after adiponectin treatment in the vascular wall *in vivo* [54,55]. Forearm bloodflow studies in humans suggest that adiponectin is closely associated not only with endothelium-dependent but also endothelium-independent vasodilation [46,56–58].

The signaling pathways by which adiponectin influences endothelial and vascular function are far from clear. Both AdipoR are present in endothelial cells with preferential expression of AdipoR1 [45,46]. Enhanced NO production in endothelial cells is dependent on AMPK activation by adiponectin [47]. Furthermore, differentiation of endothelial cells into capillary-like structures depends on this signaling intermediate [49]. Downstream of AMPK various signaling molecules have been suggested. Thus, adiponectin-induced NO production is dependent on phosphatidylinositol (PI) 3-kinase and eNOS [47], whereas differentiation into capillary-like tubes depends on PI 3-kinase and Akt [49]. In contrast, the inhibitory effect of adiponectin on TNF α -induced I κ B α phosphorylation and subsequent NF κ B activation in human endothelial cells appears to be mediated via cAMP accumulation [44]. Clearly more work is needed to precisely define the signaling pathways by which adiponectin improves vascular function and insulin sensitivity.

4. Summary and perspectives

Adiponectin has emerged in recent year as a novel adipocyte-secreted factor and therapeutic target increasing insulin sensitivity and improving vascular function not only in animal models but also in humans. However, various areas of uncertainty still need to be addressed to successfully transform our current knowledge into clinical practice. For example, a transgenic mouse model with threefold elevated circulating adiponectin concentrations has an unexpected phenotype with interscapular and intraconal fat accumulation, the latter resulting in significant exophthalmus [59]. Since AdipoR agonists might prove to be valuable agents for the treatment of insulin resistance, obesity, and cardiovascular disease, the signaling properties of both receptors which appear to be coupled to AMPK have to be better elucidated. Most recently, T-cadherin has been suggested as a novel receptor for hexameric and high-molecular-weight forms of adiponectin and needs to be better characterized as well [60]. Furthermore, it is far from clear which fragments and oligomeric states of adiponectin are important for its beneficial effects not only *in vitro* but also *in vivo*. Moreover, a recent paper by Wong et al. [61] suggests that at least seven adiponectin paralogs exist which might also have beneficial effects on insulin sensitivity and cardiovascular disease and might substitute for adiponectin function *in vivo*. Clearly, the exciting story of adiponectin will continue and perhaps lead

the way to novel treatment options for insulin resistance, obesity, and vascular dysfunction.

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