Abstract

The discoveries of leptin and adiponectin were breakthroughs in the field of metabolic diseases. Adipose cells produce both proteins and release them into the circulation. Leptin acts as a fundamental signal for the brain to modulate food intake as a function of energy status. Loss of leptin function results in obesity. Although a biological role for adiponectin has not been firmly established, clinical and experimental observations indicate that low plasma levels contribute to the pathogenesis of insulin resistance, type 2 diabetes and cardiovascular diseases in obese or overweight patients. Adiponectin circulates as several multimeric species, including a high-molecular-weight form thought to be the most clinically relevant. Adiponectin exerts anti-atherogenic effects by targeting vascular endothelial cells and macrophages and insulin-sensitizing effects, mainly predominantly in muscle and liver. The best-characterized molecular mechanism mediating adiponectin's metabolic and vascular activities involved stimulation of AMP kinase activity. Adiponectin signaling pathways comprise at least two putative receptors (AdipoR1 and AdipoR2). Ways to enhance adiponectin bioactivity are actively being sought. In obesity, reducing chronic adipose-tissue inflammation and macrophage infiltration into it could be beneficial to reverse downregulation of adiponectin gene expression by pro-inflammatory cytokines. Pharmacologically, thiazolidinediones and cannabinoid-1 receptor blockers (e.g., rimonabant) increase plasma adiponectin and gene expression in adipocytes. Finally, AdipoR activation to mimic adiponectin actions could prove beneficial to reduce metabolic risk factors in conditions, such as obesity, where low adiponectinemia prevails.

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1. Introduction

The discovery in the mid 1990s that adipose tissue releases specific proteins into the blood stream was a breakthrough in the field of obesity and metabolic diseases. Among various cell types that compose adipose tissue, adipocytes themselves produce two major proteins: leptin and adiponectin. Adipose production is the principal, if not exclusive, contributor to circulating levels of both molecules. By acting on peripheral target tissues through specific receptors, leptin and adiponectin qualify as hormones. Leptin acts as a fundamental signal for the brain to modulate food intake as a function of energy status. Reduction or loss of leptin function, due either to genetic or nutritional factors, causes obesity [1]. In contrast, a specific role for adiponectin has not been fully elucidated. Nevertheless, numerous experimental and clinical observations clearly implicate the decreased adiponectin bioactivity in obesity-linked complications, including cardiovascular diseases (CVD) and insulin resistance. In this review, I will focus on adiponectin and analyze recent progress on the pathophysiological role of this adipose tissue hormone and its relevance in human physiology.

2. History of adiponectin discovery

In reference to its homology with the complement factor C1q, adiponectin was first named “adipocyte complement-related protein of 30 kDa” (ACRP30). It was identified in 1995 as a protein secreted by murine 3T3-L1 adipocytes and present at high levels in mouse sera [2]. Shortly thereafter, the same protein was cloned but given the name of AdipoQ [3]. That study revealed for the first time that adipose expression of AdipoQ was lower in obese subjects. The human adiponectin gene was cloned through systematic sequencing of an adipose-tissue library, where it was the most frequently found transcript, and thus, given the name apM1 for “adipose most abundant gene transcript 1” [4]. Finally, the protein has also been purified from human plasma under the name of gelatin-binding protein of 28 kDa (GBP28) [5]. Unlike leptin, whose discovery in 1994 generated a frenzy of intense research, interest in adiponectin remained low until 1999–2000, when it was realized that obesity is associated with lower circulating adiponectin levels, with a more detrimental effect of type 2 diabetes (T2D) and coronary artery disease (CAD) on this parameter [6,7].

In 1999, a potential antiatheroslerotic action of adiponectin was indicated by pioneering in vitro studies, which showed that adiponectin inhibits monocyte adhesion to aortic endothelial cells and suppresses macrophage-to foam cell transformation [8–10]. Later, vascular anomalies were found in adiponectin-deficient mice, namely neointimal thickening and increased proliferation of vascular smooth muscle cells in response to external arterial injury [11,12]. Conversely, adiponectin administration to apolipoprotein E-deficient mice reduced the size of the atheroslerotic lesions that appear spontaneously in this model [13,14]. More recently, studies in adiponectin-deficient mice revealed new roles for adiponectin: protecting the heart against ischemia reperfusion injury [15] and acting as an endogenous antithrombotic factor [16]. Several epidemiological studies conducted in humans, identified hypo adiponectinemia as an independent risk factor for CVD, consistent with an adiponectin vasculoprotective action [8,17,18].

In 2001, a longitudinal study in a nonhuman primate model of diet-induced obesity showed that plasma adiponectin decreased progressively with the development of obesity and insulin resistance, preceding the onset of T2D [19]. That observation was a major contribution to the hypothesis that low adiponectin levels were causally related to diminution of insulin sensitivity. The metabolic phenotype of adiponectin knockout mice supports that postulate. Although, the results of the first analyses indicated mild or absent insulin resistance in adiponectin-deficient mice fed on a normal diet [11,20,21], a recent reevaluation of this model revealed that hepatic-glucose production was increased in the absence of adiponectin [22]. Moreover, when exposed to a high-fat regimen, adiponectin-deficient mice developed glucose intolerance, supporting the idea that adiponectin protects against diet-induced insulin resistance [11,20,22]. In agreement, prospective case control studies in obesity-prone Pima Indians and the general population indicated that individuals with high adiponectin concentrations were less likely to develop T2D than those with low concentrations [23,24].

3. Cellular and molecular mechanisms of adiponectin functions

3.1. Molecular structure of adiponectin

Adiponectin monomers have an amino-terminal collagen-like domain and a carboxy-terminal globular domain that generate trimers, hexamers and high-molecular-weight (HMW) multimers (reviewed in [25]). The three multimeric forms are found in the circulation, associated with several serum proteins recently characterized in humans [26]. The adiponectin globular head is also detected in the trimeric form in human and mouse plasmas, although at low concentrations [27,28]. Adding to this complexity, a family of seven proteins homologous to adiponectin has been identified [29] that might exhibit partial functional redundancy with adiponectin. It has not yet been clearly established which adiponectin form(s) is (are) biologically active. Based on clinical observations (see below), the current consensus is that the HMW form is the more clinically relevant. The recent development of a new ELISA system for selective measurement of human adiponectin multimers [30,31] will certainly help clarify this issue.

3.2. Skeletal muscles and liver are the main adiponectin targets

The first identified metabolic action of adiponectin was the capacity of its globular head to curtail the rise of plasma free-fatty acids following a high-fat meal in mice, an effect attributed to its stimulation of fatty-acid oxidation in muscles [27]. Enhanced lipid catabolism, leading to reduced tissue triglyceride contents and improved insulin sensitivity was confirmed in insulin resistant mice receiving adiponectin [28].
The other well-established metabolic effect of adiponectin is to lower hepatic-glucose production, demonstrated in response to acute adiponectin administration in mice and to cultured hepatocytes [32,33]. This function is corroborated by the phenotype of adiponectin-deficient mice, which have higher rates of endogenous glucose production than wild-type mice during euglycaemic-insulin clamp [22]. In patients with T2D [34,35] or nonalcoholic fatty liver disease [36], an inverse relationship between plasma adiponectin and endogenous glucose production was reported, which supports an adiponectin role in negatively controlling hepatic-glucose output.

3.3. AMPK activation mediates adiponectin actions

These metabolic effects of adiponectin are similar to those elicited by activation of the 5'-AMP-activated kinase (AMPK) in liver and muscles [37–39], leading to the hypothesis that adiponectin could act through the stimulation of this enzyme. That postulate was confirmed by a series of experimental findings showing that AMPK inactivation precludes adiponectin stimulation of fatty-acid oxidation in muscles and inhibition of gluconeogenesis in liver [40,41]. Recently, adiponectin was shown to increase mitochondrial numbers and function in skeletal muscles through an AMPK-dependent mechanism [42].

AMPK activation also mediates several cellular processes influenced by adiponectin in vascular endothelial cells and the heart that might participate in its protective effect against CVD. AMPK signaling in endothelial cells is required for adiponectin proangiogenic [44,45] and antiapoptotic effects [46], stimulation of nitric oxide (NO) production [47], and reduction of myocardial infarct size and myocardial apoptosis in a mouse model of heart ischemia–reperfusion [15].

Taken together, these observations highlight AMPK’s role as a major downstream component of adiponectin signaling, mediating both its metabolic and cardiovascular effects. Notably, the capacity to modulate AMPK activity is shared by a number of endogenous (nutrients, hormones) and exogenous (thiazolidinediones (TZD), metformin) molecules. The mechanisms by which these factors, including adiponectin, interact with the kinase are under intense investigation [37–39].

The results yielded by a series of in vitro and in vivo experiments led to the concept that all adiponectin forms can effectively activate AMPK in muscle, while the presence of HMW multimers is required to elicit a biological effect in liver [40,42,48]. These observations raised the possibility of distinct receptors with different binding affinities and tissue distributions, which was confirmed by the cloning of two putative adiponectin receptors, AdipoR1 and AdipoR2 [49]. AdipoR1 is a high-affinity receptor for globular adiponectin, while AdipoR2 binds both full-length and globular forms of the hormone. In mice, AdipoR1 is most abundant in skeletal muscles and AdipoR2 is primarily expressed in the liver. The AdipoR amino-acid sequences predicted that they would be integral membrane proteins, with seven transmembrane domains, and having an internal N-terminus and external C-terminus (opposite to the configurations of other reported seven-transmembrane-domain G protein-coupled receptors). In mice, the simultaneous targeted disruption of AdipoR1 and AdipoR2 abrogates adiponectin binding and metabolic actions, resulting in increased tissue tri-glyceride contents and glucose intolerance [50]. Most recently, a pleckstrin homology-domain-containing adaptor protein, named APPL1, was shown to interact with the cytoplasmic domain of AdipoR1 [51]. In muscle cells, this interaction is stimulated by adiponectin and mediates AMPK activation and stimulation of fatty-acid oxidation. Pertinently, APPL1 also interacts with insulin-signaling molecules and could represent a molecular link between adiponectin and downstream insulin events.

In addition to AdipoR, T-cadherin was identified as a binding protein for hexameric and HMW adiponectin species [52]. This cell-surface protein is not strongly expressed in muscles and liver, but is widely distributed throughout the cardiovascular tree, more specifically on endothelial and smooth muscle cells, which both are adiponectin targets. Since T-cadherin lacks an intracellular domain, it was thought to act as a coreceptor with an unknown binding partner in HMW-adiponectin signaling in specific cell types.

4. Regulation of adiponectin bioactivity

Adiponectin biological efficacy depends on the bioavailability of its circulating forms and functional capacity of its receptors. Currently, both the downstream signaling events and the regulation of AdipoR gene expressions in adiponectin target tissues are not well characterized. The authors of one study on mice reported that AdipoR1 and R2 expressions in liver and muscles were inversely correlated with plasma insulin during fasting and refeeding, and were lower in genetically obese mice [53]. Those changes were not found in rats [54]. Similarly, direct insulin reduction of AdipoR1 expression was observed in a murine-myocyte cell line [53] but not in human myotubes [55]. Further studies are needed to determine to what extent AdipoR-expression modulation and/or signaling contributes to modifying adiponectin sensitivity in pathophysiological settings.

Adiponectin production by the adipocytes is a multistep process that can be regulated at the level of gene expression, secretion and/or formation of the multimeric forms of the protein. The molecular mechanisms involved in adiponectin secretion and multimerization and their regulation have not been deciphered. More is known about the regulation of adiponectin gene expression. In obese subjects, adipose tissue is characterized by heightened oxidative stress [56], chronic inflammation and macrophage infiltration [57,58]. Reactive-oxygen species (ROS) [56] and pro-inflammatory cytokines [59,60] are potent inhibitors of adiponectin gene expression in cultured adipocytes and could, therefore, contribute to lowering adiponectin release by “obese” adipose tissue. In support of this hypothesis, a recent study conducted on monozygote twins discordant for obesity showed an inverse relationship between adiponectin and macrophage-marker (CD68) gene expression in subcuta-
neous adipose tissue [61]. Notably, adiponectin itself exerts anti-inflammatory impact on endothelial cells [8,62] and macrophages [10,63,64]. Thus, decreased adiponectin production in obesity could aggravate inflammation and macrophage pro-inflammatory status within the adipose tissue, thereby creating a “vicious cycle” to lower adiponectin release. As discussed below, exogenous nutritional and pharmacological factors have been found to increase plasma adiponectin and adipose gene expression, but their mechanisms remain only partially elucidated.

5. Clinical relevance of adiponectin

In humans, a broad spectrum of deleterious consequences has been associated with lower adiponectinemia. It includes enhanced risks of T2D and CVD, but the association between circulating adiponectin concentrations and CVD risk is moderate compared to the strong relationship with T2D risk [65]. Emerging evidence suggests that low adiponectin levels favor the development of hepatic fibrosis (reviewed in [66]), aggravate fibro-inflammatory lesions in the liver [67] and might also raise the risk of malignancies (reviewed in [68]). Reduced adiponectin levels mainly stem from lower levels of its HMW form in patients with CVD or insulin resistance [46,69]. Human adiponectin gene mutations, which specifically impair the formation of HMW adiponectin hexamers, have consistently been associated with T2D [48]. Those observations suggest that the HMW-adiponectin form is the most pathologically relevant. Thus, it is clinically pertinent to identify a means of restoring normal adiponectin levels and, more specifically, the HMW form.

In obese subjects, weight loss, even moderate, raises plasma adiponectin levels by increasing the HMW-multimer concentration [46,70]. Although not established in humans, observations in rodents indicate that n-3 polyunsaturated fatty acids (n-3 PUFA) dietary supplementation enhances plasma adiponectin concentrations in models of obesity and diet-induced insulin resistance [71–73]. Those effects could rely, at least in part, on the reduction of the inflammatory adipose-tissue state and macrophage infiltration elicited by weight loss [57,58] or n-3 PUFA supplementation [74].

Since the advent of TZD, a class of insulin-sensitizing drugs used to treat T2D, several studies addressed the question of whether this action might be mediated through an upregulation of adiponectin. It is now clearly established that TZD administration dose dependently increases circulating adiponectin levels in animal models of obesity and humans [75–78]. Thiazolidinediones are potent agonists of the transcription factor of peroxisome proliferator-activated receptor-gamma (PPARγ) that transactivates the promoter of the adiponectin gene [79]. In contrast to n-3 PUFA, TZD enhances adiponectin gene expression in obese mice without decreasing macrophage infiltration into adipose tissue [80]. That observation suggests that PPARγ activation might overcome the inhibitory effect of macrophage-derived pro-inflammatory cytokines on adiponectin-promoter activity. The TZD stimulatory effect specifically affects the HMW form of adiponectin, via a mechanism that remains to be determined [80,81]. Recently, rimonabant, the first selective cannabinoid-1 receptor (CB1) blocker to enter clinical trials, was shown to induce body weight loss and lower CVD risk factors in overweight and obese patients [82–85]. In the RIO-lipids study, rimonabant led to significantly weight loss (~5.4 ± 0.4 kg) and diminished waist circumference (~4.7 ± 0.5 cm), increased HDL-cholesterol (+8.1 ± 1.5%) and lowered triglycerides (~12.4 ± 3.2%), as compared to a placebo. Pertinently, rimonabant increased plasma adiponectin (+46.2%), in correlation with increased HDL-cholesterol and partly independent of weight loss. In obese rats, rimonabant raised adiponectin gene expression in adipose tissue, where the CB1 receptor is expressed [86]. Moreover, rimonabant directly stimulated adiponectin gene expression in an adipocyte line [86]. All these observations suggest that the endocannabinoid system exerts a strong negative effect on adiponectin gene expression through the CB1 receptor. Stimulation of adiponectin production in the context of CB1 blockade might explains, at least partially, the consistent and weight-loss-independent effect of rimonabant on metabolic risk factors [83].

In addition to increasing circulating adiponectin, it could be beneficial to enhance the activity of its receptors in settings associated with low adiponectinemia like obesity. In this context, the recent unexpected discovery that osmotin, an ubiquitous plant-defense protein, mimics adiponectin’s effects in cultured mammalian myocytes, raises the possibility that “natural” adiponectin agonists do exist and opens new avenues to be explored in devising therapeutic strategies to treat metabolic diseases [87].

6. Conclusion

Our rapidly growing knowledge on adiponectin biology has revealed the complexity of this fascinating protein (Fig. 1). From a fundamental research perspective, the specific biological role of adiponectin is not clear. Available data highlight its capacity to improve whole-body insulin sensitivity by reducing ectopic triglyceride accumulation in insulin-sensitive tissues and decreasing hepatic-glucose production, and by positively influencing cardiovascular functions. However, these effects do not appear to be essential, as suggested by the relatively mild phenotype of adiponectin-deficient mice, in sharp contrast to the early and massive obesity due to leptin deficiency. Indeed, it is only under metabolic (high-fat diet, obesity) or cellular (vascular injury, atherosclerotic lesion, myocardial infarct) stress conditions that a reduction or lack of adiponectin is associated with deleterious consequences. From a clinical perspective, those observations provide that adiponectin replenishment, potentially through the supplementation of specific hexameric form(s), will compensate for the metabolic and cardiovascular impairments associated with low adiponectin levels. Finally, adiponectin-receptor agonists could reserve major therapeutic usefulness, particularly in obese patients with low circulating adiponectin levels, to improve their metabolic and cardiovascular functions.
Fig. 1. Schematic representation of adiponectin regulation and currently known mechanisms of metabolic and vascular effects.

Abbreviations: ROS: reactive-oxygen species; n-3 PUFA: n-3 polyunsaturated fatty acids; TZD: thiazolidinediones; NO: nitric oxide; APPL1: a pleckstrin homology domain-containing adaptor protein; AMPK: 5′-AMP-activated kinase; CB1: cannabinoid-1 receptor.

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References


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