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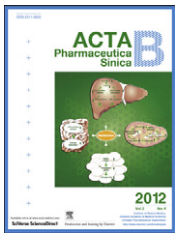

REVIEW

Adiponectin and lipid metabolism in skeletal muscle

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Abstract White adipose tissue (WAT) is a key energy depot in humans and most animals. Traditionally, it is believed that WAT passively accumulates triglycerides or releases fatty acids to accommodate systemic energy metabolism. However, recent studies have demonstrated that WAT also actively participates in energy metabolism mainly through its secretion of cytokines and hormones. Therefore, at this time, WAT is recognized as an endocrine organ. Adiponectin is one of the key adipocyte-derived hormones that regulate systemic or tissue lipid and glucose metabolism. In contrast to most other adipocyte-derived hormones, adiponectin increases insulin sensitivity and improves lipid and glucose metabolism. Although the insulin-sensitizing function of adiponectin has been well established, recent studies have demonstrated that adiponectin also regulates metabolism through pathways independent of insulin signaling. Due to the massive tissue mass of skeletal muscle, lipid uptake and subsequent fatty acid oxidation in skeletal muscle have a big impact on maintaining systemic energy homeostasis. Furthermore, adiponectin gene expression is regulated by energy intake. Therefore, adiponectin serves as a coordinator of energy balance amongst WAT, skeletal muscle and other tissues. We summarize the regulatory effects of adiponectin on lipid and glucose metabolism in skeletal muscle. Future research directions have also been proposed.

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1. Introduction

Adiponectin is adipocyte-derived hormone with aprominent function of increasing insulin sensitivity. Unlike other adipokines, such as leptin and resistin, adiponectin gene expression and circulating levels are inversely correlated with adiposity[1,2]. Furthermore, a decrease in blood adiponectin levels in the prediabetic state precedes the reduction in insulin sensitivity[3], suggesting hypoadiponectinemia may contribute to the development of insulin resistance in obesity and type 2 diabetes[3–6]. Thus, in the past decade, tremendous efforts have been committed to studying the roles and the underlying mechanisms by which adiponectin improves energy metabolism and insulin sensitivity. Increasing fatty acid oxidation in skeletal muscle is one of the important mechanisms that may be the basis of the insulin-sensitizing effect of adiponectin[7,8]. Recent studies revealed that, independent of insulin signaling, adiponectin enhances triglyceride (TG) catabolism, fatty acid uptake, and mitochondrial biogenesis, which further supports the importance of adiponectin in regulating lipid metabolism in skeletal muscle. In this review, we will briefly summarize general backgrounds of adiponectin and discuss the progress and detailed findings about the underlying mechanism of adiponectin-improved lipid metabolism in skeletal muscle.

2. Adiponectin gene structure

The human adiponectin gene spans 16 kb in chromosome 3 and is composed of three exons from 18–4,277 bp in size with consensus splice sites[9–11]. A basic promoter and an intronic enhancer have been identified in the human adiponectin gene. Similar to that of other adipocyte-derived hormones, adiponectin gene transcription is under the control of adipocyte master transcription factors including peroxisome proliferator-activated receptors γ (PPARγ) and CCAAT enhancer binding protein α (C/EBPα)[12,13]. Several other transcription factors have been found to be able to bind adiponectin gene and regulate its transcription[14,15].

Adiponectin protein is composed of an N-terminal signal sequence, a globular domain near the C terminus, and a collagen-like domain[16]. The adiponectin is a 30 kD protein of 247 amino acids. During secretion, adiponectin forms several different multimeric protein complexes in adipocytes[17]. The basic structure is the trimer. Adiponectin trimers are able to form higher-ordered complexes through the noncovalent binding of two trimers (hexamers) and six trimers (18 mers). Based on the migration speeds during electrophoresis, these higher-ordered complexes are described as low molecular weight (LMW, trimers), medium molecular weight (MMW, hexamers) and high molecular weight (HMW, 12–18 mers) forms of adiponectin[11,18]. While HMW forms comprise the major forms of intracellular adiponectin, LMW forms comprise the major part of circulating adiponectin[19]. A study suggested that blood HMW levels may be more closely correlated with systemic insulin sensitivity when compared with other multimeric adiponectin, and the ratio between HMW and total adiponectin may be more precise than total adiponectin for demonstrating the relationship between adiponectin and insulin resistance[20]. However, which forms of adiponectin are biologically active is still controversial[19–21].

3. Tissue expression pattern of adiponectin

Although the adiponectin gene was first cloned and primarily expressed in adipose tissue[11], studies have reported that adiponectin is also expressed in some non-adipose tissues including central nervous system (CNS)[22–25]. By studying adiponectin mRNA and protein, several peripheral tissues have been shown to express adiponectin, although the function of the locally-expressed adiponectin remains unclear. Adiponectin protein was detected in endothelial cells of portal vessels and liver sinusoids of patients with steatosis[23]. Bone-forming cells also expressed adiponectin[22]. Cultured human osteoblasts have increased adiponectin expression and secretion into the medium during differentiation[22]. In addition, adiponectin mRNA levels increased in osteoblasts with treatment of dietary fatty acids[22]. The expression of adiponectin is also observed in skeletal muscle[24]. Inflammatory cytokine treatment induced adiponectin expression in skeletal muscle both *in vivo* and *in vitro*[26,27]. More interestingly, recent studies have shown that adiponectin is also expressed in the brain[25]. Adiponectin protein localized in the luteinizing hormone, growth hormone, follicle-stimulating hormone, and thyroid-stimulating hormone-producing cells in the pituitary gland of brain, suggesting that locally-expressed adiponectin may regulate systemic metabolism through CNS[25]. However, the physiological roles of CNS-expressed adiponectin remain to be elucidated. It should be pointed out that despite the fact that adiponectin gene expression has been identified in some non-adipose tissues, the remarkably high levels of adiponectin expression and protein secretion rate in adipocytes indicate that adipose tissue plays a dominant role in maintaining adiponectin concentrations in the circulation.

4. Adiponectin and diseases

Adiponectin circulates at very high concentrations in humans and mice. It accounts for up to 0.05% of total plasma protein[1,11]. Unlike other adipokines whose concentrations increase with the expansion of fat tissue mass, adiponectin gene expression and circulating levels are inversely correlated with adiposity[1]. Furthermore, a reduction in the body weight of obese subjects increases plasma adiponectin concentrations, suggesting that obesity-associated hypoadiponectinemia is reversible[28].

Adiponectin increases insulin sensitivity in various tissues[28]. The main mechanism by which adiponectin enhances insulin sensitivity appears to be due to improved lipid and glucose metabolism[29–33]. When globular adiponectin was overexpressed in leptin-deficient mice, insulin resistance was ameliorated and the expression levels of genes related to fatty acid oxidation were increased in skeletal muscle[34]. Another study showed that transgenic mice with a deletion in the collagenous domain of adiponectin displayed substantially increased levels of full-length, oligomeric adiponectin complexes[35]. These mice had increased lipid clearance and improved hepatic insulin sensitivity, which may be associated with increased 5′-AMP-activated protein kinase (AMPK) activity in the liver[35].

Circulating adiponectin levels are decreased in patients with cardiovascular disease, and epidemiological studies indicated that low levels of adiponectin are a predictor of the later development

of myocardial infarction[36,37]. In addition, circulating adiponectin levels are negatively correlated with plasma TGs, low-density lipoprotein cholesterol, and were positively correlated with high-density lipoprotein cholesterol, independent of body mass index[38,39]. In addition, epidemiological studies reproducibly indicated that serum adiponectin concentrations were negatively correlated with vascular inflammatory markers and manifestations of fibrinogen, hypertension, and endothelial dysfunction[40–42]. These findings suggest that there is a close association of adiponectin with cardiovascular diseases.

Tissue inflammation has been well known for its association with multiple diseases including alcoholic and non-alcoholic fatty liver disease. A primary systemic marker of tissue inflammation is C-reactive protein (CRP)[43]. CRP levels in the circulation are inversely related to serum adiponectin levels[43]. In addition, hypoadiponectinaemia is associated with nonalcoholic hepatic steatosis in obese subjects[44], and adiponectin has been shown to have anti-inflammatory effects in the liver and reduces steatosis and hepatomegaly in mouse models of alcoholic and non-alcoholic fatty liver disease[45].

Adiponectin also plays a role in the development and progression of several obesity-related malignancies. *In vivo* studies indicate that circulating levels of adiponectin are negatively associated with the risk of malignancies associated with obesity and insulin resistance, which include endometrial cancer, postmenopausal breast cancer, leukemia, and colon cancer, gastric cancer, and prostate cancer[46–51].

Underlying mechanisms that may link adiponectin with carcinogenesis include indirect effects *via* modifying hormone and cytokine levels such as insulin and tumor necrosis factor α (TNFα), and direct effects through inhibiting mitogenic growth factors related to cell proliferation[52]. Therefore, it has been generally accepted that adiponectin is a hormone involved in reducing the risk of obesity-related diseases.

5. Adiponectin signaling

Several plasma membrane proteins have been proposed as adiponectin receptors[7,53]. A human skeletal muscle library was screened and a single cDNA that encodes a protein now called adiponectin receptor 1 (AdipoR1) was first revealed. Database screening further discovered the second adiponectin receptor (AdipoR2) which is derived from a distinct gene[7]. AdipoR1 is ubiquitously expressed, with the most abundance in skeletal muscle, whereas AdipoR2 is mainly expressed in the liver. Although both AdipoR1 and R2 have multiple transmembrane domains, they are not G-protein coupled receptor[7]. Furthermore, in contrast to the topology of classical G-protein coupled receptors, the N-terminal region is intracellular and the C-terminal region of AdipoR is extracellular[7]. AdipoR1 has a high affinity with globular adiponectin, but a low affinity with full-length adiponectin, whereas AdipoR2 has an intermediate affinity with both full length and globular adiponectin[7]. Studies show that APPL1 (adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1) binds to the intracellular domain of both AdipoRs and mediates some of the actions of adiponectin[54,55]. AMPK can be activated by adiponectin and is another downstream protein in the adiponectin signaling cascade[7,8,56].

6. Adiponectin regulates lipid metabolism in skeletal muscle

6.1. *Adiponectin enhances fatty acid oxidation in skeletal muscle*

Increased fatty acid oxidation is amongst the initially identified metabolic effects of adiponectin, and has been considered an important mechanism through which adiponectin increases insulin sensitivity. Studies have suggested that activation of AMPK probably plays an important role in mediating the simulative effects of adiponectin on fatty acid oxidation[8,57]. In support of this, adiponectin treatment increased AMPK phosphorylation and fatty acid oxidation in the skeletal muscle of mice, whereas dominant-negative AMPK abolished those effects[7,8]. In cultured C2C12 myotubes, adiponectin treatment increased PPARα activity and its downstream gene expression, such as acyl-CoA oxidase and carnitinepalmitoyltransferase 1[57]. However, inhibition of either AMPK or p38 MAPK (mitogen-activated protein kinase) attenuated the effects of adiponectin on fatty acid oxidation and PPARγ target gene expression. Furthermore, while an AMPK inhibitor inhibited the activation of p38 MAPK, a p38 MAPK inhibitor had no effect on AMPK activation. This study clearly reveled that adiponectin induces fatty acid oxidation in muscle cells through the sequential activation of AMPK, p38 MAPK, and PPARα[57].

Fatty acids are mainly transported and stored as TGs. There are two pools of fatty acids for oxidative metabolism in skeletal muscle: circulating TGs and intramyocellular TGs. Lipoprotein lipase (LPL) acts as a door keeper in tissue fatty acid metabolism by hydrolyzing blood TGs[58]. LPL catalyzes TGs in chylomicrons and very low density lipoprotein (VLDL) particles, thereby providing non-esterified fatty acids and 2-monoacylglycerol for tissue utilization[58]. Besides its effects on fatty acid oxidation, adiponectin appears to increase VLDL-TG catabolism in skeletal muscle. Fasting plasma TG levels were significantly decreased in mice with elevated adiponectin in circulation[59]. Interestingly, the TG-lowering effect of adiponectin was not due to a reduction in hepatic VLDL-TG secretion, but rather was due to VLDL-TG catabolism through an increase in postheparin plasma lipoprotein lipase (LPL) activity. Adiponectin overexpression did not alter LPL expression and activity in mouse WAT, liver, and heart. However, skeletal muscle LPL activity as well as its gene expression level was increased by 41% after viral vector-mediated increase in blood adiponectin[59]. The effect of adiponectin on LPL has been shown in other studies. Human studies indicate that plasma adiponectin levels are positively associated with postheparin LPL activity[60,61]. It was also reported that adiponectin increased TG clearance by increasing LPL expression in WAT in female adiponectin transgenic mice[35]. Furthermore, adiponectin overexpression also increased the gene expression of VLDL receptor, an important factor for VLDL-TG catabolism, in skeletal muscle[59]. These results suggest that adiponectin increases VLDL catabolism in skeletal muscle, which should provide fatty acids as substrates for oxidation[59]. However, it is still unknown whether adiponectin alters intramyocellular TG mobilization.

6.2. *Adiponectin stimulates mitochondrial biogenesis in skeletal muscle*

Mitochondria are cellular power plants that convert metabolites of nutrients into ATP. It has been reported that subjects

with insulin resistance or type 2 diabetes have reduced mitochondrial content[62] and decreased electron transport chain activity in total[62,63], intramyofibular, and subsarcolemal mitochondria[64]. In addition to mitophagy and mitochondrial fusion and fission, biogenesis is important in maintaining mitochondrial content. Recently, the stimulative effects of adiponectin on mitochondrial biogenesis in skeletal muscle have been highlighted. Animal studies indicate that adiponectin increases mitochondrial biogenesis and oxidative capacity in skeletal muscle[65,66]. Activated AMPK and increased peroxisome proliferator-activated receptor γ coactivator1 α (PGC1 α) have been suggested to mediate the regulatory effects of adiponectin on mitochondrial biogenesis and function[8,57,65,67]. In addition, muscle-specific AdipoR1 knockout mice exhibited insulin resistance at least partially due to a reduction in mitochondrial content and activity in skeletal muscle[65]. Those results demonstrate that adiponectin and/or adiponectin signaling plays an indispensible role in regulating mitochondrial biogenesis and function in mice.

A human study also supports the roles of adiponectin in mitochondrial biogenesis in skeletal muscle[67]. The relationship between adiponectin and mitochondrial function was investigated in muscle from humans who were predisposed to type 2 diabetes. Individuals with a family history of type 2 diabetes exhibit skeletal muscle insulin resistance and mitochondrial dysfunction. In addition, adiponectin levels strongly correlate with mitochondrial DNA content in human skeletal muscle[67]. Furthermore, treatment of primary cultured human myotubes with adiponectin resulted in increased mitochondrial biogenesis, palmitate oxidation, and citrate synthase activity, and reduced the production of reactive oxygen species[67]. On the other hand, knocking down AdipoR1, R2, or both by siRNA inhibited adiponectin-mediated effects on mitochondrial function[67]. These data demonstrate that adiponectin enhances mitochondrial biogenesis and oxidative metabolism in the skeletal muscle.

6.3. Underlying mechanisms through which adiponectin enhances mitochondrial biogenesis and improves lipid metabolism in skeletal muscle

PGC-1α is a transcriptional coactivator and is well known for its role in controlling mitochondrial biogenesis[65,68]. The PGC-1α gene expression is regulated by various physiological stimulations and molecular factors. Of those, in response to exercise, PGC-1α is partially up-regulated by Ca^{2+} signaling through molecules such as Ca^{2+}/calmodulin-dependent protein kinase (CaMK) in skeletal muscle[69]. Interestingly, adiponectin stimulates Ca^{2+} influx *via* AdipoR1, thereby activating Ca^{2+}/calmodulin-dependent protein kinase kinase (CAMKK)β, which is an upstream signal of CaMK[65]. These events induced PGC-1α expression. Furthermore, adiponectin stimulates expression of SIRT1, which deacetylates and activates PGC-1α, indicating that adiponectin stimulates both PGC-1α expression and activation[65]. In contrast, muscle-specific AdipoR1 knockout abolished the adiponectin-induced increase in intracellular Ca^{2+} influx and activation of CaMKK, AMPK, and SIRT1[65]. Furthermore, muscle-specific AdipoR1 knockout mice exhibited reduced PGC1α expression, increased PGC-1α acetylation, and decreased mitochondrial count and activity in skeletal muscle[65]. These results indicate that adiponectin/AdipoR1 regulate mitochondrial biogenesis and function through $Ca^{2+}$and AMPK/SIRT1 dependent mechanisms[65].

There are other pathways that can also activate PGC-1α or mediate the simulative effects of adiponectin on mitochondrial biogenesis. p38 MAPK is a downstream signal in the adiponectin pathway[7,55,70]. Activation of p38 MAPK increases not only PGC-1α expression but also its activity[71–73]. Inhibition of p38 MAPK completely blocks Ca^{2+}-induced PGC-1α expression[74]. These results indicate that p38 MAPK plays an indispensible role in mediating adiponectin-stimulated PGC-1α expression, activation, and mitochondrial biogenesis in skeletal muscle.

It has been well reported that adiponectin induces p38 MAPK activation. Similar to other MAPK members, p38 MAPK is activated by MAPK kinase (MKK)-mediated phosphorylation, and is deactivated by MAPK phosphatase (MKP)-catalyzed de-phosphorylation[75]. Therefore, p38 MAPK activity is determined by the counterbalance of MKKs and MKPs[70]. APPL1 has been shown to selectively transduce signals from the adiponectin receptor to the TGFβ-activated kinase1-MAPK kinase (MKK) 3/p38 MAPK pathway[70]. Our recent study further investigated how adiponectin induces p38 MAPK and its downstream activation[66]. In addition to the involvement of MKK, our study also found that adiponectin reduces the protein levels of MKP1 in mouse skeletal muscle[66]. Furthermore, MKP1 overexpression attenuated adiponectin-enhanced PGC-1α gene expression and mitochondrial biogenesis in C2C12 myotubes[66]. Knocking down MKP1 protein expression led to enhanced p38 MAPK activation and to higher PGC-1α expression and mitochondrial biogenesis in skeletal muscle[66]. These results indicate that the suppression of MKP1 expression is one of the underlying mechanisms through which adiponectin stimulates p38 MAPK/PGC-1α signaling and mitochondrial biogenesis in skeletal muscle[66].

7. Summary

Adiponectin is an adipocyte-secreted hormone that improves lipid and glucose metabolism. In addition to the insulin sensitizing effect, adiponectin directly enhances fatty acid oxidation in skeletal muscle through its own signaling or other pathways including p38 MAPK/PGC-1α. Although adiponectin stimulates mitochondrial biogenesis in skeletal muscle, it is still largely unknown how adiponectin increases mitochondrial oxidative metabolism.

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