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Adiponectin and Energy Homeostasis

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Abstract

White adipose tissue (WAT) is the premier energy depot. Since the discovery of the hormonal properties of adipose-secreted proteins such as leptin and adiponectin, WAT has been classified as an endocrine organ. Although many regulatory effects of the adipocyte-derived hormones on various biological systems have been identified, maintaining systemic energy homeostasis is still the essential function of most adipocyte-derived hormones. Adiponectin is one adipocyte-derived hormone and well known for its effect in improving insulin sensitivity in liver and skeletal muscle. Unlike most other adipocyte-derived hormones, adiponectin gene expression and blood concentration are inversely associated with adiposity. Interestingly, recent studies have demonstrated that, in addition to its insulin sensitizing effects, adiponectin plays an important role in maintaining energy homeostasis. In this review, we summarize the progress of research about 1) the causal relationship of adiposity, energy intake, and adiponectin gene expression; and 2) the regulatory role of adiponectin in systemic energy metabolism.

Keywords

Adiponectin; obesity; adipocyte; calorie restriction; insulin

1 Introduction

Storing energy is the primary function of white adipose tissue (WAT). In humans and most animals, chemical energy can be stored in WAT as triglyceride (TG)-enriched lipid droplets [1]. Due to the small mass of lipid droplet and high energy density, WAT has been considered as the most efficient energy depot. Under physiological conditions, WAT mass varies according to the status of systemic energy metabolism. After prolonged positive energy imbalance, excessive energy is stored in WAT which increases its tissue mass. In contrast, when food intake does not meet energy demands, WAT releases fatty acids as energy supply through lipolysis, which reduces WAT mass.

Obesity is a disease condition with overly enlarged WAT mass, which is characterized by increased adipocyte number (hyperplasia) and cellular size (hypertrophy). Due to ample food supply and changes in life style, obesity incidence has more than doubled worldwide

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since 1980 (WHO, May 2012). Most importantly, the increase in incidences of obesity has been found to be associated with many medical issues. For example, a clinical study revealed that the increase in the prevalence of type 2 diabetes is closely linked to the upsurge of obesity [2]. About 90% of type 2 diabetes is attributable to excess weight gain [2]. These observations raise a series of questions including whether obesity is solely a consequence of prolonged energy imbalance and what the role of WAT in systemic metabolism is. Recent studies have convincingly demonstrated that WAT is not only an energy storage depot, but also an endocrine organ. The discovery of the endocrine property of WAT and the regulatory effects of adipocyte-derived hormones on energy metabolism have clearly demonstrated that WAT plays an active role in maintaining energy homeostasis [3–6].

Adiponectin is an adipocyte-derived hormone with a prominent function in improving insulin sensitivity. Unlike other adipocyte-derived hormones, adiponectin gene expression and blood concentrations are inversely associated with body mass index [7]. Decrease in circulating adiponectin in the prediabetic state precedes the development of insulin resistance [8]. Therefore, hypoadiponectinemia has been considered to be an underlying mechanism of insulin resistance in obesity and type 2 diabetes [6, 8–10]. In the last two decades, enormous efforts have been committed to understand how adiponectin gene expression is regulated and how obesity reduces adiponectin gene expression and blood adiponectin levels. With the progress of these studies, it is clear now that, although dietary fat and adiposity are associated with hypoadiponectinemia, adiponectin gene expression is causally linked with energy metabolism. Furthermore, emerging evidence suggests that, similar to leptin, adiponectin is another adipocyte-derived hormone that actively regulates energy homeostasis [11]. In the following sections, we will focus on the regulatory effects of energy intake on adiponectin gene expression and the regulatory role of adiponectin in energy metabolism.

2 The relationship of energy intake and adiponectin gene expression

Energy balance determines WAT mass, which is obviously associated with the expression and secretion of most adipocyte-derived hormones. Previous studies showed that there is an inverse correlation between adiponectin gene expression and body fat mass. However, it is not clear whether obesity-associated decrease of adiponectin gene expression is a consequence of adipose tissue expansion or suppressed by a mechanism(s) that directly induced by prolonged positive energy imbalance. Recent studies from our group and other laboratories have demonstrated that energy intake, but not adiposity, plays an important role in controlling adiponectin gene expression.

2.1 Calorie restriction reduces body fat mass and alters expression of adipocyte-derived hormones

Reducing energy intake and/or increasing energy expenditure are ideal therapeutic approaches for obesity, if positive energy imbalance is the cause of obesity. Calorie restriction (CR) is the most common regimen for energy intake studies. CR has received considerable attention due to its beneficial effects on reducing the occurrence of chronic diseases and extending lifespan in experimental animals [12, 13]. A decrease in daily calorie

intake by 20 to 40% of baseline requirement improved insulin sensitivity, and reduced atherosclerotic lesion development, inflammatory response, and production of reactive oxygen species [12, 14–16]. The profound effects of CR are at least partially accredited to decrease in adipose tissue mass and body weight. CR may increase lipolysis to a great extent and therefore, induce a reduction in adipocyte size [13]. Another key factor mediating favorable effects of CR on the functions of adipose and other tissues are changes in adipocyte-derived hormone expression levels. Adipocyte-derived hormones affect diverse metabolic processes, including glucose and lipid metabolism, insulin action, angiogenesis, vascular remodeling, and inflammation [17, 18]. To date, more than 25 adipocyte-derived hormones or adipokines have been discovered and examined. Studies have shown that CR or body weight reduction changes the levels of adipocyte-derived hormones beneficially [13, 19, 20]. Of those adipocyte-derived hormones, the up-regulation of adiponectin level by CR has been highlighted as a key underlying mechanism for CR-induced improvement of metabolism.

2.2 CR increases adiponectin gene expression and blood levels in humans and animals

The positive effect of CR on adiponectin expression has been observed in human subjects. Approximately 10 to 20% weight reduction by CR in obese subjects significantly increased adiponectin gene expression in WAT and blood adiponectin levels [21–24]. In addition, anorexic patients who had very low calorie intake exhibited 30% increase in circulating adiponectin levels [25]. Consistently, insulin sensitivity was markedly improved in these subjects [25]. However, controversial results have also been reported in other human studies. CR for 3 to 6 weeks reduced body weight by 7–12% in obese subjects, but had no effect on circulating adiponectin concentrations [26–29]. In addition, CR in healthy and normal-weight women was associated with a modest but significant decrease of circulating adiponectin levels [30]. Possible explanation about the discrepancy between these studies may be the variation in characteristics of subjects (obese vs. lean) and amount and speed of weight loss [30].

Changes in blood levels of metabolic hormones usually occur within a few minutes to hours following a meal. However, circulating adiponectin levels appear not to acutely respond to a meal. When subjects were fed 3 undefined meals over 22 hours, there was no significant fluctuation in blood adiponectin levels [22, 31]. Another study showed that postprandial plasma adiponectin levels were unchanged over 180 minutes in lean subjects after breakfast [32]. In addition, a study compared the postprandial response of adiponectin over 6 hours between normal subjects and first-degree relatives of type 2 diabetes patients after HF diet consumption [33]. Although the T2D relatives were insulin resistant and had increased adiposity compared to control subjects, postprandial levels of adiponectin was not different from fasting levels whereas the postprandial levels of insulin, triglyceride and free fatty acids were significantly changed in both groups [33]. These data demonstrate that circulating adiponectin levels in both insulin-sensitive and -resistant subjects do not acutely respond to calorie intake.

Similar to human subjects, CR increases adiponectin gene expression and circulating levels in almost all animals [4–6, 24, 34, 35]. When 40 percent of CR was applied to rats for 2 to

20 months, significantly increased adiponectin levels as well as reduction in blood glucose and insulin levels were observed in all groups of rats maintained on CR diet [6], suggesting the positive effects of CR on circulating adiponectin levels may be independent of age and the periods of CR.

2.3 Role of calorie intake and WAT mass in CR-induced adiponectin gene expression

CR is by far the most effective physiological intervention that increases adiponectin gene expression and blood levels [3, 5, 6]. However, CR generally accompanies with reduction in body fat mass. Therefore, it is not easy to discriminate whether reduction of energy intake or/and in WAT mass contribute the effect of CR-induced adiponectin gene expression. We had employed several feeding regimens and mouse models to address this question. Our study showed that CR increased adiponectin gene expression in WAT and blood adiponectin levels in both low fat (LF) and high fat (HF) diet-fed C57BL/6 mice [4]. However, although HF pair-fed C57BL/6 mice received the same amount of calories as LF ad libitum-fed mice, HF diet clearly increased adiposity but showed no significant effects on adiponectin gene expression and blood adiponectin level [4]. In addition, when HF-fed C57BL/6 mice were applied for different feeding regimens and treatments: a low-fat control diet, a 30% CR regimen, a treadmill exercise regimen with a low-fat control diet, or continuation of HF diet, both CR and exercise reduced adiposity by 35–40%, but only CR increased adiponectin levels and insulin sensitivity [36]. Several human studies have reported that hypoadiponectinemia is not closely associated with body fat content [37–40]. For example, when obese women underwent a 12-week aerobic exercise program, their body and fat weight were reduced by 5.9%, but the expression and circulating levels of adiponectin was unchanged [41]. Together, these results indicate that energy intake is important in controlling adiponectin expression and WAT mass itself may play a minor role in maintaining blood adiponectin concentrations.

However, a human study had showed that increased adiponectin gene expression levels by very short-term CR may be associated with the extent of subjects' body mass index (BMI) in a certain condition. When the effect of 2 day acute CR and subsequent refeeding (70% reduction in subjects' usual calorie intake) on adiponectin gene expression was investigated in subcutaneous fat of obese subjects, CR induced 33% increase in the adiponectin mRNA levels, whereas refeeding induces a 32.8% fall [42]. However, the obese subjects who showed an acute response by 2 day CR had a higher basal level of adiponectin mRNA and significantly lower BMI compared to the subjects who showed weak or no adiponectin mRNA response. In certain conditions, a high degree of adiposity and a low basal expression level of adiponectin may be a potential factor blunting the up-regulating effect on adiponectin gene expression by an acute CR [42]. Furthermore, some studies indicate that the levels of adiponectin are negatively related to central adipose tissue [43–46] and positively associated with subcutaneous adipose tissue [43]. Therefore, the loss of visceral fat by CR in obese subjects may cause increase of adiponectin levels. On the other hands, CR-mediated subcutaneous fat loss in lean healthy subjects may result in reduced adiponectin levels [30]. More studies are necessary to clarify environmental or physiological factors that may also contribute to CR-induced adiponectin gene expression in humans.

2.4 CR increases adiponectin gene expression, but not protein half-life

When the half-life of blood adiponectin was measured in C57BL/6 mice after the 24 weeks of feeding regimens, neither CR nor HF feeding displayed any significant effect on blood adiponectin half-life in C57BL/6 mice [4]. In addition, when the circulating levels of multimeric isoforms of adiponectin were measured, the multimeric forms of adiponectin increased or reduced proportionally with total adiponectin levels in LF-CR, HF-CR, or HF-ad libitum fed mice [4]. These results indicate that energy intake may controls circulating adiponectin levels through a mechanism(s) at gene expression and/or protein secretion levels rather than through altering blood adiponectin clearance rate.

2.5 Calorie intake, but not dietary fat, is a key player for regulating adiponectin expression

HF diet has been widely used for inducing obesity in animal models that exhibit reduced adiponectin gene expression in WAT [47–49]. However, it was unclear whether energy intake or dietary fat content reduces adiponectin gene expression in WAT of obese animals. We had conducted a study to specifically address this question using mouse models and feeding regimens. Our study showed that when total energy intakes were kept at the same levels between LF and HF-fed mice, CR increased serum adiponectin levels, but no differences were observed between LF-CR and HF-CR mice [4]. In addition, serum adiponectin were at similar levels between LF-ad libitum and HF-pair-fed mice [4]. Similarly in human subjects, when comparing changes in adiponectin levels with changes in the fat content of eucaloric diets in non-diabetic lean and obese subjects, there were large differences in circulating adiponectin levels between lean and obese individuals. However, group mean values for adiponectin level were not altered significantly with a change in fat content of a eucaloric diet in lean and obese subjects [50]. Those results indicate that the total amount of calorie intake rather than the source of calorie may play a more important role in controlling adiponectin levels.

2.6 Transcription factors that mediate CR-enhanced adiponectin transcription

CR alters the expression of a large number of genes associated with lipid and glucose metabolism [51]. Many enzymes and transcription factors are involved in these processes. It is known that NAD-dependent deacetylase sirtuin 1 (SIRT1) plays an important role in mediating CR-induced metabolic adaptation. CR increased SIRT1 protein levels in WAT in mouse models [4, 52]. In contrast, SIRT1 protein levels were significantly reduced in WAT of genetically obese mice (db/db) and HF-diet induced obese mice [53]. SIRT1 is known for increasing adiponectin transcription in adipocytes by activating Foxo1 and enhancing Foxo1 and C/EBP α interaction [53]. Therefore, increased SIRT1 plays an important role in mediating CR-induced increase of adiponectin gene transcription. Furthermore, other studies have reported that SIRT1 also stimulates adiponectin protein secretion [54, 55].

Peroxisome proliferator-activated receptors (PPARs) regulate numerous genes related to energy metabolism [56, 57]. CR regulates the expression and activity of PPARs in various tissues [4, 58, 59]. PPAR γ is a master transcription factor of adipocyte differentiation and lipogenesis in adipocytes [56]. PPAR γ is a potent transcription factor that directly up-regulates adiponectin gene expression at the transcriptional level. Due to the opposite effects of PPAR γ and CR on adipogenesis, it would be assumable that CR reduces PPAR γ

transactivity in WAT. However, results of PPAR γ expression from CR studies were not consistent. For example, some studies showed that 30% CR did not change the expression levels of PPAR γ in both liver and adipose tissues of mice [58, 59]. In contrast, although CR increased PPAR γ mRNA expression levels in WAT of LF or HF-fed mice, the protein levels were unchanged [4]. We also found that CR actually reduced the expression levels of PPAR γ -target genes, including aP2 and fatty acid synthase in WAT of mice [4]. Consistently, it has been reported that CR inhibits PPAR γ transactivity [51]. However, further studies are required to elucidate the role of PPAR γ in CR-induced increase of adiponectin gene expression in WAT. On the other hands, CR significantly increased PPAR α protein levels as well as its gene expression, but decreased both PPAR β/δ gene and protein expression levels in the liver of mice [59]. CR did not change mRNA levels of RXR isoforms (α , β/δ , and γ) [59], which form a heterodimer with PPAR at the target gene. Similar to PPAR γ , PPAR α regulates adiponectin gene transcription through PPRE at the adiponectin promoter [60]. In line with this report, our study showed that the treatment of finofibrate, a PPAR α agonist, robustly increased adiponectin mRNA level in adipocyte [4]. Adiponectin mRNA levels in WAT and blood adiponectin levels were remarkably lower in PPAR α gene knockout mice than that in wild type control mice. Furthermore, CR failed to increase circulating adiponectin levels as well as its gene expression in WAT of PPAR α knockout mice [4]. Therefore, we proposed that both SIRT1 and PPAR α mediate the stimulatory effect of CR on adiponectin expression in adipocytes.

3 The regulatory role of adiponectin in energy homeostasis

Insulin is pivotal in regulating energy metabolism. The insulin sensitizing function of adiponectin has been well established. Therefore, it has been assumed that adiponectin plays a role in maintaining energy homeostasis by enhancing insulin sensitivity. However, recent studies have suggested that, in addition to insulin signaling, adiponectin may directly participate in controlling energy metabolism.

3.1 Adiponectin possesses the properties of a starvation hormone

To cope with the unstable food supply, human and most animals have developed a hormonal system to provide a relatively consistent chemical energy supply by regulating energy intake, storage, and metabolic rate. In terms of energy metabolism, some hormones have been characterized as starvation hormones, which enhance energy storage by stimulating food intake and suppressing energy expenditure. In contrast, to prevent excessive energy storage within body, some hormones inhibit food intake and increase energy expenditure. These hormones are referred as satiety hormones. The starvation hormone characteristics of adiponectin have been observed in animal studies [61, 62]. A mouse study examined the roles of adiponectin on the hypothalamus and found that adiponectin is involved in regulating energy homeostasis by regulating food intake and energy expenditure [62]. In parallel with the concept that total energy intake may play a key role in adiponectin expression, serum and cerebrospinal fluid levels of adiponectin increased during fasting and reduced after refeeding [62]. In addition, adiponectin stimulated food intake and adiponectin-deficient mice fed a HF diet exhibited reduced food intake. On the other hand, adiponectin reduced energy expenditure and HF-fed adiponectin-deficient mice exhibit

increased energy expenditure, showing lower body weight than HF-fed control mice [61, 62]. These results suggest that adiponectin may serve as a starvation hormone. It is worth to point it out that adiponectin inhibits Ucp1 gene expression in mouse brown adipose tissue [62, 63]. However, further studies are required to verify whether reduced Ucp1 gene expression in BAT mediates the inhibitory effect of adiponectin on energy expenditure.

In contrast, serum leptin levels are inversely related to adiponectin during fasting and refeeding conditions. Because leptin is a satiety hormone which inhibits food intake, central adiponectin/leptin signaling may represent the physiological pathway by which food intake is regulated by adipocyte-derived hormones [62].

3.2 Adiponectin regulates energy metabolism in a tissue-specific manner

3.2.1 Adiponectin enhances mitochondrial biogenesis and oxidative metabolism in skeletal muscle—Skeletal muscle is the largest tissue in human subjects and most animals. Energy consumption in skeletal muscle plays an important role in maintaining energy homeostasis. Mitochondria are power plants of most eukaryotic cells. Recently, the stimulative effects of adiponectin on mitochondrial biogenesis in skeletal muscle have been highlighted [64–66]. Some studies even reported that skeletal muscle also expresses adiponectin, which may regulate glucose or lipid metabolism in skeletal muscle by an autocrine manner [67–69]. Due to the high concentration of adiponectin in circulation and low expression level of adiponectin in skeletal muscle, further studies are required to determine the physiological significance of skeletal muscle-secreted adiponectin in energy metabolism. However, regardless of the origin of adiponectin, most available data suggest that adiponectin improves skeletal muscle oxidative metabolism through its own receptors and downstream signaling [70–72]. Animal studies indicate that adiponectin increases mitochondrial biogenesis and oxidative capacity in skeletal muscle [65, 73]. Muscle-specific AdipoR1 knockout mice exhibited insulin resistance at least partially due to reduction in mitochondria content and activity in skeletal muscle [73]. In addition, a human study also supported the stimulative effects of adiponectin on mitochondrial biogenesis in skeletal muscle [64]. The relationship between adiponectin and mitochondrial function was investigated in muscle from humans who are 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 [64]. Furthermore, adiponectin-treated primary cultured-human myotubes displayed increased mitochondrial biogenesis, palmitate oxidation, and citrate synthase activity. On the other hand, the down-regulation of AdipoR1 and AdipoR2 expressions by siRNA inhibited adiponectin-mediated effects on mitochondrial function [64]. Those data demonstrate that adiponectin is involved in mitochondrial biogenesis and oxidative metabolism in the skeletal muscle of both animals and human.

Activated AMP-activated protein kinase (AMPK) and increased peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α) have been suggested to mediate the stimulative effects of adiponectin on mitochondrial biogenesis and function [64, 66, 72, 73]. Our recent study demonstrated that adiponectin increases skeletal muscle mitochondrial

biogenesis by suppressing mitogen-activated protein kinase phosphatase-1 [65], which may be a key step to connect an adiponectin receptor signaling pathway with PGC-1 α gene expression. Together, those studies indicate that adiponectin improving metabolism is not limited to the increase in insulin sensitivity.

3.2.2 Adiponectin inhibits lipolysis in adipocytes—AdipoR1 and AdipoR2 had been identified as the main adiponectin receptors and expressed in WAT [74–76]. Adiponectin may regulate metabolism in WAT by an autocrine effect or indirectly through enhancing insulin sensitivity. A direct regulatory effect was identified by recent studies. Human and animal studies have clearly demonstrated that adiponectin improves lipid and glucose metabolism. Due to the prominent effect of adiponectin on enhancing insulin signaling, most studies attribute these beneficial effects to improved insulin signaling in skeletal muscle and liver. Emerging evidence suggests that adiponectin directly regulates lipid metabolism in fat. Adiponectin transgenic female FVB mice exhibit increased body weight and fat tissue mass [77]. In addition, modestly increased adiponectin completely rescued the diabetic phenotype in ob/ob mice with significant expansion of adipose tissue [61]. Recent studies have revealed a direct inhibitory effect of adiponectin on lipolysis in both mouse and human adipocytes [78, 79]. Significantly increased lipolysis was observed in both adiponectin gene knockout mice and primary adipocytes from these mice [78]. Regarding the underlying mechanism, our mouse study showed that adiponectin suppresses hormone-sensitive lipase activation without altering adipose triglyceride lipase and CGI-58 expression in adipocyte [78]. Moreover, adiponectin reduced protein levels of the type 2 regulatory subunit RII α of protein kinase A by reducing its protein stability. Ectopic expression of RII α abolished the inhibitory effects of adiponectin on lipolysis in adipocytes [78]. Similar inhibitory effects of adiponectin on lipolysis were reported in human adipocytes [79]. However, this study reported that adiponectin inhibited spontaneous and catecholamine-induced lipolysis in human adipocytes of non-obese subjects through an AMPK-dependent mechanism [79]. Although the underlying mechanisms of adiponectin-inhibited lipolysis are different in human and mouse adipocytes, those studies provide an explanation about how adiponectin improves circulating lipid profiles. However, more studies are necessary to claim the importance of adiponectin-mediated inhibition of lipolysis in the development of obesity because adiponectin expression is reduced in obesity [71].

4 Conclusions

By using genetic animal models and more precise metabolic approaches, recent studies have revealed broader regulatory effects of adiponectin on energy metabolism. Although more studies are required, available information strongly suggests that, as an adipocyte-derived starving hormone, adiponectin maintains energy homeostasis in favoring systemic energy conservation through improving energy efficiency in major metabolic tissues such as skeletal muscle and WAT. On the other hand, the amount of energy intake, but not dietary fat content and WAT mass, appears to be a key factor in controlling adiponectin expression and circulating concentration.

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