

Adiponectin: action, regulation and association to insulin sensitivity

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Summary

Adiponectin is a novel adipocyte-specific protein, which, it has been suggested, plays a role in the development of insulin resistance and atherosclerosis. Although it circulates in high concentrations, adiponectin levels are lower in obese subjects than in lean subjects. Apart from negative correlations with measures of adiposity, adiponectin levels are also reduced in association with insulin resistance and type 2 diabetes. Visceral adiposity has been shown to be an independent negative predictor of adiponectin. Thus, most features of the metabolic syndrome's negative associations with adiponectin have been shown. Adiponectin levels seem to be reduced prior to the development of type 2 diabetes, and administration of adiponectin has been accompanied by lower plasma glucose levels as well as increased insulin sensitivity. Furthermore, reduced expression of adiponectin has been associated with some degree of insulin resistance in animal studies indicating a role for hypoadiponectinaemia in relation to insulin resistance. The primary mechanisms by which adiponectin enhance insulin sensitivity appears to be through increased fatty acid oxidation and inhibition of hepatic glucose production. Adiponectin levels are increased by thiazolidinedione treatment, and this effect might be important for the enhanced insulin sensitivity induced by thiazolidinediones. In contrast, adiponectin levels are reduced by pro-inflammatory cytokines especially tumour necrosis factor- α . In summary, adiponectin in addition to possible anti-inflammatory and anti-atherogenic effects appears to be an insulin enhancer, with potential as a new pharmacologic treatment modality of the metabolic syndrome and type 2 diabetes.

Keywords: Adiponectin, insulin sensitivity, regulation.

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Introduction

In recent years, the perception of the adipose tissue being solely an energy storage organ has extended to include an endocrine organ that plays a pivotal role in relation to energy homeostasis and metabolism. Apart from secreting free fatty acids (FFA), adipose tissue produces and releases numerous proteins and substances with autocrine, paracrine and endocrine functions. These proteins appear to have various biological functions such as regulation of energy intake and energy expenditure, regulation of glucose and lipid metabolism, as well as anti- and pro-inflamma-

tory effects (1). An increasing body of evidence indicates that some of these adipose-tissue-derived molecules are involved in the pathophysiology of obesity-related insulin resistance and atherosclerosis (2–4). In the present review, the recently discovered adipose tissue-derived protein, adiponectin, will be discussed with focus on its action and regulation.

Adiponectin

Adiponectin is a secreted protein of 247 amino acids, produced exclusively by adipocytes (5). Structurally, adiponec-

tin has homology to tumour necrosis factor- α (TNF- α), and sequence homology (43%) to the complement protein C1q (6). Adiponectin consists of three domains including a globular domain near the C terminus, a signal sequence at the N terminus, and a collagen-like domain (6).

Three of these collagen domains assemble to form a stable collagen triple helix, and two to six of these trimers multimerize to form a 'bouquet'. In the circulation adiponectin exists in at least two forms, as a hexamer (two trimers) called low molecular weight (LMW) oligomer and as high molecular weight (HMW) oligomers consisting of four to six trimers (5,7). Oligomerization of adiponectin depends on disulphide bond formation mediated by Cys39 (7). HMW oligomers constitute the major part of intracellular adiponectin, whereas the predominant form of adiponectin in the circulation is LMW oligomers (8). Monomer forms of adiponectin have not been found in plasma (7). Very recently, Scherer's group (8) suggested that the HMW adiponectin complex is the active form of this protein, and that the ratio between HMW and total adiponectin (HMW + LMW) is more accurate than total adiponectin reflecting the association of adiponectin to insulin sensitivity. Despite this elegant study, which of the adiponectin isoforms are biologically active still remains controversial (9).

The adiponectin protein can undergo proteolytic cleavage, leading to the formation of a globular form of adiponectin containing only the globular head domain (10). The pharmacological effect of this globular fragment of adiponectin appears to be stimulation of β -oxidation in skeletal muscle, whereas full-length adiponectin decreases hepatic glucose output (10–12). Thus, the primary site of action as well as the mode of action seems to be different for globular and full-length adiponectin. Furthermore, the protein undergoes post-translational modification including hydroxylation and glycosylation (13).

The adiponectin gene is located on chromosome 3q27, and consists of three exons and two introns. This region of the chromosome has also been found to be the locus for other candidate genes with phenotypes related to features of the metabolic syndrome (14). Comuzzie *et al.* (15) have identified quantitative trait loci with effects on plasma adiponectin levels, indicating a strong genetic contribution to the level of circulating adiponectin.

Various conditions affect the gene expression of adiponectin in adipose tissue. For example, adiponectin gene expression is increased 50–100-fold during differentiation of 3T3-L1 adipocytes (5,16) indicating that adiponectin is a marker of mature adipocytes. In accordance with these data obtained with clonal preadipocytes, we found the expression of adiponectin mRNA to be induced nearly 100-fold during differentiation of human preadipocytes in primary culture (Fig. 1). After 13–16 d of culture, about 70–80% of the cells were differentiated into mature adipocytes,

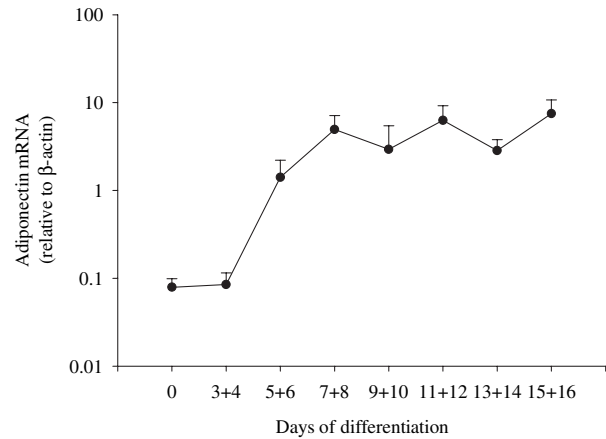


Figure 1 Adiponectin mRNA levels during human preadipocyte differentiation (A.S. Lihn *et al.* unpubl. data).

and already after 5 d of differentiation the adiponectin mRNA level was substantially increased ($P < 0.05$, $n = 6$) (Fig. 1).

In contrast to what is the case for most adipose-tissue-produced proteins, plasma adiponectin levels are found to be lower in obese subjects than in lean subjects, and strong negative correlations between plasma adiponectin levels and body mass index (BMI) have been shown both in humans and in animals (17–19). In accordance with these findings, the adiponectin mRNA levels are also lower in adipose tissue from obese as compared with lean subjects (16,20). Furthermore, adiponectin gene expression and protein levels are higher in subcutaneous than in intra-abdominal adipose tissue (20,21), albeit this has not been a consistent finding (22,23). Preferential accumulation of AT in the gluteofemoral region ('gynoid obesity') has been associated with protective effects especially with respect to cardiovascular disease risk (24). Interestingly, adiponectin mRNA levels do not seem to differ between abdominal and gluteo/femoral subcutaneous adipose tissue (20). Differences in adiponectin gene expression in relation to various adipose tissue depots is, however, still not fully elucidated (21).

Epidemiology

Adiponectin is found abundantly in the circulation with concentrations between 2 and 20 $\mu\text{g mL}^{-1}$, accounting for up to 0.05% of total serum protein (5,17). As mentioned, plasma adiponectin levels are lower in obese subjects as compared with lean subjects (17–19). Women have about 40% higher circulating levels of adiponectin than men (17,18), and the level of androgens may play a role for these gender differences because androgens appears to have an inhibitory effect on adiponectin (25). In addition, women display higher serum proportions of HMW adiponectin as compared to men (8).

Adiponectin levels are reduced in patients with cardiovascular disease (26) and in diabetics (27) and from epidemiological studies low levels of adiponectin are found to be a predictor of the later development of type 2 diabetes (28,29) and myocardial infarction (30,31).

Moreover, negative correlations between circulating adiponectin and insulin resistance have been shown repeatedly (18,32,33). Furthermore, plasma adiponectin is negatively correlated with plasma triglycerides, low-density lipoprotein (LDL)-cholesterol, and positively correlated with high-density lipoprotein (HDL)-cholesterol (18,33). Visceral adiposity has been shown to be an independent negative predictor of adiponectin (34), and close negative correlations have been shown between adiponectin levels and liver fat content (34). Thus, most features of the metabolic syndrome negative associations with adiponectin have been shown.

Adiponectin and insulin sensitivity

In rhesus monkeys genetically predisposed to develop insulin resistance, Hotta *et al.* (35) showed that circulating adiponectin levels decrease in parallel with the development of insulin resistance, and thus prior to the onset of diabetes. In a group of first-degree relatives (FDR) to patients with type 2 diabetes we have found that FDR were characterized by being more insulin resistant, and they had significantly lower adiponectin mRNA levels in adipose tissue (36). Adiponectin gene expression was found to correlate positively with insulin sensitivity in control subjects, but not in FDR. These results suggest that adiponectin gene expression is dys-regulated in relation to insulin resistance prior to the development of type 2 diabetes.

Not only obesity, where fat mass is increased, but also lipodystrophy, where fat is lost partially or totally, is associated with the development of insulin resistance (37). Both lipodystrophy and the so-called HIV-associated lipodystrophy syndrome (HALS), which is a syndrome characterized by body fat redistribution and metabolic abnormalities including insulin resistance (37), are associated with low plasma adiponectin and low expression of adiponectin in the adipose tissue (38–41). These data indicate that reduced plasma adiponectin levels might play a role for lipodystrophy related insulin resistance. Using a mouse model with lipodystrophy and insulin resistance, Yamauchi *et al.* (42) found that these mice were hyperinsulinemic, hyperglycaemic, and they had no adiponectin in serum. Systemic infusion of physiological doses of recombinant adiponectin, alone or in combination with leptin, ameliorated hyperglycaemia and hyperinsulinaemia, suggesting that insulin resistance of lipoatrophic mice might be caused at least partially by a deficiency in adipocytokines such as adiponectin and leptin.

Injection of recombinant adiponectin to wild-type mice as well as to various models of insulin resistant mice resulted in a significant acute decrease in plasma glucose levels (12). This glucose lowering effect was independent of plasma insulin levels, and was also observed in mice with insulin secretion deficiency, indicating that the effect most likely was mediated by enhancing insulin action. Importantly, only full-length adiponectin lowered plasma glucose levels in this study. In contrast, Fruebis *et al.* (10) found that injection of globular but not full-length adiponectin reduced plasma glucose levels. Different approaches for the production of the recombinant proteins as well as for the post-translational modification were used in the two studies, which might explain the different findings.

Apart from affecting blood glucose levels, it has been suggested that adiponectin plays a role in reducing the plasma concentration of FFA (10,43). This effect has been indicated by data from both adiponectin treatment (10) and adiponectin knockout studies (43), and it might be important for the insulin sensitizing effects of adiponectin. Interestingly, adiponectin knockout (KO) mice on normal chow displayed normal fasting plasma levels of glucose, insulin and FFA; however, when fed a high-fat/high-sucrose diet, these mice developed severe insulin resistance and increased plasma FFA concentrations (43). When subjected to adenoviral overproduction of adiponectin, the diet-treated adiponectin KO mice displayed improved insulin sensitivity and decreased plasma levels of FFA, glucose and insulin. Based on these adiponectin knockout studies, Maeda and colleagues suggested that hypoadiponectinaemia caused by overnutrition is linked to the development of insulin resistance and diabetes.

Recently, Xu *et al.* (44) demonstrated that adiponectin might also decrease the hepatic fat content. They administered adiponectin to mice with fatty liver diseases and this resulted in alleviation of both steatosis and hepatomegaly. These effects were at least in part attributed to enhanced hepatic fatty acid oxidation and decreased hepatic fatty acid synthesis. The increase in hepatic lipid oxidation by adiponectin might also play a role for the beneficial effect of adiponectin on hepatic glucose metabolism.

Recently, two reports have described mouse models with transgenic-induced hyperadiponectinaemia, albeit two different approaches were used (45,46). First, Yamauchi *et al.* (45) investigated the effects of over-expressing adiponectin by analysing globular adiponectin transgenic mice with leptin deficiency. They found that these mice showed amelioration of insulin resistance and diabetes. Concomitantly, they observed increased expression of molecules involved in fatty acid oxidation in skeletal muscles. Later, Combs *et al.* (46) have generated a transgenic mouse which displays substantially increased levels of native, full-length, oligomeric adiponectin complexes. This hyperadiponectinaemia was found to increase lipid clearance, improve

hepatic insulin sensitivity, and improve oral glucose tolerance. Moreover, they found increased 5'-AMP-activated protein kinase (AMPK) activity in the liver. Thus, consistent with the results of the pharmacological studies, these two studies suggest that the effects and mechanism of action differ between globular and full-length adiponectin.

The results of adiponectin KO mice studies are, however, conflicting, and Ma *et al.* (47) were not able to demonstrate insulin resistance either of KO mice on normal chow or after 7 months of feeding with a high-fat diet. In contrast, Kubota *et al.* (48) observed mild insulin resistance in heterozygous adiponectin deficient mice and moderate insulin resistance in homozygous adiponectin deficient mice. The observed differences in the phenotypes of the KO mice might be caused by different knockout methods and the genetic background of the animals. However, taken together, the adiponectin deficiency studies indicate that adiponectin plays a protective role against the development of insulin resistance.

Mode of action

Adiponectin has various biological functions including insulin sensitizing (27), anti-atherogenic (45), anti-inflammatory (49), anti-angiogenic and anti-tumour functions (50). The recent discovery of adiponectin receptors (51) has helped in elucidating the more specific intracellular pathways involved in the action of adiponectin. The adiponectin receptor 1 (AdipoR1) was found to be predominantly expressed in skeletal muscle, but may be ubiquitously presented, whereas the expression of adiponectin receptor 2 (AdipoR2) was most abundant in the liver. Both receptors are related to G protein-coupled seven transmembrane domain receptors; however, the sequence homology of both AdipoR1 and AdipoR2 with this type of receptors is low. Furthermore, the N terminal is intracellular and the C terminus is extracellular, which is opposite to the topology of classical G protein-coupled receptors (51). The receptors have also been shown to be markedly expressed in pancreatic β -cells (52), macrophages and atherosclerotic lesions (53) as well as in the brain (51). AdipoR1 appears to be a high-affinity receptor for globular adiponectin, as well as a low-affinity receptor for full-length adiponectin, and it mediates AMPK activation, increase in glucose uptake and fatty acid oxidation in skeletal muscle (51). In contrast, AdipoR2 is an intermediate-affinity receptor for both globular and full-length adiponectin, which seems to be predominantly responsible for mediating the effects of full-length adiponectin in the liver presumably also through activation of AMPK (51). Adiponectin infusion decreases expression of hepatic gluconeogenic enzymes, inhibits glucose production, and enhances the hepatic effect of insulin (54). Recently, Pajvani *et al.* (8) showed that injection of HMW adiponectin, but

not LMW adiponectin, reduced plasma glucose levels, and that an increase in the proportion of HMW adiponectin correlates with improved hepatic insulin sensitivity. In contrast, no such correlation was found between the ratio HMW/total adiponectin and peripheral insulin sensitivity, indicating that the primary site of action of HMW adiponectin is in the liver. Furthermore, Tsao *et al.* (55) showed that hexamers and HMW adiponectin might activate the nuclear factor- κ B pathway. Thus, tissue specificity of receptor distribution and differential ligand interactions indicate related, but distinct, physiological pathways mediating the effects of adiponectin.

Very recently it has been shown that adiponectin also mediates effects in the brain. Qi and co-workers (56) have found the adiponectin concentration in the cerebrospinal fluid (CSF) to be 1–4% of the serum concentration indicating a transport of adiponectin from the serum to CSF. Intracerebroventricular (icv) injection of adiponectin reduced body weight of normal mice without affecting food intake. In parallel, increased oxygen consumption and uncoupling protein-1 expression in brown adipose tissue was observed, indicating increased thermogenesis. Because icv injection of adiponectin had no effect in Agouti mice, these effects of adiponectin seemed to be mediated through the melanocortin pathway, indicating that some of the biological effects of adiponectin are mediated through the brain. It is, however, important to emphasize the involvement of the specialized brown adipose tissue for these effects of adiponectin. Because humans have virtually no brown adipose tissue, it is an open question whether central effects of adiponectin does play a role in human beings.

Regulation

The half-life of adiponectin in serum is long being 2.5–6 h (7,57), and circulating adiponectin levels display diurnal variation with a nocturnal decline and maximum levels in the late morning (58). Furthermore, ultradian pulsatility has been observed in circulating adiponectin levels (58). It is noteworthy that important regulation of adiponectin might take place at the transcriptional, the translational, as well as at the post-translational level, which includes protein modification, secretion and oligomerization. Finally, degradation and excretion of adiponectin might be an important regulatory site for circulating adiponectin levels as well. To date, little is known about adiponectin clearance, however, both renal and hepatic clearance have been suggested (59,60).

Although lack of variation in circulating adiponectin levels after caloric-restriction-induced weight loss has been found (61,62), most studies have shown increased plasma adiponectin levels in relation to both traditionally induced weight loss (27) and weight loss after gastric surgery (63,64). The lack of increase in adiponectin levels after

weight loss in some studies might be a consequence of a smaller weight loss in these studies than in most of the other reported studies. Exercise training without a concomitant weight loss has not been found to increase plasma adiponectin levels (65,66) indicating that exercise and weight loss improve insulin sensitivity by at least partially different mechanisms, and that adiponectin only plays a role for the enhanced insulin sensitivity observed after weight loss (65).

TNF- α and interleukin-6 (IL-6) are expressed at higher levels in adipose tissue from obese patients, and they have been shown to attenuate insulin sensitivity *in vivo* and *in vitro* (67–70). Several studies have pointed to a role of especially TNF- α but also IL-6 in the regulation of adiponectin levels. Fasshauer *et al.* (71) showed that TNF- α down-regulate adiponectin mRNA levels in 3T3-L1 cells. These results were confirmed and extended by Maeda *et al.* (72), who demonstrated inhibition of both adiponectin gene expression and production by TNF- α . They, furthermore, revealed that this inhibition was mediated by suppression of the promoter activity of the adiponectin gene. In humans, TNF- α has been shown to reduce the gene expression and secretion of adiponectin from preadipocytes (73) as well as from adipose tissue fragments (38). In accordance with these *in vitro* data, data from human and rodent *in vivo* studies have shown negative associations between TNF- α and plasma adiponectin (38,74), and between TNF- α mRNA in adipose tissue and circulating adiponectin concentrations (38,75). Thus, TNF- α and adiponectin indeed seem to antagonize each other, regulating the expression of the other, and acting in an antagonist manner in modulating insulin action. It might be speculated that the increased levels of TNF- α and IL-6 in relation to metabolic disorder, such as obesity and lipodystrophy, may play a role for down-regulating adiponectin in these conditions.

The effect of insulin on adiponectin is still not fully elucidated. Scherer *et al.* (5) and Lodish *et al.* (76) found that insulin stimulates adiponectin secretion from 3T3-L1 cells within 2 h. Later it was shown that insulin induced adiponectin gene expression in human visceral adipocytes *in vitro* (77). In contrast, Fasshauer *et al.* (71) showed a dose- and time-dependent inhibition of 3T3-L1 adipocyte adiponectin mRNA levels with a significant reduction after 4 h. Hyperinsulinaemia during a hyperinsulinemic euglycemic clamp has been shown to decrease circulating adiponectin levels, indicating that high levels of insulin might reduce plasma adiponectin concentrations (36,78). Multivariate regression analyses have pointed at fasting plasma insulin levels as an independent determinant of plasma adiponectin (19,32,33), however, this has not been a consistent finding (27). Thus, at present there is no clear evidence that insulin *per se* might down-regulate adiponectin gene expression, secretion or plasma levels.

It is suggested that adiponectin plays an important role in lipid metabolism, however, whether FFA regulate adiponectin levels remains unclear. Staiger *et al.* (79) demonstrated a slight increase in circulating adiponectin levels 6 h after start of FFA-infusion. Furthermore, they showed that administration of acipimox, which lowers plasma FFA levels, did not affect plasma adiponectin levels. In contrast, Bernstein *et al.* (80) recently showed acute down-regulation of plasma adiponectin concentrations by acipimox treatment. The issue of possible FFA-induced regulation of adiponectin warrants further investigations.

Because catecholamines have been associated with impairment of insulin sensitivity, several studies have investigated the effects of β -adrenergic stimulation on adiponectin levels. By the use of different approaches, they all find that β -adrenergic agonists and c-AMP analogs inhibit adiponectin gene expression and secretion, suggesting that β -adrenergic down-regulation of adiponectin might play a role in the development of insulin resistance (73,81,82).

Thiazolidinediones (TZD) which are PPAR- γ agonists and which are used in the treatment of type 2 diabetes have been found *in vitro* to stimulate the production of adiponectin (72,83). The potential importance of adiponectin as a target for the insulin-sensitizing action of TZD is underscored by the substantial increase in plasma adiponectin levels in response to treatment with TZDs (72,78,83). Because PPAR- γ is predominantly expressed in adipose tissue and adipose tissue appears to be essential for TZD induced improvement in insulin sensitivity, this up-regulation of adiponectin by TZD suggests that adiponectin plays an important role in mediating the anti-diabetic effect of TZDs. During treatment with other anti-diabetic drugs such as metformin insulin sensitivity is improved, however, without a concomitant increase in adiponectin levels (41,83). Altogether, these data suggest an emerging paradigm of adiponectin playing an important role as a pharmacological target mediating the anti-diabetic effects of TZDs.

Discussion

Adiponectin appears to be an essential adipocytokine with pivotal biological effects. It is important to realize that this adipocytokine is circulating in concentrations exceeding the concentrations of any other known hormone, though still there is much uncertainty with regard to its primary physiological role especially in healthy subjects. The paradoxical inverse relationship between this adipocyte-specific molecule and BMI seems to be unique. Furthermore, the negative correlation is even stronger between adiponectin and visceral adiposity. Although the mechanism causing this reduction in adiponectin levels with increasing visceral adipose tissue mass is unclear, it seems likely to be an adipose tissue derived factor, which is secreted in higher

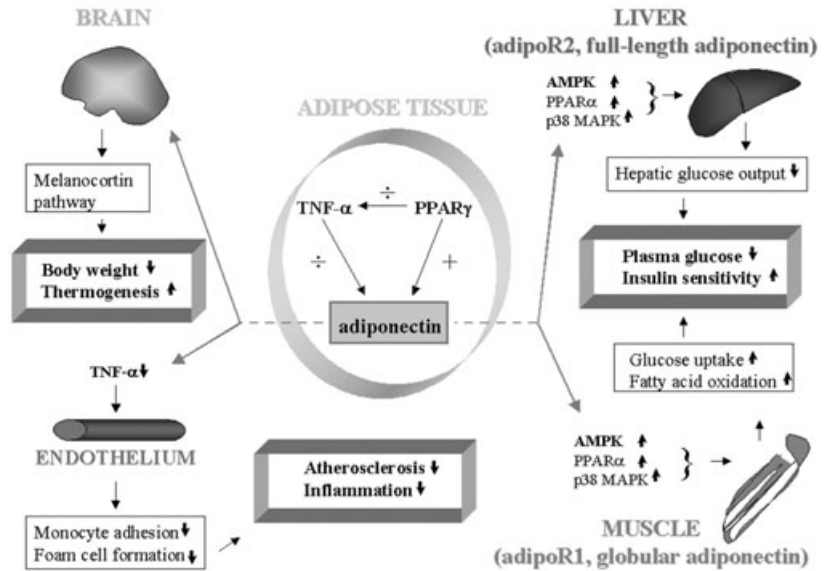


Figure 2 Illustration of target tissues, and proposed mode of action and regulation of adiponectin.

amounts, when adipose tissue is accumulated. Because TNF- α expression is positively correlated with BMI, and several lines of evidence indicate a mutual negative regulation between TNF- α and adiponectin, TNF- α could be the adipocytokine, which is suppressing adiponectin levels when fat mass is increased. However, at present this is a hypothesis, and other mechanisms are possible including the increase in adipocyte cell size *per se*.

Because adiponectin is relatively stably present in plasma, with little evidence of being an acutely regulated protein, this could indicate that the major physiological role of endogenous adiponectin is to adapt to long-term metabolic dysregulation. It could be suggested, that in healthy subjects adiponectin protects against the development of insulin resistance and atherosclerosis, however, when exposed to an increase in energy balance followed by an increase in fat mass, adiponectin concentrations are suppressed. Consequently, the risk of developing features of the metabolic syndrome will increase.

From the present literature, an emerging paradigm of adiponectin as an insulin enhancer is evolving. The suggested mechanisms appear to depend on adiponectin isoforms. Full-length adiponectin seems to be the predominant form of endogenous adiponectin, and especially HMW oligomers have been related to metabolic effects. The primary site of action for full-length adiponectin appears to be the liver, where it activates AMPK (Fig. 2). By still uncertain mechanisms, this leads to a decrease in hepatic glucose output.

In contrast, globular adiponectin, which might be less important as a physiological molecule, but with pharmacological potential, seems to act predominantly in skeletal muscles through adipoR1 receptors causing increased glucose uptake and fatty acid oxidation (Fig. 2). As stressed

above, the effects and physiological importance of different adiponectin isoforms is an issue of controversy, and further investigations are required to address this particular issue.

Thus, although increasing evidence is lending strong support to the hypothesis that adiponectin is a key player in the insulin-sensitizing mechanism, the question still remains whether the most important physiological role of adiponectin is in relation to insulin sensitivity, as a protector of atherosclerosis, in relation to low-grade inflammation, or as a modulator of lipid metabolism.

It is clear that adiponectin or adiponectin receptor agonists have potential as new drugs in the treatment of obesity-related health consequences. Up-regulation of the suppressed endogenous adiponectin production in obesity using, for example, TZD could be an alternative approach both for dietary and pharmacological intervention.

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