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MINIREVIEW

Adiponectin and Its Role in the Obesity-Induced Insulin Resistance and Related Complications

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Summary

It is now generally accepted that adipose tissue acts as an endocrine organ producing a number of substances with an important role in the regulation of food intake, energy expenditure and a series of metabolic processes. Adiponectin is a recently discovered protein produced exclusively by adipocytes. A number of studies have shown that obesity, insulin resistance and atherosclerosis are accompanied by decreased adiponectin levels and that adiponectin replacement under experimental settings is able to diminish both insulin resistance and atherosclerosis. The aim of this review is to summarize the current knowledge about the physiology and pathophysiology of adiponectin and to discuss its potential in the treatment of insulin resistance and atherosclerosis.

Key words

Adipose tissue • Adiponectin • Leptin • Insulin resistance • Atherosclerosis • Obesity

Introduction

New advances in biomedical sciences are continuously changing our views on the role of different tissues and organs in the human body. The adipose tissue represents one of the most typical examples of this notion. It is now generally accepted that in addition to its classical function as an energy storage depot, adipose tissue represents an important and very active endocrine organ that produces a number of hormones and other substances with significant roles in the regulation of insulin sensitivity and other physiological processes (Havel 2002). Discovery of the first adipose tissue-derived hormone leptin by Friedman´s group in 1994 (Zhang *et al.* 1994) started a flurry of studies searching for other hormones produced by the adipose tissue.

The reason for the deep interest in adipose tissue-derived hormones lies in the growing incidence of obesity in the developed countries of the Western World. It is now clear that the presence of obesity substantially increases the risk of related comorbidities such as insulin resistance, diabetes, dyslipidemia, hypertension and others (Reaven 2002). The combination of the above mentioned pathologies is now commonly referred to as the metabolic syndrome or syndrome X (Reaven 1992). The close link between obesity and its related complications has been well established, but the precise mechanism directly linking one to each other is not clear, as yet.

Until now a number of hormones produced by adipose tissue has been discovered and their role in the human body is being unraveled. Further studies including ours suggested that leptin is an important regulator of food intake and energy expenditure that links peripheral adipose energy stores to the hypothalamic satiety center and serves as a very sensitive marker of the body fat content and metabolic activity (Haluzík *et al.* 1999a,b,c,d, Havel 2002, Křížová *et al.* 2003). Adipose tissue was found to be the source of other hormones, such as TNF-α, PAI-1, resistin and others that are increased in obesity and that, at least under experimental settings, are accompanying or possibly can induce obesity-related insulin resistance, diabetes and/or atherosclerosis (Hube and Hauner 1999, Juhan-Vague *et al.* 2000, Steppan *et al.* 2001). Adiponectin has now been added on the list as a new and a very exciting player in the field of obesity-related insulin resistance and atherosclerosis. This new hormone produced exclusively by adipocytes differs from its predecessors in at least one important feature. While all of the currently known adipose-derived hormones related to insulin resistance are increased by obesity, adiponectin production and concentrations actually decrease in obese subjects. The fact that obesity is the state of adiponectin deficiency makes this hormone a very tempting target for possible therapeutic interventions focusing on the possibility that adiponectin treatment may improve obesity-related insulin resistance and atherosclerosis. The aim of this review is to summarize the present knowledge about the discovery, physiology and pathophysiology of adiponectin. Attention will be focused on the possible causal relationship between adiponectin deficiency and insulin resistance/atherosclerosis.

Identification of adiponectin, regulation of adiponectin gene expression

Adiponectin was identified as a protein expressed and produced by differentiated murine 3T3-L1 adipocytes (Scherer *et al.* 1995). It was also independently cloned and named AdipoQ by Hu *et al.* (1996). The human homologue of adiponectin was originally described as the most frequent transcript in female human adipose tissue when sequencing random DNA library clones and it was named APM1 (adipose most abundant gene transcript 1) (Maeda *et al.* 1996). The adiponectin protein was purified simultaneously and independently from human plasma as one of the proteins with a high affinity for gelatin-cellulose resins (Nakano *et al.* 1996).

Human adiponectin gene is located on chromosome 3q27, and it codes for a 244 amino acid polypeptide. The primary sequence of adiponectin contains a signal peptide at the N-terminus, short hypervariable region with no homology among different species, collagenous region and C-terminal half of the protein with a globular domain (Tsao *et al.* 2002). The globular domain shares sequence homology with C1q protein, adiponectin thus belongs to the C1q globular domain protein family. The biological function of most proteins of this family is yet only partially understood or completely unknown. Interestingly, in addition to sequence homology with C1q adiponectin has also structural homology with the TNF-α cytokine family.

Adiponectin is expressed exclusively in white and according to some reports also in brown adipose tissue (T37i brown adipocyte cell line) (Viengchareun *et al.* 2002). Adiponectin gene regulation includes a number of hormonal and environmental factors. Adiponectin gene expression in white adipose tissue is decreased by obesity, glucocorticoids, β-adrenergic agonists and TNF-α and increased by leanness, cold exposure, adrenalectomy and IGF-1 (Fasshauer *et al.* 2002, Makimura *et al.* 2002). There are somewhat conflicting reports concerning the influence of insulin on the adiponectin gene expression. Some authors have reported an increase of adiponectin gene expression in 3T3-L1 adipocytes *in vitro* after a short-term insulin stimulation (Scherer *et al.* 1995), while others found a decrease in adiponectin gene expression after a more prolonged exposure to insulin (Fasshauer *et al.* 2002). It seems that insulin is a very important regulator of adiponectin gene expression that may have different effects depending on the dose and the duration of action. It should be stressed that most of the hormonal actions described above were studied under *in vitro* conditions which may not necessarily reflect the true *in vivo* situation.

Adiponectin in experimental models of obesity and insulin resistance

It was demonstrated in several experimental studies that both adipose adiponectin mRNA expression and plasma adiponectin levels are decreased in most rodent models of obesity (Hu *et al.* 1996, Yamauchi *et al.* 2001), although this is not absolutely true in all situations. We measured adipose adiponectin gene expression and its plasma levels in 7-week-old leptin-deficient *ob/ob* mice on the two genetic backgrounds (C57BL/6J and FVB/N) and their wild type littermates (Haluzík *et al.*, unpublished results). A twofold decrease

in circulating adiponectin and a 10-fold decrease in adiponectin gene expression was found in FVB/N *ob/ob* mice relative to strain-matched controls. In contrast, we found no differences in circulating adiponectin levels between C57BL/6J *ob/ob* mice and their wild type littermates, despite a 3-fold decrease of adiponectin gene expression in *ob/ob* mice. It thus seems that there is not necessarily a close correlation between adiponectin gene expression and its plasma levels. This can partly be explained by the possibility that increased total fat mass in obese individuals can temporarily compensate for decreased adiponectin production per unit of fat. Indeed, others have shown a decrease in both circulating adiponectin levels and their gene expression in older C57BL/6J *ob/ob* mice with more pronounced obesity and diabetes (Yamauchi *et al.* 2003). Adiponectin levels were also decreased by high-fat diet-induced obesity in monkeys (Hotta *et al.* 2001). In fact, the drop of adiponectin levels in this study preceded the decrease in insulin sensitivity and the development of type 2 diabetes.

The most compelling evidence about the role of adiponectin in the development of insulin resistance and atherosclerosis was brought by the transgenic mouse models with adiponectin gene knockout. Maeda *et al.* (2002) showed that adiponectin-knockout (KO) mice had delayed clearance of free fatty acids in the plasma, low levels of fatty-acid transport protein 1 mRNA in muscle, high levels of TNF-α mRNA in adipose tissue and high plasma TNF-α concentrations. In addition, despite having normal glucose tolerance when fed by regular diet, adiponectin KO mice exhibited more severe high-fat diet-induced insulin resistance with reduced insulin-receptor substrate 1-associated phosphatidylinositol 3 kinase activity in muscles than their wild type littermates. Adenovirus-mediated adiponectin expression in adiponectin KO mice completely reversed the phenotype. Kubota *et al.* (2002) independently created another transgenic murine model lacking adiponectin and found a decreased insulin sensitivity in adiponectin KO mice even on a regular diet. Moreover, adiponectin-deficient mice showed twofold more neointimal formation in response to external vascular cuff injury than wild type mice, strongly suggesting a direct role of adiponectin in the development of atherosclerosis. In contrast, the adiponectin knockout model developed by Ma *et al.* (2002) showed completely different phenotype from the two models described above. In this study, authors found no impact of adiponectin deficiency on insulin sensitivity under either normal or high-fat diet conditions. In addition, adiponectin KO mice displayed increased fatty acid oxidation relative to wild type littermates. The reason for such a discrepancy between the phenotypes of transgenic mice made by Maeda and Kubota relative to Ma´s model is not completely clear. It is, however, possible that the latter knockout is not complete enough and enables the production of some adiponectin fragments that can at least in part serve as a substitute for physiological functions of full length adiponectin.

Adiponectin: clinical observations

Plasma adiponectin levels in humans range from 0.5 to 30 μg/ml, which is about 1000-fold higher than he concentrations of most other hormones such as leptin, insulin etc. In fact, adiponectin accounts for 0.01 % of total human plasma proteins and is the most abundant adipose tissue protein (Stefan and Stumvoll 2002). A number of clinical studies showed a decrease of adiponectin levels in obese humans relative to lean subjects (Arita *et al.* 1999, Hotta *et al.* 2001, Yang *et al.* 2001). For example, Arita *et al.* (1999) found a negative correlation between body mass index and plasma adiponectin levels in Japanese men and women. Interestingly, there were marked variations in adiponectin levels even among obese subjects (adiponectin concentration varied from 1.9 to 17 μg/ml in this study). Adiponectin levels were also significantly higher in females relative to the males. Negative correlation between plasma adiponectin levels and body mass index or body fat was further supported by studies of Weyer *et al*. (2001) performed on Caucasian and Pima Indian populations.

In another study, adiponectin levels were compared in three groups of subjects: non-diabetic individuals, diabetic subjects with coronary artery disease and diabetic subjects without coronary artery disease (Hotta *et al.* 2000). Plasma adiponectin levels were decreased in diabetic as compared to non-diabetic individuals. This decrease was more pronounced in patients who had both diabetes and coronary artery disease. In the study by Weyer *et al.* (2001) plasma adiponectin concentrations were correlated with various parameters of insulin sensitivity. Adiponectin levels correlated positively with insulin-stimulated whole body glucose disposal as measured by the euglycemic hyperinsulinemic clamp and negatively with serum insulin levels. Other studies found an inverse relationship between plasma adiponectin and serum triglyceride levels as well as fasting and postprandial plasma glucose concentrations (Hotta *et al.* 2000, Weyer *et al.* 2001).

In contrast to decreased adiponectin levels in obese individuals, the weight loss was found to enhance adiponectin concentrations (Hotta *et al.* 2000, Yang *et al.* 2001). As briefly mentioned above, leanness is accompanied by increased adiponectin levels. Delporte *et al.* (2002) showed that malnourished anorexia nervosa patients with extremely decreased body fat content have markedly higher adiponectin levels relative to age- and gender-matched controls. In our study (Pařízkova *et al.* unpublished data) we measured adiponectin levels in patients with restrictive and purgative form of anorexia nervosa, subjects with bulimia nervosa and healthy controls. We found significantly increased adiponectin levels in patients with a restrictive form of anorexia nervosa relative to other groups, while patients with bulimia nervosa tended to have lower adiponectin concentrations than those from other groups.

Another factor that markedly affects adiponectin levels is the stimulation of peroxisome proliferator-activated receptor gamma (PPAR-γ). The treatment with PPAR-γ receptor agonists, thiazolidine-diones, increased circulating adiponectin levels under both experimental conditions in rodent models of obesity (Combs *et al.* 2002) and in patients with obesity/type 2 diabetes (Maeda *et al.* 2001), while metformin or PPAR-α agonists had no effect. It thus seems that part of the insulin-sensitizing effect of thiazolidinediones might be mediated by an increase of adiponectin levels.

Further evidence for the role of adiponectin in the obesity and diabetes comes from genetic studies. In a recently performed genome-wide scan on a large group of human subjects two quantitative trait loci related to metabolic syndrome components were identified on chromosomal location 3q27 where the adiponectin gene is located (Kissebah *et al.* 2000). In other studies, the association between type 2 diabetes and single nucleotide polymorphisms at position 45 and 276 (Hara *et al.* 2002) and in the proximal promoter and exon 3 of the adiponectin gene (Vasseur *et al.* 2002) has been reported.

Pharmacological effects of adiponectin: insulin resistance

Since convincing evidence has been reported on the association of decreased adiponectin levels with obesity and insulin resistance, a number of laboratories have tried to explore the possibility that hypoadiponectinemia plays a causative role in these diseases by testing the effects of adiponectin replacement. Administration of the globular domain of adiponectin was accompanied by a weight loss and a decrease of plasma glucose, free fatty acids and triglycerides in mice consuming a high-fat/high-sucrose diet (Fruebis *et al.* 2001). Recombinant adiponectin treatment reduced serum glucose in normal and diabetic rodents without stimulating insulin secretion and markedly enhanced the ability of insulin to suppress glucose production by isolated hepatocytes (Berg *et al.* 2001). The same group showed by using the euglycemic hyperinsulinemic clamp technique that the same, i.e. adiponectin sensitization of the liver tissue to insulin action, is also true under *in vivo* conditions in mice. Yamauchi *et al.* (2002) recently showed that both globular domain and full-length adiponectin stimulated 5′-AMP-activated protein kinase in the muscle and that only full-length adiponectin did so in the liver. This suggests that adiponectin action on glucose metabolism may be mediated by enhanced 5′-AMP-activated protein kinase that in turn increases fatty acid oxidation and glucose uptake.

Pharmacological effects of adiponectin: atherosclerosis

In addition to increased sensitivity of adiponectin-deficient mice to vascular injury-induced neointimal proliferation, an increasing number of studies is showing antiatherosclerotic effects of adiponectin treatment. For example, Yamauchi *et al.* (2003) showed that the administration of adiponectin globular domain to a classical model of accelerated atherosclerosis apolipoproteinE(ApoE)-deficient transgenic mice, or the double transgenic ApoE/leptin-deficient mice led to amelioration of atherosclerosis in both models. This effect was accompanied by reduced expression of class A scavenger receptor and TNF-α. Okamoto *et al.* (2002) tested the influence of adenovirus-mediated full-length recombinant adiponectin overexpression on the number of atherosclerosis-related parameters in ApoE-deficient mice. Similarly to the previously mentioned study, adiponectin treatment reduced the atherosclerotic lesion formation by 30 %. Immunohistochemical analyses demonstrated that adiponectin migrated to foam cells in the fatty streak lesions. Adiponectin treatment significantly suppressed the expression of vascular cell adhesion molecule-1 and of class A scavenger receptor.

Two *in vitro* studies further revealed a possible mechanism of adiponectin action on the development of atherosclerosis. Arita *et al.* (2002) showed that recombinant adiponectin suppressed human aortic smooth muscle cell proliferation and migration through direct binding with platelet-derived growth factor and inhibition of growth factor-induced ERK signaling. Ouchi *et al.*

(2001) found that adiponectin suppressed macrophage-to-foam cell transformation of human monocyte-derived macrophages by reducing the expression of class A macrophage scavenger receptors.

Conclusions and future directions

The discovery of adiponectin undoubtedly represents a very important step in our attempts to further understand the mechanism of obesity-induced insulin resistance and atherosclerosis. In contrast to other known adipocyte-derived hormones that are generally increased in obesity, adiponectin concentrations are decreased in obese individuals. This fact together with the promising results of experimental studies suggests the possibility that adiponectin replacement might become a new pharmacological approach to treatment of insulin resistance and/or atherosclerosis. Despite this promising implication, there is still a number of crucial steps to be performed to fully understand the biology of adiponectin, e.g. identification of the adiponectin receptor and the exact mechanism of adiponectin action. From the clinical point of view, human studies with recombinant adiponectin administration will be necessary in order to test the effectiveness of this compound in the treatment of insulin resistance and/or atherosclerosis in clinical medicine.

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