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MINIREVIEW

Adiponectin, an Adipocyte-Derived Protein

J. NEDVÍDKOVÁ, K. SMITKA, V. KOPSKÝ, V. HAINER

Institute of Endocrinology, Prague, Czech Republic

This article is dedicated to Prof. MUDr. Vratislav Schreiber, DrSc. on the occasion of his 80th birthday

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Summary

Adipose tissue is a hormonally active tissue, producing adipocytokines which may influence activity of other tissues. Adiponectin, abundantly present in the plasma increases insulin sensitivity by stimulating fatty acid oxidation, decreases plasma triglycerides and improves glucose metabolism. Adiponectin levels are inversely related to the degree of adiposity. Anorexia nervosa and type 1 diabetes are associated with increased plasma adiponectin levels and higher insulin sensitivity. Decreased plasma adiponectin levels were reported in insulin-resistant states, such as obesity and type 2 diabetes and in patients with coronary artery disease. Activity of adiponectin is associated with leptin, resistin and with steroid and thyroid hormones, glucocorticoids, NO and others. Adiponectin suppresses expression of extracellular matrix adhesive proteins in endothelial cells and atherosclerosis potentiating cytokines. Anti-atherogenic and anti-inflammatory properties of adiponectin and the ability to stimulate insulin sensitivity have made adiponectin an important object for physiological and pathophysiological studies with the aim of potential therapeutic applications.

Key words

Adiponectin • Adipose tissue • Energy metabolism • Animal and human studies

Introduction

Adipose tissue secretes a large number of physiologically active peptides that often share properties with cytokines, and are therefore collectively referred to as „adipocytokines“, e.g. leptin, tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6) or resistin (Fig. 1). Some of these molecules are almost exclusively secreted by the adipose tissue. It is also likely that some of these adipocytokines mediate the systemic effects of obesity on health. Adipocytokine, adiponectin (Apn), also referred as 30-kDa adipocyte complement-related protein (Acrp 30), gelatin-binding protein-28 and Apn Q (Maeda *et al.* 1996, Nakano *et al.* 1996) is encoded by gene APM1, which has been mapped to chromosome 3 q 27 (Vasseur *et al.* 2003). Apn, 244 amino acid collagen-like protein, abundantly synthesized and secreted by the adipose tissue, has structural homology to complement factor C1q and collagen VIII and X. Apn circulates in the plasma as a hexamer of relatively low molecular weight (LMW) and a larger multimeric structure of high molecular weight (HMW) (Pajvani *et al.* 2003) in relatively high

concentrations (5 to 30 μg/ml, 0.01 % of total plasma protein), by three orders more than other hormones, at higher levels in women than in men (Scherer *et al.* 1995). Serum levels of this protein correlate with systemic insulin sensitivity. Reduced plasma levels of Apn may play a role in pathogenesis of obesity and diabetes type 2 (Statnick *et al.* 2000, Haluzík *et al.* 2004). A physiological role for Apn has not yet been fully established.

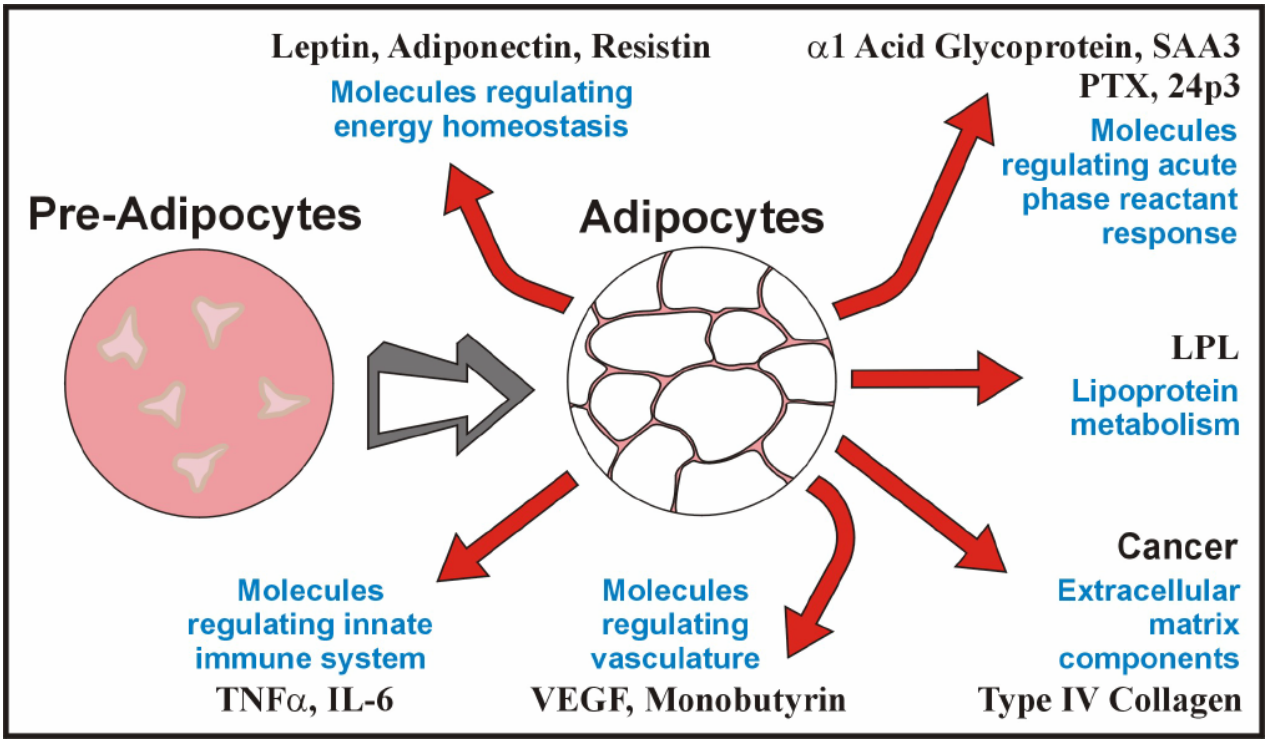

Fig. 1. The role of adipocytes in energy homeostasis, immune system function and cancer. Adipose tissue plays a major role in problems associated with prolonged hyperglycemia. Hyperglycemia induces a production of acute phase reactants in adipose tissue, including alpha 1 acid-glycoprotein, serum amyloid A3 (SAA3), lipocalin (24p3), paclitaxel (PTX). The adipocytes produce vascular endothelial growth factor (VEGF) in response to insulin and catecholamines. Monobutyrin (1-butyryl-glycerol) is a novel angiogenic and vasoactive factor secreted by differentiating adipocytes. LPL-lipoprotein lipase. Type VI collagen, a soluble extracellular matrix protein abundantly expressed in adipocytes, is upregulated in adipocytes during tumorigenesis.

Animal studies

Experimental data obtained on some animal models suggest that a reduction of Apn expression is associated with obesity and insulin resistance. The expression of Apn may be activated during adipogenesis, but a feedback inhibition on its production may be involved in the development of obesity (Diez and Iglesias 2003). It was demonstrated that the expression of adipogenic genes was suppressed during the development of obesity and diabetes mellitus in mice. These observations suggest the existence of a feedback inhibitory pathway (Nadler *et al.* 2001). The decrease in plasma Apn levels preceded the development of insulin resistance and diabetes in rhesus monkeys (Hotta *et al.* 2001). This study showed that low plasma Apn may contribute to the pathogenesis of insulin resistance and diabetes mellitus in animals (Diez and Iglesias 2003). Apn knock-out mice showed delayed clearance of free fatty acid from plasma and low levels of fatty acid transport protein 1 mRNA in muscles. There was no evidence of insulin resistance when Apn knock-out mice were fed a regular chow. Some observations indicate that Apn deficiency contributes to the induction of insulin resistance and that Apn may play a protective role against insulin resistance (Maeda *et al.* 2002, Ma *et al.* 2002).

Administration of recombinant Apn in pharmacological studies reduced serum glucose in normal and diabetic rodents without stimulation of insulin secretion. Full length Apn molecule produced in mammalian cells in culture is more effective in enhancing insulin sensitivity than that produced in bacterial cells. This could be attributed to post-transcriptional modifications of endogenous Apn in eucaryotic cells.

Plasma membrane receptors and the control of adiponectin synthesis

Adiponectin receptor 1 (AdipoR1) is abundantly expressed in skeletal muscle, whereas adiponectin receptor 2 (AdipoR2) is predominantly expressed in the liver. These two Apn receptors are predicted to contain seven transmembrane domains, but to be structurally and functionally distinct from G-protein-coupled receptors (Yamauchi *et al.* 2003). These authors supposed that receptors serve for globular (AdipoR1) and full-length (HMW) Apn molecules (AdipoR2 binds both). Experimentally activated expression or suppression of AdipoR1/R2 support the conclusion that they mediate increased AMP kinase and PPAR ligands activities, as well as fatty-acid oxidation and glucose uptake by Apn (Yamauchi *et al.* 2003).

The mechanism responsible for the control of Apn synthesis has not been determined in detail so far. The expression and secretion of Apn from adipocytes are reduced significantly by TNF-α (Fasshauer *et al.* 2002a,b). TNF-α is one of the candidate molecules responsible for causing insulin resistance. The recent study has shown that insulin reduces the level of Apn mRNA in a dose- and time-dependent fashion (Fasshauer *et al.* 2002a,b). Also β-adrenergic agonists (Zhang *et al.* 2002) and glucocorticoid are reported to inhibit Apn gene expression and secretion, suggesting that decreased Apn production could play a role in catecholamine- or glucocorticoid-induced insulin resistance. Finally, the stomach-derived peptide, ghrelin, inhibits Apn gene expression (Ott *et al.* 2002). Peroxisome proliferator-activated nuclear receptor-γ (PPARγ) and liver receptor homolog-1 (LRH-1) play significant roles in the transcriptional activation of Apn gene *via* the peroxisome proliferator-activated receptor gamma response element (PPRE) and the LRH-RE in its promoter.

Peroxisome proliferator-activated nuclear receptors (PPARs) and regulation of energetic metabolism

The PPARs are nuclear receptor isoforms with key roles in the regulation of lipid and glucose metabolism. PPARγ and PPARα and probably also PPARδ have effects of promoting insulin sensitization in the context of obesity. PPARγ and PPARα have anti-inflammatory effects and reduce the progression of atherosclerosis in animals (α ,γ) or in humans (α). Apn is induced by PPARγ agonists. Synthetic PPARγ agonist administered to differentiated adipocytes cultured *in vitro* increased Apn mRNA (Chinetti *et al.* 2004). PPARs act as DNA response elements in heterodimer form with retinol and other cofactors in control of many adipocyte genes (Rocchi and Auwerx 1999). PPARγ abundant in fat tissue induces adipocyte differentiation and it is also an insulin sensitizer *in vivo* (Diez and Iglesias 2003). It was thought that the effects of PPARγ in adipose tissue are crucial in explaining its role in insulin sensitization. More recent studies have highlighted the contribution of the other tissues (Picard and Auwerx 2002). The upregulation of the Apn pathway by PPARγ may play a role in the increasing β-oxidations of lipids, leading to decreased triglycerides from the liver and muscle (Maeda *et al.* 2001).

Thiazolidinediones (TZD), TNF-α and adiponectin

Thiazolidinediones, PPAR-γ agonists, enhanced the expression and release of mediators of insulin resistance originating in adipose tissue (e.g. increased free fatty acids, decreased Apn) in a way that results in net improvement of insulin sensitivity in muscle and liver (Stumvoll 2003). TZD normalized or increased Apn mRNA expression and Apn secretion in adipose tissue of obese mice (Maeda *et al.* 2001). TZD also enhanced Apn promotor activity and restored inhibitory effect of TNF-α on this promotor (Diez and Iglesias 2003). TNF-α is a key modulator of adipocyte metabolism, with direct role in several insulin-mediated processes, including glucose homeostasis and lipid metabolism and is a major contributor to the development of adipose tissue insulin resistance (Sethi and Hotamisligil 1999).

Sympathetic nervous system (SNS) and adiponectin

Elevated levels of catecholamines, due to SNS hyperactivity, play a role in the development of insulin resistance. Reduced Apn mRNA levels were almost completely reversed by pretreatment of adipocytes with propranolol, a β-adrenergic antagonist (Diez and Iglesias 2003). Administration of a β-agonist isoprenaline and cAMP to mice or human adipocytes in culture showed an inhibitory effect on Apn gene expression and Apn secretion in both subcutaneous and visceral adipose tissues (Delporte *et al.* 2002, Fasshauer *et al.* 2002a,b). Treatment with isoprenaline reduced Apn mRNA levels in a dose-dependent manner in 3T3-L1 adipocytes (Diez and Iglesias 2003).

Adiponectin stimulates production of nitric oxide (NO) in vascular endothelial cells

Adiponectin exerts its vascular actions by direct stimulation of NO production in endothelial cells using phosphatidylinositol 3-kinase pathways involving phosphorylation of endothelial NO synthase (eNOS) by AMP-activated protein kinase (AMPK) and stimulating new blood vessel growth and taking part in vasodilatator actions and increasing blood flow. Thus Apn mimics vascular as well as metabolic actions of insulin. The fact that insulin and adiponectin regulate activation of eNOS by slightly different mechanisms suggest that therapies designed to increase Apn levels may be beneficial in treatment of insulin resistance, diabetes, vascular complications and atherosclerosis (Chen *et al.* 2003).

Conclusions from human studies

Adiponectin, leptin, and resistin are specific fat-derived hormones that affect human fuel homeostasis and insulin action and may also be involved in haematopoiesis and immunity. Clear relationship exists between Apn and fat mass in humans. Apn release is positively correlated with fat cell size and negatively with body mass index (BMI). Apn release is significantly lower in omental than in subcutaneous adipose tissue (Johnson *et al.* 2003). In contrast to leptin, Apn levels are significantly reduced not only in obese subjects (Arita *et al.* 1999, Haluzík *et al.* 2004), but also in patients with some of the disease states associated with obesity, such as type 2 diabetes (Hotta *et al.* 2000) and coronary artery disease (Ouchi *et al.* 1999). The trend towards increased Apn on a high-fat diet in more insulin-sensitive subjects is suggestive of increased capacity for fat oxidation and may be protective against development of type 2 diabetes (Berk *et al.* 2003). Apn serum concentrations were negatively correlated with the increase in muscle intracellular lipids after dietary lipid challenge. Suppression of lipid oxidation by hyperinsulinemia prevents effects of Apn on muscle intracellular lipid stores. Apn promotes lipid oxidation in humans (Thamer *et al.* 2003). The HMW protein affects hepatic gluconeogenesis through improved insulin sensitivity, and LMW Adiponectin stimulates β-oxidation in muscle. Pajvani *et al.* (2003) showed that the ratio, and not the absolute amounts, between two Apn molecular forms (HMW to LMW) is crucial in determining the insulin sensitivity.

On the other hand, in anorexia nervosa characterized by chronic self-starvation and severe weight loss, starvation-induced depletion of fat stores, is accompanied by alterations of circulating adipocytokines. We found that plasma leptin and likely resistin levels are decreased in anorectic patients, while plasma Apn levels are increased (our unpublished results). In anorexia nervosa patients, control women and obese women, plasma Apn was negatively correlated not only with BMI and body fat mass, but also with serum leptin concentration, fasting insulin and calculated insulin resistance (Matsubara *et al.* 2002, our observations). Apn was inversely associated with insulin resistance in nondiabetic subjects, independently of age, blood pressure, adiposity and serum lipids (Matsubara *et al.* 2003). Another study performed in subjects with normal weight, has shown that plasma Apn is negatively correlated with BMI, systolic and diastolic blood pressure, fasting plasma glucose, insulin, insulin resistance, total and LDL-cholesterol, triglycerides and uric acid, and positively correlated with HDL-cholesterol (Yamamoto *et al.* 2002). Serum Apn was positively associated with HDL-cholesterol in both diabetic and nondiabetic subjects. Caucasian have higher serum adiponectin levels compared with Indo-Asians (Valsamakis *et al.* 2003). On the contrary, plasma Apn concentrations are significantly increased in type 1 diabetic patients compared with healthy controls (Imagawa *et al.* 2002). Experimental evidence suggest that Apn may play a protective role against atherosclerosis (Haluzík *et al.* 2004). Hyperinsulinemia caused a significant decrease of Apn plasma levels under euglycemic conditions. Hypoadiponectinemia might at least partly be a link between hyperinsulinemia and vascular disease in metabolic syndrome X (Diez et Iglesias 2003). A significant negative correlation was found between plasma Apn concentration and mean systolic and diastolic blood pressure, suggesting that Apn contributes to the clinical course of hypertension (Adamczak *et al.* 2003). Adiponectin, leptin and interleukin-6 are associated with impaired fibrinolysis in obese hypertensive patients (Skurk *et al.* 2002). Apn concentrations seem to be gender-dependent, being higher in women than in men (Yamamoto *et al.* 2002). It was observed that weight loss induces an increase in Apn levels in obesity (Yang *et al.* 2001).

Circulating Apn levels were found to be suppressed fivefold in patients with severe insulin resistance due to dominant-negative PPARγ mutations,

thus suggesting that Apn may be a biomarker of *in vivo* PPARγ activation (Combs *et al.* 2002).

Similar to the animal models, TZD treatment should enhance endogenous Apn production in humans (Maeda *et al.* 2001). TZD increases circulating Apn levels in normal subjects and in obese and type 2 diabetic patients. Plasma Apn levels in diabetic patients were increased more than twofold after three months of rosiglitazone therapy (6.7±0.7 vs. 15.1±2.0 mg/ml) and remained elevated after 6 months of rosiglitazone therapy. There was a tendency towards an increase in Apn mRNA expression after 24-h incubation of human adipose tissue with either rosiglitazone or pioglitazone. The results may suggest that in humans TZD affects Apn at the transcriptional level (Lihn *et al.* 2003).

Apn is a novel determinant of bone mineral density and visceral fat (Lenchik *et al.* 2003). This peptide also stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and other signaling pathways in endothelial cells (Ouchi *et al.* 2003). Fernandez-Real *et al.* (2003) observed interaction of Apn with the endocrine system and inflammatory parameters. Their findings suggest that circulating adiponectin differentially modulates insulin action and that the thyroid axis, inflammatory cytokines and the adrenal cortex may participate in this modulation. The carboxy-terminal globular structure of Apn, through its use of gC1q receptor found in mitochondria of the thyroid, could be a regulator of thyroid hormone production (Soltys *et al.* 2000). Additional evidence for a role of thyroid hormones in the regulation of Apn expression comes from a recent study showing increased Apn levels in mice exposed to cold (Yoda *et al.* 2001). It was postulated that Apn could regulate body temperature and basal metabolic rate in response to changing environmental conditions. It was then concluded that Apn might play a role in thermogenesis. These data suggest that thyroid and adrenal activity modulates Apn expression and Apn possesses anti-atherogenic and anti-inflammatory properties. A recent study has shown that estradiol is negatively and indirectly associated with Apn, whereas there is no association between serum adiponectin and leptin, cortisol, or free testosterone levels (Gavrila *et al.* 2003). However, Nishizawa *et al.* (2002) observed that testosterone leads to a reduction in plasma Apn.

In summary, adiponectin is a fat-derived hormone with antidiabetic properties. The ability of adiponectin to increase insulin sensitivity in conjunction with its anti-inflammatory and anti-atherogenic properties have made this novel adipocytokine a promising therapeutic tool for the future, with potential applications in states associated with low plasma adiponectin levels.

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Reprint requests

J. Nedvídková, Institute of Endocrinology, Národní 8, 116 94 Prague 1, Czech Republic. Fax: 22490 5325, e-mail: jnedvidkova@endo.cz