Adiponectin and resistin – new hormones of white adipose tissue

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Summary

Adiponectin and resistin are recently described secretory products of adipose tissue. Adiponectin is secreted by fat cells and circulates in the blood. Plasma adiponectin concentration is reduced in obese animals and humans and in patients with type 2 diabetes mellitus. Adiponectin stimulates fatty acids oxidation, decreases plasma triglycerides, and improves glucose metabolism by increasing insulin sensitivity. In addition, adiponectin inhibits the inflammatory process and possibly atherogenesis by suppressing the migration of monocytes/macrophages and their transformation into foam cells. Plasma adiponectin is lower in patients with ischemic heart disease than in body mass index-matched healthy individuals. Hypoadiponectinemia may contribute to insulin resistance and accelerated atherogenesis associated with obesity. Resistin/FIZZ3 is a member of the newly discovered cysteine-reach secretory protein family, referred to as 'resistin-like molecules' (RELM) or 'found in inflammatory zone' (FIZZ), together with FIZZ1/RELMα and FIZZ2/RELMβ. Each of these has unique tissue distribution. Both resistin and FIZZ1/RELMα are expressed in adipose tissue. Initial studies in rodents suggested that resistin is upregulated in obesity and may be involved in the development of insulin resistance. Later studies failed to confirm this hypothesis and demonstrated reduced resistin expression in adipose tissue of obese animals. In human adipose tissue resistin is detectable at a very low level, and there is no relationship between resistin expression and obesity. Although the role of resistin in linking human obesity with type 2 diabetes is thus questionable, this protein is detected in peripheral blood monocytes, suggesting its possible role in inflammatory processes.

key words: obesity • diabetes mellitus • atherosclerosis


Word count: 4079
Tables: –
Figures: –
References: 51

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BACKGROUND

Obesity is a growing health problem in well-developed countries. Overweight and obesity increase morbidity and mortality associated with numerous complications, such as impaired glucose tolerance/type 2 diabetes mellitus, hyperlipidemia, arterial hypertension and atherosclerosis. These consequences of obesity, referred to as ‘metabolic syndrome’, are usually attributed to insulin resistance and hyperinsulinemia; however, their pathogenesis has not been completely elucidated [1–3].

White adipose tissue (WAT) was for a long time regarded as a relatively passive site of energy storage. This energy is accumulated in the form of triglycerides during periods of excess food consumption and mobilized when calorie intake is inadequate. Recent studies indicate that WAT is an endocrine organ producing numerous proteins with broad biological activity. The secretory products of WAT, collectively referred to as ‘adipocytokines’, include leptin, tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), transforming growth factor β (TGF-β), plasminogen activator-inhibitor 1 (PAI-1), angiotensinogen, adipin, acylation-stimulating protein and metallothionein. Proteins secreted by adipose tissue play an important autocrine role in WAT physiology and are involved in obesity-associated complications, such as insulin resistance, endothelial dysfunction, arterial hypertension and atherosclerosis [4]. This brief review describes two recently discovered WAT-derived proteins: adiponectin and resistin.

ADIPONECTIN

Structure, synthesis, and regulation of expression

Adiponectin was independently characterized by four groups using different methods. Adiponectin cDNA was isolated from the human adipose tissue library and was called apM1 (AdiPose Most Abundant gene transcript) [5]. Scherer et al. [6] cloned mouse adiponectin cDNA and found that the respective protein, called Acrp30 (adipocyte complement-related protein of 30 kDa) is rapidly upregulated during differentiation of preadipocytes to adipocytes. Another group identified the same protein in rats and mice and termed it adipoQ [7]. Finally, human adiponectin protein was isolated from plasma as gelatin binding protein of 28 kDa (GBP28) by Nakano et al. [8].

Human adiponectin contains 244 aminoacid residues and consists of a 20-residue signal sequence, an N-terminal region without homology to any known proteins, a collagen-like region, and a C-terminal globular domain. The molecule shares sequence homology with type VI and type X collagens, complement component Clq, precerbellin and the hibernation-regulated proteins hib 20, 25 and 27. The three-dimensional structure of its C-terminal globular domain is similar to that of TNF-α, even though there is no sequence homology at the primary structure level. It is possible that adiponectin is proteolytically cleaved after secretion, because mouse serum contains both full-length protein and small amounts of shorter 25 kDa molecules recognized by antibodies against the C-terminal region [9]. A smaller form of adiponectin containing the C-terminal domain with a molecular weight of 27 kDa has been detected, also in human plasma [10]. This cleavage product has shown higher biological activity than native adiponectin in some studies. Adiponectin is abundant in plasma and accounts for 0.01% of total plasma proteins in humans [11] and even 0.05% in rodents [7]. Under normal conditions the adiponectin gene is expressed exclusively in adipose tissue. However, adiponectin mRNA also appears in hepatocytes after treatment with carbon tetrachloride or interleukin-6 [12].

The synthesis and secretion of adiponectin is regulated by several mechanisms. Insulin stimulates adiponectin gene expression and its secretion from cultured 3T3-L1 adipocytes [6]. Both insulin and insulin-like growth factor-1 (IGF-1) also increase adiponectin synthesis in adipocytes isolated from human visceral adipose tissue [13]. Peroxisome proliferator-activated receptors (PPAR), which belong to the nuclear hormone receptor superfamily, are involved in the regulation of adiponectin synthesis. PPARα agonists (fibrates) decrease adiponectin mRNA abundance in white adipose tissue of obese db/db mice, which lack functional leptin receptors [14]. Moreover, chronic treatment with the PPARα agonist, rosiglitazone, reduces adiponectin expression in this obesity model [14]. In contrast, in another study [9], rosiglitazone enhanced adiponectin expression in high fat diet-fed db/db mice, as well as in wild type lean C57 mice, and the same was observed in vitro in cultured 3T3-L1 adipocytes. Maeda et al. [15] also observed stimulation of adiponectin gene expression and increased circulating adiponectin concentration in obese mice and insulin-resistant obese humans by the PPARγ agonists, thiazolidinediones. Because adiponectin improves glucose tolerance by increasing insulin sensitivity (see below), the effect of thiazolidinediones on adiponectin secretion may explain, at least partially, the hypoglycemic effect of these drugs in patients with type 2 diabetes mellitus. TNF-α produced by white adipose tissue is markedly upregulated in obesity and contributes to insulin resistance by interfering with insulin receptor signaling [16]. This cytokine suppresses adiponectin expression in WAT [15,17], whereas thiazolidinediones prevent this inhibitory effect of TNF-α [15]. Thus, insulin resistance induced by TNF-α may be partially explained by the inhibition of adiponectin secretion, and reversal of the effect of TNF-α by thiazolidinediones may contribute to the insulin-sensitizing action of these drugs.

Fat cells specifically express adrenergic β3 receptors, which stimulate lipolysis through the mechanism dependent on cyclic AMP-protein kinase A. Stimulation of the cAMP-PKA pathway by the β-adrenergic agonist isoproterenol, the adenylyl cyclase activator forskolin, or the synthetic cAMP analogue dibutyryl-cAMP reduces the level of adiponectin mRNA in 3T3-L1 adipocytes; this effect is blocked by the β-adrenergic antagonist propranolol, and by protein kinase A inhibitor H-89 [17,18]. However, in vivo administration of...
the specific β3-receptor agonist BRL-35135 had no effect on adiponectin expression in db/db mice [14]. It is possible that the direct suppressive effect of an adrenergic agonist is counterbalanced in vivo by indirect stimulation of adiponectin production due to improvement of insulin sensitivity and glycemic control resulting from body weight reduction in BRL-35135-treated animals.

No adiponectin receptors have been identified as yet. However, specific saturable peptide binding inhibited by anti-adiponectin antibodies has been observed in cultures of human aortic endothelial cells [19]. The effect of adiponectin in these cells is partially mediated by cyclic AMP and protein kinase A. Thus it is likely that adiponectin acts through cell surface receptors coupled to adenylate cyclase. Adiponectin can partially exert its effects through receptors for complement C1q components. Antibodies against this receptor block the effect of adiponectin in peripheral monocytes, but not in bone marrow progenitor cells [20].

Little is known about the degradation of plasma adiponectin; however, the kidneys may be involved in this process, because the plasma level of this protein markedly increases in patients with advanced renal failure [21].

**Hypoadiponectinemia in obesity and type 2 diabetes mellitus**

One of the most interesting features of adiponectin is that, in contrast to other adipocytokines which are markedly upregulated in obesity, its adipose tissue expression and plasma concentration is reduced in overweight and obese subjects. This has been observed in different animal models of obesity, such as leptin-deficient ob/ob mice [7], leptin-resistant db/db mice [9], high fat diet-fed mice [9], as well as in obese humans [7,11]. In rhesus monkeys (Macaca mulatta), which spontaneously develop obesity and subsequently often progress to type 2 diabetes mellitus, plasma adiponectin declines at an early phase of obesity and remains decreased after the development of diabetes [22]. In addition, longitudinal changes in insulin sensitivity in individual animals are correlated with changes in plasma adiponectin. In humans, plasma adiponectin concentration negatively correlates with body mass index, percent body fat, waist/hip ratio, fasting insulin concentration [23] and plasma triglycerides [24], but positively with plasma cholesterol contained in high-density lipoproteins. Moreover, surgical treatment of morbid obesity by gastric partition surgery results in elevation of plasma adiponectin concentration, which is significantly correlated with body weight reduction as well as with the decrease in waist and hip circumferences [25]. Weight reduction achieved by low-calorie diet also increases plasma adiponectin both in nondiabetic and in diabetic patients [25]. In addition, the adiponectin level is lower in patients with impaired glucose tolerance or type 2 diabetes mellitus than in age and body mass index-matched subjects with normal glucose tolerance, and correlates negatively with plasma glucose measured at 2 hours in the oral glucose tolerance test [22,23]. The adiponectin mRNA level is lower in omental and, to a lesser extent, in subcutaneous adipose tissue of diabetic patients than in lean normoglycemic controls [26]. Because adiponectin possesses anti-inflammatory properties and improves glucose tolerance (see below), hypoadiponectinemia may contribute to the pathogenesis of atherosclerosis and type 2 diabetes mellitus, which are frequent complications of obesity. Interestingly, the diabetes-susceptibility locus has been mapped to human chromosome 3q27, where the adiponectin gene is located [27].

The mechanism whereby adiponectin secretion is reduced in obese subjects is not clear. Since adiponectin is stimulated by insulin and inhibited by TNF-α, insulin resistance and enhanced TNF-α expression may contribute to this effect. An interesting observation was recently made by Halleux et al. [13], who found that adiponectin expression decreased when visceral adipose tissue was isolated and cultured in vitro. This effect was reduced by decreasing the amount of tissue cultured per dish. In addition, the effect was prevented by inhibitors of transcription and translation. The authors suggest that increasing the mass of WAT induces the expression of an as-yet-unidentified protein which destabilizes adiponectin mRNA and thus reduces adiponectin protein synthesis.

**The effect of adiponectin on lipid and carbohydrate metabolism**

Adiponectin reduces the plasma concentration of fatty acids and triglycerides in mice models of obesity and hyperlipidemia [9]. The effect is mediated by accelerated fatty acid oxidation in muscle cells, which leads to decreased cellular triglyceride content [9,10]. Adiponectin increases expression of the proteins involved in fatty acid metabolism, such as acyl-CoA oxidase and uncoupling protein-2 (UCP-2), in skeletal muscles [9]. In contrast to muscle cells, adiponectin had no effect on fatty acid oxidation in cultured hepatocytes. The C-terminal fragment of adiponectin reduces the elevation of plasma free fatty acids and triglycerides induced by high fat/high sucrose meal in mice [10]. Adiponectin has no effect on intestinal absorption of fatty acids because it also ameliorates postprandial lipemia in animals receiving lipids intravenously rather than high-fat meal. Adiponectin also has no effect on adipose tissue hormone-sensitive lipase, indicating that reduction of plasma fatty acids results from accelerated tissue uptake rather than inhibition of lipolysis [10]. Adiponectin can improve fatty acid catabolism either directly or by stimulating the expression of peroxisome proliferator activated receptor-α, which regulates the enzymes involved in lipid metabolism [9].

Animal studies have demonstrated that adiponectin reduces hyperglycemia in different models of obesity/diabetes mellitus, such as high fat diet-fed C57 mice, leptin-resistant db/db mice, wild type KK mice and KK’ mice (mice made obese by overexpression of agouti protein) [9,28]. Because plasma insulin is reduced simultaneously with glucose, the hypoglycemic effect of adiponectin...
Adiponectin is not associated with stimulation of insulin secretion, but rather with increased insulin sensitivity. The C-terminal fragment of adiponectin reduces postprandial hyperglycemia in mice [10]. This effect is not accompanied by any changes in plasma insulin, glucagon and leptin levels. Several mechanisms may contribute to the insulin-sensitizing effect of adiponectin. First, increased fatty acid catabolism improves insulin sensitivity, since both circulating fatty acids and tissue triglycerides are involved in the pathogenesis of insulin resistance [29]. Secondly, it has been demonstrated that the C-terminal globular domain of adiponectin is much more effective in improving insulin sensitivity than the full-length peptide. This fragment markedly augments insulin-induced tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) and of protein kinase B (Akt kinase) in skeletal muscles [9]. Combs et al. [30] have observed that intravenous adiponectin infusion has no effect on glucose uptake by tissues, glycolysis and glycogen synthesis, but reduces hepatic glucose production by reducing the expression of enzymes involved in gluconeogenesis. Although the effect of adiponectin on TNF-α in adipose tissue has not yet been studied, this hormone suppresses both TNF-α secretion and signaling in macrophages/vascular endothelial cells. If the same is true for adipocytes, reduced activity of TNF-α could improve insulin sensitivity in this tissue. Thus, the insulin-sensitizing effect of adiponectin may result from four different mechanisms: 1) increased lipids oxidation, 2) direct inhibiting effect of adiponectin may result from four different mechanisms: 1) increased lipids oxidation, 2) direct binding of oxidized LDLs and their uptake by macrophages. By contrast, adiponectin specifically inhibits specific scavenger receptors class A type I, which are responsible for uptake of modified low-density lipoproteins (LDLs) by macrophages. These effects are not associated with inhibition of food intake. In contrast, adiponectin rather stimulates food intake, but simultaneously increases body temperature, suggesting a stimulatory effect on energy expenditure [9,10].

Adiponectin and atherosclerosis

Several studies have indicated that adiponectin possesses anti-inflammatory properties and thus may negatively modulate the process of atherogenesis. One of the initial steps in atherogenesis is adherence of monocytes to endothelial cells and their migration into subendothelial space, where they take up oxidized lipoproteins and transform them into foam cells. Adiponectin dose-dependently suppresses TNF-α-stimulated adherence of monocytes to cultured human endothelial cells. This effect results from inhibition of the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1). TNF-α increases, whereas adiponectin reduces the amount of these proteins and the respective mRNAs in endothelial cells [31]. The mechanism of adiponectin action in endothelial cells has been further investigated. TNF-α activates nuclear transcription factor NFkB in these cells by stimulating protein kinase NIK (NFkB inducing kinase), which phosphorylates the NFkB inhibitor, IκB, initiating its degradation and thus leading to NFkB activation. NFkB stimulates the expression of cytokines and adhesion molecules involved in the inflammatory process. Adiponectin inhibits TNF-α dependent phosphorylation and degradation of IκB. The effect of adiponectin is specific for the IκB-NFkB pathway, since no changes in the phosphorylation of other proteins induced by TNF-α have been observed. The inhibition of IκB phosphorylation is most likely mediated by the cAMP-protein kinase A pathway, because it is mimicked by the membrane-permeable cAMP analogue, dibutylr-cAMP, and blocked by inhibitors of either adenylyl cyclase or protein kinase A [19]. In addition, adiponectin decreases the cholesterol esters content in macrophages by about 50% and inhibits transformation of macrophages to foam cells in vitro. The effect is mediated by decreased expression of scavenger receptors class A type I, which are responsible for uptake of modified low-density lipoproteins (LDLs) by macrophages. By contrast, adiponectin has no effect on class B (CD36) scavenger receptor expression. In addition, adiponectin inhibits specific binding of oxidized LDLs and their uptake by macrophages [32]. Furthermore, adiponectin specifically inhibits proliferation of myelomonocytic bone marrow progenitor cells and induces their apoptosis by reducing the expression of the antiapoptotic gene Bcl-2 [20]. Adiponectin also inhibits proliferation of human peripheral blood monocytes, reduces their phagocytic activity, and inhibits TNF-α expression stimulated by lipopolysaccharide, but not by interleukin-1 or interleukin-6 [20]. Thus, adiponectin can suppress atherosclerosis by inhibiting the adherence of monocytes, reducing their phagocytic activity and decreasing the accumulation of modified lipoproteins in the vascular wall.

These data suggest that adiponectin deficiency associated with obesity and/or type 2 diabetes may contribute to accelerated atherosclerosis in these states. In support of this, the circulating adiponectin concentration has been found to be lower in patients with ischemic heart disease than in age- and body mass index-matched controls [31]. Similar results have been observed among patients with type 2 diabetes mellitus [22]. However, adiponectin is found in the subendothelial space of carotid arteries which injured by a catheter [33] and in atherosclerotic lesions with injured endothelium in human abdominal aorta [32]. Thus, it is also possible that the lower plasma adiponectin in these patients is secondary to accelerated degradation of the protein due to its accumulation in the vessel wall. A recently published first prospective study [21] has shown that low levels of adiponectin are related to subsequent cardiovascular events in hemodia-
lyzed patients. This study confirms that hypoadiponec-tinemia plays a causative role in atherogenesis, at least in patients with end-stage renal disease.

**RESISTIN**

**Structure, tissue distribution, and regulation of expression**

Resistin is a member of the newly-discovered family of cysteine-rich secretory proteins called 'resistin-like molecules' (RELM) or 'found in inflammatory zone' (FIZZ). The first member of the family, FIZZ1/RELMα, was identified as a 111-aminoacid protein in bronchoalveolar lavage fluid obtained from mice with ovalbumin-induced allergic pulmonary inflammation [34]. In control mice, FIZZ1/RELMα mRNA is found in the lung, where it is expressed in large airways in small discrete clusters of epithelial cells and in scattered non-neuronal cells adjacent to neurovascular bundles in peribronchial stroma, as evidenced by in situ hybridization and immunohistochemistry. During allergic pulmonary inflammation, FIZZ1/RELMα expression markedly increases with widespread uniform expression in the bronchial mucosal epithelial cells, and it also appears in type II alveolar pneumocytes, but not in alveolar bronchial mucosal epithelial cells, and it also appears in increases with widespread uniform expression in the heart, tongue, mediastinum, and skeletal muscles [34]. In the rat, resistin is expressed in white, and to a much lesser extent in brown adipose tissue, do not contain resistin mRNA [34]. In the rat, resistin is expressed in white, and to a much lesser extent in brown adipose tissue [36]. Unlike FIZZ1/RELMα, resistin is not expressed in rodent WAT, but most likely appear in different cell types. Resistin is secreted to the medium by cultured adipocytes and circulates in plasma in both rats and mice, indicating that it is indeed the secretory product of adipose tissue [37].

All resistin-like molecules contain 10 cysteine residues with identical spacing within the protein C-terminus. This is a unique feature of this new protein family. Both resistin and FIZZ2/RELMβ contain an additional 11th cysteine residue close to their N-termini. When expressed in heterologous cells, these two members of the family are secreted as disulphide-linked dimers connected with an intermolecular SS bond formed by these unpaired cysteines, whereas the remaining cysteine residues most likely form intramolecular bridges. By contrast, FIZZ1/RELMα is secreted as a monomer because it lacks this additional 11th cysteine [38].

The regulation of resistin expression is controversial. Some studies demonstrated that rosiglitazone, a PPARγ receptor agonist belonging to thiazolidinediones, inhibited resistin expression in cultured 3T3-L1 adipocytes [39], in isolated mature adipocytes in vitro [37] and in db/db mice in vivo [14]. These observations were not confirmed by Way et al. [40], who observed stimulation of resistin by PPARγ agonists in obese rodents. In contrast to resistin, FIZZ1/RELMα expression in WAT was not altered by rosiglitazone treatment in db/db mice [14]. Activators of PPARα receptors have no effect on resistin but stimulate FIZZ1/RELMα expression in adipose tissue of db/db mice [14]. The effect of insulin is also controversial. In 3T3-L1 adipocytes, insulin down-regulated resistin expression [39], whereas in vitro studies in obese Zucker rats [40] and in streptozotocin-induced diabetes in mice [36] showed a stimulatory effect of this hormone. Dexamethazone upregulates resistin expression in adipocytes, indicating an important role for glucocorticoids [39]. Selective β, adrenergic receptor agonists have no effect on resistin mRNA either in 3T3-L1 adipocytes in vivo [39], or in db/db mice in vivo [14]. In contrast, β, agonists stimulate FIZZ1/RELMα mRNA in the WAT of db/db mice [14]. Unlike specific β, agonists, a less specific β, agonist, isoproterenol, decreases resistin mRNA in 3T3-L1 adipocytes, an effect mimicked by an adenylate cyclase activator, forskolin, and blocked by a β-receptor antagonist, propranolol [41]. Plasma resistin concentration decreases following fasting and returns to normal level after refeeding [3,37].

**Resistin in obesity**

Initial studies have demonstrated that obesity induced by a high-fat diet, mutation of the leptin gene (ob/ob mouse) or leptin receptor gene (db/db mice), is associated with elevated circulating resistin concentrations. Intraperitoneally-administered resistin elevates blood glucose and insulin concentration in mice, and impairs hypoglycemic response to insulin infusion. In addition, anti-resistin antibodies decrease blood glucose and improve insulin sensitivity in obese mice [37]. Resistin suppresses insulin-stimulated glucose uptake in cultured 3T3-L1 adipocytes, and this effect is prevented by anti-resistin antibodies. These data suggest that resistin induces insulin resistance and that hyperresistinemia contributes to impaired insulin sensitivity in obese rodents [37]. The suppressive effect of thiazolidinediones on resistin secretion found in some studies may...
contribute to the insulin-sensitizing effect of this class of drugs. However, other data do not confirm these results. Way et al. [40], Moore et al. [14], and Iay et al. [42] have observed reduced resistin mRNA in WAT in different models of mouse obesity, such as dietary-induced obesity, o1b1 mice, db/db mice and KK' mice. In rats fed high-fructose diet, a model characterized by hyperinsulinemia, hyperglycemia, hypertriglyceridemia and hypertension, adipose tissue resistin expression is also decreased [43]. In addition, TNF-a, which is upregulated in obesity, suppresses resistin gene expression and protein secretion by 3T3-L1 adipocytes [44]. The level of FIZZ1/RELM mRNA was also reduced in WAT of db/db mice [14].

Studies in humans are even more controversial. Resistin mRNA is undetectable in WAT of lean subjects [45]. Although resistin transcript is found in the WAT of obese individuals, there is no correlation between body weight, adiposity and insulin resistance, and resistin mRNA level [45,46]. Resistin is expressed in stromovascular fraction of WAT and in peripheral blood monocytes [45,47], but its mRNA is not detectable in human fat cells even by very sensitive RT-PCR method, either in lean or in insulin resistant, obese and diabetic patients [47]. Species differences in cellular resistin distribution may be partially explained by recent observation that in humans, in contrast to rodents, resistin is highly expressed in cultured preadipocytes but barely detectable in mature fat cells [46]. Thus, the role of resistin and other members of the FIZZ/RELM family in humans remains to be established. These proteins may be involved in the regulation of cell proliferation and differentiation. Resistin has been found to inhibit adipocyte differentiation [36]. Recombinant FIZZ1/RELM inhibits the nerve growth factor (NGF)-mediated survival of rat embryonic dorsal root ganglion neurons and NGF-stimulated calcitonin gene-related peptide (CGRP) expression in adult neurons [54]. Given the expression of FIZZ1/RELM in inflammatory regions, and of resistin in inflammatory cells [45,47], another possibility is their involvement in chronic inflammatory reactions associated with obesity [48-50].

**Conclusions and Perspectives**

The identification of adiponectin and resistin as secretory products of white adipose tissue is intriguing from both theoretical and clinical points of view. Adiponectin is the first adipocytokine which is downregulated in obesity, and the mechanism of this negative regulation remains obscure. Resistin belongs to a newly-discovered protein family, with no homology to any previously-known proteins. The tissue-specific expression of three different RELM/FIZZ proteins suggests that their functions are divergent. The hypoglycemic effect of adiponectin helps us understand the mechanisms of insulin resistance and the action of insulin sensitizing drugs, thiazolidinediones. Hypoadiponectinemia probably contributes to the chronic inflammatory process associated with obesity, leading to endothelial dysfunction and atherosclerosis. Finally, adiponectin is a potentially promising hypoglycemic drug. Its advantages in comparison to insulin are: 1) its beneficial, reducing effect on body weight, 2) the inhibition of atherogenesis, and 3) the fact that the effect of adiponectin is not impaired in obesity. However, many issues require further study. Adiponectin and resistin receptors and their mechanisms of action have not been identified. The role of resistin in insulin resistance awaits elucidation. The clear picture initially created by data obtained in rodents [37] has been subsequently confused, particularly in human studies. Consequently, the etymology of the name ‘resistin’ has evolved from ‘hormone inducing insulin resistance’ to ‘resistant to definition of its function’ [51]. Finally, the effect of both hormones on other pathological processes involved in cardiovascular complications of obesity, especially on renal sodium handling, as well as vascular and myocardial hypertrophy, remains to be elucidated.

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