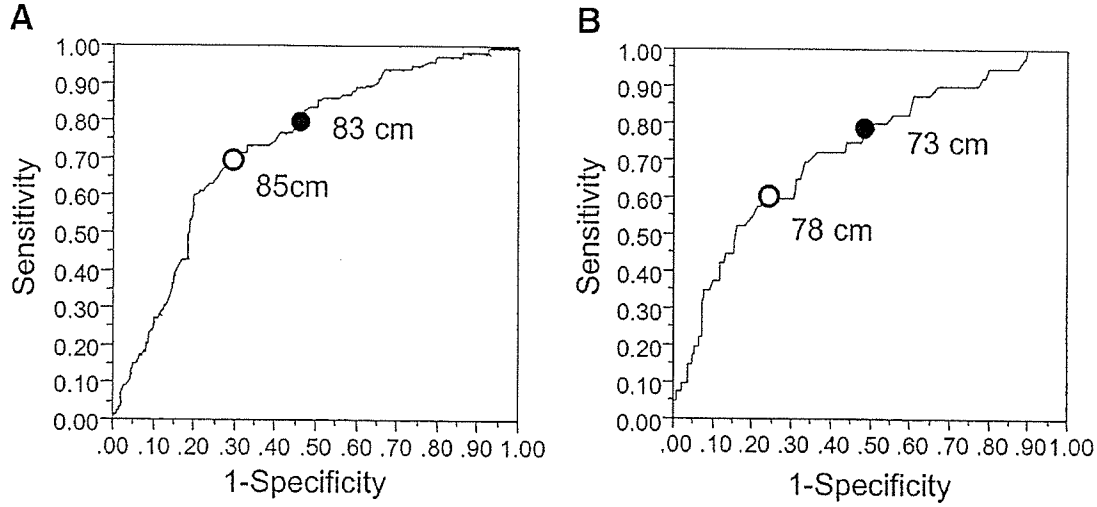

Figure 1—*The ROC curves for waist circumference to predict the presence of two or more risk factors of the metabolic syndrome, as defined by the NCEP III except for waist circumstance, in men (A) and women (B). O, cutoff waist circumference yielding the maximal sensitivity plus specificity for predicting the presence of multiple risk factors. ●, cutoff waist circumference yielding at least 80% sensitivity for predicting the presence of multiple risk factors.*

by the NCEP III was 43.9% in men and 34.5% in women. The prevalence of impaired fasting glucose was 24.8% in men and 10.9% in women. The prevalence of multiple risk factors was 28.7% in men and 14.1% in women.

We plotted the ROC curve to determine the cutoff values of waist circumference in relation to the detection of multiple risk factors for the Japanese population (Fig. 1). According to the ROC curve, the cutoff level yielding the maximal sensitivity plus specificity for predicting the presence of multiple risk factors was 85 cm in men and 78 cm in women. The sensitivity and specificity using these cutoff values were 70.9 and 69.8%, respectively, in men and 60.0 and 77.1%, respectively, in women. Alternatively, given that waist circumference criteria is used for the first screening of subjects as a prerequisite for the diagnosis of metabolic syndrome, setting a cutoff level to obtain a high sensitivity of at least 80% may be justified, even if it possibly considerably decreases specificity. According to the ROC curve in this study, an optimal cutoff value for waist circumference to detect multiple risk factors was 83 cm in men and 73 cm in women, with a corresponding specificity of 54.0 and 47.1%, respectively (Fig. 1).

CONCLUSIONS— In the present study, we proposed an optimal cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population: 85 cm in men and 78 cm in women, yielding the maximal sensitivity plus specificity, or 83 cm in men and 73 cm in women, yielding at least 80% sensitivity for predicting the presence of multiple risk factors. It apparently seems that the cutoff point of waist circumference described in the present study is much shorter than that recently proposed by the IDF, especially in women. However, it should be taken into consideration that there was a difference in the method of measuring waist circumference between this study and in the criteria outlined by the IDF; we measured waist circumference at the "mid" level and the IDF measured at the umbilical level. Waist circumference at the umbilical level is thought to be several centimeters longer than that measured at the "mid" level in women, whereas values measured at the "mid" and umbilical levels tend to be very similar in men. Thus, appropriate cutoff points for waist circumference at the umbilical level would be ~80 cm in women and ~85 cm in men. Further studies must be performed to elucidate the most suitable method of measuring waist circumference and its most appropriate cutoff point.

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Adiponectin and Adiponectin Receptors

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Metabolic syndrome is thought to result from obesity and obesity-linked insulin resistance. Obesity in adulthood is characterized by adipocyte hypertrophy. Adipose tissue participates in the regulation of energy homeostasis as an important endocrine organ that secretes a number of biologically active "adipokines."

Heterozygous peroxisome proliferator-activated receptor-γ knockout mice were protected from high-fat diet induced obesity, adipocyte hypertrophy, and insulin resistance. Systematic gene profiling analysis of these mice revealed that adiponectin/Acrp30 was overexpressed. Functional analyses including generation of adiponectin transgenic or knockout mice have revealed that adiponectin serves as an insulin-sensitizing adipokine. In fact, obesity-linked down-regulation of adiponectin was a mechanism whereby obesity could cause insulin resistance and diabetes.

Recently, we have cloned adiponectin receptors in the skeletal muscle (AdipoR1) and liver (AdipoR2), which appear to comprise a novel cell-surface receptor family. We showed that AdipoR1 and AdipoR2 serve as receptors for globular and full-length adiponectin and mediate increased AMP-activated protein kinase, peroxisome proliferator-activated receptor-α ligand activities, and glucose uptake and fatty-acid oxidation by adiponectin. Obesity decreased expression levels of AdipoR1/R2, thereby reducing adiponectin sensitivity, which finally leads to insulin resistance, the so-called "vicious cycle." Most recently, we showed that osmotin, which is a ligand for the yeast homolog of AdipoR (PHO36), activated AMPK via AdipoR in C2C12 myocytes. This may facilitate efficient development of adiponectin receptor agonists.

Adiponectin receptor agonists and adiponectin sensitizers should serve as versatile treatment strategies for obesity-linked diseases such as diabetes and metabolic syndrome. (*Endocrine Reviews* 26: 439–451, 2005)

Abbreviations: ACC, Acetyl-coenzyme-A carboxylase; AMPK, AMP-activated protein kinase; apoE, apolipoprotein E; EGF, epidermal growth factor; gAd, globular adiponectin; HF, high-fat; HMW, high molecular weight; PI, phosphatidylinositol; PPAR, peroxisome proliferator-activated receptor; PR, pathogenesis-related; siRNA, small interfering RNA; SNP, single nucleotide polymorphism; TG, triglyceride.

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I. Introduction

HIGH-FAT (HF) diet-induced insulin resistance associated with obesity is a major risk factor for diabetes and cardiovascular diseases, the prevalence of which is increasing sharply (1, 2). However, the molecular basis for this association remains to be elucidated. The adipose tissue itself serves as the site of triglyceride (TG) storage and free fatty acid/glycerol release in response to changing energy demands (1). Adipose tissue also participates in the regulation of energy homeostasis as an important endocrine organ that secretes a number of biologically active adipokines such as free fatty acid (3), adipsin (4), leptin (5), plasminogen activator inhibitor-1 (6), resistin (7), and TNF-α (8). Adiponectin is one such adipokine that has recently attracted much attention. In this review, we will describe recent progress made in adiponectin research with particular emphasis on the role of adiponectin in the regulation of insulin sensitivity and the development of insulin resistance. Other aspects of adiponectin research have been reviewed elsewhere (9–14).

II. Identification and Molecular Structure

A. Identification

Adiponectin was originally identified independently by four groups using different approaches. Mouse cDNAs for

adiponectin, termed Acrp30 (15) and AdipoQ (16), were cloned by differential display before and after differentiation of mouse 3T3-L1 and 3T3-F442A cells. Human adiponectin cDNA was isolated by large-scale random sequencing of a 3′-directed human adipose tissue cDNA library (17). Human adiponectin was also purified from plasma as a gelatin binding protein, GBP28 (18).

B. Molecular structure and multimeric form of adiponectin

Adiponectin structurally belongs to the complement 1q family (19–21) (Fig. 1) and is known to form a characteristic homomultimer (22) (Fig. 2). It has been demonstrated that simple SDS-PAGE under nonreducing and non-heat-denaturing conditions clearly separates multimeric species of adiponectin (23) (Fig. 2). Adiponectin in human or mouse serum and adiponectin expressed in NIH-3T3 cells or *Escherichia coli* forms a wide range of multimers from trimers and hexamers to high molecular weight (HMW) multimers (23) such as dodecamers and 18 mers, as demonstrated by ourselves and other groups (22, 24, 25) (Fig. 2).

Adiponectin can exist as full-length or a smaller, globular fragment; however, almost all adiponectin appears to exist as full-length adiponectin in plasma. Lodish's group reported that a small amount of globular adiponectin was detected in human plasma (26) (Fig. 1). It has been proposed that the globular fragment is generated by proteolytic cleavage, and recently it has been shown that the cleavage of adiponectin by leukocyte elastase secreted from activated monocytes and/or neutrophils could be responsible for the generation of the globular fragment of adiponectin (27). However, the pathophysiological importance of adiponectin cleavage by leukocyte elastase *in vivo* remains to be determined.

Oligomer formation of adiponectin depends on disulfide bond formation mediated by Cys-39 (28). Interestingly, a mutant adiponectin with a substitution of Cys by Ser at codon 39, which formed a trimer and readily underwent proteolytic cleavage, showed much more potent bioactivity, such as reduction of glucose output from primary hepatocytes, than wild-type adiponectin with a HMW.

Hydroxylation and glycosylation of the four lysines in the collagenous domain of adiponectin have been shown to play important roles in enhancing the ability of subphysiological concentrations of insulin to inhibit gluconeogenesis in hepatocytes (29). Adiponectin was reported to be an α2,8-linked disialic acid-containing glycoprotein, although the biological functions of the disialic acid epitope of adiponectin remain to be elucidated (30).

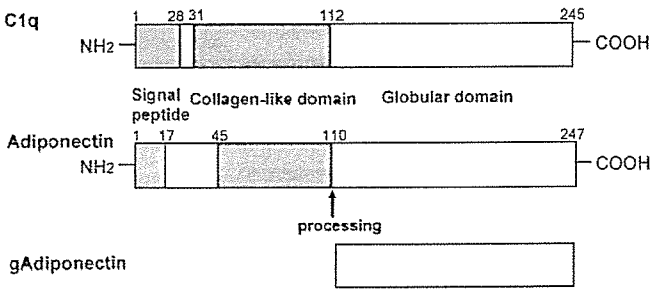

FIG. 1. Structure and domains of adiponectin. Adiponectin, also known as Acrp30, AdipoQ, and GBP28, was originally identified independently by four groups using different approaches (15–18). Adiponectin is composed of an N-terminal collagen-like sequence and a C-terminal globular region. A small amount of a processed globular form was reported to be present in human plasma (26).

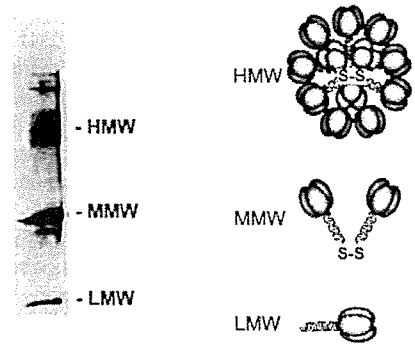

FIG. 2. Multimer formation of adiponectin. Human serum was subjected to SDS-PAGE under nonreducing, non-heat-denaturing conditions, and multimer forms of adiponectin were detected using antiadiponectin antibody (23). MMW, Medium molecular weight; LMW, low molecular weight; S–S, disulfide bridge.

III. Adiponectin and Insulin Resistance

A. Low plasma adiponectin levels and insulin resistance

Spiegelman's group reported that adiponectin expression is exclusive to adipose tissue and that the mRNA expression of adiponectin was reduced in obese diabetic murine model db/db mice (16). Plasma levels of adiponectin have also been reported to be significantly reduced in obese/diabetic mice and humans (16, 31, 32). Moreover, plasma adiponectin levels have been shown to be decreased in patients with cardiovascular diseases (33, 34), hypertension (35), or metabolic syndrome (36). Thus, reductions in plasma adiponectin levels are commonly observed in a variety of states frequently associated with insulin resistance. However, whether this apparent parallelism between low plasma adiponectin levels and insulin resistance represents a cause and effect relationship was not known.

B. Insulin-sensitizing effects of adiponectin

The insulin-sensitizing effect of adiponectin was first identified by three independent groups in 2001 (26, 31, 37). We previously generated heterozygous PPAR (peroxisome proliferator-activated receptor) γ knockout mice that remained insulin-sensitive on a HF diet (38). In an attempt to identify insulin-sensitizing molecules secreted from white adipose tissue of heterozygous PPARγ knockout mice, oligonucleotide microarray analysis was carried out using white adipose tissue (39). Adiponectin as well as leptin expression was up-regulated. Leptin was previously shown to be a major insulin-sensitizing adipokine (40).

To verify the direct insulin-sensitizing effect of adiponectin *in vivo*, an insulin-resistant lipoatrophic diabetic mouse model that displays both adiponectin and leptin deficiency was employed (41). Replenishment of a physiological dose of recombinant adiponectin to the lipoatrophic diabetic mice significantly ameliorated insulin resistance (31). Moreover,

insulin resistance in lipoatrophic mice was completely reversed by the combination of physiological doses of adiponectin and leptin, but only partially by either adiponectin or leptin alone (31). These data clearly indicate that adiponectin has a direct insulin-sensitizing action. These data also suggest that leptin and adiponectin may be the two major insulin-sensitizing hormones secreted from adipose tissue.

We also studied whether adiponectin can improve insulin resistance and diabetes in murine models of type 2 diabetes, characterized by obesity, insulin resistance, and hyperglycemia. Serum adiponectin levels were decreased in KKAy mice on a HF diet compared with those under a high-carbohydrate diet (31) (Fig. 3). Lower serum adiponectin levels in KKAy mice on the HF diet were partially restored by replenishment of recombinant adiponectin. Importantly, replenishment of adiponectin significantly ameliorated HF diet-induced insulin resistance and hypertriglyceridemia (31) (Fig. 3). These data suggest that the insulin resistance associated with HF diets and obesity is caused at least in part by the decreases in adiponectin linked to those circumstances. The data suggest that the fat-derived hormone adiponectin is decreased in obesity and deficient in lipoatrophy, and that reduction in adiponectin plays causal roles in the development of insulin resistance in these models.

Scherer's group has reported that an acute increase in circulating adiponectin levels triggers a transient decrease in basal glucose levels by inhibiting both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production in both wild-type mice and a type 2 diabetes mouse model (37, 42), consistent with the proposal that adiponectin sensitizes the body to insulin. Lodish's group reported that a proteolytic cleavage product of adiponectin increases fatty-acid oxidation in muscle and causes a decrease in plasma glucose and weight loss in mice (26).

These data raise the possibility that the replenishment of adiponectin may provide a novel treatment modality for insulin resistance and type 2 diabetes.

IV. Mouse Models

The chronic effects of adiponectin on insulin resistance *in vivo* were investigated by generating globular adiponectin transgenic mice (43, 44) or adiponectin-deficient mice (45–47). Globular adiponectin transgenic mice were generated and crossed with ob/ob mice (45). Globular adiponectin transgenic ob/ob mice showed partial amelioration of insulin resistance and diabetes, but not of obesity (43). These data suggested that chronic elevation of globular adiponectin has a direct insulin-sensitizing effect independent of white adipose tissue mass.

Scherer's group reported that transgenic mice with a deletion in the collagenous domain of adiponectin displayed 3-fold elevated levels of circulating adiponectin, raised lipid clearance and lipoprotein lipase activity, and improved insulin-mediated suppression of endogenous glucose production, thereby improving insulin sensitivity (44). In rats, sustained peripheral expression of adiponectin by the transgene also offset the development of diet-induced obesity (48).

Globular adiponectin transgenic mice were also crossed with apolipoprotein E (apoE)-deficient mice to study whether globular adiponectin can inhibit atherosclerosis *in vivo* (43). apoE-Deficient mice are hypercholesterolemic and spontaneously develop severe atherosclerosis. We compared the extent of atherosclerotic lesions of globular adiponectin transgenic apoE-deficient mice to that in control apoE-deficient mice. Although serum parameters such as total cholesterol, TG, glucose, and insulin were not altered, the *en face* Sudan IV-positive lesion areas of the arch and the descending aorta were significantly smaller in globular adiponectin transgenic apoE-deficient mice than in control apoE-deficient littermates (43). Similar results were obtained by using adenoviral-mediated overexpression of adiponectin in apoE knockout mice (49). Thus, overexpression of adiponectin resulted in marked reduction of atherosclerotic lesion formation. Together with the observations that adiponectin can ameliorate diabetes and hyperlipidemia, adiponectin can re-

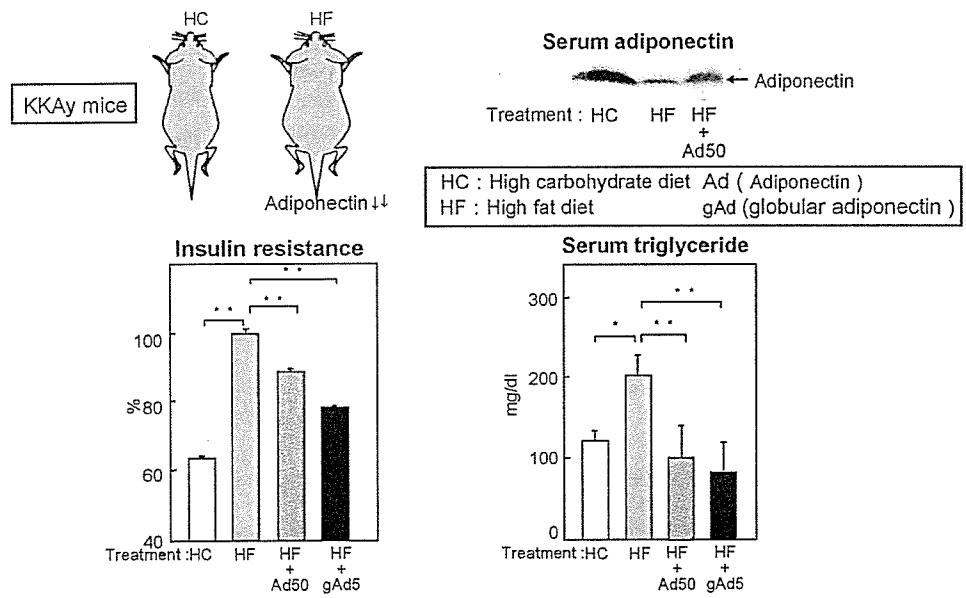

FIG. 3. Replenishment of adiponectin reversed insulin resistance and metabolic syndrome in a murine model of type 2 diabetes. Serum adiponectin levels were decreased in mice on a HF diet compared with those in mice on a high-carbohydrate (HC) diet. Lower serum adiponectin levels in mice on the HF diet were partially restored compared with those in mice on the HC diet by replenishment of recombinant adiponectin, which significantly ameliorated HF diet-induced insulin resistance. *, $P < 0.05$; **, $P < 0.01$, between the two groups indicated.

duce atherosclerosis both via direct effects on vascular wall and via reduction in risk factors.

To determine the physiological role of adiponectin, we and others have generated adiponectin knockout mice and reported that adiponectin-deficient mice exhibited characteristics of the metabolic syndrome such as insulin resistance, glucose intolerance, hyperlipidemia, and hypertension (35, 45, 46).

We and others also studied the role of adiponectin in vascular wall using adiponectin knockout mice (45, 50). We placed a cuff around the femoral artery to induce inflammation of the adventitia and subsequent neointimal formation 2 wk after cuff placement. Intimal thickness was significantly greater (2-fold) in adiponectin knockout mice than in the wild-type mice. Thus, adiponectin plays a protective role against neointimal formation in response to injury (45, 50).

V. Mechanism of Action of Adiponectin

A. *Insulin-sensitizing actions*

1. Adiponectin reduces tissue TG content and up-regulates insulin signaling. Interestingly, in skeletal muscle, adiponectin increased expression of molecules involved in fatty-acid transport such as CD36, in combustion of fatty-acid such as acyl-coenzyme A oxidase, and in energy dissipation such as uncoupling protein 2. These changes led to decreased tissue TG content in skeletal muscle (31).

Increased tissue TG content has been reported to interfere with insulin-stimulated phosphatidylinositol (PI) 3-kinase activation and subsequent glucose transporter 4 translocation and glucose uptake, leading to insulin resistance (3). Thus, decreased tissue TG content in muscle may contribute to improved insulin signal transduction. This was demonstrated in skeletal muscle of lipoatrophic mice treated with adiponectin, in which increases in insulin-induced tyrosine phosphorylation of insulin receptor and insulin receptor substrate-1 and insulin-stimulated phosphorylation of Akt were seen (31).

2. Adiponectin activates PPARα. Based on the data that treatment of lipoatrophic or obese diabetic mice with adiponectin or overexpression of adiponectin in ob/ob mice resulted in increased expression levels of PPARα target genes such as CD36, acyl-coenzyme A oxidase, and uncoupling protein 2, we hypothesized that adiponectin could activate PPARα (31) (Fig. 4).

Consistent with this hypothesis, adiponectin indeed increased the expression levels of PPARα *in vivo* (31). These data suggested that adiponectin increased fatty-acid combustion and energy consumption, presumably via PPARα activation at least in part, which led to decreased TG content in the liver and skeletal muscle and thus coordinately increased *in vivo* insulin sensitivity.

Endogenous PPARα ligand activities were measured *in vitro* to further clarify the mechanisms by which adiponectin activated PPARα (31, 43). Interestingly, the treatment of C2C12 myocytes with adiponectin for 6 h significantly increased PPARα ligand activities (43) and at the same time fatty-acid oxidation *in vitro*.

3. Adiponectin activates AMP kinase. We next examined the effects of treatment of adiponectin for a shorter time period

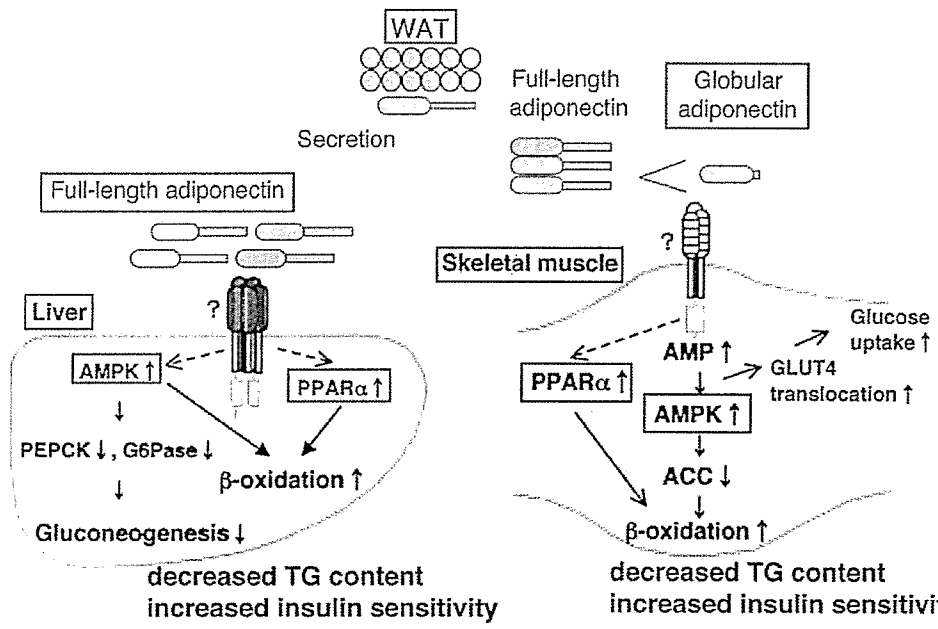

FIG. 4. Adiponectin can activate AMPK and PPARα in the liver and skeletal muscle. In skeletal muscle, both globular and full-length adiponectin activate AMPK, thereby stimulating phosphorylation of ACC, fatty-acid oxidation, and glucose uptake. Adiponectin activates PPARα, thereby also stimulating fatty-acid oxidation and decreasing tissue TG content in muscle. In the liver, only full-length adiponectin activates AMPK, thereby reducing molecules involved in gluconeogenesis and increasing phosphorylation of ACC and fatty-acid oxidation. Adiponectin activates PPARα, thereby stimulating fatty-acid oxidation and decreasing tissue TG content in the liver. These alterations all increase insulin sensitivity *in vivo* (101). WAT, White adipose tissue; PEPCK, phosphoenolpyruvate carboxykinase; G6Pase, glucose-6-phosphatase G6Pase.

(51). Treatment of C2C12 myocytes with adiponectin for 1 h stimulated fatty-acid oxidation. Although actinomycin D had no effect on the increase in fatty-acid oxidation stimulated by adiponectin for 1 h, it suppressed fatty-acid oxidation stimulated by the PPARα agonist Wy-14,643. Moreover, treatment of C2C12 myocytes for 1 h stimulated glucose uptake. We hypothesized that adiponectin may stimulate β-oxidation and glucose uptake via AMP-activated protein kinase (AMPK) during a period shorter than 6 h (51).

Globular adiponectin and full-length adiponectin stimulated phosphorylation and activation of AMPK in skeletal muscle, whereas only full-length adiponectin did so in the liver (51). In parallel with its activation of AMPK, adiponectin stimulated phosphorylation of acetyl coenzyme-A carboxylase (ACC), fatty-acid combustion, glucose uptake, and lactate production in myocytes, and also stimulated phosphorylation of ACC and caused a reduction in molecules involved in gluconeogenesis in the liver, which can account for the acute glucose-lowering effects of adiponectin *in vivo* (51). Blocking AMPK activation by use of a dominant negative mutant inhibited each of these effects, indicating that stimulation of glucose utilization and fatty-acid combustion by adiponectin occurs through activation of AMPK. Our data may provide a novel paradigm that an adipocyte-derived hormone activates AMPK, thereby directly regulating glucose metabolism and insulin sensitivity *in vitro* and *in vivo* (51) (Fig. 4).

The group of Lodish and Ruderman also showed that the adiponectin/ACRP30 globular domain enhanced muscle fat oxidation and glucose transport via AMPK activation and ACC inhibition (52). More recently, AMPK was reported to be involved in glucose uptake stimulated by the globular domain of adiponectin in primary rat adipocytes (53). Because leptin has also been shown to stimulate AMPK in skeletal muscle (54), activation of AMPK may be a common mechanism by which insulin-sensitizing adipokines such as adiponectin and leptin increase insulin sensitivity.

Scherer's group also reported that in adiponectin transgenic mice, reduced expression of gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase was associated with elevated phosphorylation of AMPK in liver (44). The same group reported that adiponectin is found as two forms in serum, as a lower molecular weight trimer-dimer and a HMW complex (28). Female subjects display significantly higher levels of the HMW complex in serum than do male subjects (23, 28, 55–57). Levels of the HMW complex appeared to be negatively regulated by insulin. In accordance with this, the amount of HMW adiponectin complex, but not the total amount of adiponectin, was recently reported to be correlated with a thiazolidinedione-mediated improvement in insulin sensitivity (55).

B. Antiatherosclerotic actions

Adiponectin has been reported to have direct antiatherosclerotic effects (58–67). Adiponectin was demonstrated to strongly inhibit the expression of adhesion molecules, including intracellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin (Fig. 5). Adiponectin was also shown to inhibit TNF-α-induced nuclear factor-κB activation through the inhibition of IκB phosphorylation (61). Suppression of nuclear factor-κB by adiponectin might be a major molecular mechanism for the inhibition of monocyte adhesion to endothelial cells (62). Adiponectin also inhibits the expression of the scavenger receptor class A-1 of macrophages, resulting in markedly decreased uptake of oxidized low-density lipoprotein by macrophages and inhibition of foam cell formation (63). In addition, in cultured smooth muscle cells, adiponectin attenuated DNA synthesis

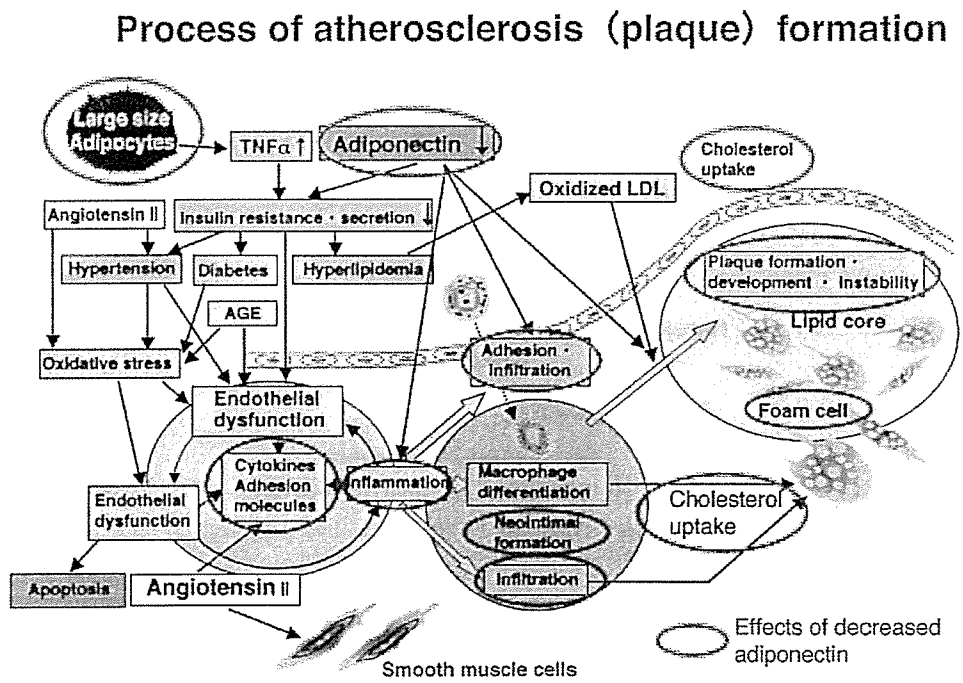

FIG. 5. Suppression of atherosclerosis by adiponectin. Adiponectin inhibits atherosclerosis and plaque formation at least via suppression of two processes: 1) suppression of neointimal formation by inhibiting the expressions of inflammatory cytokines and adhesion molecules; and 2) suppression of uptake of cholesterol by inhibiting the expression of scavenger receptors. LDL, Low-density lipoprotein.

induced by growth factors including platelet-derived growth factor, heparin-binding epidermal growth factor (EGF)-like growth factor, basic fibroblast growth factor, and EGF, as well as cell proliferation and migration induced by heparin-binding EGF-like growth factor (64). This inhibition was shown to be attributable to the inhibition of signal transduction through ERK. More recently, selective suppression of endothelial cell apoptosis via AMPK activation by the HMW form of adiponectin has been reported (65).

VI. Alterations in Adiponectin Gene Are Associated with Human Diabetes

Independent of these functional analyses carried out *in vitro* and in animal models, data from human genetic studies on adiponectin also support the role of adiponectin as a determinant of susceptibility to insulin resistance and type 2 diabetes. By use of affected sib-pair analysis, complete genome mapping of type 2 diabetes genes in Japanese was performed (68). The genome scans revealed at least nine chromosomal regions linked to type 2 diabetes in Japanese people. Among these, three chromosomal regions (3q, 15q, and 20q) are the same regions as previously reported in other ethnic groups. Among these three chromosomal regions, interestingly, the 3q27 chromosomal region contains the adiponectin gene.

We screened for the adiponectin gene and identified 10 relatively common single nucleotide polymorphisms (SNPs) in the Japanese population (Fig. 6). One such SNP, SNP 276 in intron 2 (G *vs.* T), showed interesting phenotypes with respect to plasma adiponectin levels, insulin resistance, and susceptibility to type 2 diabetes (69) (Fig. 7). Subjects with the G/G genotype had lower plasma adiponectin levels than those with the T/T genotype. Subjects with the G/G genotype at position 276 had a higher insulin resistance index than those with T/T. Importantly, subjects with the G/G genotype at position 276 were at increased risk for type 2 diabetes. The odds ratio was slightly greater than 2 (69) (Fig. 8). Similar associations for the adiponectin gene with susceptibility to type 2 diabetes have also been reported in other ethnic groups (70–72). In German and American Caucasians, the SNP 276, either independently or as a haplotype together with SNP 45 in exon 2, was shown to be associated with obesity and insulin resistance (71, 72). In French Caucasians, two SNPs in the promoter region of the adiponectin gene, SNP-11377 and SNP-11391, were significantly associated with hypoadiponectinemia and type 2 diabetes (70). Taken together, these data strongly support the hypothesis that adiponectin plays a pivotal role in the pathogenesis of type 2 diabetes.

Several cross-sectional studies have reported that adiponectin levels were decreased in subjects with type 2 diabetes and are inversely correlated with insulin resistance. However, no studies had investigated whether adiponectin protects subjects from diabetes or the extent of risk of developing diabetes in subjects with hypoadiponectinemia. Recently, matched case-control studies in subjects recruited from a large cohort have examined the protective effect of adiponectin against diabetes. One study was performed in severely obese Pima Indian subjects, who have the highest known prevalence of obesity and type 2 diabetes in the world, to assess the role of adiponectin independent of the effects of obesity (73). Subjects with high concentrations of adiponectin were 40% less likely to develop type 2 diabetes than those with low concentrations after adjustment for body mass index (BMI), indicating that adiponectin could be used as a predictor of future development of type 2 diabetes in addition to the established risk parameters, such as BMI.

In addition to the relatively common SNPs, eight mutations in the human adiponectin gene have been reported (69, 74, 75), some of which were significantly related to diabetes and hypoadiponectinemia (23, 75). Among human adiponectin mutations, Arg112Cys and Ile164Thr mutants did not assemble into trimers, which caused impaired secretion from the cell (23). These mutants are clinically associated with hypoadiponectinemia. The Gly84Arg and Gly90Ser mutants were able to assemble into trimers and hexamers but were unable to form HMW multimers (the HMW multimers are thought to be larger than heximers), which are clinically associated with diabetes. These data raised the possibility that HMW multimers have more potent insulin-sensitizing effects than trimers and hexamers (23).

These data suggest that impaired multimerization of adiponectin may be among the causes of a diabetic phenotype or hypoadiponectinemia in subjects having these mutations. Thus, not only the total concentrations but also the multimer distribution should always be considered when interpreting plasma adiponectin levels in health as well as various disease states (23–25).

VII. Cloning of Adiponectin Receptors AdipoR1 and AdipoR2

We believe that cloning of the adiponectin receptor should facilitate studies on the regulation of glucose and lipid me-

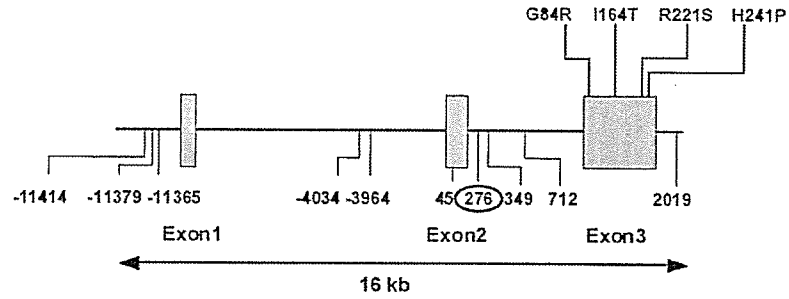

FIG. 6. Schema of genomic structure and polymorphic variants of the adiponectin gene. Exon-intron organization of the gene is indicated by *closed boxes*. *Arrows* show the positions of the polymorphic variants identified. *Numbers* indicate locations relative to the A of the ATG of the initiator Met of the adiponectin gene. Rare mutations with amino acid substitutions are also described (23, 70, 75).

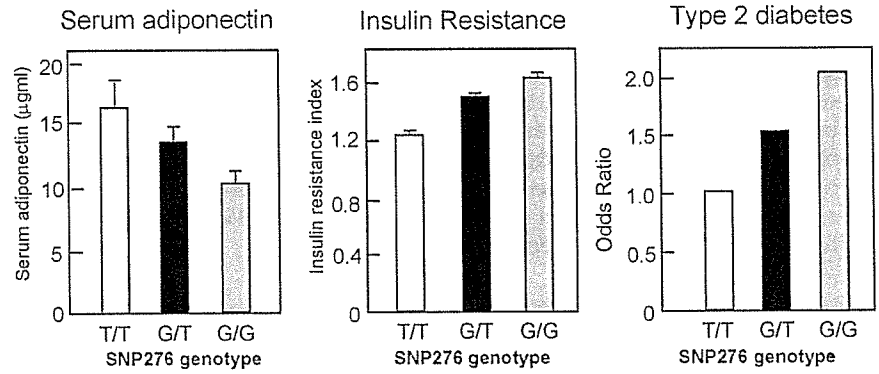

FIG. 7. Effects of SNP 276 in intron 2 of the adiponectin gene on serum adiponectin, insulin resistance, and susceptibility to type 2 diabetes. The effects of SNP 276 in intron 2 on plasma adiponectin levels, insulin resistance, and susceptibility to type 2 diabetes were studied. On the *left*, subjects with the G/G genotype had lower plasma adiponectin levels than those with the T/T genotype. In the *middle*, subjects with the G/G genotype at position 276 had a higher insulin resistance index than those with T/T. Importantly, on the *right*, subjects with the G/G genotype at position 276 were at increased risk for type 2 diabetes. The odds ratio was slightly greater than 2.

tabolism, the molecular causes of diabetes and atherosclerosis, and the development of antidiabetic and antiatherosclerotic drugs. We isolated cDNA for adiponectin receptors (AdipoR) that mediate the antidiabetic effects from human skeletal muscle cDNA library by screening for globular adiponectin binding (76).

The cDNA analyzed encoded a protein designated human AdipoR1 (Fig. 8) (76). This protein is conserved from yeast to man (especially in the seven transmembrane domains). Interestingly, this yeast homolog YOL002c plays a key role in metabolic pathways that regulate lipid metabolism such as fatty-acid oxidation (77).

Because there may be two distinct adiponectin receptors, we searched for a homologous gene in the human and mouse databases. We found only one gene that was significantly homologous (67% identity in amino acids) to AdipoR1, which was termed AdipoR2 (Fig. 8) (76). AdipoR1 was ubiquitously expressed and most abundantly expressed in skeletal muscle, whereas AdipoR2 was most abundantly expressed in mouse liver. It was reported that adiponectin receptors were expressed in pancreatic β-cells, and that fatty acids may regulate their expression levels (78). GH is reported to be a positive regulator of AdipoR2 in 3T3-L1 adipocytes (79).

AdipoR1 and AdipoR2 appeared to be integral membrane proteins; the N terminus was internal, and the C terminus was external, which is opposite to the topology of all other reported G protein-coupled receptors (Fig. 8) (76). AdipoR1 and AdipoR2 may form both homo- and heteromultimers. Scatchard plot analysis revealed that AdipoR1 is a receptor for globular adiponectin, whereas AdipoR2 is a receptor for full-length adiponectin (76). Suppression of AdipoR1 with small interfering RNA (siRNA) reduced the increase in fatty-acid oxidation by globular adiponectin. Suppression of AdipoR2 with siRNA reduced the increase in fatty-acid oxidation by full-length adiponectin (Fig. 9) (76).

Thus, we have isolated cDNA-encoding adiponectin receptors (AdipoR1 and R2). Expression of AdipoR1/R2 or suppression of AdipoR1/R2 supports our conclusion that AdipoR1 and R2 serve as receptors for globular and full-length adiponectin and mediate increased AMPK, PPARα ligand activities and fatty-acid oxidation and glucose uptake by adiponectin (Fig. 9) (57).

Lodish's group reported that T-cadherin was capable of binding adiponectin in C2C12 myoblasts, but not in the liver or hepatocytes (80).

VIII. Regulation of Adiponectin Receptors

A. Regulation of expression levels of AdipoR1 and AdipoR2

We first examined whether the expressions of AdipoR1 and/or AdipoR2 were regulated under physiological and/or pathophysiological states (81). The levels of AdipoR1 and AdipoR2 mRNA expression in the liver and skeletal muscle increased after fasting, and refeeding rapidly restored these to levels equal to the original fed state. AdipoR1 and AdipoR2 mRNA increased significantly in skeletal muscle of

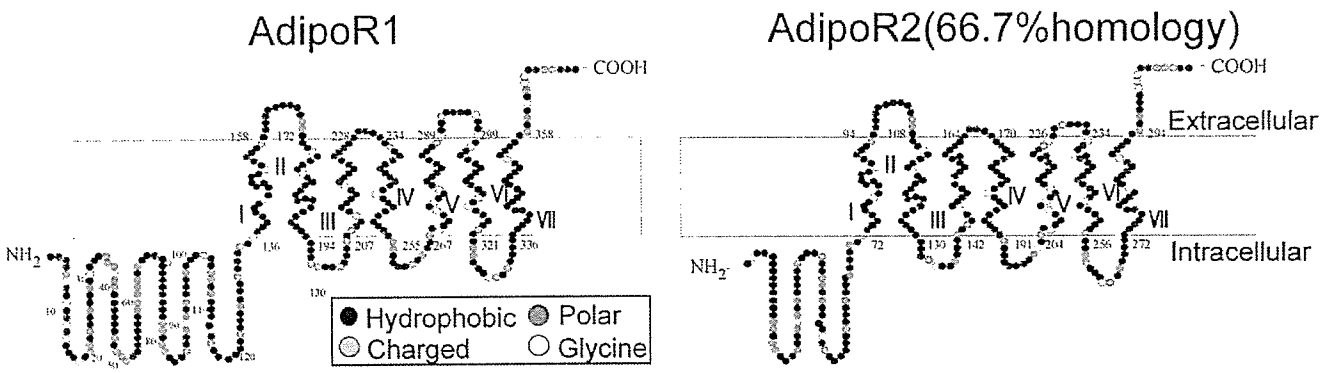

FIG. 8. Proposed structure of adiponectin receptors and their expression in various tissues. cDNA encoding adiponectin receptors (AdipoR1 and R2) were isolated. AdipoR1 was ubiquitously expressed and most abundantly expressed in skeletal muscle, whereas AdipoR2 was most abundantly expressed in mouse liver (76).

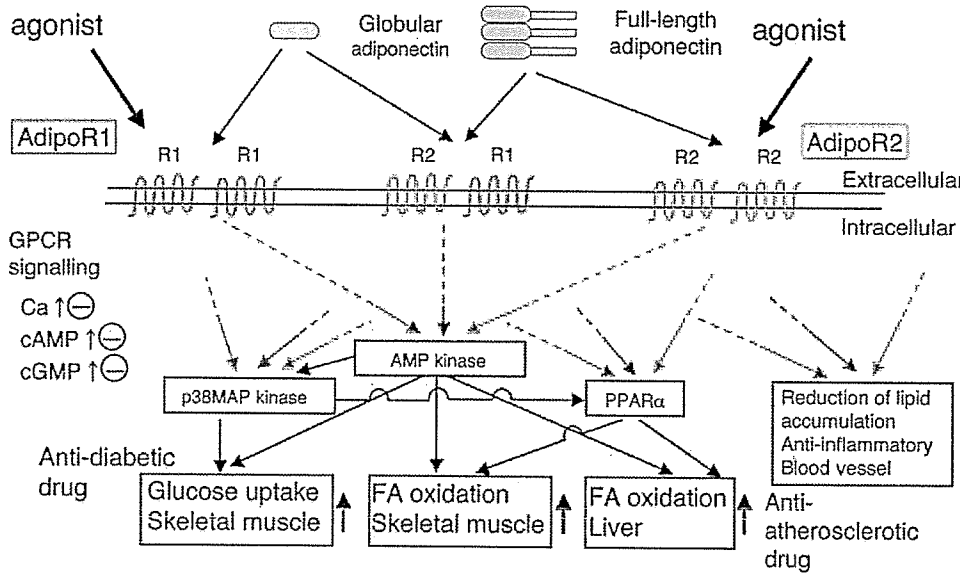

FIG. 9. Molecular mechanisms of adiponectin action. cDNA encoding adiponectin receptors (AdipoR1 and R2) was isolated. Expression of AdipoR1/R2 or suppression of AdipoR1/R2 supports the conclusion that AdipoR1 and R2 serve as receptors for globular and full-length adiponectin and mediate increased AMPK, PPARα ligand activities, and fatty-acid oxidation and glucose uptake by adiponectin. Molecular cloning of AdipoR1 and R2 should facilitate the designing of novel antidiabetic and antiatherogenic drugs with AdipoR1 and R2 as molecular targets (76, 101). FA, Fatty acid; GPCR, G protein-coupled receptor.

mice rendered hypoinsulinemic/hyperglycemic with streptozotocin, and both AdipoR1 and AdipoR2 mRNA were almost completely restored by insulin treatment. These observations suggested that insulin may negatively regulate AdipoR1/R2 mRNA levels (81). The PI3-kinase inhibitor LY 294002 and constitutively active form of Foxo (Forkhead box, class O) 1 revealed that insulin repressed AdipoR1/R2 mRNA expressions via activation of PI3-kinase and inactivation of Foxo1 (81).

The expressions of both AdipoR1 and AdipoR2 were significantly decreased in muscle and adipose tissue of insulin-resistant ob/ob mice, which exhibited hyperglycemia and hyperinsulinemia, as compared with control mice (81) (Fig. 10). Scatchard plot analysis revealed that both high-affinity and low-affinity binding sites for globular adiponectin (gAd) and adiponectin binding in skeletal muscles of ob/ob mice were reduced as compared with those of wild-type mice, findings that are consistent with the fact that the numbers of both AdipoR1 and AdipoR2 were reduced. Moreover, adiponectin-induced activation of AMPK was impaired in skeletal muscle of ob/ob mice. These data suggest that adiponectin resistance was observed in ob/ob mice, which exhibited decreased expression levels of AdipoR1 and AdipoR2 (81) (Fig. 10).

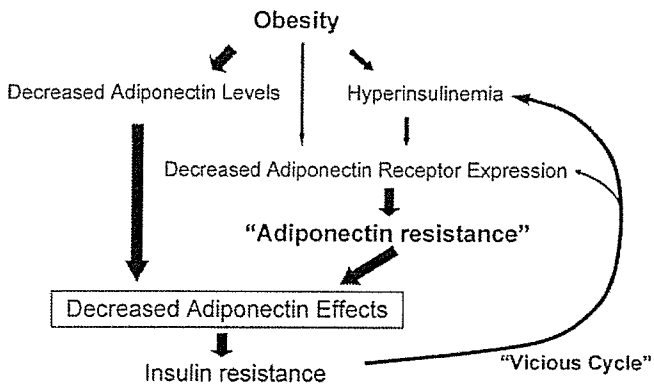

FIG. 10. Obesity, adiponectin resistance, and insulin resistance. Plasma adiponectin levels were decreased in obesity, which may play causal roles in the development of insulin resistance. The expression levels of AdipoR1/R2 were also decreased in obesity. Obesity decreased expression levels of AdipoR1/R2, thereby reducing adiponectin sensitivity, which finally led to insulin resistance, the so-called "vicious cycle". These data also suggest that not only agonism of AdipoR1/R2 but also strategies to increase AdipoR1/R2 may be a logical approach to provide a novel treatment modality for insulin resistance and type 2 diabetes (81).

We and others have previously shown that plasma adiponectin levels were decreased in obesity. This reduction may play a causal role in the development of insulin resistance. In the same study, we have also shown that obesity decreased the expression levels of AdipoR1/R2, thereby reducing adiponectin sensitivity, which finally leads to insulin resistance, the so-called "vicious cycle" (61) (Fig. 10).

A correlation has been reported between adiponectin receptor gene expression and insulin sensitivity in nondiabetic Mexican Americans with or without a family history of type 2 diabetes (82). Adiponectin receptor expression in skeletal muscle of type 2 diabetic patients was also reported to be decreased (83).

Our data suggest that not only agonism of AdipoR1/R2 but also strategies to increase AdipoR1/R2 may be a logical approach with which to provide a novel treatment modality for insulin resistance and type 2 diabetes.

IX. Adiponectin Hypothesis

Based upon the significant body of evidence discussed in this review, obtained from our and other laboratories, we propose the following adiponectin hypothesis (Fig. 11). Reduced adiponectin levels were caused by interactions of genetic factors such as SNPs in the adiponectin gene itself and environmental factors causing obesity such as a HF diet. Reduced adiponectin actions also resulted from down-regulation of adiponectin receptors linked to obesity. These reductions of adiponectin actions may play a crucial causal role in the development of insulin resistance, type 2 diabetes, metabolic syndrome, and atherosclerosis (Fig. 11).

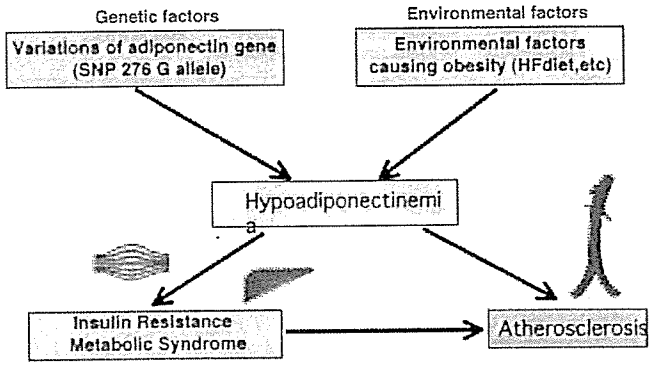

FIG. 11. Adiponectin hypothesis for insulin resistance, metabolic syndrome, and atherosclerosis. Reduced adiponectin levels can be caused by genetic factors such as SNP 276 in the adiponectin gene itself. Reduced adiponectin levels can also be caused by lifestyle changes causing obesity such as a HF diet. Both functional and genetic studies on adiponectin strongly suggest that reduced adiponectin levels play a causal role in the development of insulin resistance, type 2 diabetes, and atherosclerosis (101).

X. Adiponectin and Adiponectin Receptors as Therapeutic Targets

According to our adiponectin hypothesis, a therapeutic strategy for type 2 diabetes, metabolic syndrome, and cardiovascular diseases may include the up-regulation of plasma adiponectin, up-regulation of adiponectin receptors, or the development of AdipoRs agonists.

A. Up-regulation of plasma adiponectin

Insulin sensitizer PPARγ agonists have been shown to increase adiponectin levels in mice (31) and humans (84), as well as in 3T3L1 adipocytes *in vitro* (31). These effects seem to be associated with small-sized adipocytes (39), adipocytes differentiation (85, 86), direct transcriptional activation of genes via peroxisome proliferator response element (87–91), and increased insulin action (92). Interestingly, both PPARγ agonists and adiponectin have been shown to increase insulin sensitivity and ameliorate atherosclerosis. To test whether the PPARγ agonist-mediated improvement in insulin sensitivity and/or amelioration of atherosclerosis was dependent on adiponectin is very important, and thus it is very interesting to see the effects of PPARγ agonists in adiponectin knockout mice.

B. Up-regulation of adiponectin receptors and development of AdipoRs agonists

The evidence described in this review indicates that reductions in plasma adiponectin levels and adiponectin receptors may play major roles in the development of insulin resistance, type 2 diabetes, metabolic syndrome, and cardiovascular diseases that are linked to obesity. With this in mind, one therapeutic strategy may be to up-regulate plasma adiponectin levels, which has already been discussed. The other strategy may be to up-regulate adiponectin receptors or to stimulate adiponectin receptors using small molecule agonists. We would like to introduce two interesting examples of attempts to develop such drugs.

Dr. Staels' group reported that adiponectin receptors are expressed in human macrophages and that their expression levels may be regulated by agonists of the nuclear receptors PPARα, PPARγ, and liver X receptor (93).

Osmotin is a pathogenesis-related (PR)-5 family of plant defense proteins that induces apoptosis in the yeast. Dr. Bressan's group at Purdue University isolated and selected yeast clones that exhibited hypersensitivity to osmotin, sequenced their cDNA inserts, and found that PHO36/YOL002c, the yeast homolog of AdipoR, is a receptor for osmotin (94) (Fig. 12).

X-ray crystallographic studies revealed that both globular adiponectin and osmotin consist of antiparallel β-strands arranged in the shape of a β-barrel. The domain I (lectin-like domain) of osmotin can be overlapped with adiponectin, suggesting that the two proteins share the lectin-like domain (94) (Fig. 12).

Interestingly, osmotin could activate AMP kinase in C2C12 myocytes. More importantly, suppression of AdipoRs expression by siRNA markedly reduced phosphorylation of AMP kinase induced by osmotin. These data suggest that osmotin activates AMP kinase via AdipoRs in mammalian C2C12 myocytes (94).

Osmotin is a member of a large PR-5 protein family, which is both ubiquitous (fruits and vegetables, *etc.*) and diverse. PR-5 proteins are also extremely stable and may remain active even when in contact with the human digestive or respiratory systems. Osmotin, which is a ligand for the yeast homolog of AdipoR (PHO36), activates AMP kinase via AdipoR in C2C12 myocytes. These data raise the possibility that further research examining similarities in adiponectin and

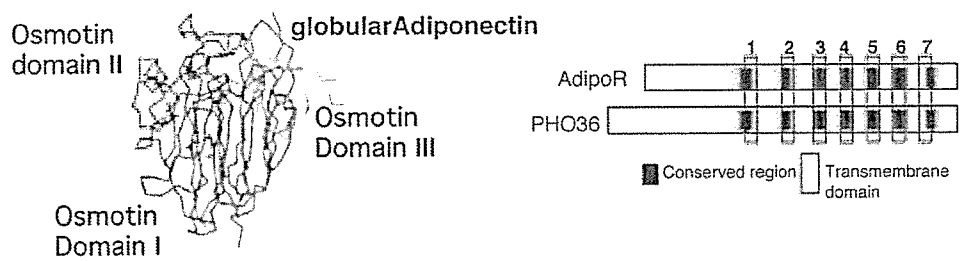

FIG. 12. Osmotin, which is a ligand for the yeast homolog of AdipoR (PHO36), activates AMP kinase via AdipoR in C2C12 myocytes. Osmotin is a member of a large PR-5 protein family, which is both ubiquitous (fruits and vegetables, *etc.*) and diverse. PR-5 proteins are also extremely stable and may remain active even when in contact with the human digestive or respiratory systems. These facts raise the possibility that further research examining similarities in adiponectin and osmotin may facilitate the development of potential adiponectin receptor agonists (94).

osmotin may facilitate the development of potential adiponectin receptor agonists (94).

C. Pleiotropic effects of adiponectin in relation to metabolic syndrome

In this review, we have stated that adiponectin increases insulin sensitivity in the liver and skeletal muscle and that adiponectin also reduces atherosclerosis. In addition to these effects, adiponectin also seems to have pleiotropic effects, particularly in relation to metabolic syndrome. Obesity has been reported to be associated with a higher incidence of certain cancers. Recently, adiponectin was reported to induce antiangiogenesis and antitumor activity via caspase-mediated endothelial cell apoptosis (95). Moreover, fatty liver and/or liver fibrosis are often associated with metabolic syndrome. Adiponectin was reported to alleviate alcoholic and nonalcoholic fatty liver diseases (96, 97) and liver fibrosis (98) in mice. Furthermore, it is possible that adiponectin stimulates insulin secretion and/or regulates energy homeostasis (99, 100). Further studies will be needed to determine the physiological and pathophysiological roles of AdipoR1 and AdipoR2 in these actions.

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