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Nuclear Receptors as Targets for Drug Development: Molecular Mechanisms for Regulation of Obesity and Insulin Resistance by Peroxisome Proliferator-Activated Receptor γ, CREB-Binding Protein, and Adiponectin

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Abstract. Obesity is defined as increased mass of adipose tissue, conferring a higher risk of cardiovascular and metabolic disorders such as diabetes, hyperlipidemia, and coronary heart disease. To investigate the role of transcriptional factors, which are involved in adipocytes differentiation and adiposity, we have generated peroxisome proliferator-activated receptor (PPAR) γ or CREB-binding protein (CBP)-deficient mice by gene targeting. Heterozygous PPARγ-deficient mice were protected from the development of insulin resistance due to adipocyte hypertrophy under a high-fat diet. Heterozygous CBP-deficient mice showed increased insulin sensitivity and were completely protected from body weight gain induced by a high-fat diet. PPARγ or CBP deficiency results in increased effects of hormones such as adiponectin and leptin. Adiponectin was decreased in obesity and lipoatrophy, and replenishment of adiponectin ameliorated insulin resistance. Moreover, adiponectin-deficient mice showed insulin resistance and atherogenic phenotype. Finally, cDNA encoding adiponectin receptors (AdipoR1/R2) have been identified by expression cloning. The expression of AdipoR1/R2 appears to be inversely regulated by insulin in physiological and pathophysiological states such as fasting/refeeding, insulin deficiency, and hyperinsulinemia models, and it is correlated with adiponectin sensitivity. These results facilitate the understanding of molecular mechanisms of adiponectin actions and obesity-linked diseases such as diabetes and atherosclerosis and propose the molecular targets for anti-diabetic and anti-atherogenic drugs.

Keywords: peroxisome proliferator-activated receptor (PPAR) γ, CREB-binding protein (CBP), adiponectin, adiponectin receptor, insulin resistance

Introduction

Insulin resistance induced by a high-fat diet and associated with obesity is a major risk factor for diabetes, atherosclerosis, and cardiovascular diseases. However, the molecular basis for that association remains to be elucidated. The adipose tissue itself serves as the site of triglyceride (TG) storage and free fatty acid (FFA)/glycerol release in response to changing energy demands. It is not simply a store of excess energy, but also secretes a variety of proteins into circulating blood that influence systemic metabolism. These include leptin (1), adiponectin (2 – 5), tumor necrosis factor (TNF) α (6), plasminogen-activator inhibitor type 1 (PAI-1) (7), adipsin (8), and resistin (9); these are collectively known as adipocytokines (10). This article focuses on the role of adipocytes and its related molecules such as peroxisome proliferator-activated receptor (PPAR) γ, CREB (cAMP response element-binding protein)-binding protein (CBP), and adiponectin, which have impor-

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tant roles in regulating adiposity and insulin resistance.

Heterozygous PPARγ-deficient mice were protected from high-fat diet-induced adipocyte hypertrophy and insulin resistance

PPARγ is a ligand-activated transcription factor and a member of the nuclear hormone receptor superfamily that functions as a heterodimer with a retinoid X receptor (RXR) (11, 12). Agonist-induced activation of PPARγ is known to cause adipocyte differentiation and insulin sensitivity (13, 14). To investigate the role of PPARγ in vivo, we have generated PPARγ-deficient mice by gene targeting (15). Homozygous PPARγ-deficient mice were embryonic lethal due to placental dysfunction. Unexpectedly, we found that weight gain and an increase in white adipose tissue mass under a high-fat diet was significantly less in heterozygous PPARγ-deficient mice than wild-type mice. Histological analyses revealed that the size of adipocytes from heterozygous PPARγ-deficient mice was significantly smaller than that of adipocytes from wild-type mice under a high-fat diet. Quite unexpectedly, the glucose-lowering effect of insulin was larger in heterozygous PPARγ-deficient mice than in wild-type mice, indicating that under a high-fat diet, heterozygous PPARγ-deficient mice were more insulin sensitive than wild-type mice. These phenotypes were abrogated by PPARγ agonist treatment. Heterozygous PPARγ-deficient mice showed overexpression and hypersecretion of leptin despite the smaller size of adipocytes and decreased fat mass, which may explain these phenotypes at least in part. These results suggested that PPARγ mediates high-fat diet-induced obesity, adipocyte hypertrophy, and insulin resistance. As shown in Fig. 1, in wild-type mice, a high-fat diet promotes adipocyte hypertrophy, which converts small adipocytes into large adipocytes, which in turn induce factors such as TNFα and free fatty acids, thereby causing insulin resistance. In heterozygous PPARγ-deficient mice, adipocyte hypertrophy and development of insulin resistance under a high-fat diet are partially protected against (15).

Both heterozygous PPARγ deficiency and PPARγ agonist improved insulin resistance, which is associated with decreased TG contents in liver and muscle and prevention of adipocytes hypertrophy

The relationship between PPARγ and insulin sensitivity is highly controversial. We attempted to explain how insulin resistance could be improved by two opposite PPARγ activity states, supraphysiological activation of PPARγ and moderate reduction. We did so by using heterozygous PPARγ-deficient mice and a pharmacological activator of PPARγ in wild-type mice (16). Supraphysiological activation of PPARγ by PPARγ agonist thiazolidinediones (TZD) stimulates adipogenesis, which promotes a flux of FFA from liver and muscle into white adipose tissue (WAT), leading to a decrease in TG content in liver and muscle and

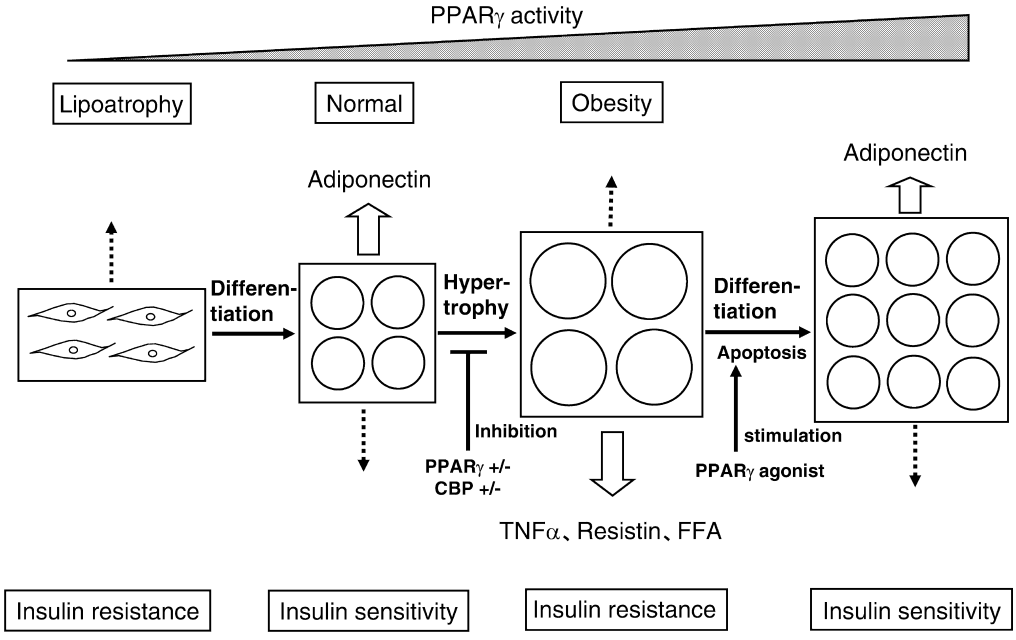

Fig. 1. The mechanisms by which PPARγ regulates insulin sensitivity and anti-atherosclerosis.

improvement of insulin sensitivity at the expense of increased WAT mass, i.e. obesity. In contrast, moderate reduction of PPARγ activity observed in untreated heterozygous PPARγ-deficient mice decreases TG content in WAT, skeletal muscle, and liver. This effect is due to a combination of increased leptin expression by antagonism of PPARγ-mediated suppression of the gene, thereby reducing expression of lipogenic enzymes, and consequent activation of the PPARα pathway in liver, brown adipose tissue (BAT), and skeletal muscle, leading to an increase in expression of UCP2 and enzymes involved in β-oxidation. Moreover, although heterozygous PPARγ deficiency and TZD have opposite effects on total WAT mass, heterozygous PPARγ deficiency decreases lipogenesis in WAT, whereas TZD stimulate adipocyte differentiation and apoptosis, thereby both preventing adipocyte hypertrophy, which is associated with alleviation of insulin resistance presumably due to decreases in free fatty acids. These observations indicated that although by different mechanisms, both heterozygous PPARγ deficiency and PPARγ agonist improve insulin resistance, which is associated with decreased TG content of muscle/liver and prevention of adipocyte hypertrophy (16).

Heterozygous CBP-deficient mice showed increased insulin sensitivity despite lipodystrophy

The CBP protein is a co-activator for several transcription factors with a wide range of important biological functions such as sterol regulatory element-binding proteins (SREBPs), CCAAT/enhancer-binding proteins (C/EBPs), nuclear receptors (including PPARs), and signal transducers and activators of transcription (STATs) (11, 17 – 24). These transcription factors are well known to have important biological functions regarding glucose and lipid metabolism, which prompted us to investigate the physiologic role of CBP in vivo using CBP-deficient mice, which were generated previously (25 – 27). As CBP-null mice died during embryogenesis (25 – 27), we used heterozygous CBP-deficient mice (27, 28). Interestingly, only WAT weight per body weight of heterozygous CBP-deficient mice was markedly decreased compared with that of wild type mice in contrast to other tissues, including BAT. Heterozygous CBP-deficient mice were completely protected from high-fat diet – induced body weight gain. Moreover, despite the phenotype of lipodystrophy, which exhibits severe insulin resistance in human disease, heterozygous CBP-deficient mice had a higher insulin sensitivity and increased glucose tolerance compared with wild-type mice both on the high-carbohydrate and high-fat diet. Furthermore, the serum adiponectin levels in heterozygous CBP-deficient mice were significantly higher than those of wild-type mice, and leptin sensitivity was also increased in heterozygous CBP-deficient mice. As shown in Fig. 1, these increased effects of insulin-sensitizing hormones secreted from WAT, as well as diminution of molecules causing insulin resistance, such as FFA and TNFα, may explain, at least in part, the phenotypes of heterozygous CBP-deficient mice (28).

Adiponectin reversed insulin resistance associated with both lipoatrophy and obesity

Adiponectin is an adipocyte-derived hormone, which was originally identified independently by four groups (2 – 5). Genome-wide scans have mapped a susceptibility locus for type 2 diabetes and metabolic syndrome to chromosome 3q27 (29 – 31), where the gene encoding adiponectin is located. Serum Adiponectin levels are reported to be decreased in obesity (4, 32). Moreover, we demonstrated that the decreased expression levels of adiponectin coincided with insulin resistance in murine models of altered insulin sensitivity (33). Insulin resistance in lipoatrophic diabetes might be due to deficiency of adipocytokines that sensitize tissues to insulin. To determine the role of adipocytokine deficiency in the development of insulin resistance in lipoatrophic mice, we administered adiponectin and leptin to these mice. 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 (33). We next studied whether adiponectin can improve insulin resistance and diabetes in *db/db* and KKA*y* mice, two different mouse models of type 2 diabetes characterized by obesity, hyperlipidemia, insulin resistance, and hyperglycemia. Serum adiponectin levels in *db/db* mice or KKA*y* mice were decreased compared with their wild-type control mice. Replenishment of adiponectin reversed hyperglycemia and hyperinsulinemia of these obese mice (33). Adiponectin decreased insulin resistance by decreasing triglyceride content in muscle and liver in obese mice, through increased expression of molecules involved in both fatty-acid combustion and energy dissipation in muscle (33). These data indicate that the replenishment of adiponectin might provide a novel treatment for insulin resistance and type 2 diabetes.

Adiponectin stimulated glucose utilization and fatty-acid oxidation by activating 5'-AMP-activated protein kinase (AMPK)

The activation of AMPK by muscle contraction and

hypoxia has been reported to increase fatty-acid oxidation (34, 35) in skeletal muscle. The activation of AMPK has also been shown to stimulate glucose uptake independent of its action on fatty acid in skeletal muscle (36) and to reduce expression levels of molecules involved in gluconeogenesis such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) in hepatocytes (37). Adiponectin suppresses hepatic glucose production (38) and also stimulates oxidation of fatty acids primarily in skeletal muscle and the liver (33), thereby preventing the accumulation of lipids in insulin target tissues, which can lead to the amelioration of insulin resistance (33). Thus, we investigated the role of AMPK in the signal transduction of adiponectin in the liver and skeletal muscle (39). Adiponectin stimulated phosphorylation and activation of AMPK in skeletal muscle and liver. Adiponectin increased phosphorylation of acetyl coenzyme A carboxylase (ACC), fatty-acid oxidation, glucose uptake in C2C12 myocytes, phosphorylation of ACC, and reduction of molecules involved in gluconeogenesis in the liver (Fig. 2). Blocking AMPK activation by dominant-negative mutant inhibits each of these effects, indicating that stimulation of glucose utilization and fatty-acid oxidation by adiponectin occurs through activation of AMPK (39). The observations that exercise (34, 35), antidiabetic adipokines such as adiponectin and leptin (40), and the antidiabetic drug metformin (41) activate AMPK suggest that AMPK plays crucial and central roles in the regulation of energy expenditure and glucose and lipid metabolism.

Disruption of adiponectin caused insulin resistance and neointimal formation and overexpression of globular adiponectin protected apolipoprotein E (apoE)-deficient mice from atherosclerosis

It has been reported that adiponectin may have putative anti-atherogenic properties in vitro such as suppression of endothelial inflammatory response and vascular smooth muscle cell proliferation, as well as macrophage-to-foam cell transformation in vitro (42, 43). Thus we generated adiponectin-deficient mice to directly investigate whether adiponectin has a physiological protective role against atherosclerosis in vivo (44). Homozygous adiponectin-deficient mice showed moderate insulin resistance and glucose intolerance and showed twofold more neointimal formation in response to external vascular cuff injury than wild-type mice (44). To examine whether overexpression of adiponectin is protective against atherosclerosis in vivo, we analyzed globular adiponectin (gAd) transgenic (Tg) mice crossed with a well-established animal model of atherosclerosis, apoE-deficient mice (45). Despite similar plasma glucose and lipid levels on an apoE-deficient background, gAd Tg apoE-deficient mice showed amelioration of atherosclerosis, which was associated with decreased expression of class A scavenger receptor and TNFα (45). These studies provide direct evidence that adiponectin plays a protective role against atherosclerosis in vivo.

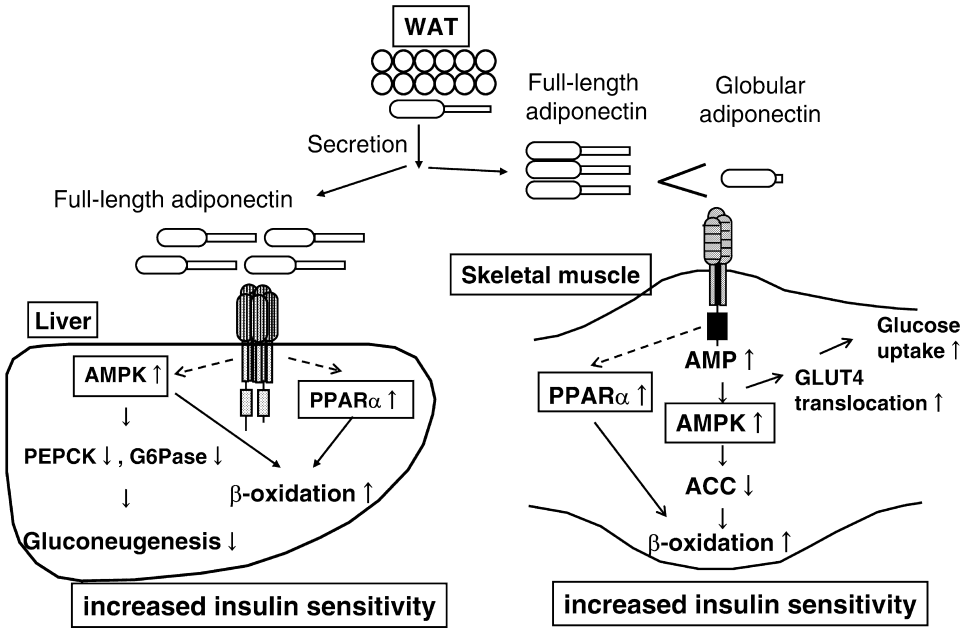

Fig. 2. Molecular mechanisms of insulin sensitizing effects of adiponectin in muscle and liver.

Cloning of adiponectin receptors and regulation of their expression levels by insulin

Cloning of adiponectin receptor should facilitate studies on the regulation of glucose and lipid metabolism, the molecular causes of diabetes and atherosclerosis, and the development of anti-diabetic and anti-atherosclerotic drugs. We cloned the cDNAs encoding adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) by expression cloning (46). Expression of AdipoR1/R2 or suppression of AdipoR1/R2 expression by small-interfering RNA supported that they bind to adiponectin and mediate increased AMP kinase and PPARα ligand activities, as well as fatty-acid oxidation and glucose uptake by adiponectin (46). We next determined whether the expressions of AdipoR1/R2 are altered in physio-

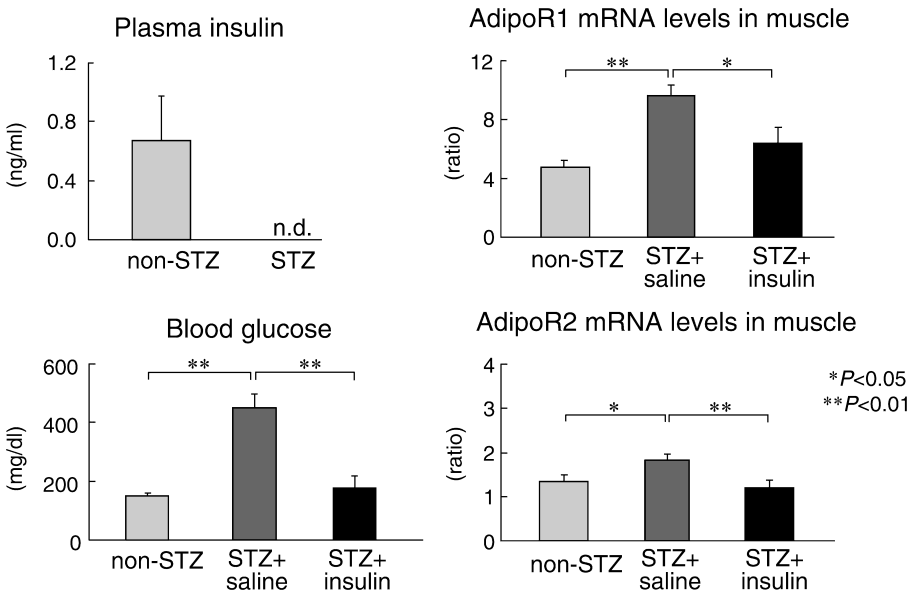

Fig. 3. Streptozotocin treatment increased AdipoR1/R2 expressions, whereas insulin decreased them.

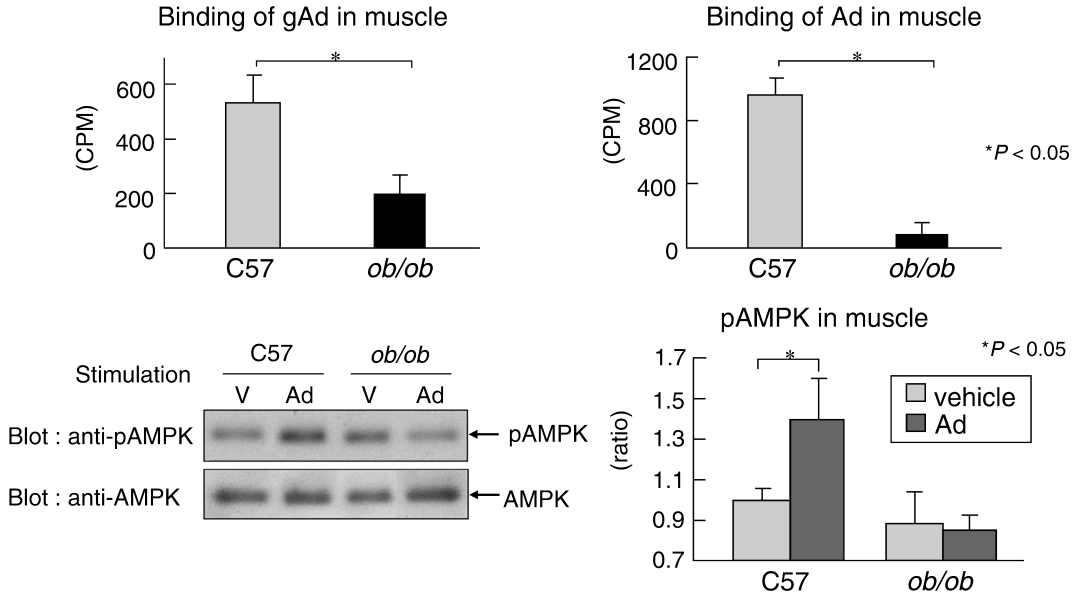

Fig. 4. Adiponectin (Ad) had a higher binding to the membrane fractions of muscle of wild-type (C57) mice than *ob/ob* mice. Adiponectin was able to activate AMPK in skeletal muscle of wild-type mice, whereas adiponectin was unable to activate AMPK in skeletal muscle of *ob/ob* mice.

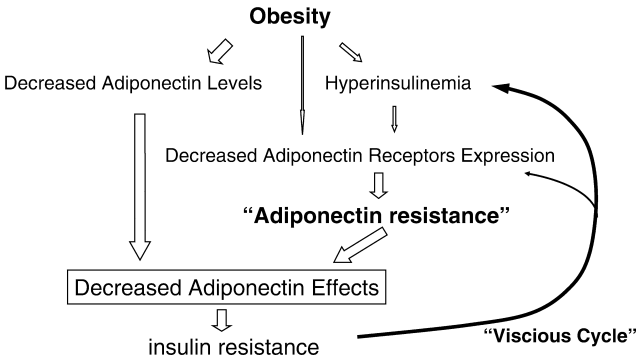

Fig. 5. Decreased adiponectin effects and insulin resistance (Hypothesis).

logical and pathophysiological states (47). We showed that the expressions of AdipoR1/R2 in skeletal muscle and liver were significantly increased in fasted mice and decreased in refed mice. Insulin deficiency induced by streptozotocin (STZ) increased and insulin replenishment reduced the expression of AdipoR1/R2 in vivo (Fig. 3). Incubation of hepatocytes or myocytes with insulin reduced the expression of AdipoR1/R2 via the PI3-kinase/Foxo1-dependent pathway (48) in vitro. Moreover, the expressions of AdipoR1/R2 in obese diabetic *ob/ob* mice were significantly decreased in skeletal muscle and adipose tissue, which were correlated with decreased adiponectin binding to membrane fractions of skeletal muscle and decreased AMP kinase activation by adiponectin (Fig. 4). This study demonstrated that insulin negatively regulates the expression levels of adiponectin receptors via the PI3-kinse/Foxo1 pathway. Our 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 (Fig. 5).

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