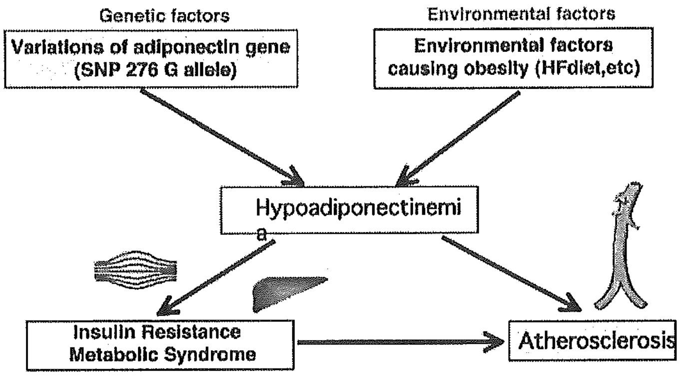

FIG. 11. Adiponectin hypothesis for insulin resistance, metabolic syndrome, and atherosclerosis. Reduced adiponectin levels can be caused by genetic factors such as SNP 276 in the adiponectin gene itself. Reduced adiponectin levels can also be caused by lifestyle changes causing obesity such as a HF 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

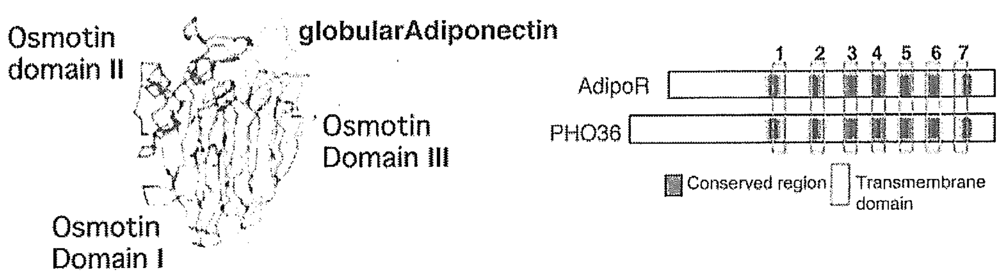

FIG. 12. Osmotin, which is a ligand for the yeast homolog of AdipoR (PHO36), activates AMP kinase via AdipoR in C2C12 myocytes. Osmotin is a member of a large PR-5 protein family, which is both ubiquitous (fruits and vegetables, *etc.*) and diverse. PR-5 proteins are also extremely stable and may remain 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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