UPDATE ARTICLE

Role of Adiponectin in disease

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ABSTRACT

Obesity and obesity related disorders play an important role in clinical medicine. Adipose tissue is an active metabolic tissue that secretes multiple metabolically active soluble mediators called as adipokines. Adiponectin, a prototypical adipokine is important because of its beneficial effects on glucose and lipid metabolism. Adiponectin levels are decreased in obesity and disease states such as diabetes and cardiovascular diseases. Direct administration of adiponectin has been shown to be beneficial in animal models of obesity, diabetes and atherosclerosis. This article will survey the physiological functions and therapeutic options available with adiponectin. [IJEM 2007;(3&4):31-34]

Key words: adiponectin, insulin resistance, obesity, thiazolidinedione, type 2 diabetes mellitus.

INTRODUCTION

Adipose tissue is an important endocrine organ secreting multiple metabolically active proteins termed adipokines. Some well known adipokines including leptin(1), tumor necrosis factor (TNF)- (2), plasminogen activated inhibited (PAI)–1 (3), adipsin(4), resistin(5), interleukin (IL) - 6 and adiponectin.

Newly discovered adipokines include visfatin(6) and retinol binding protein – 4 (RBP 4), which was found to be up regulated in adipose tissue of adipose specific GLUT 4 knockout mice(7).

Adiponectin is a novel collagen like protein synthesized by white adipose tissue that circulates at relatively high (2 – 20 μg/ ml) serum concentration. It has gained importance for its role in glucose and lipid metabolism(8). Multiple studies have shown a strong positive relationship between adiponectin and insulin sensitivity(9-13). More recent studies have shown a role for adiponectin in cardiovascular disease(14,15).

Chemical Structure

Adiponectin structurally belongs to the soluble defense collagen super family, sharing significant homology with collagen X, collagen VIII and compliment factor C1Q. The basic structure is a 247 amino acid protein with four domains. A hyper variable amino terminal, a variable region followed by a collagenous domain and a carboxy terminal globular domain(16) (Figure 1).

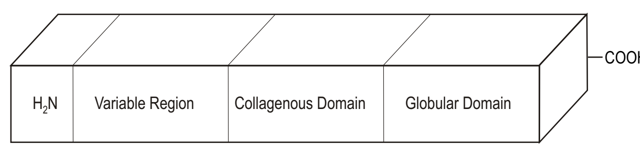

Figure 1: Structure of Adiponectin

Adiponectin undergoes post translational modification during its secretion from adipocytes. Several lysine and proline residues within the collagenous domain are hydroxylated. Hydroxyl lysine residues at position 68, 71, 80 and 104 are further modified by a glucosyl (1 – 2 galactosyl group).

Oligomerization of Adiponectin

Monomeric forms of Adiponectin undergo transformation into multiple forms including trimers, hexamers and high molecular weight (HMW) oligomers(16-19) (Figure 2). These forms range in size from 7 – 90 kDa trimers to approximately 500 kDa high molecular weight forms.

The relative distribution of adiponectin among these

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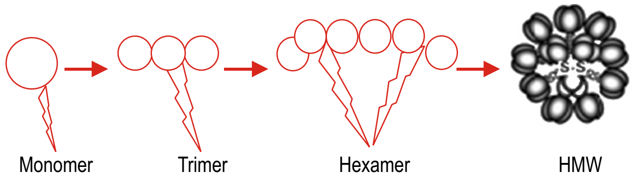

Figure 2: Oligomerization of Adiponectin

multimeric forms differs between the adipose tissue and the circulation with high molecular weight forms dominating in plasma(19,20).

Scherer et al defined a new index, S_A, as the ratio of HMW form to the total Adiponectin is equal to HMW/(HMW + LMW) where the total Adiponectin equals the sum of high (HMW) and low (LMW) molecular weight forms. They showed that S_A had a stronger correlation with insulin sensitivity than total adiponectin levels at both baseline and after thiazolidinedione treatment(16).

Several single nucleotide polymorphisms (SNP) of the Adiponectin gene have been identified, SNP 45 and SNP 276 being the most common. In the Japanese population, SNP 276 was associated with lower plasma Adiponectin levels and higher insulin resistance and increase risk for type 2 diabetes.

Mechanism of action

One potential mechanism of Adiponectin has been suggested by identification of two transmembrane receptors. Adipo R1, which is predominantly expressed in the skeletal muscles, shows a preference for globular Adiponectin (gAd), whereas Adipo R 2 which is predominantly expressed in liver shows a preference for full length Adiponectin(21). Kadowaki's group has shown that Adiponectin acts through activation of AMP kinase and PPAR in both liver and skeletal muscles, which results in stimulation of fatty acid oxidation and decreased triglyceride content in skeletal muscle and liver(22).

Physiological role

Over past several years, the functions of Adiponectin have been extensively studied in numerous animal models and invitro systems. It is now appreciated that Adiponectin is a multifunctional protein that regulates insulin sensitivity, energy homeostasis, vascular reactivity, inflammation, cell proliferation and tissue remodeling. Thus far identified targets of adiponectin include liver, skeletal muscle, adipose tissue, brain, pancreas, macrophages and blood vessels (Figure 3).

Epidemiology

Low levels of adiponectin are associated with adverse metabolic states such as diabetes, metabolic syndrome, dyslipidemia, lipodystrophy, and atherosclerotic cardiovascular disease(23,24,25). Both gender and ethnicity also effect adiponectin levels. Adiponectin levels are generally lower in men compared with women. Women also have higher content of the HMW forms adiponectin. Higher plasma levels of adiponectin are found in Caucasians

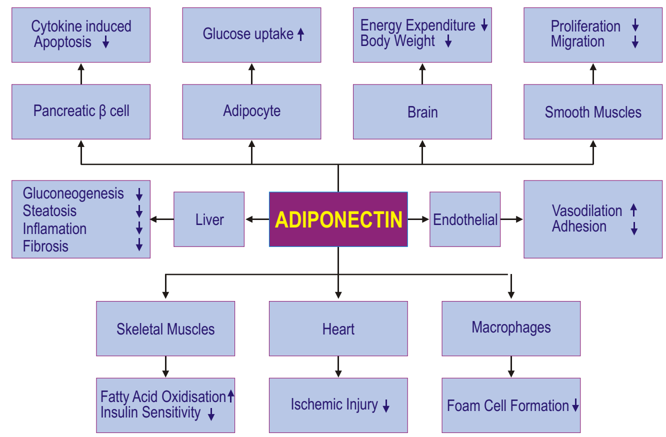

Figure 3: Physiological Role of Adiponectin

compared with body mass index [BMI]-matched Indo-Asians and Blacks.

In contrast to other adipokines which increase as the fat mass increases, circulation levels of adiponectin are paradoxically decreased in obese subject compared with lean subjects. On the other hand weight reduction by gastric partition surgery or calorie reduction leads to an increase in plasma level of adiponectin. There is a strong inverse correlation between plasma level of adiponectin and measure of adiposity; including BMI and total fat mass. Furthermore hypoadiponectinemia has been found to be closely associated with both congenital and HIV related lipodystrophy, a disease characterized by body fat redistribution

Adiponectin and Insulin sensitivity

Multiple animal and human studies have shown a correlation between plasma adiponectin levels and insulin sensitivity. Decline in plasma levels of adiponectin seems to identify insulin resistance before development of overt diabetes. Low plasma levels of adiponectin are observed in severe forms of diabetes and insulin resistance like type 2 diabetes, gestational diabetes, diabetes associated with lipodystrophy(26,27,28).

Adiponectin and Cardiovascular Diseases

Adiponectin is inversely correlated with traditional cardiovascular risk factor including blood pressure, heart rate, low-density lipoproteins (LDL), cholesterol and triglycerides levels and positively related to high density lipoprotein (HDL), cholesterol level. Hypo adiponectinemiaema has been found to be independent risk factor for endothelial dysfunction, and regardless of insulin resistance(11). In addition, the association of low levels of adiponectin with coronary artery disease and Ischemic cerebrovascular disease was also reported to be independent of classical cardiovascular risk factors such as diabetes, dyslipidemia and hypertension.

Adiponectin and chronic liver disease

Many recent studies demonstrated a close association of low adiponectin levels with non alcoholic fatty liver disease

(NAFLD) and non-alcoholic steatohepatosis (NASH)(29). In contrast to NAFLD and NASH, plasma levels of adiponectin are significantly elevated in patients with liver disease. Adiponectin was reported to alleviate alcoholic and nonalcoholic fatty liver disease and liver fibrosis in mice. Further studies will be needed to determine the physiological and pathophysiological roles of Adipo R1 and Adipo R2 in these .

Adiponectin and Cancers

A strong inverse association between plasma adiponectin levels and risk of both breast cancer and endometrial cancer has recently been reported. Plasma adiponectin levels in patients with gastric cancer were reported to be much lower than in control subject. Hypo adiponectinemia was found to be an independent predictor for future development of colorectal cancer. Recently, adiponectin was reported to induce antiangiogenesis and antitumour activity via caspace mediated endothelial cell apoptosis(30).

Therapeutic effects of Adiponectin

Administration of adiponectin has been shown to improve insulin sensitivity in mouse models of diabetes and lipoatrophy.In both wild type mice and mouse models of type 1 and type 2 diabetes intraperitoneal injection of full length adiponectin resulted in a significant reduction of glucose levels. Similar results were shown by Yamauchi *et al* using systemic infusion of the globular domain of adiponectin in mouse models of obesity, diabetes and lipoatrophy, full length forms of adiponectin was without effect(31). Yamauchi *et al* showed that transgenic mice over expressing gAd demonstrated protection from high-fat-fed-induced insulin resistance. Yamauchi *et al* demonstrated in a mouse model for atherosclerosis (apolipoprotein E deficient) that gAd can protect against atherosclerosis(32). Ouchi *et al* showed that adiponectin suppressed macrophage-to- foam cell transformation in vitro .They also demonstrated the effects of adiponectin to suppress monocyte adhesion to endothelium, myeloid differentiation and macrophage cytokine production and phagocytosis, all important steps in the development of vascular disease(33-34).

Adiponectin Up regulation as a Therapeutic Option

Results obtained from animal experiments and human epidemiological studies support the role of adiponectin as a potential target for developing novel therapeutic agents against obesity related disease. However this would be difficult to achieve in clinical setting, owing to the large protein structure of adiponectin and the need for post translational modification . Thus therapeutic possibilities have focused on the upregulation of adiponectin through indirect methods such as thiazolinedione therapy or weight loss.

It has been shown that thiazolinedione treatment results in elevated circulating levels of adiponectin in mice and humans(35). These effects seem to be associated with small-sized adipocytes, adipocytes differentiation with increased synthesis and/or secretion of Adiponectin. Besides direct transcriptional activation of genes via peroxisome proliferator response element and increased insulin action. Interestingly, both PPARg agonists and adiponectin have been shown to increase insulin sensitivity and ameliorate atherosclerosis(36). Rimonabant a selective cannabinoid (CB1) receptor antagonist acts on the adipocyte CB1 receptors and increases secretion of adiponectin.

Weight loss is another strategy for increasing adiponectin levels .Several studies have demonstrated an increase in adiponectin levels after significant weight loss induced by gastric bypass surgery. Significant weight loss mean 14% reduction in BMI through intensive life style changes can result in increase in adiponectin levels. The other strategy may be to up-regulate adiponectin receptors or to stimulate adiponectin receptors using small molecule agonists.

CONCLUSION

It is now known that adipose tissue is a dynamic endocrine organ secreting multiple adipokines. Adiponectin is an important adipokine that is secreted only by adipose tissue and circulates at highly abundant levels. Adiponectin has an important role in carbohydrate and lipid metabolism as seen in the association of low levels of adiponectin with disease state such as insulin resistance, type 2 diabetes and cardiovascular diseases.

Though administration of Adiponectin has shown benefits in improving insulin resistance and atherosclerosis in animal models, human trials have not been possible. Indirect methods for raising adiponectin levels include thiazolidinedine therapy and weight loss. Thiazolidinedones have a significant effect on adiponectin levels and may have an added advantage of increasing the HMW forms In addition to these effects; adiponectin also seems to have pleiotropic effects, particularly in relation to metabolic syndrome.

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