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COMMENTARY

Role of multimeric forms of adiponectin in metabolic disorders

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ABSTRACT

Adiponectin, also called Acrp30, is a 30-kDa protein that circulates in the blood at high levels (2-10 µg/ml in human) and constitutes 0.01% of the total plasma protein. In contrast to other adipokines such as leptin, adiponectin is believed to be an anti-inflammatory and insulin-sensitizing hormone whose levels are reduced in obesity. Adiponectin can exist in the blood as a trimer, with the potential to associate into hexamers and finally into multimers of high molecular weight (HMW) species. Adiponectin primarily mediates its insulin-sensitizing effects through various signaling proteins including the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK). Recent reports suggest the anti-inflammatory and cytoprotective effects of adiponectin are mediated by direct activation of PI3K-Akt pathway. Interestingly adiponectin is also reported to decrease body weight by centrally mediated stimulation of energy expenditure.

Keywords: *Obesity, diabetes, diabesity, adiponectin, multimeric forms, metabolic disorders*

Introduction

Adiponectin, also called Acrp30, is a 30-kDa protein that circulates in the blood at high levels (2-10 µg/ml in human) and constitutes 0.01% of the total plasma protein. In contrast to other adipokines such as leptin, adiponectin is believed to be an anti-inflammatory and insulin-sensitizing hormone whose levels are reduced in obesity.[1,2] Adiponectin can exist in the blood as a trimer, with the potential to associate into hexamers and finally into multimers of high molecular weight (HMW) species.[3] Studies suggest that HMW adiponectin is the most metabolically active multimer. For example, the proportion of HMW adiponectin, rather than the total level, is associated with the beneficial effects of thiazolidinediones.[2,3] Furthermore, HMW adiponectin appears to modulate the antiatherogenic properties of adiponectin.[2,3] Interestingly, although secreted primarily by adipocytes, levels of this hormone are paradoxically reduced in obesity. Similarly, decreased adiponectin levels were seen in parallel with the progression of insulin resistance and T2D in nonhuman primates4, suggesting that maintaining high circulating adiponectin levels may be a potential approach to preventing the development of these disorders.

Mechanisms of adiponectin

Adiponectin primarily mediates its insulin-sensitizing effects through various signaling proteins including the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK).[5] Recent reports suggest the anti-inflammatory and cytoprotective effects of adiponectin are mediated by direct activation of PI3K-Akt pathway. Interestingly adiponectin is also reported to decrease body weight by centrally mediated stimulation of energy expenditure.[6]

Multimeric forms of adiponectin

There are very little data assessing the metabolic significance of adiponectin multimeric forms. There was one recent article showing that the ratio of HMW to total adiponectin, not the total adiponectin level per se, was responsible for favorable metabolic effects.[7] The authors found that the ratio of HMW to total adiponectin, and not total adiponectin, was correlated with insulin sensitivity in humans and rodents, and it was increased by thiazolidinedione drugs in proportion to increments in hepatic insulin sensitivity manifested by a decrease in fasting hepatic glucose output.[7] In addition, administration of HMW but not LMW adiponectin lowered glucose in mice. In contrast, other studies have shown that LMW (hexamer) and HMW adiponectin are equally effective in activating nuclear factor-κB and that both the adiponectin monomer and trimer are capable of stimulating AMPK, whereas LMW and HMW adiponectin produce no effect. Thus, the manner and extent to which adiponectin multimeric forms may exert differential biological activity remains unclear. Nevertheless, these data have important and far-ranging implications regarding previous data because

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epidemiological studies have assessed total immunoreactive adiponectin, not multimeric forms. When glucose disposal rate was analyzed as a continuous variable, HMW and LMW adiponectin and the ratio of HMW to total adiponectin were positively correlated with glucose disposal rate. These associations persist even after controlling for effects of body adiposity and fat distribution, indicating that the relationships between total, HMW, and LMW adiponectin are independent of total body fat or fat distribution. These findings are in agreement with functional studies indicating that adiponectin multimers activate the AMPK pathway, which in turn induces fatty acid oxidation, glucose uptake, and lactate production in myocytes.[8]

Higher levels of total adiponectin and HMW adiponectin were correlated with higher levels of the more cardioprotective large HDL particles as well as with higher HDL particle size, together with decreased concentrations of both large VLDL particles and small LDL particles. Typically, the associations between HMW adiponectin and the various lipoprotein subclass parameters were higher than those observed for total adiponectin; these data reflect the colinearity between total and HMW adiponectin and suggest that the lipoprotein effects of total adiponectin are mainly driven by the more biologically active HMW multimer.[9]

Concluding remarks

It is HMW quantity, not total adiponectin or the ratio of multimeric forms, which is primarily responsible for these relationships. Still, the role of LMW adiponectin deserves further exploration because it was also correlated with insulin sensitivity and basal lipid oxidation. HMW adiponectin is an important biomarker for the metabolic syndrome and could play a pathogenic role in the development of the insulin resistance.

Conflict of interest

Dr. Arulmozhi Kandasamy is the managing editor of Diabesity.

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