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Signaling mechanisms underlying the insulin-sensitizing effects of adiponectin

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Adiponectin is an insulin-sensitizing adipokine with protective effects against a cluster of obesity-related metabolic and cardiovascular disorders. The adipokine exerts its insulin-sensitizing effects by alleviation of obesity-induced ectopic lipid accumulation, lipotoxicity and chronic inflammation, as well as by direct cross-talk with insulin signaling cascades. Adiponectin and insulin signaling pathways converge at the adaptor protein APPL1. On the one hand, APPL1 interacts with adiponectin receptors and mediates both metabolic and vascular actions of adiponectin through activation of AMP-activated protein kinase and p38 MAP kinase. On the other hand, APPL1 potentiates both the actions and secretion of insulin by fine-tuning the Akt activity in multiple insulin target tissues. In obese animals, reduced APPL1 expression contributes to both insulin resistance and defective insulin secretion. This review summarizes recent advances on the molecular mechanisms by which adiponectin sensitizes insulin actions, and discusses the roles of APPL1 in regulating both adiponectin and insulin signaling cascades.

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Introduction

According to the World Health Organization, more than 1.4 billion adults are overweight, and more than half a billion are obese worldwide. Obesity is the major contributor to type 2 diabetes mellitus (T2DM) and cardiovascular diseases, both of which are top causes of disability and death in the elderly population. Insulin resistance, characterized by the impaired ability of insulin to exert its metabolic and vascular actions in its target tissues, is the primary mediator that causally links obesity with diabetes and cardiovascular diseases [1]. Furthermore, obesity is closely associated with aberrant production and functions of adipokines secreted from dysfunctional adipose tissues [2].

Intensive research over the last decade has provided novel insights into how dysregulation of adipokines links obesity and insulin resistance [2]. In obesity, elevated production of pro-inflammatory adipokines and reduced synthesis of anti-inflammatory and insulin-sensitizing factors such as adiponectin, promote the development of insulin resistance. Adiponectin, one of the most abundant adipokines secreted from adipocytes, possesses protective effects against diabetes and cardiovascular diseases, at least in part through its insulin-sensitizing activity [3]. The insulin and adiponectin signaling pathways interact extensively and regulate each other at multiple levels. The synergistic actions between insulin and adiponectin play a central role in maintaining energy and vascular homeostasis. Here, we review the molecular basis underlying the metabolic and vascular actions of adiponectin and insulin, and the cross-talk between these two intimately linked signaling pathways, which may be coordinated in part by the adaptor protein APPL1.

Insulin signaling cascades and insulin resistance

In response to elevated glucose levels, insulin is secreted from pancreatic β cells to maintain euglycemia by suppressing hepatic glucose production and by enhancing glucose uptake in skeletal muscle and adipose tissues [1]. In addition, insulin regulates β cell mass, insulin secretion, endothelial function and vascular tone [1]. Insulin signaling is initiated by the binding of insulin to insulin receptor (IR), leading to activation of its intrinsic tyrosine kinase. Activation of insulin receptors elicits tyrosine phosphorylation of insulin receptor substrate (IRS) proteins, which serve as docking platforms for the p85 regulatory subunit of the phosphatidylinositol 3-kinase (PI3K), resulting in the generation of phosphatidylinositol 3,4,5-triphosphate at the plasma membrane. This activation of the PI3K pathway promotes membrane recruitment and activation of Akt and its downstream targets, which in turn inhibits gluconeogenesis and promotes glucose uptake and vaso-relaxation. In addition, insulin also activates the mitogen-activated protein kinase (MAPK) pathway, which is important for the proliferative and lipogenic actions of insulin [1]. In obesity, a number of risk factors, including ectopic lipid accumulation, endoplasmic reticulum stress and systemic inflammation, contribute to the development of insulin resistance, a common denominator of T2DM and cardiovascular diseases [1,4]. A growing body of evidence suggests that selective insulin resistance in the PI3K/Akt pathway but preserved or augmented MAPK signaling cascade contributes to the insulin resistance-associated cardio-metabolic disorders, such as augmented hepatic lipogenesis and glucose production, and vasoconstriction [4,5].

Adiponectin: an insulin-sensitizing adipokine

Adipose tissue is now recognized as a major endocrine and secretory organ releasing a wide range of protein factors and signals, collectively termed adipokines. Many adipokines participate in the regulation of insulin sensitivity in a paracrine and/or endocrine manner [2]. Aberrant production and/or function of these adipokines are causally associated with obesity-induced insulin resistance and metabolic dysregulation. While most of adipokines are pro-inflammatory and impair insulin actions, adiponectin possesses anti-inflammatory, insulin-sensitizing and anti-diabetic activities [2]. In humans, both adipose mRNA expression and plasma levels of adiponectin correlate positively with the indexes of insulin sensitivity [6], and a reduced plasma level of adiponectin (hypoadiponectinemia) was observed in obese individuals and patients with insulin resistance, T2DM and cardiovascular