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Review

Modulation of adiponectin as a potential therapeutic strategy

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ABSTRACT

Adiponectin is produced predominantly by adipocytes and plays an important role in metabolic and cardiovascular homeostasis through its insulin-sensitizing actions and anti-inflammatory and anti-atherogenic properties. Recently, it has been observed that lower levels of adiponectin can substantially increase the risk of developing type 2 diabetes, metabolic syndrome, atherosclerosis, and cardiovascular disease in patients who are obese. Circulating adiponectin levels are inversely related to the inflammatory process, oxidative stress, and metabolic dysregulation. Intensive lifestyle modifications and pharmacologic agents, including peroxisome proliferator-activated receptor-γ or α agonists, some statins, renin-angiotensin-aldosterone system blockers, some calcium channel blockers, mineralocorticoid receptor blockers, new β-blockers, and several natural compounds can increase adiponectin levels and suppress or prevent disease initiation or progression, respectively, in cardiovascular and metabolic disorders. Therefore, it is important for investigators to have a thorough understanding of the interventions that can modulate adiponectin. Such knowledge may lead to new therapeutic approaches for diseases such as type 2 diabetes, metabolic syndrome, cardiovascular disease, and obesity. This review focuses on recent updates regarding therapeutic interventions that might modulate adiponectin.

Contents

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1. Introduction

Adiponectin is produced predominantly by adipocytes and plays an important role in metabolic and cardiovascular homeostasis. Circulating adiponectin levels may act as a biologic marker—and decreased levels of circulating adiponectin may act as a mediator—for the pathophysiology in type 2 diabetes (T2D), metabolic syndrome, obesity, and atherosclerosis [1,2].

In humans, a low-calorie, high-unsaturated fat diet and/or exercise can help delay or prevent T2D and cardiovascular disease (CVD) and is associated with increased circulating adiponectin levels [3]. Thus, lifestyle modifications can have beneficial effects on glucose and lipid metabolism, insulin sensitivity, and atherosclerosis. Increased adiponectin levels may contribute directly or indirectly to the delay and/or prevention of T2D and CVD.

Several intervention trials have evaluated the efficacy of pharmacotherapies in increasing circulating concentrations of adiponectin. For example, treatment with peroxisome proliferator-activated receptor-α (PPAR-α) or γ (PPAR-γ) agonists and certain statins (e.g., pravastatin) resulted in increased adiponectin levels [4,5]. Other drugs used to treat CVD, including angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), also resulted in increased adiponectin levels [6]. In addition, natural compounds used in foods or nutritional supplements (e.g., resveratrol and S-adenosylmethionine) demonstrated anti-inflammatory actions, which were associated with increased adiponectin levels [7,8].

Adiponectin has insulin-sensitizing, anti-inflammatory, and antioxidant effects [9,10]. These properties may help explain the inverse associations between circulating adiponectin levels and diseases including CVD, T2D, metabolic syndrome, and obesity [1,2].

Several reviews have been published on adiponectin; however, there are few articles that focus on modulating adiponectin levels as a potential therapeutic strategy [11]. This review discusses 1) characteristics of adiponectin and adiponectin receptors, 2) pathophysiology of diseases (e.g., T2D and CVD) that are potentially regulated by adiponectin, and 3) possible therapeutic strategies to regulate circulating adiponectin levels or to activate adiponectin receptors. The current review is based on original and review papers that were selected from these points of view.

2. Structural characteristics and molecular functions of adiponectin

2.1. Chemical structure of adiponectin and adiponectin receptors

Since its discovery in 1995, adiponectin has drawn considerable attention because of its anti-inflammatory, antidiabetic, antiatherogenic, and cardioprotective properties [12]. Adiponectin is a 30 kDa protein composed of a collagenous domain at N-terminal and a globular domain at C-terminal. The adiponectin gene is located on chromosome 3q27, which is a diabetes susceptibility locus. The plasma concentration of adiponectin is (2–20 μg/mL) is greater than most hormones and inflammatory cytokines [12].

Adiponectin is found in low-molecular-weight (LMW) (e.g., trimer and hexamer) and high-molecular-weight (HMW) forms (e.g., dodecamers and octadecamers) in human serum [13]. The biosynthesis and secretion of adiponectin oligomers in adipocytes are regulated via molecular chaperones in the endoplasmic reticulum, including ERp44 (ER protein of 44 kDa), Ero1-Lα (ER oxidoreductase 1-Lα), and DsbA-L (disulfide-bond A oxidoreductase-like protein). ERp44 inhibits the secretion of adiponectin oligomers via thiol-mediated retention [14]. In contrast, Ero1-Lα releases HMW adiponectin that is blocked by ERp44.

HMW adiponectin formation requires an intermolecular disulfide bond between highly conserved cysteine residues that are located in the hypervariable region. Hydroxylation and glycosylation of conserved lysine residues within its collagen-like domain contribute to posttranslational changes in the intracellular assembly and HMW adiponectin secretion. LMW adiponectin is the predominant form in the circulation, and HMW adiponectin is the predominant form in intracellular adiponectins. The HMW isoform of adiponectin appears to have an important role in cardiometabolic conditions. A recent study showed that high HMW adiponectin levels were associated with lower risk of CVD in middle-aged adults with high blood glucose [15].

Adiponectin receptor (AdiopR) has a specific distribution and characteristics. AdiopR1 is a high-affinity receptor in the globular domain of adiponectin and is primarily expressed in skeletal muscle. In contrast, AdipoR2 has an intermediate affinity for both forms of adiponectin and is abundant in the liver [16]. AdipoR1 and AdipoR2 modulate AMP kinase and PPAR ligand activity and mediate fatty acid oxidation and glucose uptake [16]. Adiponectin receptors are also expressed in pancreatic β-cells and their expressions are increased by exposure to oleate as a free fatty acid, suggesting adiponectin and its receptors are involved in insulin secretory function [17]. The adapter signaling protein APPL1 is located downstream from AdipoR1 and AdipoR2 and links the liver kinase B1 to AMP kinase signaling in various tissues [18]. AdipoR1 and AdipoR2 also play an important role in adiponectin signaling in endothelial cells.

AdipoR1 and AdipoR2 expression levels are substantially decreased in nondiabetic subjects who have family history of T2D [19]. AdipoR1 and AdipoR2 levels have also been positively associated with obesity [20]. Recently, the expression of AdipoR1 in skeletal muscle was shown to be significantly higher in obese subjects compared with lean controls; however, no differences were noted in patients with T2D [21]. These data suggest that mRNA expression of AdipoR1 and AdipoR2 may be regulated via different mechanisms in certain conditions (e.g., T2D and obesity). Thus, the specific structure of adiponectin, its post-translational modifications, and receptors may aid in ameliorating metabolic and cardiovascular abnormalities.

2.2. Molecular function of adiponectin related to insulin sensitivity and atherosclerosis

Several studies suggest that adiponectin has insulin-sensitizing properties, resulting in a better metabolic profile. Adiponectin activates AMP kinase in skeletal muscle and liver tissues, thereby stimulating phosphorylation of acetyl coenzyme-A carboxylase (ACC), fatty acid oxidation, and glucose uptake [22]. Adiponectin