Role of adiponectin in metabolic and cardiovascular disease

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Under disease conditions including obesity (insulin resistance) and diabetes, dysregulation of adipokines such as tumor necrosis factor (TNF)-α, leptin, resistin, and adiponectin contribute to the development of metabolic and cardiovascular disease. Unlike other adipokines, adiponectin has been shown to be a therapeutic target for metabolic syndrome and cardiovascular disease. Circulating levels of adiponectin are markedly reduced in obese, diabetic, hypertensive, and coronary artery disease patients as well as experimental animal models of insulin resistance and diabetes. Recently, the small molecule adiponectin receptors (AdipoRs) agonist was discovered and suggested that the agonist is a novel therapeutic target for the treatment of type 2 diabetes linked to obesity in an experimental mouse model. This review will focus on signaling pathways involved in adiponectin and its receptors and the role of adiponectin in metabolic and cardiovascular disease including insulin resistance, cardiomyopathy, and cardiovascular dysfunction.

Keywords: Adiponectin receptors, AdipoRON, AMPK, PPARα

INTRODUCTION

Metabolic syndrome including insulin resistance, hypertension, and type 2 diabetes, is more linked to the development of cardiovascular complications such as stroke and cardiac arrest (Arnlov et al., 2010). Adipose tissue produces a number of bioactive substances known as adipokines including tumor necrosis factor (TNF)-α, leptin, resistin, and adiponectin (Deng and Scherer, 2010). Under disease conditions including obesity (insulin resistance) and type 2 diabetes, dysregulation of these adipokines contribute to the development of metabolic and cardiovascular disease (Guzik et al., 2006; Tilg and Moschen, 2006). Adiponectin is a 30 KDa protein abundantly secreted from adipocytes and circulates at high concentration in the blood (3–30 µg/mL) as three oligomeric complexes (Ouchi et al., 2003a; Tsao et al., 2003). Unlike other adipokines, adiponectin plays a protective role against the development of metabolic disorder and related atherosclerotic vascular disease (Matsuda et al., 2002; Okamoto et al., 2000; Zoccali et al., 2002). In the rodent models, deletion of adiponectin is associated with the increased inflammatory actions under conditions of stresses such as over-nutrition and ischemic insult (Maeda et al., 2002; Nawrocki et al., 2006; Shibata et al., 2005). Circulating levels of adiponectin are markedly reduced in obese (Arita et al., 1999), diabetic (Hotta et al., 2000), hypertensive (Adamczak et al., 2003), and coronary artery disease (Kumada et al., 2003; Nakamura et al., 2004) patients as well as experimental animal models of insulin resistance and diabetes (Lee et al., 2011; Lee et al., 2012). In addition, a number of clinical observations demonstrated that serum hypoadiponectinemia is associated with impaired endothelial-dependent vasodilation (Ouchi et al., 2003b), hypertension (Chow et al., 2007), myocardial infarction (Pischon et al., 2004), and coronary artery disease (Kiris et al., 2006). This review will focus on 1) signaling pathways involved in adiponectin and its receptors and 2) the role of adiponectin in metabolic and cardiovascular disease including insulin resistance, cardiomyopathy, and vascular dysfunction.
ADIPONECTIN AND ADIPONECTIN RECEPTORS

Adiponectin secreted from adipose tissue binds to two distinct adiponectin receptors (AdipoR1 and AdipoR2) identified and exerts its anti-diabetic effects through activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPARα) pathways in liver and skeletal muscles as well as amelioration of vascular dysfunction through activation of endothelial nitric oxide (NO) production and anti-atherogenic effects through inhibition of inflammation in the various vasculature (Okamoto et al., 2002; Omae et al., 2013; Yamauchi et al., 2003; Yamauchi et al., 2002). Adiponectin consists of 247 amino acids and circulates in the bloodstream as three different oligomeric complexes including trimer (3), hexamer (6) and high molecular weight multimer (12-18) (Magkos and Sidossis, 2007). Adiponectin receptors contain seven transmembrane domains, but they are distinct from G-protein-coupled-receptors (GPCR) structurally and functionally (Wess, 1997; Yamauchi et al., 2003). Replenishment of adiponectin has been shown to ameliorate insulin resistance, glucose intolerance, and vascular function in animal models (Cao et al., 2009; Yamauchi et al., 2002; Yamauchi et al., 2001), while hypoglycemic effects of adiponectin in liver was abrogated in the double knockout of AdipoR1 and 2 in the mouse model (Yamauchi et al., 2007). The beneficial effect of adiponectin in insulin-sensitive organs including skeletal muscle and liver appears to be mediated by an increase in glucose utilization and fatty-acid oxidation via activation of AMPK and PPARα (Kadowaki and Yamauchi, 2005). AdipoR1 is abundantly expressed and activates AMPK in skeletal muscle, while in liver, AdipoR2 is predominantly expressed and regulated glucose and lipid metabolism, inflammation, and oxidative stress through PPARα (Cao et al., 2009; Kadowaki and Yamauchi, 2005; Savage et al., 2005; Yamauchi et al., 2001). In addition, adiponectin played a protective role in the pathogenesis of vascular diseases by promoting NO production as well as inhibiting inflammation and oxidative stress. For example, deficiency of adiponectin showed impairment of endothelium-dependent vasodilation (Ouchi et al., 2003b; Shimabukuro et al., 2003). Recently, Okada-Iwabu et al. (2013) have implicated that orally active AdipoR agonists (AdipoRON) showed similar effects to adiponectin via AdipoR1 and 2 in the both liver and skeletal muscle of experimental diabetic mouse model, suggesting that adiponectin receptors could be a promising therapeutic target for the treatment of type 2 diabetes.

ADIPONECTIN AND CHRONIC DISEASE

Obesity, insulin resistance, and diabetes

Insulin resistance linked to obesity is a major risk factor for type 2 diabetes and cardiovascular disease. The skeletal muscle and liver, which are the principal storage for glucose and fatty acids, are responsible for energy homeostasis (Savage et al., 2005). Obesity and/or high fat diet feeding increased free fatty acids (FFA) in circulation and result in insulin resistance (Dresner et al., 1999). Elevated FFA reduced insulin-stimulated glucose disposal and resulted in the reduction of glycogen synthesis in both skeletal muscle and liver (Boden and Shulman, 2002). It is well established that glycogen synthesis was reduced in diabetic subjects compare to normal individuals (Shulman et al., 1990). In both liver and skeletal muscle, adiponectin reduced triglyceride content and improved insulin signaling by increasing gene expression involved in fatty acid oxidation (Yamauchi et al., 2001). Previous studies have shown that adiponectin increased insulin sensitivity, resulting in decreases in both serum glucose and hepatic glucose production by inhibiting expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production (Berg et al., 2001; Combs et al., 2001).

Cardiomyopathy

In addition to beneficial effect on insulin-sensitive organs, some experimental animal studies implicate that the overexpression of adiponectin protects heart from ischemia-reperfusion injury, cardiomyopathy, and cardiac dysfunction, whereas its deficiency exacerbates cardiac damage owing to stress response Shibata et al., 2005; Tao et al., (2007). Shibata et al showed that adiponectin deficiency increased myocardial infarction (30 min ischemia-24 h reperfusion), apoptosis, and inflammatory cytokine (TNF-α), while adiponectin supplementation by injection of adenoviral vectors expressing adiponectin diminished infarct size, cardiac apoptosis, and TNF-α production in part, through activation of both AMPK- and COX2-dependent signaling pathways (Shibata et al., 2005). In another study by Tao et al. (2007), they also showed that adiponectin knock-out mice enhanced myocardial infarct size (30 min ischemia-3 h or 24 h reperfusion) and apoptosis, while acute administration of globular adiponectin attenuated myocardial ischemia-reperfusion injury, in part, through anti-oxidant (decreased gp91phox and superoxide production) and anti-nitrative mechanisms (decreased iNOS and peroxynitrite). Taken together, these studies suggest that adiponectin play an important role in protecting ischemia and reperfusion injury by inhibiting apoptosis.
Table 1. Expression of adiponectin receptors in vascular cells and vasculatures

| Species | Vascular beds or Cell Line | Gender | AdipoR (1 or 2) | Method used | Disease | Reference |
|---------|---------------------------|--------|----------------|-------------|---------|-----------|
| Mouse (db/db) | Coronary arterioles | Male | 1 (=), 2 (↓) | WB | Type 2 diabetes | Zhang et al., 2010 |
| Mouse (db/db) | Aorta | Male | 1 (↑), 2 (↓) | WB | Type 2 diabetes | Wong et al., 2011 |
| Rat (Brown norway) | Retinal ECs | Male | 1, 2 | Immunofluorescence | - | Lyzogubov et al., 2012 |
| Rat (Wistar) | Aorta | Male | 1 (↓), 2 (↓) | PCR | Type 1 diabetes | Guo et al., 2012 |
| Rat (Sprague dawley) | Coronary artery VSMCs | Male | 1 (↓), 2 (↓) | PCR | Insulin resistance | Shen et al., 2012 |
| Pig | Retinal arterioles | - | 1, 2 | Immunohistochemistry | - | Omae et al., 2013 |
| Human | HUVECs | - | 1, 2 | WB | - | Zheng et al., 2011 |
| Human | Human aortic ECs | - | 1, 2 | PCR | - | Zhang et al., 2009 |
| Human | Human artery SMCs | - | 1, 2 | PCR | - | Shi et al., 2008 |
| Human | Human aortic ECs | - | 1, 2 | PCR | - | Tan et al., 2004 |

Adiponectin is an adipose tissue-derived protein that appears to play an important role in preventing and ameliorating insulin resistance, diabetes, and related cardiovascular dysfunction. Diminished level of adiponectin was observed in obese, diabetic, and coronary artery disease patients and has been reported to be a useful predictor of diabetes and cardiovascular disease in human. To date, two adiponectin receptors including AdipoR1 and 2 were identified and it is known that the receptors are required for beneficial action of adiponectin. The anti-diabetic drugs such as thiazolidinediones (TZDs) increase adiponectin in both animals and
human (Hiuge-Shimizu et al., 2011; Tao et al., 2010). Recently, the small molecule AdipoRs agonist, AdipoRON was discovered by Okada-Iwabu et al. (2013) and they suggested that the agonist is a novel therapeutic target for the treatment of type 2 diabetes lined to obesity in an experimental diabetic mouse model. Considering previous studies, a number of studies have shown that administration of adiponectin has beneficial effects on endothelial-dependent vasodilitation and inhibition of atherosclerotic via NO-mediated signaling pathway. In this case, it is very tempting to speculate that the AdipoRs agonist could be a novel therapeutic target for treatment of vascular dysfunction. Further studies will facilitate a better understanding of the mechanism underlying agonists for AdipoRs in the development of therapeutic intervention in vascular disease.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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Adiponectin and chronic disease

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