Review Article

JER

http://dx.doi.org/10.12965/jer.140100

Journal of Exercise Rehabilitation 2014;10(2):54-59

Role of adiponectin in metabolic and cardiovascular disease

Sewon Lee[1], Hyo-Bum Kwak[2,*]

[1]Dalton Cardiovascular Research Center, University of Missouri-Columbia, MO, USA
[2]Department of Kinesiology, Inha University, Incheon, Korea

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.

*Corresponding author: Hyo-Bum Kwak
Department of Kinesiology, Inha University, 100 Inha-ro, Nam-gu, Incheon 402-751, Korea
Tel: +82-32-860-8183, Fax: +82-32-860-8188, Email: kwakhb@inha.ac.kr
Received: March 31, 2014 / Accepted: April 15, 2014

pISSN 2288-176X
eISSN 2288-1778

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 (PPAR)α 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 $gp91^{phox}$ 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 apopto-

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 Aorta	Male	1 (=), 2 (↓) 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 (↓)	PCR	Type 1 diabetes	Guo et al., 2012
Rat (Sprague dawley)	Coronary artery VSMCs	Male	1 (↓), 2 (↓)	PCR	Type 1 diabetes	Shen et al., 2012
Rat (Sprague dawley)	Aorta	Male	1 (↓), 2 (↓)	WB	Insulin resistance (16 wk High-fat diet)	Li et al., 2010
Pig	Retinal arterioles	-	1, 2	Immunohistochemisty	-	Omae et al., 2013
Human	HUVECs	-	1, 2	WB	-	Zheng et al., 2011
Human	HUVECs	-	1, 2	WB	-	Zhang et al., 2009
Human	Human airway SMCs	-	1, 2	PCR	-	Shin et al., 2008
Human	Human aortic ECs	-	1, 2	PCR	-	Tan et al., 2004

db/db, leptin receptor mutated mouse; ECs, endothelial cells; SMCs, smooth muscle cells; VSMCs, vascular SMCs; HUVECs, human umbilical vein endothelial cells; PCR, polymerase chain reaction; WB, western blotting.

sis, inflammation, and oxidative/nitrative stress.

Vascular dysfunction and atherosclerosis

Previous studies in human demonstrated that hypoadiponectinemia is associated with vascular dysfunction and a good predictor of endothelial function of coronary artery (Okui et al., 2008; Shimabukuro et al., 2003). Consistent with clinical studies, deficiency of adiponectin in mice impaired endothelial-dependent vasorelaxation (Lee et al., 2011; Lee et al., 2012; Ouchi et al., 2003b). On the other hand, the overexpression of adiponectin ameliorated vascular dysfunction induced by metabolic abnormalities in both animal model and human subject (Lee et al., 2012; Shimabukuro et al., 2003). Some studies also implicated the possible action of adiponectin in the development of atherosclerotic plaques, which occurs infiltration of monocyte to the vasculature where they differentiate into macrophage (Chinetti et al., 2004; Zhu et al., 2008). Interestingly, it was reported that replenishment of adiponectin reduced atherosclerotic lesion in apolipoprotein E (apoE) knock-out mice (Okamoto et al., 2002). Another pathway in which adiponectin has protective effect on vascular system through anti-oxidant activity is by augmenting the production of endothelial NO as well as inhibiting oxidative stress. It is reported that adiponectin has the ability to increase NO production by eNOS phosphorylation and decreased NO inactivation by inhibiting superoxide production in the vasculature and endothelial cells (Cao et al., 2009; Chen et al., 2003). Even though a number of studies have shown that reduced adiponectin levels were observed in metabolic and cardiovascular disease, it is not clear whether these diseases cause reduction of AdipoRs in blood vessels and vascular cells including endothelial and smooth muscle cells. A summary of studies examining the expression of AdipoRs in vasculatures and vascular cells is provided in Table 1. Considering the literature, both AdipoR1 and 2 are expressed in endothelial and vascular smooth muscle cells of various vascular bed including aorta, coronary arterioles, and retinal artery. A few studies have demonstrated that the experimental mouse model of type 2 diabetes decreased protein expression of AdipoR2 without alteration of AdipoR1 in aorta and coronary arterioles (Wong et al., 2011; Zhang et al., 2010). One promising therapeutic strategy to combat diabetes and vascular disease may be to up-regulate AdipoRs or activate the receptors with agonists to increase sensitivity of adiponectin. In this perspective, the small molecule AdipoRs agonist proposed by Okada-Iwabu et al. (2013) would be interesting topic to determine whether the agonist could ameliorate vascular dysfunction in cerebral and coronary arteries.

CONCLUSIONS

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

http://dx.doi.org/10.12965/jer.140100

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 vasodilation and inhibition of atherosclerosis 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.

ACKNOWLEDGMENTS

This work was supported by Inha University Research Grant.

REFERENCES

Adamczak M, Wiecek A, Funahashi T, Chudek J, Kokot F, Matsuzawa Y. Decreased plasma adiponectin concentration in patients with essential hypertension. Am J Hypertens 2003;16:72-75.

Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79-83.

Arnlov J, Ingelsson E, Sundstrom J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation 2010;121:230-236.

Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med 2001;7:947-953.

Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. Eur J Clin Invest 2002;32:14-23.

Cao Y, Tao L, Yuan Y, Jiao X, Lau WB, Wang Y, Christopher T, Lopez B, Chan L, Goldstein B, Ma XL. Endothelial dysfunction in adiponectin deficiency and its mechanisms involved. J Mol Cell Cardiol 2009;46:413-419.

Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. J Biol Chem 2003;278:45021-45026.

Chinetti G, Zawadski C, Fruchart JC, Staels B. Expression of adiponectin receptors in human macrophages and regulation by agonists of the nuclear receptors PPARalpha, PPARgamma, and LXR. Biochem Biophys Res Commun 2004;314:151-158.

Chow WS, Cheung BM, Tso AW, Xu A, Wat NM, Fong CH, Ong LH, Tam S, Tan KC, Janus ED, Lam TH, Lam KS. Hypoadiponectinemia as a predictor for the development of hypertension: a 5-year prospective study. Hypertension 2007;49:1455-1461.

Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. J Clin Invest 2001;108:1875-1881.

Deng Y, Scherer PE. Adipokines as novel biomarkers and regulators of the metabolic syndrome. Ann N Y Acad Sci 2010;1212:E1-E19.

Dresner A, Laurent D, Marcucci M, Griffin ME, Dufour S, Cline GW, Slezak LA, Andersen DK, Hundal RS, Rothman DL, Petersen KF, Shulman GI. Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. J Clin Invest 1999;103:253-259.

Guo Z, Zhang R, Li J, Xu G. Effect of telmisartan on the expression of adiponectin receptors and nicotinamide adenine dinucleotide phosphate oxidase in the heart and aorta in type 2 diabetic rats. Cardiovasc Diabetol 2012;11: 94.

Guzik TJ, Mangalat D, Korbut R. Adipocytokines - novel link between inflammation and vascular function? J Physiol Pharmacol 2006;57:505-528.

Hiuge-Shimizu A, Maeda N, Hirata A, Nakatsuji H, Nakamura K, Okuno A, Kihara S, Funahashi T, Shimomura I. Dynamic changes of adiponectin and S100A8 levels by the selective peroxisome proliferator-activated receptor-gamma agonist rivoglitazone. Arterioscler Thromb Vasc Biol 2011;31:792-799.

Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-1599.

Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev 2005;26:439-451.

Kiris I, Tekin I, Yesildag A, Vural H, Oyar O, Sirin B, Okutan H, Ibrisim E.

Inverse relationship between adiponectin levels and subclinical carotid atherosclerosis in patients undergoing coronary artery bypass grafting. Int Heart J 2006;47:855-866.

Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, Arita Y, Okamoto Y, Shimomura I, Hiraoka H, Nakamura T, Funahashi T, Matsuzawa Y, Osaka CADSGCad. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003;23:85-89.

Lee S, Park Y, Dellsperger KC, Zhang C. Exercise training improves endothelial function via adiponectin-dependent and independent pathways in type 2 diabetic mice. Am J Physiol Heart Circ Physiol 2011;301:H306-314.

Lee S, Zhang H, Chen J, Dellsperger KC, Hill MA, Zhang C. Adiponectin abates diabetes-induced endothelial dysfunction by suppressing oxidative stress, adhesion molecules, and inflammation in type 2 diabetic mice. Am J Physiol Heart Circ Physiol 2012;303:H106-115.

Li R, Xu M, Wang X, Wang Y, Lau WB, Yuan Y, Yi W, Wei X, Lopez BL, Christopher TA, Wang XM, Ma XL. Reduced vascular responsiveness to adiponectin in hyperlipidemic rats--mechanisms and significance. J Mol Cell Cardiol 2010;49:508-515.

Lyzogubov VV, Tytarenko RG, Bora NS, Bora PS. Inhibitory role of adiponectin peptide I on rat choroidal neovascularization. Biochim Biophys Acta 2012;1823:1264-1272.

Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 2002;8:731-737.

Magkos F, Sidossis LS. Recent advances in the measurement of adiponectin isoform distribution. Curr Opin Clin Nutr Metab Care 2007;10:571-575.

Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, Kumada M, Okamoto Y, Nagaretani H, Nishizawa H, Kishida K, Komuro R, Ouchi N, Kihara S, Nagai R, Funahashi T, Matsuzawa Y. Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. J Biol Chem 2002;277:37487-37491.

Nakamura Y, Shimada K, Fukuda D, Shimada Y, Ehara S, Hirose M, Kataoka T, Kamimori K, Shimodozono S, Kobayashi Y, Yoshiyama M, Takeuchi K, Yoshikawa J. Implications of plasma concentrations of adiponectin in patients with coronary artery disease. Heart 2004;90:528-533.

Nawrocki AR, Rajala MW, Tomas E, Pajvani UB, Saha AK, Trumbauer ME, Pang Z, Chen AS, Ruderman NB, Chen H, Rossetti L, Scherer PE. Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. J Biol Chem 2006;281:2654-2660.

Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, Yamaguchi M, Tanabe H, Kimura-Someya T, Shirouzu M, Ogata H, Tokuyama K, Ueki K, Nagano T, Tanaka A, Yokoyama S, Kadowaki T. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature 2013;503:493-499.

Okamoto Y, Arita Y, Nishida M, Muraguchi M, Ouchi N, Takahashi M, Igura T, Inui Y, Kihara S, Nakamura T, Yamashita S, Miyagawa J, Funahashi T, Matsuzawa Y. An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. Horm Metab Res 2000;32:47-50.

Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, Ohashi K, Sakai N, Shimomura I, Kobayashi H, Terasaka N, Inaba T, Funahashi T, Matsuzawa Y. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation 2002;106:2767-2770.

Okui H, Hamasaki S, Ishida S, Kataoka T, Orihara K, Fukudome T, Ogawa M, Oketani N, Saihara K, Shinsato T, Shirasawa T, Mizoguchi E, Kubozono T, Ichiki H, Ninomiya Y, Matsushita T, Nakasaki M, Tei C. Adiponectin is a better predictor of endothelial function of the coronary artery than HOMA-R, body mass index, immunoreactive insulin, or triglycerides. Int J Cardiol 2008;126:53-61.

Omae T, Nagaoka T, Tanano I, Yoshida A. Adiponectin-induced dilation of isolated porcine retinal arterioles via production of nitric oxide from endothelial cells. Invest Ophthalmol Vis Sci 2013;54:4586-4594.

Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, Okamoto Y, Ohashi K, Nagaretani H, Kishida K, Nishizawa H, Maeda N, Kobayashi H, Hiraoka H, Matsuzawa Y. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation 2003a;107:671-674.

Ouchi N, Ohishi M, Kihara S, Funahashi T, Nakamura T, Nagaretani H, Kumada M, Ohashi K, Okamoto Y, Nishizawa H, Kishida K, Maeda N, Nagasawa A, Kobayashi H, Hiraoka H, Komai N, Kaibe M, Rakugi H, Ogihara T, Matsuzawa Y. Association of hypoadiponectinemia with impaired vasoreactivity. Hypertension 2003b;42:231-234.

Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291:1730-1737.

Savage DB, Petersen KF, Shulman GI. Mechanisms of insulin resistance in humans and possible links with inflammation. Hypertension 2005;45:828-833.

Shen X, Li H, Li W, Wu X, Ding X. Pioglitazone prevents hyperglycemia induced decrease of AdipoR1 and AdipoR2 in coronary arteries and coronary VSMCs. Mol Cell Endocrinol 2012;363:27-35.

Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, Funahashi T, Ouchi N, Walsh K. Adiponectin protects against myocardial

 http://dx.doi.org/10.12965/jer.140100

ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. Nat Med 2005;11:1096-1103.

Shimabukuro M, Higa N, Asahi T, Oshiro Y, Takasu N, Tagawa T, Ueda S, Shimomura I, Funahashi T, Matsuzawa Y. Hypoadiponectinemia is closely linked to endothelial dysfunction in man. J Clin Endocrinol Metab 2003;88:3236-3240.

Shin JH, Kim JH, Lee WY, Shim JY. The expression of adiponectin receptors and the effects of adiponectin and leptin on airway smooth muscle cells. Yonsei Med J 2008;49:804-810.

Shulman GI, Rothman DL, Jue T, Stein P, DeFronzo RA, Shulman RG. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by 13C nuclear magnetic resonance spectroscopy. N Engl J Med 1990;322:223-228.

Tan KC, Xu A, Chow WS, Lam MC, Ai VH, Tam SC, Lam KS. Hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation. J Clin Endocrinol Metab 2004;89:765-769.

Tao L, Gao E, Jiao X, Yuan Y, Li S, Christopher TA, Lopez BL, Koch W, Chan L, Goldstein BJ, Ma XL. Adiponectin cardioprotection after myocardial ischemia/reperfusion involves the reduction of oxidative/nitrative stress. Circulation 2007;115:1408-1416.

Tao L, Wang Y, Gao E, Zhang H, Yuan Y, Lau WB, Chan L, Koch WJ, Ma XL. Adiponectin: an indispensable molecule in rosiglitazone cardioprotection following myocardial infarction. Circ Res 2010;106:409-417.

Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772-783.

Tsao TS, Tomas E, Murrey HE, Hug C, Lee DH, Ruderman NB, Heuser JE, Lodish HF. Role of disulfide bonds in Acrp30/adiponectin structure and signaling specificity. Different oligomers activate different signal transduction pathways. J Biol Chem 2003;278:50810-50817.

Wess J. G-protein-coupled receptors: molecular mechanisms involved in receptor activation and selectivity of G-protein recognition. FASEB J 1997;11:346-354.

Wong WT, Tian XY, Xu A, Yu J, Lau CW, Hoo RL, Wang Y, Lee VW, Lam KS, Vanhoutte PM, Huang Y. Adiponectin is required for PPARgamma-mediated improvement of endothelial function in diabetic mice. Cell Metab 2011;14:104-115.

Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohteki T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kitamura T, Shimizu T, Nagai R, Kadowaki T. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003;423:762-769.

Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002;8:1288-1295.

Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941-946.

Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, Ito Y, Kamon J, Tsuchida A, Kumagai K, Kozono H, Hada Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Awazawa M, Takamoto I, Froguel P, Hara K, Tobe K, Nagai R, Ueki K, Kadowaki T. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 2007;13:332-339.

Zhang H, Park Y, Zhang C. Coronary and aortic endothelial function affected by feedback between adiponectin and tumor necrosis factor alpha in type 2 diabetic mice. Arterioscler Thromb Vasc Biol 2010;30:2156-2163.

Zhang P, Wang Y, Fan Y, Tang Z, Wang N. Overexpression of adiponectin receptors potentiates the antiinflammatory action of subeffective dose of globular adiponectin in vascular endothelial cells. Arterioscler Thromb Vasc Biol 2009;29:67-74.

Zheng Q, Yuan Y, Yi W, Lau WB, Wang Y, Wang X, Sun Y, Lopez BL, Christopher TA, Peterson JM, Wong GW, Yu S, Yi D, Ma XL. C1q/TNF-related proteins, a family of novel adipokines, induce vascular relaxation through the adiponectin receptor-1/AMPK/eNOS/nitric oxide signaling pathway. Arterioscler Thromb Vasc Biol 2011;31:2616-2623.

Zhu W, Cheng KK, Vanhoutte PM, Lam KS, Xu A. Vascular effects of adiponectin: molecular mechanisms and potential therapeutic intervention. Clin Sci 2008;114:361-374.

Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cutrupi S, Parlongo S, Malatino LS, Bonanno G, Seminara G, Rapisarda F, Fatuzzo P, Buemi M, Nicocia G, Tanaka S, Ouchi N, Kihara S, Funahashi T, Matsuzawa Y. Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. J Am Soc Nephrol 2002;13:134-141.