AdipoRon may be benefit for atherosclerosis prevention

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ABSTRACT

Atherosclerosis has serious role in coronary arteries diseases; so it is important to establish effective strategies for prevention or even treatment of atherosclerosis. Adiponectin, as one of the most abundant adipokines, has insulin sensitivity, anti-inflammatory and anti-atherogenic properties. Disturbed adiponectin actions through its receptor, (AdipoR1 and AdipoR2) may be involved in atherosclerosis development. Some adiponectin effects are mediated by AMPK and PPAR-α-signaling. AdipoRon is an orally active synthetic molecule which can bind to AdipoR1, Adipo R2 and activate them. AdipoRon can activate AdipoR1-AMPK-PGC-1α pathway and AdipoR2-PPAR-α pathway. Some studies indicated insulin sensitivity, anti-apoptotic and anti-oxidative effect of AdipoRon. We hypothesize that AdipoRon has anti-atherosclerotic effect and may suppress atherosclerosis processes. With confirmation the benefit role of AdipoRon on atherosclerosis, it may be used in patients at risk of atherosclerotic development.

Keywords: Adiponectin, Adiponectin receptors, AdipoRon, Atherosclerosis, Cardiovascular diseases

Introduction

Cardiovascular diseases (CVDs) have major role in world mortality. 17.5 million of people die each year from CVDs, nearly 31% of all death (1). Atherosclerosis is one of the significant underlying factors of CVDs (2), so it is important to establish effective strategies for prevention or even treatment of atherosclerosis. Adiponectin as one of the most abundant adipokines, is secreted by adipose tissue (3). Human gene coding for adiponectin has close association with diabetes and CVDs susceptibility (4). Anti-inflammatory, anti-atherogenic and insulin sensitivity properties of adiponectin have been proved by several studies (5-8). Adiponectin function is mediated through its receptors: AdipoR1 and AdipoR2 (6). Disturbed adiponectin actions through its receptors may have role in atherosclerosis development (6). Some metabolic effects of adiponectin are mediated by AMPK and PPAR-α signaling pathway. PPAR-α has significant role in suppression of atherogenic and inflammatory process likely by inhibiting NF-κB signaling (9). Also PPAR-α affect monocytes recruitment to early atherosclerotic lesion (an initial step in atherosclerosis) (10). AMPK pathway has several function in cellular metabolism including glucose and lipid metabolism (11, 12). AMPK activation by adiponectin is suppressed in adiponectin-null mice. Moreover AdipoR2 disturbance causes the reduction in adiponectin-induced PPAR-α signaling and concurrently deletion of AdipoR1 and AdipoR2 promotes insulin resistance and glucose intolerance (13).

Adiponectin has important vascular protective function by improvement of eNOS activity and NO production, these effects are mediated by AMPK-mediated phosphorylation of eNOS (14). AdipoR1 and R2 involved in this process (15). In addition, anti-apoptotic effect of adiponectin in endothelial cells is mediated by AMPK signaling (16). It should be noted that endothelial and smooth muscle cells apoptosis are injurious for plaque stability (17). Adiponectin inhibits foam cell formation by several mechanisms (18). This protein suppresses the production of inflammatory cytokines and adhesion molecules (19), thereby inhibits monocyte adhesion to endothelium (20). Adipor overexpression enhances this inhibitory effects of adiponectin, it is suggested that AdipoR have critical role in modulating the anti-inflammatory effects of adiponectin on the endothelium (21).

In vitro and in vivo studies have indicated the anti-oxidative effect of adiponectin (22-24). On the other hand, oxidative stress studies increased in AdipoR1 and AdipoR2-deficient mice. It is suggested that adiponectin-AdipoR pathway involves in the inhibition of oxidative stress (13, 22). There is some difficulty to convert adiponectin to a practical drug
form, so application of adiponectin receptor agonists is suggested (25). AdipoRon is an orally active synthetic molecule which is discovered by Okada-Iwabu et al., it can bind to AdipoR1, Adipo R2 and activate them (26). This substance attenuates insulin resistance and glucose intolerance, also improved lipid metabolism in high-fat diet mice. AdipoRon can activate AdipoR1-AMPK- PGC-1α pathway and AdiopR2-PPAR-α pathway. The researchers suggest that AdipoRon may perform major effects of adiponectin including enhanced insulin sensitivity, suppressive effects on cardiovascular disease and cancers (27, 28).

In vitro studies showed that AdipoRon activates AMPK pathway. Oral administration of AdipoRon ameliorate post ischemic myocardial apoptosis via dependent and independent AMPK pathway (29). It seems that AdipoRon has anti-oxidative effect, since meaningfully enhances expression of antioxidative enzymes genes including manganese superoxide dismutase and reduced markers of oxidative stress such as thiobarbituric acid reactive substance in skeletal muscle of mice. AdipoRon decreased expression of genes involved in encoding pro-inflammatory cytokines in the liver and with adipose tissue of mice (29).

Conclusion
Because adiponectin has anti atherosclerotic effect, we think that AdipoR agonists such as AdipoRon may also have this effect. No study up to now has examined the effects of AdipoRon on atherosclerosis processes. If the studies confirmed our hypothesis, AdipoRon may be a new suitable choice in atherosclerosis prevention in patients at risk of this disease.

Conflict of interest
None.

References:
1. Cardiovascular diseases (CVDs). Available at: http://www.who.int/cardiovascular_diseases/en/ cited 2016 Apr 21.
2. Autieri MV. Pro- and anti-inflammatory cytokine networks in atherosclerosis. Int Sch Res Not [serial online] 2012. Available from: http://www.hindawi.com/journals/isrn/2012/987629/ abs/. cited 2014 Apr 7.
3. Esfahani M, Movahedian A, Baranchi M, Goodarzi MT. Adiponectin: an adipokine with protective features against metabolic syndrome. Iran J Basic Med Sci 2015; 18:430–442.
4. Stumvoll M, Tschritter O, Fritsche A, Staiger H, Renn W, Weisser M, et al. Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. Diabetes 2002; 51:37–41.
5. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipatrophy and obesity. Nat Med 2001; 7:941–946.
6. Yamauchi T, Iwabu M, Okada-Iwabu M, Kadowaki T. Adiponectin receptors: a review of their structure, function and how they work. Best Pract Res Clin Endocrinol Metab 2014 28:15–23.
7. Lim S, Quon MJ, Koh KK. Modulation of adiponectin as a potential therapeutic strategy. Atherosclerosis. 2014 Apr;233(2):721–8.
8. Pileiro R, Iglesias MJ, Gallego R, Raghay K, Eiras S, Rubio J, Diéguez C, Guallís O, González-Juanatey JR, Lago F. Adiponectin is synthesized and secreted by human and murine cardiomyocytes. FEBS Lett. 2005 Sep 26;579(23):5163–9.
9. Lee WS, Kim J. Peroxisome proliferator-activated receptors and the heart: lessons from the past and future directions. PPAR Res 2015; 2015:271983.
10. Neve BP, Frucht JC, Staelens B. Role of the peroxisome proliferator-activated receptors (PPAR) in atherosclerosis. Biochem Pharmacol 2000; 60:1245–1250.
11. Russell RR, Li J, Coven DL, Pypaert M, Zechner C, Palmeri M, et al. AMP-activated protein kinase mediates ischemic glucose uptake and prevents postischemic cardiac dysfunction, apoptosis, and injury. J Clin Invest 2004; 114:495–503.
12. Hopkins TA, Ouchi N, Shi Bata R, Walsh K. Adiponectin actions in the cardiovascular system. Cardiovasc Res 2007; 74:11–18.
13. Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 2007; 13:332–339.
14. 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.
15. Cheng KK, Lam KS, Wang Y, Huang Y, Carling D, Wu D, et al. Adiponectin-induced endothelial nitric oxide synthase activation and nitric oxide production are mediated by APPL1 in endothelial cells. Diabetes 2007; 56:1387–1394.
16. Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, et al. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circ Res 2004; 94:227–31.
17. Kodex MM, Herman AG. Apoptosis in atherosclerosis: beneficial or detrimental? Cardiovasc Res 2000; 45:736–746.
18. Ouchi N, Kihara S, Aita Y, Nishida M, Matsuyama A, Okamoto Y, et al. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation 2001; 103:1057–1063.
19. Motoshina H, Wu X, Mahady K, Goldstein BJ. Adiponectin suppresses proliferation and superoxide generation and enhances eNOS activity in endothelial cells treated with oxidized LDL. Biochem Biophys Res Commun 2004; 315:264–271.
20. Ouedraogo R, Gong Y, Berzins B, Wu X, Mahady K, Hough K, et al. Adiponectin deficiency increases leukocyte–endothelium interactions via upregulation
of endothelial cell adhesion molecules in vivo. J Clin Invest 2007; 117:1718-1726.
21. Zhang P, Wang Y, Fan Y, Tang Z, Wang N. Overexpression of adiponectin receptors potentiates the antiinflammatory action of sub effective dose of globular adiponectin in vascular endothelial cells. Arterioscler Thromb Vasc Biol 2009; 29:67-74.
22. Matsuda M, Shimomura I. Roles of adiponectin and oxidative stress in obesity-associated metabolic and cardiovascular diseases. Rev Endocr Metab Disord 2014; 15:1-10.
23. Cao Y, Tao L, Yuan Y, Jiao X, Lau WB, Wang Y, et al. Endothelial dysfunction in adiponectin deficiency and its mechanisms involved. J Mol Cell Cardiol 2009; 46:413-419.
24. Kim J, Song SE, Kim YW, Kim JY, Park SC, Park YK, et al. Adiponectin inhibits palmitate-induced apoptosis through suppression of reactive oxygen species in endothelial cells: involvement of cAMP/protein kinase A and AMP-activated protein kinase. J Endocrinol 2010; 207:35-44.
25. Lee CH, Hung Y-J. Possible new therapeutic approach for obesity-related diseases: Role of adiponectin receptor agonists. J Diabetes Investig. 2015; 6: 264-266.
26. Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, et al. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature 2013; 503:493-499.
27. Caselli C, D’Amico A, Cabitati M, Prescimone T, Del Ry S, Giannessi D. Back to the heart: the protective role of adiponectin. Pharmacol Res 2014; 82:9-20.
28. Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: a review of current evidence. Endocr Rev 2012; 33:547-594.
29. Zhang Y, Zhao J, Li R, Lau WB, Yuan Y-X, Liang B, et al. AdipoRon, the first orally active adiponectin receptor activator, attenuates postischemic myocardial apoptosis through both AMPK-mediated and AMPK-independent signalings. Am J Physiol Endocrinol Metab 2015; 309:E275-282.