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AdipoRon may be benefit for atherosclerosis prevention

Maryam Esfahani [1], Nooshin Shabab [2], Massoud Saidijam [3*]

[1] Department of Biochemistry and Nutrition, Hamadan University of Medical Sciences, Hamadān, Iran
[2] Research Center for Molecular Medicine, Hamadan University of Medical Sciences, Hamadān, Iran
[3] Department of Molecular Medicine and Genetics, Research Center for Molecular Medicine, Hamadan University of Medical Sciences, Hamadān, Iran

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ABSTRACT

Atherosclerosis has serious role in coronary arteries disease,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.

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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-kβ signaling (9). Also PPAR-α affect monocytic 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 adipoR1-null mice, Moreover AdipoR2 disturbance causes the reduction in adiponectin-induced PPAR-αsignaling 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 processes(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). AdipoRs overexpression enhances this inhibitory effects of adiponectin, it is suggested that AdipoRs 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 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

*Corresponding author: Massoud Saidijam. Department of Molecular Medicine and Genetics, Research Center for Molecular Medicine, Hamadan University of Medical Sciences, Hamadān, Iran. email: saidijam@umsha.ac.ir

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 AdipoR2-PPAR-α pathway. The researchers suggest that AdipoRon may perform majority effects of adiponectin including enhanced insulin sensitivity, suppressive effects on cardiovascular disease and cancers (27, 28).

In vitro studies showed that AdipRon 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.

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