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AdipoRon, adiponectin receptor agonist improves vascular function in the mesenteric arteries of type 2 diabetic mice

Soo Kyoung Choi

Abstract

Adiponectin is one among the foremost abundant adipokines secreted from fat . An orally active synthetic adiponectin receptor agonist, adipoRon has been suggested to ameliorate insulin resistance, myocardial apoptosis, and pancreatic tumor. it's been reported that adiponectin directly induces vascular relaxation however; the chronic effect of adipoRon within the vascular dysfunction in type 2 diabetes has not been studied yet. Thus, during this study, we examined whether adipoRon improves vascular function in type 2 diabetes and what mechanism is involved. Ten to 12-week old male type 2 diabetic (db-/ db-) mice were treated with adiponectin receptor agonist (adipoRon, 10 mg/kg/everyday by oral gavage) for two weeks. Isolated mesenteric arteries were mounted within the arteriography and arterial diameter was measured. And western blot analysis was assessed. Pressure-induced myogenic response was significantly increased, whereas endothelium-dependent relaxation was significantly reduced within the mesenteric arteries from type 2 diabetic mice. Interestingly, treatment of adipoRon normalized potentiated myogenic response. However,endothelium-dependent relaxation wasn't suffering from treatment of adipoRon. The expression levels of adiponectin receptor 1, 2 and APPL 1, 2 were increased within the mesenteric arteries from Type 2 diabetic mice and treatment of adipoRon didn't affect them. Interestingly, adipoRon treatment increased the phosphorylation level of AMPK and decreased phosphorylation of MYPT1 within the type 2 diabetic mice while there was no change within the level of eNOS phosphorylation. The treatment of adipoRon improves vascular function within the mesenteric arteries from type 2 diabetic mice through endothelium-independent mechanism. it's suggested that MLCP activation through reduced phosphorylation of MYPT1 could be the dominant mechanism within the adipoRon-induced vascular effect.

An orally active synthetic adiponectin receptor agonist, AdipoRon has been suggested to ameliorate insulin resistance, and glucose tolerance. However, the chronic effect of AdipoRon within the vascular dysfunction in type 2 diabetes has not been studied yet. Thus, during this study, we examined whether AdipoRon improves vascular function in type 2 diabetes. Type 2 diabetic (db-/db-) mice were treated with AdipoRon (10 mg/kg/everyday, by oral gavage) for two weeks. weight and blood sugar levels were recorded every other day during the experimental period. Diameter of mesenteric arteries was measured. And western blot analysis was performed with mesenteric arteries. Pressure-induced myogenic response was significantly increased while endothelium-dependent relaxation was reduced within the mesenteric arteries of db-/db- mice. Treatment of AdipoRon normalized potentiated myogenic response, whereas endothelium-dependent relaxation wasn't suffering from treatment of AdipoRon. The expression levels of AdiR1, AdiR2, APPL1, and APPL 2 were increased within the mesenteric arteries of db-/db- mice and treatment of AdipoRon didn't affect them. Interestingly, AdipoRon treatment increased the phospho-AMPK and decreased MYPT1 phosphorylation in db-/db- mice while there was no change within the level of eNOS phosphorylation. The treatment of AdipoRon improves vascular function within the mesenteric arteries of db-/db- mice through endothelium-independent mechanism. we propose that MLCP activation through reduced phosphorylation of MYPT1 could be the dominant mechanism within the AdipoRon-induced vascular effect.

Adiponectin is a crucial and abundant adipokine secreted from adipocyte and regulates insulin sensitivity and energy homeostasis. The low concentration of adiponectin is related to various disease like obesity, diabetes, cardiovascular diseases [5]. Recent studies reported plasma adiponectin level was decreased within the patients with type 2 diabetes, and thiazolidinedione (TZD) administration increased the adiponectin level [6,7]. An experimental study showed that insulin resistance was ameliorated by the replenishment of adiponectin in mice [8]. Thus adiponectin has been focused as potential therapeutic target for the treatment of type 2 diabetes [9]. Adiponectin regulates cellular function via two specific receptors, adiponectin receptor 1 (AdiR1) and adiponectin receptor 2 (AdiR2) [10]. Adaptor protein containing a pleckstrin homology (PH) domain, phosphotyrosine-binding (PTB) domain, and leucine zipper motif 1 (APPL1) is that the first identified adapter protein to positively mediate intracellular adiponectin signaling. APPL1 directly binds to the intracellular domain of adiponectin receptor and positively mediates the signaling to the AMP-activated protein kinase (AMPK), p38 mitogen activated protein kinase (MAPK), and peroxisome proliferator-activated receptor α (PPARα) [11]. On the opposite hand APPL2, an isoform of APPL1, blocks APPL1-mediated insulin-sensitizing effect of adiponectin and thus negatively regulates adiponectin signaling [9]. Recently, an orally active adiponectin receptor agonist, AdipoRon, has been developed and showed similar effects to adiponectin. Like adiponectin, AdipoRon binds to both AdiR1 and

AdiR2 at a coffee molecular concentration and activates AMPK, PPAR, and peroxisome proliferator–activated receptor gamma coactivator 1–alpha (PGC1α) [12]. AdipoRon improved insulin sensitivity and glucose tolerance and lipid metabolism in cultured cells and mice [13]. Furthermore, treatment of AdipoRon improved metabolic function and extended lifetime in type 2 diabetic mice. Although effects of AdipoRon are investigated in various pathophysiological states, the consequences of AdipoRon on vascular function, specifically in type 2 diabetes haven't yet been studied. Therefore, the objectives of this study were to elucidate whether adiponectin receptor agonist, AdipoRon, improves vascular function within the mesenteric arteries of type 2 diabetic mice and, if so, to work out the mechanisms involved. After 2 weeks of treatment, mice were euthanized and mesenteric arteries were isolated and cannulated with glass micropipettes. Krebs-Henseleit (K-H) solution bubbled with a 95% O2 + 5% CO2 gas mixture was perfused into the arteries. The arteries were pressurized to 40 mmHg using pressure-servo control perfusion systems (Living Systems Instruments, St Albans, USA) for 30-minutes equilibration period. A video image analyzer, as described previously [14], monitored the vessel diameter. Intraluminal pressure was increased from 20 to 120 mm Hg in a stepwise manner to measure myogenic response. At the end of the experiments, vessels were superfused with a calcium-free K-H solution containing 1 mM ethylene glycol-bis (2-aminoethylether)-N,N,N′,N′-tetraacetic acid (EGTA) to determine passive diameter. Myogenic response was calculated as the percentage between active and passive diameters. To determine the endothelium-dependent relaxation, pressurized arteries were pre-contracted with thromboxane agonist (U-46619, 10^{-7} mol/L), and then cumulative concentrations (10^{-9} to 10^{-5} mol/L) of acetylcholine were applied.

Biography

Soo Kyoung Choi has pursued her PhD from Yonsei University and Postdoctoral studies from Tulane University. She is the Research Assistant Professor in Department of Physiology at Yonsei University. She has published more than 22 papers in reputed journals.

Soo Kyoung Choi
Yonsei University, Republic of Korea,E-mail: skchoi@yuhs.ac

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