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Effects of chemerin/CMKLR1 on aerobic exercise-induced improvement of glycolipid metabolism in atherosclerosis rats

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Objective As an adipokine and inflammatory cytokines, chemerin plays an vital role in the occurrence and severity of obesity and its related disease such as atherosclerosis (AS), type 2 diabetes and coronary artery disease, among which the regulation of chemerin on glycolipid metabolism is of great important. Chemerin exerts its main biological functions through binding to its receptor: G protein-coupled receptor chemokine-like receptor (CMKLR1). Chemerin/CMKLR1 has become potential targets for diabetes treatment. For AS, the serum level of chemerin is also related to the disorders of glycolipid metabolism as well as the size and fibrous cap maturity of AS plaques. Exercise decreased the serum level of chemerin in AS, accompanied with the improvement of glucose and lipid metabolism, which indicated the possible relation between decrease of chemerin and improvement of glycolipid metabolism. However, it is still unclear whether exercise-induced improvements of glycolipid metabolism is associated with the changes of chemerin and CMKLR1 in tissue such as livers and gastrocnemius (play key roles in the modulation of glycolipid metabolism) and the mechanism by which chemerin/CMKLR1 modulated glycolipid metabolism. Recent studies reported that chemerin is a target gene of nuclear transcription factor- peroxisome proliferator activated receptor γ (PPARγ). PPARγ links glycolipid metabolism and inflammation through its target gene-adipose triglyceride lipase (ATGL) and lipoprotein lipase (LPL), gate-keeping enzymes hydrolyzing lipids in intracellular triglyceride and plasma lipoproteins respectively. Our previous work has found that aerobic exercise decreased the level of chemerin/CMKLR1 in serum and tissues of type 2 diabetes rats by the mediation of PPARγ-ATGL and LPL. So the purposes of this study were to clarify if exercise-modulated improvement of glycolipid metabolism of atherosclerosis rats was also associated with the changes of chemerin and CMKLR1 in serum and tissues (liver and gastrocnemius), similar as in diabetes, and further its mechanisms.
Methods Twenty-seven male Sprague-Dawley (SD) rats aged 6 weeks were randomly divided into control group (Con, n=9) and atherosclerosis (AS, n=18) model rats. AS model rats were established by intraperitoneal injection of Vitamin D3 (600,000 IU/kg body weight in the first week, 100,000 IU/kg body weight in the third week and six week) in combination with 8-week high fat diet feeding. For verifying the successful establishment of AS rats, one rat from Con group and two rats from AS model group were taken randomly to determine the levels of blood glucose and lipid as well as the morphological and pathological alterations of the aorta. Then, 16 successfully established AS rats were randomly divided into AS group (n=8) and exercised AS group (EAS, n=8). EAS group rats experience 4-week moderate intensity aerobic exercise on treadmill with gradually increasing intensity, while the Con and AS rats were kept sedentary life, with all of the rats were fed with common diet during the experiments. Before and after 4-week exercise, the blood sample of the three group rats were drawn to measure the circulating levels of fasting blood glucose (FBG), triglyceride (TC), total cholesterol (TG), LDL and HDL. The serum fasting insulin (FINS) and serum chemerin were measured by ELISA. The protein levels of chemerin, CMKLR1, PPARγ, ATGL and LPL in livers and gastrocnemius were detected by Western blot. And the full-length aorta of the rats were separated to determine AS arteriosclerosis plaques with oil red O staining and histopathological examination with HE staining.

Results 1) Compared with AS rats, the disorder of glycolipid metabolism (reflected by increases in TC, TG, LDL and FINS as well as decrease in HDL in blood although no difference in serum level of FBG) were all improved in EAS rats. 2) Compared with AS rats, the atherosclerotic plaque in the aoras and the enhanced proliferation and arrangement disorder of smooth muscle cells in aorta membrane were all alleviated in EAS rats. 3) Compared with AS rats, the increased chemerin in serum and the enhancements of chemerin and CMKLR1 in liver and gastrocnemius at protein levels were all significantly decreased in EAS rats. 4) Compared with AS rats, the protein levels of PPARγ, ATGL and LPL in the livers and gastrocnemius were all increased in EAS rats.
Conclusions This study verified that: 1) the exercise-induced improvement of glycolipid metabolism in AS rats was likely to be associated with the decreases of chemerin in serum as well as of chemerin and CMKLR1 in tissues (liver and gastrocnemius). To our knowledge, it is the first report that exercise down-regulated chemerin/CMKLR1 in tissues in AS rats, and the decreases of chemerin/CMKLR1 might be related to the improvement of glycolipid metabolism in AS rats. 2) the exercise-induced decreases of chemerin/CMKLR1 in AS rats might be mediated by PPARγ and its target genes- ATGL and LPL, which need further investigations.