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Epigenetic regulation of exercise-improved LTCC and BKCa channels function in hypertension mesenteric arteries

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Objective To investigate the epigenetic mechanism of the voltage-gated L-type Ca^{2+} channel (LTCC) and the large-conductance Ca^{2+}-activated K^+ channel (BK_{Ca}) function in mesenteric arterial myocytes improved by regular aerobic exercise in hypertension.
Methods 12-week-old male SHR and WKY rats were randomly assigned to sedentary and exercise training groups, respectively. Exercise groups were performed a moderate-intensity treadmill running. After 8 weeks, patch clamp study, Ca^{2+} image, Western blot, qPCR, bisulfite sequencing PCR were used to detect the LTCC and BK_{Ca} channel currents, BK_{Ca} single channel gating properties, Ca^{2+} spark, mRNA and protein expression of LTCC α_{1c} together with BK_{Ca} α and β1 subunits, DNA methylation level of α_{1c} and β1 gene promoter region, miR-328 expression. In vitro experiment，miR-328 mimic and miR-328 inhibitor were transfected into cultured arterial myocytes to make miR-328 overexpressing or silencing, the mRNA and protein expression of α_{1c} subunits were determined after 48 h transfection.
Results 1) After 8 weeks of exercise, SBP in both exercise groups of WKY and SHR were significantly lower than that of their sedentary counterparts. 2) Exercise normalized the increased LTCC and BK_{Ca} current density of mesenteric arterial myocytes in SHR. 3) Exercise attenuated the increased single BK_{Ca} channel open Probability (*Po*) and the amplitude of Ca^{2+} spark in hypertension. 4) Exercise inhibited the upregulated mRNA and protein expression of BK_{Ca} β1 subunit in mesenteric arteries from SHR; β1 gene promoter was demethylation in hypertension, exercise increased the methylation level at β1 gene promoter of SHR. 5) The protein expression of LTCC α_{1c} subunit was significantly increased in SHR, while decreased by exercise; the expression of miR-328 in mesenteric arteries was highly negative correlation with α_{1c} subunit. 6) The miR-328 overexpression by transfecting miR-328 mimic decreased α_{1c} subunit protein level significantly, while miR-328 inhibitor made α_{1c} subunit a slight increase.
Conclusions Regular aerobic exercise efficiently reduces blood pressure of SHR, enhances β1 gene promoter methylation, mediates miR-328 inhibiting the α_{1c} expression at post-transcriptional level, which might be the epigenetic mechanism underlying exercise-improved LTCC and BK_{Ca} channels function in mesenteric arteries of hypertension.