Title: High-intensity training induces airway hyperresponsive through neuron transdifferentiation of adrenal medulla chromaffin cells

Body: Background: A high prevalence of exercise-induced bronchoconstriction (EIB) can be found in elite athletes, but the underlying mechanisms remain elusive. Objectives: We hypothesized that high-intensity training was related to the mechanisms of EIB via nerve growth factor (NGF)-induced neuron transdifferentiation of adrenal medulla chromaffin cells (AMCC). Methods: Airway responsiveness, NGF and EPI levels, and chromaffin cell structure in high/moderate-intensity training (HiTr/MoTr) rats with or without ovalbumin sensitization and the expression of NGF-associated genes in AMCC was tested. Results: Both HiTr and OVA intervention significantly increased airway resistance. HiTr significantly increased peribronchial lymphocyte infiltration, whereas OVA significantly increased various inflammatory cells infiltration especially the eosinophil level. Both HiTr- and OVA-intervention up-regulated circulating NGF level and peripherin level in AMCC, but down-regulated phenylethanolamine N-methyl transferase level in AMCC and circulating EPI level. HiTr+OVA and HiTr+ExhEx (exhaustive exercise) interventions significantly enhanced most of the HiTr effects. The elevated NGF level was significantly associated with neuronal conversion of AMCC. The levels of p-Erk1/2, JMJD3 and Mash1 were significantly increased, but the levels of p-p38 and p-JNK were significantly decreased in AMCC in HiTr and OVA rats. Injection of NGF antiserum and MoTr reversed these changes observed in HiTr and/or OVA rats. Conclusion: Our study suggests that NGF may be important in the pathogenesis of EIB by inducing neuron transdifferentiation of AMCC via MAPK pathways and decreasing circulating EPI.