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The effect of hypoxic training at different simulated altitude on the antioxidant activity mediated by Nrf2 in mice skeletal muscle

Weixiu Ji[2,1],Ying Zhang[2]
1.Beijng sport university
2.tianjin university of sport

Objective It is generally believed that the long-term hypoxic training could impact oxidation resistance. Nrf2-Keapl signaling pathway is a key pathway of cell oxidative stress reaction. This research attempts to investigate the role and mechanism of Nrf2 in oxidation resistance to hypoxic training of different oxygen concentration.
Methods Part one, 8-week-old Nrf2 knockout mice and wild type mice were divided into normoxic control group (NC), simulated altitude of 3500m hypoxic training group (3500HT) and simulated altitude of 5000m hypoxic training group (5000HT) randomly and respectively. The mice run on treadmill in speed of 12 m/min, 1h/day, 6day/week, for 4 weeks. Oxygen concentration in hypoxia was 13.3% and 10%. Mice were treated for 4 weeks, 8h/day. 48 h after the last training, the mice were sacrificed and skeletal muscles of legs were collected. Western Blot tested Nrf2 and antioxidant enzyme protein. Antioxidant enzymes mRNA were tested by RT-PCR. High quality fluorescence measurement was used to test ROS levels in skeletal muscle. Part two, The 30 C57BL/6J mice were divided into three groups: control group (WC), hypoxia group (WH), hypoxic training group (WHT). The hypoxic training arrangement was same as before. After both the interventions, the mice were sacrificed and collected skeletal muscle of legs. The expression of Nrf2, Keap1 and p-Nrf2 were analyzed by western blot. High quality fluorescence assay was done to detect ROS level in skeletal muscle of mice.
Results (1) Compared with the same type mice NC group, Nrf2 protein, the mRNA and protein of CAT, GPX-1, GCLm, the mRNA of SOD1, SOD2, HO-1 were increased in wild type mice 3500HT group. And the Nrf2 protein, the mRNA and protein of SOD1, SOD2, the mRNA of CAT, NQO-1, GCLc, GCLm mRNA, the protein of HO-1 were decreased, and the ROS levels was higher in wile type mice 5000HT group. The mRNA of CAT, HO-1 in Nrf2-KO mice 3500HT group were increased, the mRNA and protein of SOD1, the mRNA of SOD2, the protein of GCLc were decreased, but the GCLc mRNA was increased in Nrf2-KO mice 5000HT group. When compared with the same intervention wild type mice, the mRNA and protein of SOD1, GPX-1, SOD2, HO-1, the mRNA of CAT, NQO-1, GCLc, GCLm were decreased in Nrf2-KO mice 3500HT group. The mRNA of GCLm, NQO-1, the protein of GCLc, HO-1 were decreased, but the GCLc mRNA was increased. (2) Nrf2/Keap1 complex contents in mice skeletal muscle of WH and WHT groups were significantly increased compared with WC group respectively. The free Nrf2 in mice skeletal muscle of WH、WHT groups were significantly reduced compared with WC group respectively. After both types of intervention, free Keap1 had no change nearly in skeletal muscle of mice. Compared with WC group, p-Nrf2 in mice skeletal muscle of WH and WHT groups were significantly reduced. The ROS level in mice skeletal muscle of WHT group significantly increased compared with WC group mice. Conclusions: Hypoxia and hypoxia training three interventions could increase Nrf2/Keap1 combination in skeletal muscle of mice, reduce the volume of free Nrf2; Phosphorylation of Nrf2 in skeletal muscle of mice in hypoxia training group was significantly lower, which may be result in marked increase in ROS level.
Conclusions (1) Hypoxic training could affect antioxidant activity via Nrf2 in mice skeletal muscle, which is connected with the oxygen concentration. (2) Moderate hypoxia training (at the altitude of

3500m) can promote the antioxidant activity via Nrf2. However, extremely hypoxic training (at the altitude of 5000m) can restrain the antioxidant activity via Nrf2 through the inhibition of Nrf2/Keap1 dissociation.