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Effects of HIF-1 α on Nrf2-ARE antioxidant signal in mice skeletal muscle after acute exhaustive exercise

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Objective Hypoxia or exercise could lead to oxidative stress. Hypoxia inducible factor-1 (HIF-1) is an oxygen sensor and the expression of its α subunit can be regulated by hypoxia. NF-E2-related factor 2 (Nrf2) is an important modifier of cellular responses to oxidative stress. A major mechanism in defense oxidative stress is the activation of the Nrf2-ARE antioxidant pathway. But whether the increase of HIF-1 α could affect the Nrf2-ARE antioxidant signal, and further influence the oxidative stress status in vivo remains unknown. In this study, we wished to examine the effect of HIF-1 α on Nrf2-ARE antioxidant pathway in mice skeletal muscle after acute exhaustion exercise.

Methods HIF-1 α high expression (H) and C57BL/6J mice(W) were used at 20 respectively and each kind of mice were randomly divided into two groups: control (C) and exercise (E). The treadmill exercise was preformed at the acute exhaustion exercise. On the day of acute exercise, mice allocated to perform treadmill running were subject to 5% incline and 5min at 10m/min, and then increased 3m/min every 3 minutes. Mice were sacrificed at the indicated time points following treadmill running. Nrf2, phosphor-Nrf2 (Ser40), nuclear Nrf2 protein were measured by Western Blot and Nrf2-ARE binding activity, the mRNA and protein levels of Nrf2 target genes, key antioxidant enzymes (SOD1, SOD2, CAT, NQO-1) and ROS level, were also measured in skeletal muscles after the interventions.

Results (1) The results showed that compared with WC, RNA and protein expression level of Nrf2 were increased in HC skeletal muscles. Nrf2-ARE binding activity, Nrf2 target gene SOD1, SOD2, NQO-1 mRNA expression and NQO-1 protein expression were also increased in HC skeletal muscles. Meanwhile, ROS level in HC skeletal muscles decreased significantly.

(2) After the acute exhaustion exercise, high HIF-1 α expression mice (HE) had higher expression of p-Nrf2(Ser 40) and nuclear Nrf2 protein than the wide type mice(WE). The mRNA expression of SOD1 and mRNA /protein of NQO-1 in HE increased as well. In contrast, ROS level decreased significantly in HE muscles.

Conclusions The result indicated the proper high expression of HIF-1 α could promote the antioxidant capacity of skeletal muscle in mice through Nrf2-ARE pathway.