Effect of Genistein Supplementation on Exercise-Induced Inflammation and Oxidative Stress in Mice

スポーツ医科学研究領域
5019A020-1　WU Cong　　研究指導教員：鈴木　克彦　教授

Abstract

Background: Physical exercise has proven to be an effective way to maintain health status. Being physically fit and eating a well-balanced diet have been proved to be practical in the prevention of various chronic diseases. However, when the intensity or duration of exercise gets severe, it will lead to the cellular production of reactive oxygen species (ROS) which exceed the capacity of the antioxidant defense system. When the homeostatic condition of redox (oxidation-reduction) balance breaks, ROS react with cellular components including DNA, lipids, and proteins and can lead to cellular damage, which can be called short-term oxidative stress. On the other hand, this kind of episodic increase in ROS production may also induce oxidative stress, inflammation and even organ damage. When free radical damage is caused by high-intensity exercise, the pro-inflammatory mediators such as interleukin (IL)-6 and IL-1β will be induced afterwards.

Isoflavonoids is widely used as a kind of potent antioxidant supplement. Genistein (GE), which is rich in soy-derived foods, is one of the most studied isoflavonoids for its estrogenic function and anti-oxidative, anti-inflammatory activities. Previous studies have shown that GE supplementation is related to the activation of the nuclear factor erythroid 2-related factor/hemeoxygenase-1 (Nrf2/HO-1) pathway and the increase of antioxidant enzymes activities. GE has drawn special attention for its potential protective effect against exercise-induced inflammation and oxidative stress, but most previous studies used relatively long term and low-dose GE administration and the conclusions are inconsistent. The purpose of this study was to investigate the influences of oral high-dose GE administration on exercise-induced oxidative stress, inflammatory response, tissue damage and physical performance.

Methods: C57BL/6J mice were divided into four groups (n=8): control group (Con), GE administrated group (GE), exercise group (Ex) and GE administrated plus exercise group (GE + Ex). Mice in the GE and GE + Ex group were given GE orally at the dose of 200 mg/kg weight one hour before the exhaustive exercise procedure and were sacrificed immediately after exercise. Plasma, skeletal muscles and livers were sampled for analyses. Biochemical parameters were measured in the plasma. The lipid peroxidation maker thiobarbituric acid reactive substance (TBARS) and protein oxidation marker protein carbonyl concentrations were measured in plasma, liver and skeletal muscle. Furthermore, the gene expression levels of inflammation-related factors IL-6, IL-1β, tumor necrosis factor (TNF-α), cyclooxygenase-2 (COX-2), antioxidant enzymes superoxide dismutase 1 (SOD1), catalase (CAT), Nrf2 and HO-1 were measured in gastrocnemius, soleus and livers using RT-PCR.

Results: Plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels, liver IL-6, IL-1β, SOD1, CAT, HO-1 gene expression

levels and skeletal muscle IL-6, Nrf2, HO-1 gene expression levels increased immediately after exhaustive exercise. However, the gene expression levels of TNF-α and COX-2 were not altered by exercise or GE treatment in skeletal muscles or livers. TBARS and protein carbonyl concentrations in plasma and skeletal muscles were not altered by exercise or GE supplementation. Contrary to our expectations, GE supplementation increased liver protein carbonyl concentrations. On the other hand, GE supplementation significantly decreased SOD1, CAT gene expression levels in liver and Nrf2, HO-1 gene expression levels in skeletal muscle.

Discussion: In line with previous studies, we found that exhaustive exercise increased ALT and AST levels and liver inflammation-related cytokine IL-6, IL-1β gene expression levels. Also, SOD1, CAT and HO-1 gene expression levels were raised after strenuous exercise in the liver, indicating that the exercise protocol used in this study was intensive enough to induce oxidative stress in the liver tissue. However, in this study, we did not observe that GE supplementation attenuated the liver damage or inflammation. Contrary to our expectations, we observed an increase in protein carbonyl concentration in the liver. These results revealed that protein oxidation in the liver is more severe after GE treatment.

Previous studies indicated that relatively low-dose GE can activate the Nrf2 and antioxidant response elements (AREs) gene expression to protect the body from oxidative stress and inflammation. However, we observed GE has a suppressive effect on liver SOD1, CAT gene expression both in the excise group and the sedentary group in the present study. Also, HO-1 expression was slightly decreased in liver after GE administration. Under the premise of the above-mentioned view, we assumed that in this study, a single, high-dose of GE did not show any preventive effect on exhaustive exercise-induced oxidative stress. The reason might be that GE acts as a pro-oxidant by the inhibition activity of Nrf2 and downstream gene expression in the liver, thus influencing the oxidative stress systematically.

Although plenty of studies demonstrated that GE has positive effects on the relief of oxidative stress, it is not ignorable that some studies have also indicated GE exhibiting pro-oxidant potential and toxicity at high concentrations. Therefore, when considering GE in antioxidant substance and developing experiments to assess the properties, its hormetic response should be taken into consideration. Further studies are necessary to use relatively low-dose and long-term GE supplementation to elicit its health-promoting effects.

Conclusion: In conclusion, acute exercise was able to induce organ damage, inflammation and oxidative stress in skeletal muscle and liver. However, a single dose of GE supplementation before exercise did not lead to favorable antioxidant and anti-inflammatory effects in this study. Moreover, the oxidative stress in the liver was actually slightly induced by GE supplementation along with the suppression of antioxidant enzyme expression.