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Research Article

The Impact of Resistance Training With Coenzyme Q10 Supplementation on Antioxidant Value of Nuclear Factor-Erythroid-2-Related Factor 2 in Young Male Rats

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Abstract

Background: Nuclear factor-erythroid-2-related factor 2 (Nrf2) is an inducible transcription factor that improves redox balance through stimulating antioxidant gene expression.

Objectives: Studies have shown that Nrf2 can be modulated by physical exercise. However, the impact of resistance training and coenzyme Q10 supplementation has never been investigated. The aim of this study was to evaluate the effects of two months of resistance exercise and coenzyme Q10 supplementation on the expression of Nrf2 and NAD(P)quinone acceptor oxidoreductase 1 (NQO1) in young male rats.

Methods: In this semi-experimental study, a total of 36 male and young Sprague Dawley rats (age: 8 weeks) were randomly assigned into six groups as follows: resistance training (RT), training and supplementation of 200 mg/kg of rat weight (RT + Q200), training and supplementation and 300 mg/kg (RT + Q300), supplementary group with the value of 200 mg/kg (Q200), supplementary group with the value of 300 mg/kg (Q300), and control. The resistance training protocol consisted of three set of five repetitions of trained rats climbing a vertical ladder with an extra load attached to the tail, representing 30–100% of total body mass three times per week for eight weeks. The proteins levels of Nrf2 and NQO1 were measured by Western blotting technique. One-way analysis of variance (ANOVA), and in case of statistically significant difference, Tukey's post-hoc test were used to determine the difference between groups.

Results: The results showed that the expression of Nrf2 and NQO1 levels changed in the groups after the end of the period. While the expression of Nrf2 and NQO1 significantly increased in the RT and RT + Q200 groups ($P<0.001$).

Conclusion: The results of present study showed that resistance training provides a beneficial adaptation to Nrf2 and NQO1 activity, which can be further enhanced by Q10 supplementation with antioxidant effects.

Keywords: Resistance training, Nuclear factor-erythroid-2-related factor 2, Antioxidants, Coenzyme Q10 supplement

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Background

Chronic metabolic health conditions affect a large portion of the global population and have detrimental effects on healthcare, economic growth, and personal wellbeing. The increase in incidence may be due to improved disease detection, population expansion, or an aging population. Redox imbalance and low-grade chronic inflammation are highly correlated with health conditions, such as metabolic syndrome, cardiovascular disease, type 2 diabetes, neurodegenerative diseases (1-4), and liver disease.

Redox imbalance and inflammation share a cyclical relationship. Therefore, understanding a mechanism whereby there is a reduction in either one or both factors would be important for reduction of disease prevalence. As such, effective evaluation of this relationship would be beneficial to all those afflicted with reactive oxygen species (ROS) associated chronic condition. Oxidative stress is an imbalance between free radicals and antioxidants in your body. Excessive production of ROS or a deformity in the internal antioxidant protection machine, containing enzymatic and non-enzymatic antioxidants, is generally specific as oxidative pressure.

Exercise is a key instrument in the management of chronic conditions associated with inflammation and oxidative stress (5). Although the prescription of aerobic exercise is typically used to improve cardiorespiratory fitness (6), there are many other benefits to exercise such as improving lipid profile, regulating blood glucose, reducing blood pressure, and improving antioxidant capacity. Several reports have shown that resistance exercise has profound effects on the body's antioxidant defense system (7,8). In particular, the antioxidant enzyme superoxide dismutase has been reported to increase significantly in resistance trained individuals compared to their sedentary counterparts. This suggests that

exercise may be an effective method to promote a cellular protective effect through the production of endogenous antioxidants. Exercise training elicits a transient increase in ROS production through upregulation of energy production, the primary source of ROS. During exercise, oxygen delivery to acting skeletal muscle can increase 10- to 20-fold, leading to the creation of more ROS and free radicals that can attach to natural macromolecules, particularly DNA active proteins (9). Recent research has shown that ROS created within sport initiates two significant redox-delicate flagging passage, containing nuclear factor B (NF-κB) and mitogen activated protein kinase (MAPK) (10).

One of the factors that promotes the expression of antioxidant genes and the regulation of oxidative stress is the nuclear factor-erythroid-2-related factor (Nrf2), which is a transcription factor belonging to the leucine zipper protein group encoded by the NFE2L2 gene. Nrf2 is present in all tissues but is found mostly in the brain, kidneys, muscles, lungs, heart, and liver. Evidence suggests that Nrf2 is the primary transcriptional regulator of most antioxidants, including nicotinamide adenine dinucleotide phosphate oxidase, quinone dehydrogenase, NAD(P)H dehydrogenase quinone 1 (NQO1) and superoxide dismutase (11). Recently, the molecular mechanism, regulation of Nrf2 function, as well as its signaling pathways and relationship with other antioxidants have been studied. Nrf2 is closely related to the enzyme NQO1, which is a type of Flavonoids chemical with a significant part in protecting cells from the redox oxidation process induced by quinines. NQO1 is a cytosolic enzyme regulated by the keep1-Nrf2-ARE pathway, a gene that is a two-electron reductase that converts active quinone to hydroquinone. The main action of this enzyme, which is in phase two of the antioxidant pathway, is to reduce ROS formation and quinone toxicity (12). Evidence suggests that the presence or absence of this enzyme is associated with increased and decreased sensitivity to oxidative stress.

Today, antioxidant supplements are used as a factor in counteracting oxidative stress in exercise and many diseases (13-15). Coenzyme Q-10 (CoQ10) is the predominant form of ubiquinone in the human body, which is produced as an enzymatic exogenous cofactor in all living human cells and as a catalyst in proton transport. Electrons play a role in mitochondria and lysosomes and protect mitochondria against free radical damage (16, 17). Coenzyme Q-10 is mainly transported by lipoproteins in the blood and can play an antioxidant role (18). Some previous studies have shown that regular exercise reduces the expression of oxidative stress, increases antioxidants, and in general, reduces inflammation. The use of antioxidants to reduce oxidative stress caused by exercise and its associated result is one of the most questionable issues as to the use of dietary cell reinforcements antioxidants, particularly in supplement shape (19, 20).

The ambiguity of research results might bring up the issue of whether cell antioxidant supplementation within activity or orderly physical education alone has positive or negative impacts. Given that no research has been conducted on the effect of resistance training with coenzyme Q10 supplementation on Nrf2 and NQO1, the present research aimed to answer the question whether two months of weight training using coenzyme Q10 supplementation can have an effect on the antioxidant levels of Nrf2 and NQO1 in male Sprague Dawley rats.

Objectives

The current investigation tries to answer the question whether two months of weight training using coenzyme Q10 supplementation can have an effect on the antioxidant levels of Nrf2 and NQO1 in male Sprague Dawley rats.

Materials and Methods

The animals were kept according to the directive of the Animal Creature Care Advisory Group of Shiraz College of Clinical Sciences, Iran. This semi-experimental study was conducted in six groups. In order to conduct the research, 36 male rats (weight range: 180 to 200 g) were randomly assigned into six groups as follows: resistance training (RT), training and supplementation of 200 mg/kg of rat weight (RT + Q200), training and supplementation and 300 mg/kg (RT + Q300), supplementary group with the value of 200 mg/kg (Q200), supplementary group with the value of 300 mg/kg (Q300), and control.

Protocol Training

After one week of familiarity with resistance training, including eight weeks and three weeks of ascending, a 100-cm upright stepping stool with 26 stages and four centimeters of room among each progression with a slant of 85 degrees was performed. During the weight training with the appropriate weight, each training intensity was tied to the tails according to the weight of the rats. Each session consisted of three repetitions with five repetitions, with one minute of rest in between each repetition and two minutes of rest in between each repetition. In the first week, the weights attached to the tails of the rats was 30% of their body mass, which gradually increased by 10% per week and reached 100% of their body weight (21). To prepare coenzyme Q10 supplement, we first weighed 400 mg of coenzyme Q10 supplement powder from Bulk Supplement USA with an accuracy of 0.001, then we added 10 cc of olive oil to dissolve the supplement. Supplementation was provided on a weekly basis to prevent supplemental degradation, which may occur over time due to factors such as heat and exposure to direct sunlight. The daily intake of Q10 supplement was 200 and 300 mg/kg of body weight, which was calculated at the beginning of each week and was administered by gavage for eight weeks simultaneously with the training protocol into two groups: supplement-training and

supplementation (22).

Western Blot Method

The rats were sacrificed 48 hours after the last training session. The rats were first anesthetized with the expressed combination of xylazine and ketamine. The gastrocnemius muscles were separated with pliers and scissors, washed in a petri dish containing normal saline, dehydrated with a gas, placed in a cryotype. It was immediately transferred to a liquid nitrogen tank and kept temperature at -80 °C. Antibodies were used to measure the surfaces of Nrf2 and NQO1 proteins from antibodies of Santa Cruz Biotechnology (USA) and Elabscience, USA, respectively.

Statistical Analysis

In the present study, after data collection, analysis was performed using descriptive and inferential statistical methods. Kolmogorov-Smirnov test was used to determine the normality of data distribution and Levene test was used to examine the homogeneity of variance. Also, one-way analysis of variance (ANOVA) was used to investigate the significant changes in each of the research variables between different groups. If a statistically significant difference was observed, Tukey's post-hoc test was used. $P<0.00$ was considered as a significant difference. All statistical tests were performed utilizing the SPSS software version 22.

Results

The results showed that the expression of Nrf2 and NQO1 levels in the groups changed after the end of the period. The expression of Nrf2 and NQO1 significantly increased in the RT and RT + Q200 groups ($P<0.001$), while in resistance training group + Supplement (a dose of 300 mg/kg) ($P<0.07$) and two groups of supplements (at doses of 200 and 300 mg/kg) ($P<0.09$) did not change significantly. (Figure 1).

Discussion

This study evaluated the impact of Q10 supplementation and resistance training on gastrocnemius muscle Nrf2 and NQO1 levels in rats after exercise. The results showed that the expression of Nrf2 and NQO1 levels in the groups changed after the end of the period. The expression of Nrf2 and NQO1 significantly increased in the RT and RT + Q200 groups ($P<0.001$), while it increased in the Q200 and RT + Q300 groups ($P=0.9$) + Q300 ($P=0.7$).

As far as the researchers investigated, there are no studies examining the effect of resistance training and Q10 supplementation on muscle Nrf2 and NQO1. Previous research on the animal model has shown that regular exercise regulates Nrf2 protein levels and the amount of phase II antioxidant enzyme or enzyme activity (23). However, a cross-sectional study comparing the Nrf2 and Keap1 protein content of a quadriceps muscle sample of active and inactive elderly showed that physically active elderly had a higher Nrf2 and NQO1 proteins content than inactive elderly. Thus, regular exercise may reduce age-related changes in Nrf2 signaling (24). Inconsistent with our results, the jumping protocol with weight vests was tested as a type of resistance training in rats, and no change in Nrf2 expression was observed in young rats (25). Further research is needed to determine whether resistance training can induce Nrf2 signaling.

In 2015, Tsu et al examined the activity of NrF2 in the gastrocnemius muscles in response to four weeks of resistance training, which showed that the expression of NrF2 increased significantly with exercise (26). Q10 can decrease oxidative pressure and be regarded as a neutralizer of free radicals (27). It should be noted that, in the interior mitochondrial cover, Q10 acts as an electron transporter by the enzyme assemble I and assemble II to assemble III. Nrf2 and NQO1 levels increased significantly in most gatherings compared to the control group, but the expression of Nrf2 and NQO1 significantly increased in the RT and RT + Q200 groups ($P<0.001$). Nrf2 is a record divisor that attaches to the response element antioxidant (ARE), therefore is this inducing the expression of the antioxidant genes.

Kelch-like ECH-associated protein 1 (Keap1) is delivered by the isolating in protein by specific systems. In the lack of Keap1, Nrf2 is transported toward the

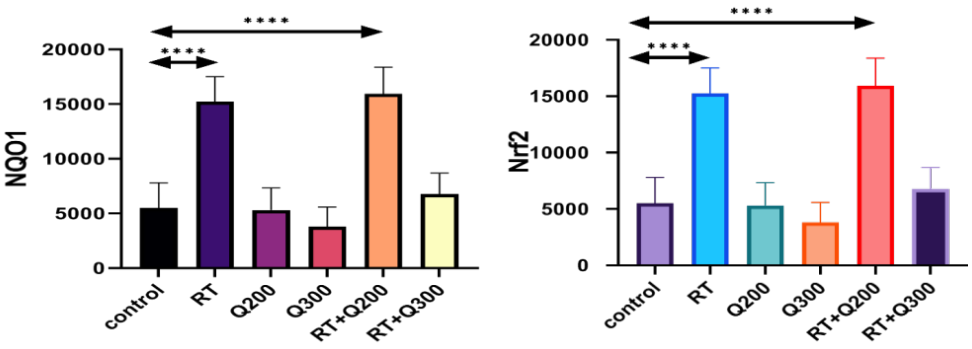

Figure 1. The Effects of RT, Q200, Q300, RT + Q200 and RT + Q300 on the Expression of Nrf2 and NQO1 in gastrocnemius muscle. Control; RT: Resistance training; Q200: Supplementary group with value 200 mg/kg; Q300: Supplementary group with value 300 mg/kg; RT + Q200: Training and supplementary group with value 200 mg/kg; RT + Q300: Training and supplementary group with value 300 mg/kg. Data are presented as the mean±SD. ****P value<0.001 was considered as significant.

core, sticks to ARE, and expresses Nrf2 genes, including NQO1 and other genes such as glutamate, cysteine ligase, and glutathione (28). Exercise activity along with Q10 supplementation showed that Nrf2, an antioxidant protein mainly produced by ROS, increased during exercise (29). According to our results, exercise stimulates Nrf2 and NQO1 transcription factors, reduces oxidative stress, and enhances antioxidant defense (30). However, the signaling pathways that lead to increased Nrf2 expression after exercise have not been fully elucidated.

One study evaluated the effect of resistance training on dialysis patients to explore the impact of weight training on NRF2 and NF-KB. NRF2 and glutathione oxidase activity were presented in the training group compared to the control group. This study also showed that resistance training improved and strengthened the antioxidant defense in these patients (31). Although the set of Nrf2-mediated antioxidant protection systems is not yet fully understood, it has been shown to be effective in responding to stimuli such as exercise. Researchers have shown that antioxidant supplements protect against alcohol-induced myopathy through oxidative stress myopathy by regulating the Nrf2-1HO- pathways (32). However, the organic premise of the exact job of mitochondrial function in this disorder is not fully unclear.

Q10 is a necessary factor in the electron transfer link and a powerful antioxidant may defend cells against oxidative pressure by inhibiting ROS. In our study, Q10 supplementation elevated Nrf2 and NQO1 levels more significantly in the exercise and supplementation groups than in the control group. In a previous report in Q10 hepatocytes, inhibiting hepatic fibrosis through ARE-Nrf2 activation, the researchers speculated that Q10-interceded Nrf2 activation can lead to stable self-acting oxidation of the quinone portion (33). Thus, our findings support the notion that weight training can increase Nrf2, which is more evident in Q10 resistance training and supplementation rats. Modulation of Nrf2 by exercise and Q10 supplementation points out the potential therapeutic role of Q10 in metabolic stress, when the requirement for energy is increased.

One of the strengths of our research is that this is the first study to examine the impact of weight training with Q10 on Nrf2 and NQO1. However, as a limitation, we could not find similar studies to compare the results.

Conclusion

The present study showed that resistance training provides a beneficial adaptation to Nrf2 and NQO activity in young male rats.

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Authors' Contribution

Laboratory studies and tests: MJS, RR; study and review: MJS and MS; analysis and interpretation of data: MJS and FD.

Conflict of Interests

The authors express that they have no conflict of interest.

Ethical Approval

The researchers received introduction letters from the Animal Care Committee at Shiraz University of Medical Sciences (code: IR.SUMS.REC.1399.639).

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