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A Comparative Study of Antifatigue Effects of Taurine and Vitamin C on Chronic Fatigue Syndrome

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Abstract

Vitamin C and taurine (TR) are well known as active components for fatigue recovery. However, the mechanism of the anti-fatigue effects of vitamin C and TR is still unclear. Our study was designed to evaluate the anti-fatigue activities of vitamin C and TR in an animal test for fatigue and to compare the activities between vitamin C and TR. **Materials and Methods:** Vitamin C, TR or their combination were orally administrated to mice once daily for 15 days, and then metabolic activities such as blood glucose, triglyceride (TG), lactate, and lactate dehydrogenase (LDH) as well as antioxidant activities such as malondialdehyde (MDA) and superoxide dismutase (SOD) were determined (evaluated) after forced swimming test (FST). **Results:** Compared with the control group, C100, C200, and T50 showed a tendency to decrease mobility in FST. Moreover, TG (C100, C200, T200), LDH (C200), lactic acid (C100) and MDA (C50, C100, C200) levels were inhibited by vitamin C and TR. **Conclusions:** These results suggest that vitamin C and TR have anti-fatigue activities in mice, with vitamin C providing a stronger effect.

Keywords

Vitamin C, Taurine, Chronic Fatigue Syndrome, Anti-Fatigue Effect

1. Introduction

Chronic fatigue syndrome (CFS) is a clinical condition defined by persistent fatigue lasting more than 6 months that is not amended by rest [1]. Chronic fatigue can cause serious health problems, and the lack of control over fatigue is

emerging as an important issue [2] [3]. There is no specific treatment except lifestyle change, and this lack of relief leads to chronic impairment of quality of life [4], CFS is associated with concentration deficiency, memory loss, muscle aches, and sleep deprivation and the global incidence of CFS and its prevalence have been steadily rising [5]. Nevertheless, there is no effective treatment to prevent CFS. Some reports have suggested that the combination of supplementation with essential nutrients and aerobic exercise is an effective approach to preventing CFS [6]. Therefore, one of the ways to suppress fatigue involves the elimination or inhibition of the production of fatigue-related metabolites during exercise. Physical fatigue is tightly associated with maintenance of the balance between nutrition and energy metabolism [7]. Water-soluble vitamins are one of the body's most important antioxidants and are involved as a co-factor in more than 150 metabolic functions [8]. Vitamin C deficiency causes clinically related diseases. Fatigue, pain, cognitive disorders, and depression-like symptoms are known symptoms of a vitamin C deficiency [9]. Therefore, it is possible that vitamin C supplements can treat the symptoms of vitamin C deficiency, including fatigue, and relieve fatigue through neuroprotective and vasoprotective effects due to its antioxidant and anti-inflammatory properties [10] [11].

Taurine is a sulfur-containing amino acid that is found abundantly in the heart, brain, retina and skeletal muscles of humans [12] and is an *in vivo* metabolite that acts as an antioxidant and antifatigue agent [13]. The major biological functions of TR vary but, include antioxidant [14] [15], anti-inflammatory [16] [17] [18] vitagene activation [19] [20], energy metabolism [21] [22], neuroprotection [23] [24] and immunomodulation [25] [26] functions. Additionally, there are many studies showing TR as an antioxidant with a role in protecting against oxidative stress in the mitochondria [27] [28] [29].

However, there are no studies on the synergistic or dose-specific effects of vitamin C and TR on the anti-fatigue effect. Here, we analyzed fatigue-causing factors in mice to determine whether there is a synergistic effect and dose-specific effects between the antifatigue effects of TR and vitamin C.

2. Materials and Methods

2.1. Materials

TR was purchased from Sigma-Aldrich (St. Louis, MO, USA). Vitamin C was obtained from Kwang Dong Pharmaceutical Co., Ltd. (Seoul, Korea). To detect MDA and SOD assay kits were purchased from Thermo Fisher Scientific (Waltham, MA, USA).

2.2. Animal Care

Twelve-week-old, male ICR mice (Orient Bio Co. Republic of Korea) were used in the experiment after acclimation for 1 week. The animal use and care protocols for this experiment were approved by the Institutional Animal Care and Use Committee (IACUC), College of Medicine, Hanyang University, Seoul, Republic

of Korea. All experiments and animal care performed in accordance with institutional guidelines (2016-0225A). Experimental animals were housed in standard cages maintained at a constant temperature of 25˚C ± 2˚C, humidity 55 ± 5%, and a 12-h light/dark cycle.

2.3. *In Vivo* Antfatigue Experimental Design

Antifatigue experiments of forced swimming, TG, glucose, lactate, LDH, MDA, and SOD tests, were performed as described in previous studies [30] [31] [32] [33]. To test the antifatigue effects of the treatments, 72 mice were randomly divided into 8 groups (n = 9) and treated for 15 days as follows: untreated group (saline); C50 group (50 mg/kg/day vitamin C); C100 group (100 mg/kg/day vitamin C); C200 group 200 mg/kg/day vitamin C); T50 group (50 mg/kg/day TR); T100 group (100 mg/kg/day TR); T200 group (200 mg/kg/day TR); and C50 + T50 group (50 mg/kg/day vitamin C and 50 mg/kg/day TR) (**Figure 1**).

2.4. Forced Swimming Test

The forced swim test (FST) carried out as described in the literature [34]. Briefly, following the last treatment with vitamin C, TR or distilled water, mice were individually placed into a glass cylinder (height: 25 cm, diameter: 10 cm) containing 10 cm of water at 23˚C - 25˚C for a 6 min swimming session. The duration of immobility defined as cessation of struggling to float motionless in the water, making only movements necessary to keep its head above water.

2.5. *In Vivo* Measurement of Biochemical Parameters

To detect the anti-fatigue effects of vitamin C and TR, blood samples of mice

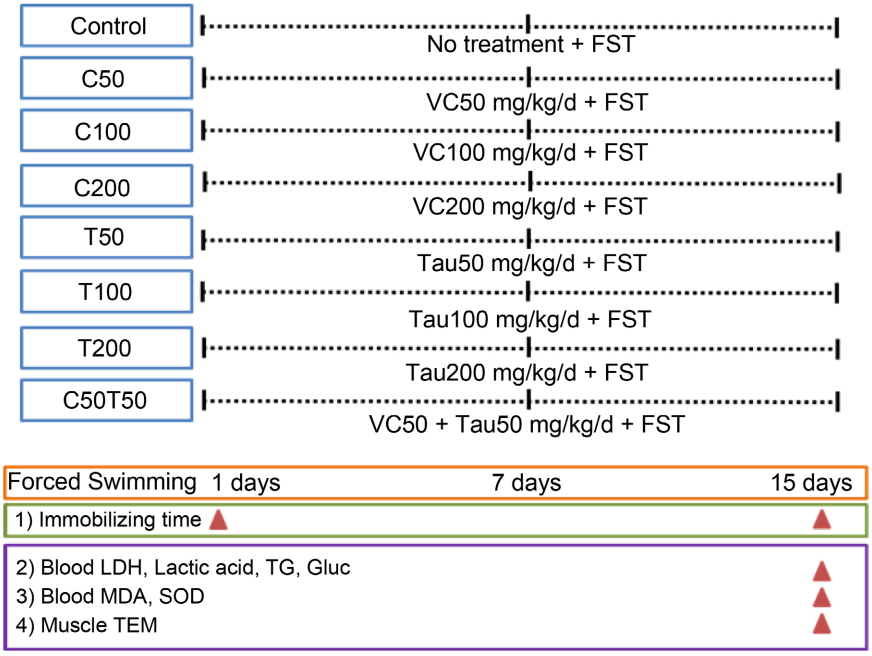

Figure 1. Schematic workflow of the experiment.

were collected, and sera were prepared by centrifugation at 3000 rpm at 4˚C for 10 min. Levels of GLU, TG, LDH, and lactic acid were determined using an autoanalyzer (Hitachi 7060, Hitachi, Japan). Levels of MDA and SOD were determined using commercially available kits from Thermo Fisher Scientific (Waltham, MA, USA).

2.6. TEM for Mitochondria of Rat Femoral Muscle

The striated muscles of the quadriceps muscle of the right lower extremity of the mice were preserved in a fixed solution containing 4% paraformaldehyde, 1.25% glutaraldehyde, and 0.1 mol/L phosphate buffer (pH 7.4). After 24 hours, sections of the fixed tissue with a thickness of 10 - 50 μm were cut and dehydrated by sequential immersion in 70%, 90%, 95%, and 100% ethanol for 10 min each. Samples were then placed in epoxy resin, sliced into ultra-thin sections, and stained with uranium acetate and lead citrate. In the stained tissue sample, the state of the mitochondria was observed by transmission electron microscopy (TEM).

2.7. Statistical Analysis

All values were expressed as mean ± S.D (n = 9). Data were analyzed using one-way ANOVA followed by subsequent multiple comparison test (Duncan). Differences were considered statistically signifiant at $p < 0.05$.

3. Results

3.1. Forced Swimming Test

On day 1 and day 15, the time (sec) of the passive (immobillity) state was recorded during the FST. On the first day of administration, the floating time in all groups was less than 100 sec (data not shown). The floating times on the 15th day of oral dosing were 171.33 ± 76.67, 172.5 ± 62.82, and 174.16 ± 40.64 sec, respectively, in the C100, C200, and T50 groups, showing short but not significantly different floating status compared with the control group (**Figure 2**).

3.2. *In Vivo* Measurement of Biochemical Parameters

Metabolic activities of blood glucose, triglycerides (TG), lactic dehydrogenase (LDH), and lactic acid, which are biochemical indicators of degree of fatigue of mice were investigated during the FST (**Figures 3-6**). There was no difference among groups in creatinine. Creatinine is a metabolite of creatine phosphate, and to increase with intense exercise (work). For glucose, there was no change after administration of vitamin C and TR. The vitamin C, T200, and C50T50 groups showed lower levels of TG compared with the 89.73 ± 31.08 mg/dl of the control group ($p < 0.05$). The utilization rate of TG increases during long-term exercise (chronic fatigue). After administration of vitamin C or TR, TG was low in the vitamin C groups (especially C100 and C200), which seemed to lower the degree of fatigue. The level of LDH showed a significant difference in both

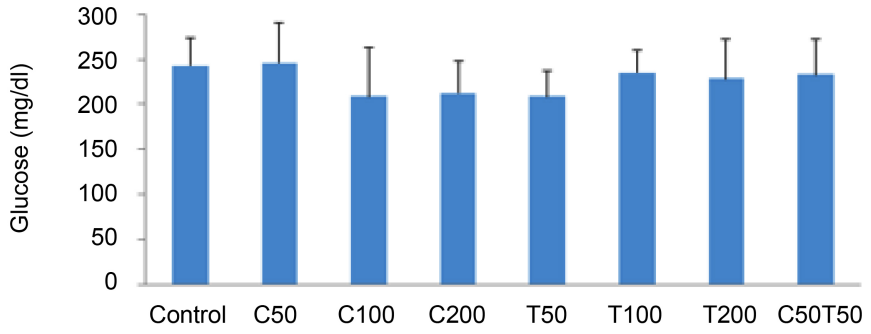

Figure 2. Effects of vitamin C and taurine on the immobility duration of mice in the forced swimming test (FST). Data shown are from the last day (day 15) of the FST. Value are expressed as mean ± SD. Ctrl, control group performed FST only; C groups were performed FST after oral administration Vitamin C 50, 100, 200 mg/kg/day, respectively; T groups were performed FST after oral administration taurine 50, 100, 200 mg/kg/day, respectively; C and T combination group were performed FST after oral administration Vitamin 50 mg/kg/day and taurine 50 mg/kg/day.

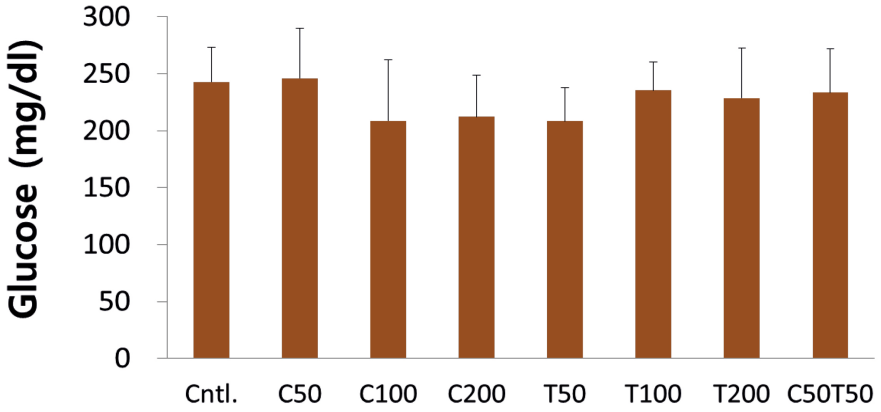

Figure 3. Effects of vitamin C and taurine on serum glucose after the forced swimming. Value are expressed as mean ± SD. The significance of differences among mean values were assessed by one-way ANOVA. (a)-(c) Mean values with the different letters are significantly different by Duncan's multiple test ($p < 0.05$). Each group listed in **Figure 2**.

vitamin C groups compared with the control group, with the lowest level in the C200 group ($p < 0.05$). The level of LDH, a fatigue-related physiological marker, showed a tendency to recover more in the vitamin C group than in the TR group. The level of lactic acid was low in the C100 group, but there was no difference between the groups. Lactic acid from LDH is produced during anaerobic metabolism, and is closely related to physical fatigue. In this study, there was a tendency for lactic acid decrease in the C100 group compared with the control group and TR group.

To investigate the antioxidant effects of vitamin C and TR, MDA, and SOD activities were measured (**Figure 7** and **Figure 8**). For MDA, there was a significant difference in both the vitamin C group and the TR group compared with the control group ($p < 0.05$). In particular, among the vitamin C group, the C50,

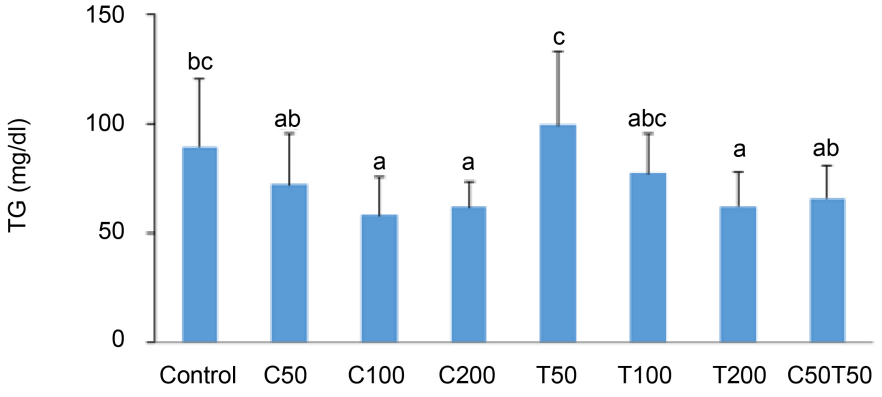

Figure 4. Effects of vitamin C and taurine on serum triglyceride (TG) after the forced swimming. Value are expressed as mean ± SD. The significance of differences among mean values were assessed by one-way ANOVA. (a)-(c) Mean values with the different letters are significantly different by Duncan's multiple test ($p < 0.05$). Each group listed in **Figure 2**.

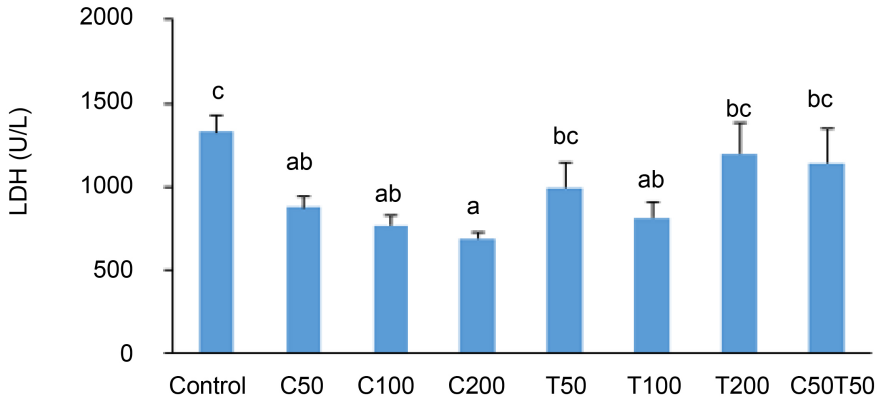

Figure 5. Effects of vitamin C and taurine on serum lactic dehydrogenase (LDH) after the forced swimming. Value are expressed as mean ± SD. The significance of differences among mean values were assessed by one-way ANOVA. (a)-(c) Mean values with the different letters are significantly different by Duncan's multiple test ($p < 0.05$). Each group listed in **Figure 2**.

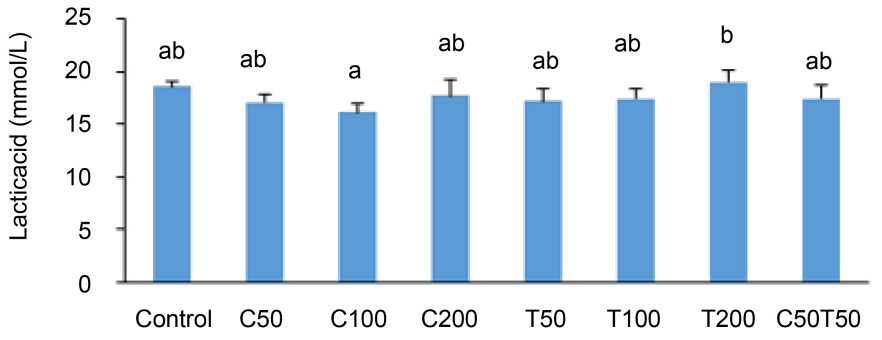

Figure 6. Effects of vitamin C and taurine on serum lactic acid after the forced swimming. Value are expressed as mean ± SD. The significance of differences among mean values were assessed by one-way ANOVA. (a)-(c) Mean values with the different letters are significantly different by Duncan's multiple test ($p < 0.05$). Each group listed in **Figure 2**.

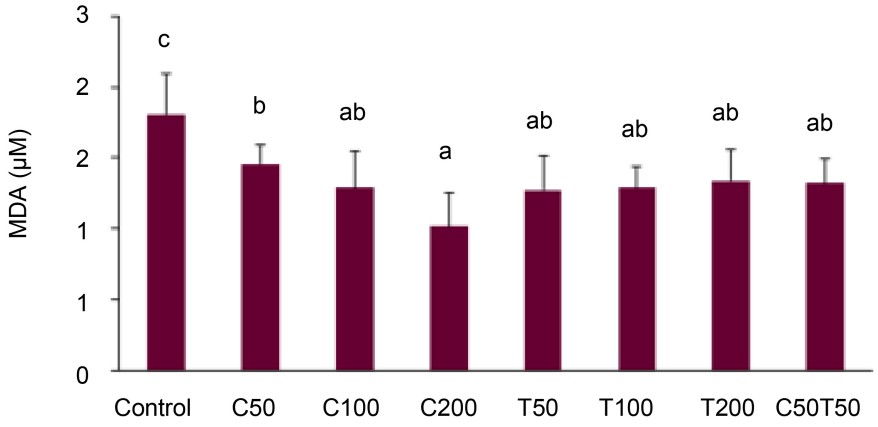

Figure 7. Effects of vitamin C and taurine on serum malondialdehyde (MDA) after the forced swimming. Value are expressed as mean ± SD. The significance of differences among mean values were assessed by one-way ANOVA. (a)-(c) Mean values with the different letters are significantly different by Duncan's multiple test ($p < 0.05$). Each group listed in **Figure 2**.

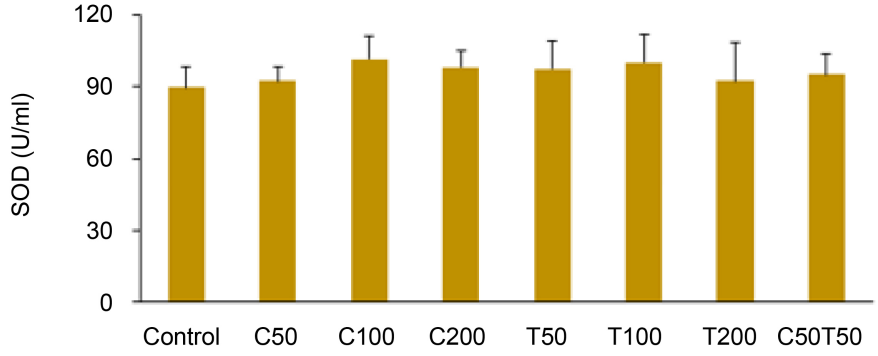

Figure 8. Effects of vitamin C and taurine on serum superoxide dismutase (SOD) after the forced swimming. Value are expressed as mean ± SD. The significance of differences among mean values were assessed by one-way ANOVA. Each group listed in **Figure 2**.

C100, and C200 groups were 1.46 ± 0.15 μM and 1.29 ± 0.28 μM, respectively showed a result of effective dose reduction to 1.02 ± 0.26 μM. The MDA level of the TR group was similar to the level of the C100 group regardless of the dose administered. MDA is known to increase lipid peroxidation by generating reactive oxygen species during strenuous exercise (work) or stress as an indicator of lipid peroxidation caused by oxidative stress. We confirmed that MDA could be reduced by administration of TR or vitamin C, and the lowest level was confirmed in the C200 group ($p < 0.05$). We predicted that SOD activity would increase due to a decrease in concentration of MDA; however, there was no significant difference in SOD among the groups, with the highest value in the C100 group showing 101.65 ± 10.33 U/ml compared with the control group 89.57 ± 10.10 U/ml.

3.3. TEM for Mitochondria of Rat Femoral Muscle

The mitochondria of the femoral muscle tissue did not show any specific differ-

ences among groups (Figure 9). As FST for 15 days does not appear to have any effect on mitochondria and muscle tissue, the effects of vitamin C and TR on mitochondria and muscle tissue must be determined with extended FST period or swimming time.

4. Discussion

Vitamin C and TR, widely used in energy drinks and functional foods, have multiple physiological functions and pharmacological benefits including anti-fatigue, antioxidant, anti-inflammatory, and neuroprotective activities [9] [10] [11] [14] [15] [16] [17] [18]. However, functional foods and energy drinks contain additives such as caffeine, ginseng, vitamins, antioxidants, and sugar in addition to vitamin C and TR. The additives complicate the determination of the effects of pure vitamin C and TR on anti-fatigue. Therefore, in this study, we attempted to determine the exact effects of only vitamin C and TR in mouse fatigue. For this, we set doses in mice of 50, 100, and 200 mg/kg/day for vitamin C (250, 500, and 1000 mg for human comparison), and of 50, 100, and 200 mg/kg/day for TR (300, 600, and 1200 mg for human comparison) and administered them to groups for 15 days. Our anti-fatigue activity tests of vitamin C and TR in FST, an effective animal model for anti-fatigue effect screening [35] [36], showed that the immobility time after FST on day 15 had a decreasing trend in mice treated with C100, C200, and T50 at 100, 200, and 50 mg/kg, respectively.

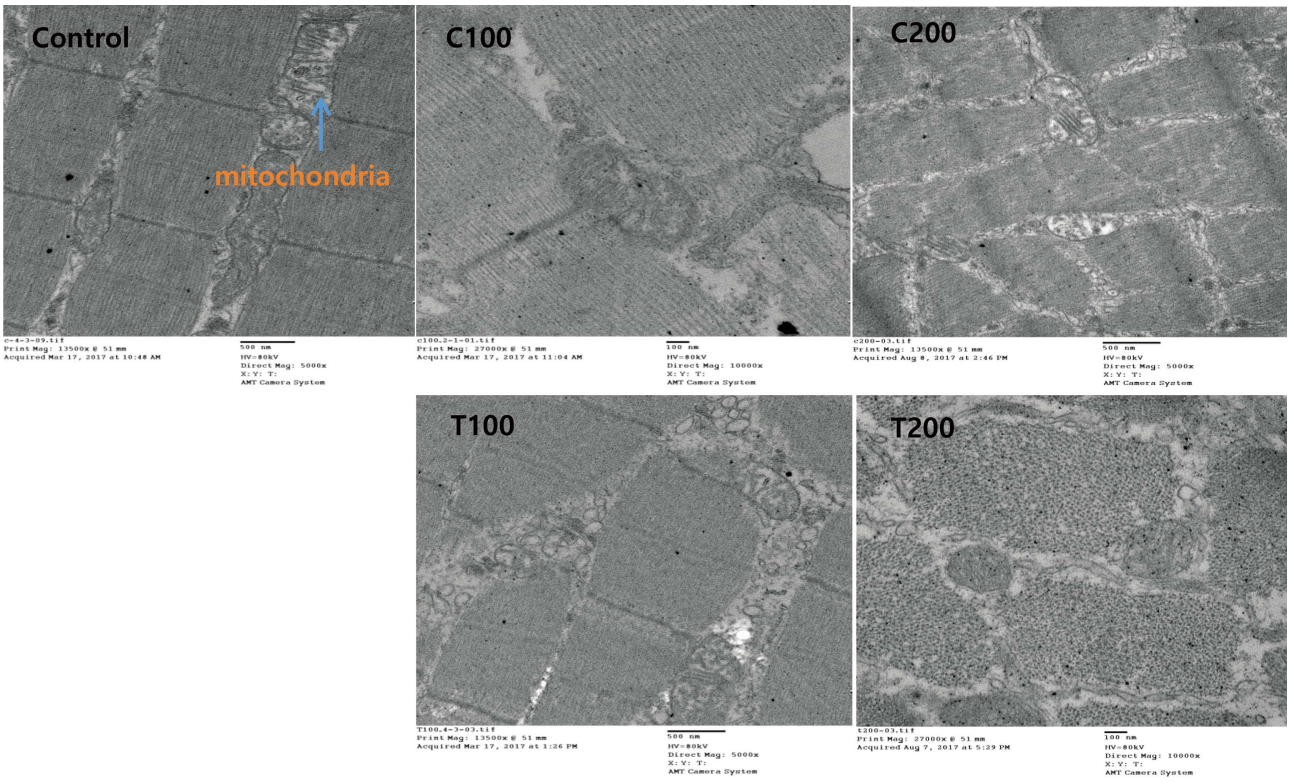

Figure 9. Effects of vitamin C and taurine on mitochondria of rat femoral muscle by TEM after the forced swimming. Each group listed in Figure 2.

Moreover, the effects of vitamin C and TR in the FST were accompanied by attenuation of FST-induced fatigue on the physiological markers relevant for fatigue.

The present study demonstrates anti-fatigue activities of vitamin C and TR in FST. Specifically, all vitamin C levels tested significantly lowered levels LDH and MDA compared with control group. LDH activity indicates the degree of lactate metabolism and represents anti-fatigue activity [37]. Some diseases are relevant to oxidative damage caused by lipid peroxidation, which can produce harmful metabolites [38]. MDA is a product of lipid peroxidation, and its elevation indicates oxidative damage to the cell membrane [39]. In the present study, the vitamin C and TR supplemented group clearly demonstrated an ability to decrease MDA formation. This result suggests that the anti-fatigue effect of vitamin C probably occurred by preventing lipid oxidation via modifying activities of several enzymes. After oral administration of vitamin C or TR for 15 days, the level of SOD was not significantly different among the groups. SOD is an enzyme that acts in the first step of the antioxidant defense system and catalyzes the conversion of free oxygen radicals to H_2O_2 [33]. It is then decomposed into non-toxic water and oxygen by the catalytic action of glutathione peroxidase or catalase [40].

In relation to this mechanism, it is expected that results that are more reliable can be confirmed through measurement of glutathione peroxidase or catalase. Since the effects of MDA and SOD were positively changed by the intake of vitamin C and TR, we believe that the improved antioxidant efficacies of vitamin C and TR can be compared through extension of the study. Another possible explanation for the anti-fatigue effect following treatment with vitamin C and TR could involve TG (or fat) mobilization during exercise, as indicated by the decrease in TG level. Such an effect might become advantageous during prolonged exercise, since better utilization of TG allows the sparing of glycogen and glucose and delays fatigue [33] [41]. We found that the level of TG in C100, C200, and T200 was significantly lower than that of the control group. This suggests that vitamin C can be helpful in maintaining an active state. Further experiments are needed to determine the mechanisms by which vitamin C can affect fat mobilization.

The performance of long-term exercise can induce apoptosis in skeletal muscle mitochondria and lead to oxidative stress and inflammation to result in fatigue. Vitamin C, an exogenous antioxidant, is a free radical scavenger. Conversely, TR, involved mitochondrial health maintenance, but taurine is not a direct radical scavenger [42]. We expected vitamin C and TR to play potential roles in the oxidative stress of mitochondria, but our results did not show any effect on oxidative stress. Further research on oxidative stress-related regulatory factors of mitochondria is needed. Taken together, some of our results show that vitamin C and TR possess anti-fatigue activity. Moreover, vitamin C100 and C200 demonstrated higher potency to induce an anti-fatigue activity compared with TR.

Therefore, the finding of vitamin C100 supports this suggestion and C200 reduced the levels of TG, LDH, and MDA compared with other groups. Further studies on extended administration period, administration pathways, and some biological mechanisms are needed to clarify these effects.

5. Conclusion

We showed that taurine has positive anti-fatigue effects, but vitamin C is more effective. Adequate doses of vitamin C for fatigue suppression and recovery in mice are considered to be between 100 and 200 mg/kg/day. We concluded that oral administration of vitamin C may be upregulated active status and inhibited chronic fatigue.

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Author Contribution

Conceptualization: JS Kang, SH Kim, YT Koo, SH Lee, DH Paik; Investigation: SH Kim; Statistical analysis: SH Kim, Hyun-Jim Kim, Semi Kim; Supervision: JS Kang; Writing—original draft: SH Kim; Writing—review & editing: JS Kang, SH Kim; All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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