Effect of Ubiquinol on Exercise and the Oxidative Stress Regulation System in SMAP1 Mice

HIROSHI MARUOKA, PT, PhD1), KENJI FUJI, PhD2), KAZUHISA INOUE, PT3)

1) School of Health and Social Services, Saitama Prefectural University: 820 San-nomiya, Kosigaya, Saitama, 343-8540, Japan. TEL: +81 48-973-0500, FAX: +81 48-973-4807, E-mail: maruoka-hiroshi@spu.ac.jp
2) Functional Food Ingredients Group, QOL Division, Kaneka Corporation

Abstract. [Purpose] This study examined how exercise capacity and the oxidative stress regulation system are affected by different amounts of consumed ubiquinol (reduced coenzyme Q10, H₂CoQ10: QH) through experiments on 23 SAMP1 mice. [Methods] The mice were randomly divided into two groups: one consuming a high amount of QH (300 mg/Kg) and the other consuming a low amount of QH (30 mg/Kg). Both groups were made to run up to their limit on a treadmill (TM) before/after consuming QH, and then each running time was measured. For the oxidative stress regulation system, the d-ROM test value (degree of oxidative stress) and BAP test value (anti-oxidant potential) were measured both in a resting state before QH consumption and after running up to the limit, and then the BAP/d-ROM ratio was calculated. The values of plasma QH and plasma ubiquinone (plasma oxidized CoQ10) were also measured, and the reduced ratio was calculated. [Results] Both groups showed a significant extension of running time. Also, a more significant extension was seen in the group consuming a high amount of QH than in the group consuming a low amount. With regard to the oxidative stress regulation system, the group consuming a high amount also showed a significant increase in d-ROM test value, plasma QH value and reduced ratio. [Conclusion] The difference in the amount of consumed ubiquinol led to an extension of running time and an increase in reduced ratio and other values.

Key words: Oxidative stress regulation system, Reduced coenzyme Q10 (H₂CoQ10), Exercise

INTRODUCTION

Oxygen is essential to maintain homeostatic function, but for some reason, some of it is changed into active oxygen (superoxide radical etc. is collectively referred to as oxidant stress), which damages body cells and tissues and causes various illnesses like lifestyle-related diseases1). The body has various defensive mechanisms against this, including an autonomic system, an endocrine system, an immune system and an oxidative stress regulation system2). In particular, the oxidative stress regulation system ensures a “balance (latent anti-oxidant potential) between the oxidative reaction (oxidative stress) and anti-oxidant reaction (anti-oxidant potential) of the body,” and how the defensive capability against oxidative stresses (anti-oxidant potential) can be improved is important. As oxygen flux to tissues increases during exercise3), the amount of oxidant stress also shows a remarkable rise. How transient or continuous exercise loaded on mice has an impact on oxidative stress and anti-oxidant potential has already been reviewed4), but there have been few studies on the relation between exercise capacity and the oxidative stress regulation system through consumption of vitamin C, which is sensitive to oxidative stress, and anti-oxidant foods containing a radical scavenger like ubiquinol (reduced coenzyme Q10, H₂CoQ10: QH)5). In addition, there have been no studies on how different amounts of consumed antioxidant foods affect exercise capacity and degree of oxidative stress. Like cholesterol, Coenzyme Q (CoQ), is biologically synthesized in the mevalonate pathway and exists in all organs and cells5). Coenzyme Q has two major functions: activating energy production and anti-oxidation. A major CoQ in mammals like humans is CoQ10, which has a side chain with ten isoprenoid units, existing as ubiquinone (oxidized CoQ10) and ubiquinol. CoQ10 is converted by reductase from an oxidized form to a reduced form in the body with NAD(P)H serving as an electron donor, and the conversion capability decreases with age6). While it has been reported that CoQ10 consumption by mice leads to an increase in plasma CoQ10 and other values7), 8), we have not seen a report that studied how different amounts of consumed antioxidant foods affect the reduced ratio.

Here, we studied the effect of different amounts of QH consumed by SAMP1 mice (38 weeks old), which were randomly divided into two groups: one...
As a result of QH consumption, both groups showed a significant extension of running time ($p<0.05$) (Table 1). Also, a more significant extension was seen in the group consuming a high amount of QH than in the group consuming a low amount ($p<0.05$). Only the group consuming a high amount of QH showed a significant increase in d-ROM test value after QH consumption in comparison with the value before QH consumption ($p<0.01$), and both groups showed a significant increase in BAP test value and BAP/d-ROM ratio ($p<0.01$) (Table 2). Comparison of the d-ROM test values of the groups showed a more significant increase after QH consumption in the group consuming a high amount ($p<0.05$). This group showed a significant increase after QH consumption in the values of plasma QH and plasma Q10 and a reduced ratio, compared with the values before QH consumption ($p<0.01$--$0.001$), while the group consuming a low amount showed a significant decrease in plasma oxidized Q10 and a significant increase in reduced ratio ($p<0.05$, $p<0.01$) (Table 3). In particular, the value of plasma QH in the group consuming a high amount showed a nearly tenfold increase. Comparison of plasma QH, plasma Q10 and the reduced ratio showed a significant increase after QH consumption in the group consuming a high amount ($p<0.001$ each). The average senescence grading score was $2.6 \pm 0.7$ in the group consuming a high amount of QH and $2.4 \pm 0.4$ in the group consuming a low amount. The
average weight was 35.7±2.2 g in the group consuming a high amount and 33.4±2.6 g in the group consuming a low amount. These values did not reveal any differences between the groups.

**DISCUSSION**

The purpose of this study was to examine the effects of different amounts of consumed QH on exercise capacity and the oxidative stress regulation system. In particular, QH is a typical supplement material, attracting attention for activating energy production and having anti-oxidation properties. Although its biological effect has been demonstrated7, 16–18, it has not been revealed how exercise capacity and the oxidative stress regulation system are affected by different amounts of consumed QH. Thus, our aim was for this to be a fundamental study for consideration of the oxidative stress system and examination of measures for improving exercise capacity. CoQ10 has an anti-fatigue action and has been used a lot in Europe and the United States for strengthening the physical aspects of athletes17, 18. Mizuno et al.19) reported that the consumption of oxidized CoQ10 by healthy individuals was effective in relieving the physical aspects of fatigue resulting from ergometer exercise. Since it was revealed that QH, when orally administered, was transformed into QH soon after it was absorbed in the small intestine, the above report essentially showed the effect of QH. In the present study, consumption of QH resulted in a significant extension of running time. This physiological effect on running time. Moreover, the group consuming a high amount of QH in the present study showed a more significant extension of running time than the group consuming a low amount, which suggested the possibility that QH consumption caused the physiological effect to be prominent. The body’s defense against oxidative lesions is not perfect, and oxidation products formed through exercise indicate oxidative stress15. In general, the effect of exercise on oxidative stress increases with the extension of running time, since oxygen is taken in into the body for the purpose of continuous production of ATP20. Exposure to such things as exercise is reported to have the possibility, potential to increase the expression of enzymes of the bio-defense system, including anti-oxidant enzymes, and proteins and control the expression of inflammation-related enzymes in response to enhanced production of oxidative stress21. It has been pointed out that the activation of these anti-oxidant enzymes is a compensatory response to increased production of oxidative stress22. The body has a vitamin C23) removal function and a CoQ10 redox cycle17, 24) defense mechanism to combat continuous exposure to oxidative stress. In the present study, along with a significant extension of running time, the group consuming a high amount of QH showed a more significant increase in d-ROM test value and, values of

### Table 1. Changes in running times

<table>
<thead>
<tr>
<th></th>
<th>Running time (min)</th>
<th>average changes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before intake</td>
<td>After intake</td>
</tr>
<tr>
<td>High</td>
<td>21.6 ± 5.5</td>
<td>36.0 ± 28.4a</td>
</tr>
<tr>
<td></td>
<td>14.4 ± 25.8</td>
<td>9.4 ± 23.7</td>
</tr>
<tr>
<td>Low</td>
<td>18.8 ± 6.3</td>
<td>28.3 ± 29.0ab</td>
</tr>
</tbody>
</table>

High, 300 mg/Kg QH consumption group (n=12); Low, 30 mg/Kg QH consumption group (n=11). a: significant by Mann-Whitney U test compared to Before intake (p<0.05), b: significant by Mann-Whitney U test compared to High (p<0.05)

### Table 2. Changes in oxidative stress

<table>
<thead>
<tr>
<th></th>
<th>d-ROM test (μCARR)</th>
<th>BAP test (μM)</th>
<th>BAP/d-ROM ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>High</td>
<td>113.8 ± 4.4</td>
<td>132.3 ± 15.4a</td>
<td>2223.2 ± 135.2</td>
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<tr>
<td>Low</td>
<td>114.7 ± 7.7</td>
<td>120.5 ± 7.7b</td>
<td>2202.5 ± 58.9</td>
</tr>
</tbody>
</table>

High, 300 mg/Kg QH consumption group (n=12); Low, 30 mg/Kg QH consumption group (n=11). a: significant by Mann-Whitney U test compared to Pre (p<0.01), b: significant by Mann-Whitney U test compared to High (p<0.05)

### Table 3. Changes in plasma concentration

<table>
<thead>
<tr>
<th></th>
<th>Plasma QH (μg/mL)</th>
<th>Plasma Q10 (μg/mL)</th>
<th>Reduced ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>High</td>
<td>0.031 ± 0.021</td>
<td>0.318 ± 0.145a</td>
<td>0.024 ± 0.006</td>
</tr>
<tr>
<td>Low</td>
<td>0.033 ± 0.023</td>
<td>0.035 ± 0.006d</td>
<td>0.030 ± 0.014</td>
</tr>
</tbody>
</table>

High, 300 mg/Kg QH consumption group (n=12); Low, 30 mg/Kg QH consumption group (n=11); plasma QH, plasma concentration of QH; Plasma Q10, plasma concentration of ubiquinone; reduced ratio, calculated from plasma QH and plasma Q10; Pre, before QH consumption; Post, after QH consumption. a: significant by Mann-Whitney U test compared to Pre (p<0.001), b: significant by Mann-Whitney U test compared to Pre (p<0.01), c: significant by Mann-Whitney U test compared to Pre (p<0.05), d: significant by Mann-Whitney U test compared to High (p<0.001)
plasma QH and plasma CoQ10 and a reduced ratio compared with the group consuming a low amount. This suggests the possibility that the CoQ10 redox cycle defense mechanism was activated as a result of increased oxidative stress by the extension of running time in the group consuming a high amount of QH. This CoQ10 redox cycle is a mechanism that maintains QH in the body by reducing enzymes and one of the important defense mechanisms that reduces exercise-induced oxidized stress occurring with exercise. In this study, both groups showed a significant increase in BAP test value and BAP/δ-ROM ratio as a result of QH consumption. Considering BAP test analyses, reducing the capacity of iron ions by plasma, the possibility was suggested that it might reflect improvement of the systemic anti-oxidant state rather than the effect of different amounts of consumed QH on plasma QH value. Therefore, it is necessary to study the plasma vitamin C level in the future. Deguchi et al.25 reported improvement of the reduced ratio, fatigue and QOL in elderly people as a result of QH consumption. The reduced ratio is largely influenced by the decrease in plasma QH value caused by oxidative stress (an increase in the plasma Q10 value) and the amount of NAD (P) H necessary for re-reduction of oxidized CoQ10. Thus, QH consumption improved the physical energy state by activating energy production, which led to improvement of the reduced ratio and fatigue. In the present study, the group consuming a high amount of QH showed a significant increase in plasma QH value and reduced ratio. The increase in plasma QH value caused a change in the dynamic state of QH in the body, suggesting the activation of the reduced enzyme system. The group consuming a low amount, however, did not show a change in plasma QH value, but a change was seen in the reduced ratio and running time. No change was observed in the plasma QH value this time, possibly because orally administered QH moved swiftly to organs and showed no apparent change. It was considered necessary to examine the levels of QH in organs in the future.

REFERENCES

17) Bowry VW, Stanley KK, Stocker R: High density lipoprotein is the major carrier of lipid hydroperoxides in human blood plasma from fasting donors. Proc Natl Acad Sci, 1992, 89: 10316–10320. [Medline] [CrossRef]