Influence of CoQ10 on Autonomic Nervous Activity and Energy Metabolism during Exercise in Healthy Subjects

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(Received November 26, 2007)

Summary Background: CoQ10 has come to be widely used as a dietary supplement, and daily intake of it has increased in recent years. CoQ10 is produced in all living organisms and is an essential coenzyme for energy synthesis in the mitochondria and an important scavenger of reactive oxygen species. Objective: This is a randomized, double-blind, placebo-controlled experiment to examine the acute effects of a single dose of CoQ10 on the autonomic nervous system (ANS) by using power spectral analysis of HRV and energy metabolism at rest and during low intensity exercise in healthy subjects. Eleven nonsmoking healthy male students (age: 26 ± 1 y) volunteered to participate in this experiment. CM5 lead ECG and gas exchange parameters were recorded 5 min before, and 30 min and 60 min after the oral administration of CoQ10 or a placebo. Following this, the subjects exercised using a stationary cycle ergometer for 10 min at 60 rpm with an intensity of 30% of heart rate reserve. During the exercise, the ECG and gas exchange parameters were recorded continuously. Results: There were no significant differences in heart rate between the CoQ10 and placebo trials at rest or during exercise. With regard to the integrated values of the spectrum, there were no significant differences in the HF power representing parasympathetic activity or LF power representing both sympathetic and parasympathetic nervous activities between the trials at any timepoint. However, during the exercise, HF power and LF power in the CoQ10 trial showed a tendency to increase compared with the placebo trial ($p < 0.1$). Total power representing the over-all ANS activity was significantly increased in the CoQ10 trial during exercise, which implied that autonomic nervous activity was augmented by CoQ10 ($p < 0.05$). CoQ10 also induced enhanced lipid oxidation as shown by the significantly lower respiratory gas exchange ratio (R) and increased fat oxidation during exercise. The results shed some light upon the relationship between the autonomic nervous activity and energy metabolism. Conclusion: These results suggested that CoQ10 may increase fat oxidation with augmented autonomic nervous activity during low intensity exercise.

Key Words CoQ10, ANS, energy metabolism, power spectral analysis of HRV

Coenzyme Q10 (CoQ10) is a naturally occurring fat-soluble ubiquinone-10 with vitamin-like properties (1, 2). CoQ10 acts in the body as an antioxidant and may have membrane-stabilizing properties (1). In addition, CoQ10 is an important factor for cellular mitochondrial respiration. CoQ10 acts in part as a redox link between flavoproteins and the cytochromes, which are needed for oxidative phosphorylation and the synthesis of adenosine triphosphate (ATP) (1, 3). In other words, CoQ10 is essential for energy production.

CoQ10 is biosynthesized and concentrated in the heart, kidneys, liver, muscle, pancreas, and thyroid gland. The content of CoQ10 in organs decreases with age (4). Although CoQ10 can be obtained from foods such as meat and fish, its content in them is very low (4). Therefore, some nutritionists have considered CoQ10 suitable as a dietary supplement. CoQ10 is now

widely used as a therapeutic substance to treat a variety of disorders such as ischemic heart disease, Parkinson's disease and diabetes mellitus (5–7). Its supplementation has been touted to improve physical and athletic stamina, muscle fatigue and weakness (8, 9).

Currently, there is no information investigating the acute efficacy of CoQ10 supplementation on energy metabolism at rest or during exercise in healthy subjects. In addition, no studies have evaluated the acute effect of CoQ10 on the autonomic nervous system. Previous study has verified that energy metabolism was modulated by the autonomic nervous system (ANS) (10, 11). The spectral analysis of heart rate variability (HRV) can evaluate the net effect of sympathetic (SNS) and parasympathetic nervous system (PNS) activity (12, 13), namely, autonomic nervous system (ANS) activity.

Accordingly, the purpose of this study was to assess the CoQ10 supplementation on ANS by using power spectral analysis of HRV and energy metabolism at rest

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and during exercise in healthy subjects.

MATERIALS AND METHODS

Subjects and informed consent. Eleven non-smoking healthy male students (age: 26 ± 1 y; height: 173.3 ± 1.7 cm; body mass: 65 ± 2.3 kg) in Kyoto University volunteered to participate in this randomized, double-blind, placebo-controlled experiment. This study examined the acute effects of CoQ10 and a placebo on autonomic nervous activity and energy metabolism at rest and during exercise. None of the subjects was taking any medication, and each subject was instructed to avoid beverages containing alcohol or caffeine and strenuous physical activity on the day before the measurements. The experiment administrator explained the purpose of the experiment, test protocol and bioactivity of CoQ10 prior to the experiment to all subjects. Then, informed consent to participate in this study was obtained from each subject. The protocol of the study was approved by the ethical committee of Kyoto University Graduate School.

Study design. Exercise intensity was defined by a target heart rate which was continuously monitored by a heart rate monitor (OEC-6102, Nihon Kohden Co., Japan). Target heart rate was calculated as 30% of the maximal heart rate reserve by the formula (14):

$$\text{Target HR} = (\text{maximal HR} - \text{resting HR}) \times 0.3 + \text{resting HR}$$

$$\text{Maximal HR} = 220 - \text{age}$$

Target heart rate was derived from the incremental cycle ergometer (CB-X 1000, NAPS, Japan) test, performed prior to the start of the experiment.

On the day preceding the exercise test, the subjects were instructed to refrain from strenuous physical exercise, tobacco and alcohol. They were instructed not to take any food or beverages during the 10 h prior to the commencement of exercise.

On the day of the experiment, all experiments were performed in the morning from 8:30 to 11:00 a.m. to minimize the circadian influence. The subject was placed in an upright seated condition for at least 20 min before the beginning of the experiment in a room at the temperature of 25°C. ECG and gas exchange parameters for each subject were recorded for 5 min as baseline (Rest1) data. Then the subjects were provided a simple breakfast (energy content 300 kcal or approximately 1,254 kJ), consisting of traditional Japanese food, and then provided one capsule of CoQ10 (30 mg, Nitto Pharmaceutical Industries, Ltd.) or a placebo (cornmeal) with a randomized order after the meal to facilitate absorption of the extremely lipophilic CoQ10. After their taking the capsules at 30 min (Rest2) and at 60 min (Rest3), ECG and gas exchange parameters were recorded for 5 min repeatedly. Following this, the subjects exercised using a stationary cycle ergometer (CB-X 1000, NAPS) for 10 min at 60 rpm with an intensity of 30% of heart rate reserve.

During rest, the subjects were instructed to breathe at a frequency of 1 breath every 4 s (0.25 Hz) in synchrony with the sound of an electric metronome, as

mentioned in our study (15), so that respiratory-linked HRV would not overlap with fluctuations in the low-frequency component. During exercise, the subjects were instructed that they could breathe freely as the respiratory rate would easily exceed the 0.25 Hz, so that low frequency HRV frequency components would not be affected by the respiration.

Data acquisition. The ECG was obtained using a CM5 lead. The analogue output of the ECG was connected to an ECG amplifier (Multi-channel Amplifier MEG-6100, Nihon Kohden Co.) and digitized using a 13 bit analogue-to-digital converter (HTB410) at a sampling of 1 kHz, using a 0.5–100 Hz band pass filter at rest and a 1.5–100 Hz filter during exercise.

Measurements of gas exchange parameters were obtained using the mixing chamber method (Aero monitor AE-300 S, Minato Medical Science, Japan). The analogue signals of fractional concentrations of O₂ and CO₂ from the gas analysis and those from the flow transducer were continuously digitized using a 13 bit analogue-to-digital converter at a sampling rate of 50 Hz. The $\dot{V}O_2$, carbon dioxide production, and expired ventilatory volume were calculated every 15 s.

All signals were stored continuously on a computer (DOS/V) for later analysis.

ECG R-R interval power spectral analysis. The heart acts in a discrete fashion with successive heartbeats leading to a series of fluctuating values of R-R intervals. In recent years, the power spectrum analysis of HRV has been proved to be a reliable non-invasive method to use for the quantitative and qualitative assessment of the activities of the cardiac sympathetic and parasympathetic nervous system in human studies (10, 13). In general, power spectrum analysis of HRV has shown two major distinct regions of periodicity in R-R intervals: the high frequency, respiration-linked component (HF, greater than 0.15 Hz) and the low frequency component (LF, less than 0.15 Hz). The HF is associated solely with activity in the parasympathetic nervous system while LF reflects mainly activity in the sympathetic nervous system, and partly activity in the parasympathetic nervous system (16, 17).

In the actual analysis, the derived R-R interval time series was aligned in 2 Hz sequences for power spectrum analysis. The DC component and linear trends were completely eliminated by digital filtering for band pass between 0.03–0.5 Hz at rest and 0.03–0.8 Hz during exercise as described elsewhere (10, 13). After passing through a Hamming-type data window, power spectrum analysis using a fast Fourier transform was performed on consecutive 256-s time series of the data for R-R intervals obtained during the experiments. We analysed LF (0.03–0.15 Hz), HF (at rest: 0.15–0.4 Hz, during exercise: 0.15–0.8 Hz), and total power (Total, at rest: 0.03–0.4 Hz, during exercise: 0.03–0.8 Hz) by integrating the spectrum for the appropriate bandwidth. Because integrated values of the basal spectrum differ greatly among individuals, the value of each placebo trial was standardized as 100%, and the other values were compared to this.

Fig. 1. Changes of activity in the autonomic nervous system following administration of CoQ10 or a placebo at rest and during exercise, as assessed from a power spectrum analysis of the R-R interval. Total: total power of the spectrum, LF: low frequency component of the spectrum, HF: high frequency component of the spectrum. The value of each placebo trial was standardized as 100%. Values represent means (SE), * $p < 0.05$, † $p < 0.1$.

Fig. 2. Changes in energy metabolism after the administration of CoQ10 or a placebo at rest and during exercise. R: respiratory exchange ratio, Fat: fat oxidation (g/min). Values represent means (SE), * $p < 0.05$.

Statistical analysis. All statistical analyses were performed using a commercial software package (SPSS version 11.5 for Windows, SPSS Inc., Chicago, IL). The effects of time, treatment and time $\times$ treatment were evaluated using 2-way ANOVA for repeated measurements; for comparisons between the trials at certain times, we used Student's paired *t*-test. *p* values of less than 0.05 were considered to be statistically significant. Data are expressed as mean $\pm$ SE.

RESULTS

Effect of CoQ10 on the power spectrum of the R-R intervals

There were no significant differences in heart rate between the CoQ10 and placebo trials at rest or during exercise [Rest1: CoQ10 63 (1.8), placebo 65 (2.2); Rest2: CoQ10 65 (1.2), placebo 66 (2.6); Rest3: CoQ10 65 (1.7), placebo 66 (2.6); exercise: CoQ10 106 (1.3), placebo 108 (2.0) beats/min, means (SE)]. With regard to the integrated values of the spectrum, there were no significant differences in the HF power or LF power between the trials at any timepoint. However, during

the exercise, HF power and LF power in the CoQ10 trial showed a tendency to increase compared with the placebo trial [HF 133.5 (18.3)%, LF 127.5 (13.0)%, means (SE), $p < 0.1$]. Total power showed no significant difference between the trials at rest, but during exercise, total power was significantly increased in the CoQ10 trial [Total 121.5 (8.9)%, means (SE), $p < 0.05$] as shown in Fig. 1.

Metabolic response to CoQ10

Figure 2 shows the changes in energy metabolism between the CoQ10 and placebo trials at rest and during exercise. $\dot{V}O_2$ (L/min) showed no significant difference between the trials at rest and during exercise. The respiratory gas exchange ratio (R) showed no significant difference between the trials at rest, but during exercise, R values in the CoQ10 trial were significantly lower than those in the placebo trial [CoQ10 0.91 (0.006), placebo 0.92 (0.002), means (SE), $p < 0.05$]. Fat oxidation increased significantly during exercise in the CoQ10 trial compared with the placebo trial [CoQ10 0.20 (0.006), placebo 0.19 (0.008) g/min,

means (SE), $p < 0.05$].

DISCUSSION

To the best of our knowledge, this is the first study to examine the effects of CoQ10 supplementation on the autonomic nervous system and energy metabolism during low intensity exercise in healthy subjects.

Since CoQ10 plays a key role in aerobic energy production, elevated serum CoQ10 levels may have a favorable effect on exercising muscles.

It has been reported that CoQ10 increased 2,3-diphosphoglycerate levels in erythrocytes (18). Because 2,3-diphosphoglycerate shifts the Hb-O₂ dissociation curve to the right, O₂ delivery to the muscles increases at a given PaO₂ (19). Therefore, ATP synthesis and lactate production may improve as a result of this increased muscular oxygenation. This could occur not only in skeletal muscle but also in cardiac and respiratory muscles. We speculate that this is the most important mechanism of action of CoQ10.

The autonomic nervous system plays an important role in energy metabolism. A change or reduction in activity of the sympathetic nervous system per se has been widely believed to contribute to the pathogenesis of obesity (20). Shihara et al. (21) have demonstrated that subjects having Trp64 polymorphism of the β -3 adrenergic receptor mutation (decreased receptor affinity for adrenaline and noradrenaline), responsible for the control of lipolysis through ANS activity, manifested a significantly lower LF power than normal subjects.

Our data showed lower R values and higher fat oxidation during exercise in the CoQ10 trial compared to those in the placebo trial. Furthermore, our HRV power spectrum data together with the gas exchange data strongly suggest that the CoQ10-induced stimulation of lipid metabolism might be mediated by enhanced overall autonomic nervous activity.

Although there was no significant difference in $\dot{V}O_2$ values, we found a higher autonomic nervous activity with lower R values and a higher fat oxidation during exercise after the administration of CoQ10. These changes may have been due to the improved O₂ utilization efficiency in peripheral tissue which resulted in enhanced fat metabolism.

Previous studies investigating the effects of CoQ10 supplementation during moderate to high-intensity exercise have been reported. Braun et al. (22) measured the exercise-induced change in $\dot{V}O_2$ max and lipid peroxidation before and after a one-month CoQ10 supplementation (100 mg daily) in twelve male bicycle racers. As compared with the placebo group, no significant change took place in maximal oxygen consumption, submaximal oxygen consumption, respiratory exchange ratio, heart rate, or total work after CoQ10 supplementation. Roberts (23) also reported no change in maximal oxygen consumption, stroke volume, or cardiac output in sedentary subjects after 4 wk of 100 mg/d CoQ10 supplementation, despite a twofold increase in serum CoQ10 concentration. These results suggested that the choice of exercise protocol—using moderate to

high-intensity exercise—may not have been as sensitive to the possible benefits of CoQ10 supplementation as would low-to-moderate-intensity exercise. The present study might confirm that the action of CoQ10 would be sensitive to low intensity exercise during which enhanced fat utilization would take place.

In conclusion, the major finding showed that CoQ10 may be increasing the fat oxidation with augmented autonomic nervous activity during low intensity exercise. The mechanism for this effect is not clear, but CoQ10 administration may be useful for the treatment of individuals with hyper-lipidemia or obesity by improving lipolysis. However, because the results of this present study were derived from a small number of subjects, the interpretation of the results should be retested in further larger doses and longer supplementation times with a larger scale study to confirm the present findings.

Acknowledgments

We would like to thank Nitto Pharmaceutical Industries, Ltd., for providing the supplement. We also thank all the subjects for their participation and cooperation during the experiment.

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