Dietary Coenzyme Q10 and Vitamin E Alter the Status of These Compounds in Rat Tissues and Mitochondria

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ABSTRACT Vitamin E (VE) and coenzyme Q (CQ) are essential for maintaining functions and integrity of mitochondria, and high concentrations of these compounds are found in their inner membranes. This study was conducted to examine the interaction between exogenously administered CQ10 and VE in rats. Male Sprague-Dawley rats (12 mo old) were fed a basal diet (10 IU VE or 6.7 mg RRR-α-tocopherol equivalent) supplemented with either 0 or 500 mg CQ10, and 0, 100 or 1310 IU VE/kg diet for 14 or 28 d. Liver, spleen, heart, kidney, skeletal muscle, brain and serum were analyzed for the levels of CQ10, CQ9 and VE. CQ10 supplementation significantly (P < 0.05) increased CQ10 concentration in the liver and spleen (total and mitochondria) and serum, but not in other organs. Interestingly, rats supplemented with CQ10 plus 100 IU VE/kg diet had significantly higher CQ10 levels in the liver and spleen, whereas those supplemented with CQ10 plus 1310 IU VE/kg diet had lower levels, compared with those supplemented with CQ10 alone. As expected, dietary VE increased VE content in all of the organs analyzed in a dose-dependent manner. However, rats fed the basal diet supplemented with CQ10 had significantly higher VE levels in liver (total and mitochondria) than those not receiving CQ10 supplementation. CQ9 levels were higher in the liver and spleen, lower in skeletal muscle and unaltered in brain, serum, heart and kidney of rats supplemented with CQ10 compared with the controls. These data provide direct evidence for an interactive effect between exogenously administered VE and CQ10 in terms of tissue uptake and retention, and for a sparing effect of CQ10 on VE. Data also suggest that dietary VE plays a key role in determining tissue retention of exogenous CQ10.

KEY WORDS: • coenzyme Q10 • vitamin E • mitochondria • rats

Coenzyme Q (CQ), which is also known as ubiquinone, is a lipid-soluble compound composed of a redox active quinoid moiety and a hydrophobic side chain made up of isoprenoid units. The number of isoprenoid units in the side chain is species specific. CQ is synthesized in all cells by enzymes present in the endoplasmic reticulum and Golgi membranes, and then transported to other cellular organelles. The biosynthesis of CQ occurs via the mevalonate pathway (Ernster and Dallner 1995, Maltese and Aprille 1985), which is also involved in cholesterol biosynthesis. The predominant form of CQ in humans is CQ10, which contains 10 isoprenoid units, whereas the main form in rodents is CQ9, which has nine isoprenoid units.

CQ is an essential cofactor in the mitochondrial electron transport chain where it accepts electrons from complexes I and II (Beyer 1992, Ernst and Dallner 1995). CQ also functions in its reduced form (ubiquinol) as an antioxidant, protecting biological membranes (Forssmark-Andree et al. 1997, Noack et al. 1994). Effective protection against oxidative damage by CQ10 has been demonstrated in liposomes, LDL, biological membranes, proteins and DNA (Forssmark et al. 1991, Indre et al. 1994, Stocker et al. 1991). Decreases in CQ10 levels have been reported in cardiac myopathies, degenerative muscle diseases and during aging (Battino et al. 1995, Kalen et al. 1989, Karlsson et al. 1990, Mortensen 1993). Most of the clinical work with CQ10 has focused on heart disease, specifically congestive heart failure and cardiomyopathy. The majority of the studies showed that treatment with CQ10 improved heart muscle function significantly without known adverse effects (Langsjoen et al. 1994). In addition to heart disease, the beneficial effects of CQ10 also have been demonstrated in patients with mitochondrial disorders (Bresolin et al. 1988, Ibara et al. 1989, Nishikawa et al. 1989, Shoffner et al. 1989).

Vitamin E (VE) is the major lipid-soluble chain-breaking antioxidant found in plasma, red cells and tissues, and plays an essential role in maintaining the integrity of biological membranes (Burton and Traber 1990, Chow 1991). VE can also react directly with peroxyl and superoxide radicals (Fukuzawa and Gebicki 1983, Niki et al. 1984). VE is functionally interrelated with a number of antioxidants, including ascorbic acid, glutathione, lipoic acid and CQ (Chan et al. 1991, Kang et al. 1990, Maguire et al. 1992, Mccay 1985, Niki et al. 1982, Packer et al. 1997). High concentrations of both CQ and VE are found in the inner membranes of mitochondria. The

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possibility of interaction between CQ and VE in terms of VE recycling was first suggested in the 1960s (Mellors and Tappel 1966). However, the bulk of the experimental evidence available concerning the interaction between these two compounds is derived from in vitro studies (Kagan et al. 1990, Lass and Sohal 1998, Maguire et al. 1992, Mellors and Tappel 1966, Stoyanovsky et al. 1995).

A number of studies have examined the interaction between VE and CQ10 with inconsistent findings. For example, Zhang et al. (1995 and 1996) showed that dietary CQ was taken up only into liver, spleen and plasma, and not into kidney, heart, muscle and brain; VE supplementation increased the levels of both endogenous and exogenous CQ in the liver and plasma, whereas dietary CQ10 had no effect on tissue VE. On the other hand, Lass et al. (1999) found that dietary CQ10 alone. To gain a better understanding of the interaction between VE and CQ10 with inconsistent findings. For example, Stoyanovsky et al. (1995).


### MATERIALS AND METHODS

**Chemicals and reagents.** Mono- and di-basic sodium phosphate were purchased from Fisher Scientific, Cincinnati, OH. HPLC-grade methanol and hexane were purchased from EM Science, Gibbstown, NJ. Ethanol (95%) was obtained from Midwest Grain Products, Pekin, IL. Potassium ferricyanide was purchased from J. T. Baker Chemicals, Phillipsburg, NJ. KCl, EDTA, Nagarse, Tris-HCl, Tris base, sucrose, Folin’s reagents, copper sulfate, sodium tetratrate, sodium carbonate and sodium hydroxide were purchased from Sigma Chemical, St. Louis, MO.

**Diets and feeding regimen.** Dietary ingredients were purchased from Dyets, Bethlehem, PA. The basal diet (AIN-93M) consisted of 14.00% vitamin-free casein, 46.57% cornstarch, 15.50% dextrose, 14.00% vitamin mix (without VE), 0.18%DL-methionine and 0.25% calcium, St. Louis, MO.

**TABLE 1**

<table>
<thead>
<tr>
<th>Coenzyme Q10 concentrations in the tissues of rats after vitamin E and coenzyme Q10 supplementation for 14 or 28 d1,2</th>
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</thead>
<tbody>
<tr>
<td>Tissue</td>
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<tr>
<td>Liver</td>
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<td>Kidney</td>
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<td>Heart</td>
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<tr>
<td>Muscle</td>
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<tr>
<td>Brain</td>
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<tr>
<td>Tissue</td>
</tr>
</tbody>
</table>

1 Rats were fed a basal diet (10 IU vitamin E/kg) supplemented with nothing (10E – Q), 500 mg coenzyme Q10/kg diet (10E + Q), 100 IU vitamin E plus 500 mg coenzyme Q10/kg diet (110E + Q), or 1310 IU vitamin E plus 500 mg coenzyme Q10/kg diet (1320E + Q) for 14 or 28 d.

2 Data are expressed as means ± se; n = 4. Different letters in a row denote significant differences, P < 0.05.
**RESULTS**

**CQ10 and VE supplementation and tissue CQ10 concentration.** CQ10 supplementation for 14 or 28 d significantly (P < 0.05) increased the CQ10 concentration in the liver, spleen and serum (Table 1) compared with the group not supplemented with CQ10. The increases in CQ10 concentrations were relatively larger in the liver and spleen of rats fed the experimental diets for 28 d than in those fed for 14 d. The levels of CQ10 in the heart, kidney, skeletal muscle and brain (Table 1) were not significantly altered by CQ10 supplementation for 14 or 28 d. Similar to the effect in the whole organs, dietary CQ10 significantly increased the CQ10 level in the mitochondria of liver (Fig. 1A) and spleen (Fig. 1B), but not heart (Fig. 1C).

Dietary VE showed a differential effect, depending on the dose, on tissue CQ10 levels; were significantly higher in the liver and spleen (Table 1) of rats supplemented with 100 IU VE/kg diet for either 14 or 28 d than in those of the controls. On the other hand, rats supplemented with 1310 IU VE/kg diet had significantly lower CQ10 levels in the liver and spleen than the respective controls. The increases of CQ10 concentration were relatively larger in the liver and spleen of rats supplemented with 100 IU VE/kg diet for 28 d than in those fed for 14 d. The CQ10 concentrations of serum, heart, kidney, skeletal muscle and brain (Table 1) were not significantly altered by dietary VE at any dose. Similar to the effect in the whole organs, supplementing 100 IU VE/kg diet significantly increased the CQ10 concentration in the mitochondria of liver (Fig. 1A) and spleen (Fig. 1B), whereas supplementing 1310 IU VE/kg diet had an opposite effect.

**CQ10 and VE supplementation and tissue levels of CQ9.** The CQ9 concentrations were significantly higher in the liver of rats fed the CQ10-supplemented diet at 14 d, and in the spleen of rats at 14 and 28 d (Table 1). On the other hand, CQ10 supplementation resulted in significantly lower CQ9 concentrations in the liver, heart, kidney, skeletal muscle and brain (Table 1) than the respective controls. The increases in CQ9 concentrations were relatively larger in the liver and spleen of rats supplemented with 100 IU VE/kg diet for 28 d than in those fed for 14 d. The CQ9 concentrations of serum, heart, kidney, skeletal muscle and brain (Table 1) were not significantly altered by CQ10 supplementation for 14 or 28 d. Similar to the effect in the whole organs, supplementing 100 IU VE/kg diet significantly increased the CQ9 concentration in the mitochondria of liver (Fig. 1A) and spleen (Fig. 1B), whereas supplementing 1310 IU VE/kg diet had an opposite effect.

**Table 2**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>10E – Q</th>
<th>10E + Q</th>
<th>110E + Q</th>
<th>1320E + Q</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14 d</td>
<td>28 d</td>
<td>14 d</td>
<td>28 d</td>
</tr>
<tr>
<td>Liver</td>
<td>1465 ± 64a</td>
<td>1500 ± 186a</td>
<td>1852 ± 63a,b</td>
<td>1666 ± 52ab</td>
</tr>
<tr>
<td>Spleen</td>
<td>13.0 ± 2.0b</td>
<td>16.6 ± 3.4a</td>
<td>19.0 ± 2.0b</td>
<td>18.0 ± 3.1c</td>
</tr>
<tr>
<td>Kidney</td>
<td>60.5 ± 2.0</td>
<td>54.6 ± 6.0</td>
<td>49.4 ± 6.4</td>
<td>63.2 ± 11.0</td>
</tr>
<tr>
<td>Heart</td>
<td>165 ± 7.6</td>
<td>160 ± 10.0</td>
<td>170 ± 23</td>
<td>196 ± 23</td>
</tr>
<tr>
<td>Muscle</td>
<td>25.6 ± 1.3b</td>
<td>30.1 ± 2.4b</td>
<td>19.5 ± 1.9ab</td>
<td>18.8 ± 1.8a</td>
</tr>
<tr>
<td>Brain</td>
<td>13.7 ± 2.0</td>
<td>12.8 ± 1.8</td>
<td>14.1 ± 1.8</td>
<td>12.5 ± 1.1</td>
</tr>
<tr>
<td>Serum</td>
<td>252 ± 50.4</td>
<td>277 ± 38</td>
<td>290 ± 38</td>
<td>353 ± 50</td>
</tr>
</tbody>
</table>

1 Rats were fed a basal diet (10 IU vitamin E/kg) supplemented with nothing (10E – Q), 500 mg coenzyme Q10/kg diet (10E + Q), 100 IU vitamin E plus 500 mg coenzyme Q10/kg diet (110E + Q), or 1310 IU vitamin E plus 500 mg coenzyme Q10/kg diet (1320E + Q) for 14 or 28 d.

2 Data are expressed as means ± SD; n = 4. Different letters in a row denote significant differences, P < 0.05.
CQ10 and VE supplementation and tissue levels of VE. Rats fed the CQ10-supplemented diets had significantly higher hepatic VE levels in both the homogenate (Fig. 2A) and mitochondria (Fig. 3). CQ10 supplementation had no significant effect on the concentration of VE in the spleen (Fig. 2B), serum (Fig. 2C), heart (Fig. 2D), kidney (Fig. 4A), skeletal muscle (Fig. 4B) or brain (Fig. 4C).

As expected, dietary VE supplementation for 14 or 28 d increased VE concentrations of liver (Fig. 2A), spleen (Fig. 2B), serum (Fig. 2C), heart (Fig. 2D), kidney (Fig. 4A), skeletal muscle (Fig. 4B) and brain (Fig. 4C) of rats in a dose-dependent manner. Similarly, VE supplementation increased VE levels in liver mitochondria in the same fashion (Fig. 3).

DISCUSSION

In agreement with studies involving relatively short-term administration of CQ10 (Lonnrot et al. 1998, Rehak and Wrigglesworth 1992, Yuzuriha et al. 1983, Zhang et al. 1995 and 1996), we also found significant increases in the CQ10 concentrations of serum, liver and spleen, but not of heart, kidney, skeletal muscle and brain of CQ10-supplemented rats. Significant increases of CQ10, however, have been found in cerebral cortex mitochondrial concentrations of CQ10 in 12 mo-old rats after oral treatment with 200 mg CQ10/kg body mass daily for 2 mo (Matthews et al. 1998), and in kidney mitochondria in 24-mo-old mice after oral CQ10 administration at a dose of 123 mg/kg body mass daily for 13 wk (Lass et al. 1999). It thus appears that treatment with high doses of CQ10 for longer periods may enable its uptake into other organs in addition to liver, spleen and serum.

Whether dietary VE influences tissue retention of CQ10 was examined in this study. We fed three different levels of VE along with 500 mg CQ10/kg diet and found that the rats supplemented with 100 IU VE/kg had significantly more CQ10 in both the homogenate and mitochondria of liver and spleen, whereas those supplemented with 1310 IU VE/kg had lower levels, compared with the control group not receiving VE supplementation. The mechanism of the enhancing effect of moderate levels and the suppressing effect of high levels of VE on tissue CQ10 found in our study is not yet clear. However, because both compounds are lipid soluble, it is possible that they may have a similar absorption/transport mechanism. A moderate increase in the dose of VE may elevate CQ absorption and/or incorporation, whereas high levels of VE may compete with CQ10 and thus suppress its absorption, transport and/or uptake.

CQ is synthesized in all the cells via the mevalonate pathway (Ernster and Dallner 1995, Maltese and Aprille 1985), and the predominant CQ homologue in rodents is CQ9. In this study, we examined the effect of dietary CQ10 and VE on endogenous CQ 9 and found that CQ9 levels were altered.
reported increased levels of VE in mice liver and skeletal muscle mitochondria after CQ10 supplementation. The results obtained from this study provide experimental evidence for an interaction in vivo between exogenously administered VE and CQ10 in terms of uptake and tissue retention. The evidence also points to an interaction between these two redox compounds at the endogenous level with respect to the liver and spleen. Moderate levels of VE in the diet enhanced the retention of dietary CQ10 in these organs, whereas high levels of VE had the opposite effect. These data suggest that VE is a key determinant of CQ10 status. The data obtained also suggest that CQ10 has a sparing effect on VE, possibly via the regeneration of VE from the tocopheroxyl radical. The implications of the interaction in relation to other functions of VE and CQ10 must be examined further.

**LITERATURE CITED**


2347