Dietary supplementation with coenzyme Q₁₀ results in increased levels of ubiquinol-10 within circulating lipoproteins and increased resistance of human low-density lipoprotein to the initiation of lipid peroxidation

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Ubiquinol-10 (CoQH₂, the reduced form of coenzyme Q₁₀) is a potent antioxidant present in human low-density lipoprotein (LDL). Supplementation of humans with ubiquinone-10 (CoQ, the oxidized coenzyme) increased the concentrations of CoQH₂ in plasma and in all of its lipoproteins. Intake of a single oral dose of 100 or 200 mg CoQ increased the total plasma coenzyme content by 80 or 150%, respectively, within 6 h. Long-term supplementation (three times 100 mg CoQ/day) resulted in 4-fold enrichment of CoQH₂ in plasma and LDL with the latter containing 2.8 CoQH₂ molecules per LDL particle (on day 11). Approx. 80% of the coenzyme was present as CoQH₂ and the CoQH₂/CoQ ratio was unaffected by supplementation, indicating that the redox state of coenzyme Q₁₀ is tightly controlled in the blood. Oxidation of LDL containing various [CoQH₂] by a mild, steady flux of aqueous peroxyl radicals resulted immediately in very slow formation of lipid hydroperoxides. However, in each case the rate of lipid oxidation increased markedly with the disappearance of 80–90% CoQH₂. Moreover, the cumulative radical dose required to reach this ‘break point’ in lipid oxidation was proportional to the amount of CoQH₂ incorporated in vivo into the LDL. Thus, oral supplementation with CoQ increases CoQH₂ in the plasma and all lipoproteins thereby increasing the resistance of LDL to radical oxidation.

Introduction

Oxidative modification of low-density lipoprotein (LDL) in the arterial wall is believed to contribute to the development of atherosclerosis [1] and may even be the primary precipitating factor in this widespread form of heart disease. Since oxidation of LDL lipids is generally thought to precede that of the apoprotein, considerable interest has been taken in oxidation of LDL lipids and in its inhibition by endogenous antioxidants, especially α-tocopherol, quantitatively the major antioxidant in plasma [2] and LDL [3]. Recently published in vitro data from this laboratory have shown that ubiquinol-10 (CoQH₂, the reduced form of coenzyme Q₁₀) is a potent antioxidant present in LDL of human blood plasma [4] (Scheme I).

We have found that treatment of LDL with a variety of oxidants including, organic peroxyl radicals generated in the water and in the lipid phases of LDL [4], copper ions, hypochlorite (Legge, L., Bowry, V.W., Barlow, T. and Stocker, R., unpublished data) and activated neutrophils [4] all result in rapid consumption of CoQH₂ and slower depletion of α-tocopherol and the carotenoids. For the neutrophils and peroxyl radicals, a marked increase in lipid hydroperoxide (LOOH) accumulation rate closely coincides with the disappearance of endogenous CoQH₂ (i.e., its oxidation to

Abbreviations: AAPH, 2,2'-azobis(2-amidinopropane hydrochloride); CEQH₂, cholesteryl ester hydroperoxides; CoQ, ubiquinone-10 (= coenzyme Q); CoQH₂, ubiquinol-10; HDL, high-density lipoproteins; LDL, low-density lipoprotein; LOOH, lipid hydroperoxides; PLOOH, phospholipid hydroperoxides; TRL, triacylglycerol rich lipoproteins; VLDL, very low-density lipoprotein.

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Scheme I
ubiquinone-10, CoQ), indicating that CoQH₂ strongly inhibits oxidation. Taken together with evidence that ischemic heart disease patients have significantly lower levels of the coenzyme in their LDL than do normal subjects [5] our 'antioxidation' data indicate that CoQH₂ may have an important in vivo anti-oxidant function(s).

If CoQH₂ is an important antioxidant one would predict that an increase in its concentration would result in increased antioxidant protection. However, the potential of the coenzyme to act as an antioxidant in plasma in vivo clearly will depend not only on its concentration, but also its distribution and redox status (CoQH₂/CoQ) among the various plasma lipoproteins. We have measured these parameters and the concentrations of other lipid antioxidants during short-term and long-term dietary CoQ supplementation. The resistance of the resulting 'in vivo supplemented LDL' towards peroxyl radical oxidation has been measured and compared with non-supplemented and exogenously (in vitro) supplemented LDL.

Material and Methods

CoQ and (all-E)-lycopene and α-carotene were generous gifts from Mitsubishi Gas Chemicals, Tokyo, Japan (trading name 'Ubidecarenone') and H. Keller (Hoffmann-La Roche), respectively. All other chemicals used were the same as previously described [4]. Lipid hydroperoxide standards were prepared as described [6]. CoQH₂ standard was made from CoQ by dithionite reduction [7] and used immediately after its preparation. Organic solvents of HPLC quality and 'nanopure' water were used throughout. All aqueous preparations and buffers were treated with Chelex-100 (Bio-Rad) to remove contaminating transition metals. Other chemicals were from Sigma and Merck and of the highest purity available.

The test subject for single dose supplantations was a 35-year-old, fasted, healthy male. An intravenous cannula was inserted in the cephalic vein for serial sample collection. After removal of the first 10 ml aliquot of blood into a heparinized syringe, CoQ was orally administered as a powder suspended in 100 ml of milk (which itself contained no significant CoQ or CoQH₂) and further blood aliquots were withdrawn at the indicated time points. For long-term supplementation, the test subjects were three healthy, male-fasted, normolipidemic males aged 31–35 years on normal diets. After a 4 day monitored run-in period, CoQ (weighed in 100 ± 1 mg portions and stored in aluminium foil at 4°C) was administered orally three times daily in the form of a fine powder suspended in 25 ml fresh milk. Blood was taken 3–4 h after either the morning, midday, or evening supplement depending on the donor. For both short- and long-term studies, the blood taken was centrifuged immediately to obtain plasma. While an aliquot of the plasma was analysed for lipids, antioxidants and lipid hydroperoxides (LOOH) as described below, the remainder was fractionated into different lipoprotein classes. The triacylglycerol-rich lipoproteins (TRL, top fraction, d < 1.06 g/ml), LDL (d = 1.06–1.006 g/ml), and high-density lipoproteins (HDL, bottom fraction, d > 1.1 g/ml) were prepared from the plasma by 30-min centrifugation in a Beckman TL-100 ultracentrifuge as described in 'procedure 7' [8] and were used immediately for experiments and analyses. Lipophilic antioxidants in hexane extracts (see below) of plasma and lipoproteins were determined by HPLC with electrochemical detection [4]. Neutral lipids (i.e., cholesterol, cholesteryl esters, and triacylglycerols) in hexane extracts were analysed by HPLC with 210 nm ultraviolet detection on a 4.6 × 250 mm, 5 μm particle size C-18 column eluted with 1:1 (v/v) tBuOH/MeOH at 1.0 ml/min. Protein concentrations were measured by the Lowry method [9].

For the oxidation experiments, LDL was isolated from ascorbate-depleted plasma [4] from a single donor before vs. after 11 days of supplementation. The LDL (2.0 ml × 1.2–2.4 mg protein/ml) was preincubated for 3 min at 37°C before adding 2.2'-azobisis(2-amidinopropane hydrochloride) (AAPH, 20 or 40 μl of 100 mM in 0.156 M NaCl) and gently shaking the resulting mixture in a waterbath at 37°C under air. At various times, 200-μl aliquots were withdrawn, added to 2 ml of cold argon flushed methanol and extracted with 10 ml of hexane. The hexane layer was evaporated in vacuo and the residue redissolved in 1:1 tBuOH/MeOH and analyzed immediately for lipid antioxidants and lipid hydroperoxides while the aqueous methanol portion was analysed for urate by HPLC with 265 nm ultraviolet detection [6]. Throughout this work, sample oxidation was inhibited by isolating and extracting the lipoproteins in argon flushed buffers and solvents, and by excluding oxygen from the subsequent hexane-evaporation and redissolving steps.

Results

Single dose response

A 100 mg oral supplement of CoQ in a fasted subject resulted in a doubling of the plasma coenzyme concentration, appearing mainly in its reduced form CoQH₂, between the second and sixth hours (Fig. 1A). A 200 mg supplement elicited a proportionately larger increase in [CoQH₂] in the same donor with a peak level reached at about 5 h (Fig 1B). The 0.7 μM rise in plasma [CoQH₂] after 100 mg CoQ supplementation (Fig. 1A) is consistent with published data showing the appearance of 0.7 μM deuterium-labeled coenzyme Q₁₀ (reduced + oxidized) in plasma following 100 mg supplementation with labeled coenzyme (d₅-CoQ₁₀).
Fig. 1. Coenzyme Q\textsubscript{10} concentrations in plasma and the various lipoproteins following a single oral dose of CoQ. The supplementation doses was 100 mg (A) or 200 mg (B) CoQ. Plasma concentrations of CoQ\textsubscript{H2} and CoQ were determined as described in Materials and Methods. In B, non-TRL data were normalized to free cholesterol contents assuming LDL and HDL contribute 70% and 15%, respectively, to plasma free cholesterol (1.1 mM). Symbols are in A: \( \circ \), \% reduced = 100CoQ\textsubscript{H2}/(CoQ\textsubscript{H2} + CoQ); \( \bullet \), plasma; and in B: \( \bullet \), plasma; \( \textbullet \), LDL; \( \text{\textbullet} \), HDL; and \( \Delta \), TRL.

Data for the various density fractions of plasma (Fig. 1B) showed that, in the short-term, CoQ\textsubscript{H2} contents of the HDL and TRL (d < 1.006 g/ml) fractions responded more strongly to the oral supplement than LDL, which carried most (= 70%) of the endogenous CoQ\textsubscript{H2} in pre-supplementation plasma. The elicited response was most dramatic in the (quantitatively minor) TRL fraction which comprised very low-density lipoproteins (VLDL) and chylomicrons. In comparison with LDL and HDL, the rapid fall-off in TRL-CoQ\textsubscript{H2} after its maximum is consistent with the relatively short half-lives of VLDL and chylomicrons in circulation. Notable rises in LDL- and HDL-[CoQ\textsubscript{H2}] at the end of the monitored period corresponded with the loss of coenzyme in TRL fraction.

The proportion of coenzyme in the reduced state, \( \%\text{CoQ}\textsubscript{H2} = 100\text{CoQ}\textsubscript{H2}/(\text{CoQ} + \text{CoQ}\textsubscript{H2}) \), was constant in plasma throughout the monitored period (Fig. 1A), a result which suggests that efficient reduction of CoQ to CoQ\textsubscript{H2} must occur either during absorption or rapidly after appearance of CoQ in blood. Regarding the latter possibility, preliminary experiments have shown that the monoprenyl homologue of CoQ, ubiquinone-1, is rapidly reduced at 37°C when added to whole blood (Surna, C. and Stocker, R., unpublished data) and further work with lipoprotein-associated ubiquinone-10 is on-going.

Long-term supplementation
Supplementation of three normolipidemic male subjects with \( 3 \times 100 \) mg CoQ/day for 11 days afforded the donor-averaged coenzyme and \( \alpha \)-tocopherol data shown in Figs. 2A–P. No overall change in the mean total carotenoid concentration [lycopene + \( \alpha \)-\( \beta \)-carotene] was observed following supplementation, e.g., the concentration in LDL remaining constant at \( \approx 0.3 \) molecules per LDL particle. Neutral lipids, i.e., cholesteryl esters, triacylglycerols and free cholesterol, determined by HPLC for each class of lipid carrier, did not change significantly during supplementation.

After 11 days of supplementation, plasma CoQ\textsubscript{H2} reached 3–5-fold higher levels than in the run-in period, depending on the donor, and on average there was a 4-fold increase in plasma [CoQ\textsubscript{H2}] from non-supplemented 0.8 \( \mu \)M to 3.2 \( \mu \)M during the latter half of the supplementation program (Fig. 2A). The highest plasma [CoQ\textsubscript{H2}] reached by an individual donor was 6.3 \( \mu \)M on day 5, a 6-fold enhancement, while the lowest response (at day 4) was a 2-fold enhancement. Similar relative increases in [CoQ\textsubscript{H2}] were found in LDL and HDL (Figs. 2E and I). Although there was an even larger (= 10-fold) increase in TRL-CoQ\textsubscript{H2} (cf. Fig. 2D and P), the increase in total coenzyme (CoQ\textsubscript{H2} + CoQ) in TRL was roughly the same as that in plasma, LDL and HDL. This was because the proportion of coenzyme in the reduced state (\%CoQ\textsubscript{H2}) increased \( \approx 2 \)-fold in TRL (Fig. 2P), while in plasma, LDL and HDL it was unchanged. Indeed, one of the interesting findings of this study was that, in spite of supplementation with the oxidized coenzyme, the 'reducant status' of the coenzyme in plasma, LDL and HDL remained constant both in the short term (see above) and over a long-term supplementation period with the 15-day mean \%CoQ\textsubscript{H2} being 79, 85 and 69%, respectively (Fig. 2D, H and L). Data obtained from fasted, non-supplemented donors are similar except that the mean \%CoQ\textsubscript{H2} in HDL was 30% lower (Bowry, V.W., Stanley, K.K. and Stocker, R., unpublished data).

\( \alpha \)-Tocopherol concentrations in both plasma and LDL exhibited a small though consistent transient increase peaking at around the fifth day of supplementation (Figs. 2B and 2F). This was not so evident in the \( \alpha \)-tocopherol/CoQ\textsubscript{H2} ratios which in plasma, LDL, HDL and TRL showed rapid (day 1) then slower decreases (Fig. 2C, G, K and O). Here, the increases in \( \alpha \)-tocopherol apparently were overwhelmed by the simultaneous and larger increases in [CoQ\textsubscript{H2}].
Oxidizability of CoQH₂ supplemented LDL

In view of the 4-5-fold increase in [CoQH₂] and the putative role of CoQH₂ as an LDL antioxidant (Introduction), it was of interest to test whether in vivo supplemented LDL was correspondingly less susceptible to radical oxidation. For this purpose, AAPH was chosen as the oxidizer because at 37°C it generates a reproducible, steady flux of well defined radicals (d/dt[RÖO·] = 1.1 × 10⁻⁶ [AAPH] s⁻¹) [10] in the aqueous phase of the LDL preparation [11,12] (Scheme II).

Oxidations were performed using LDL from the same donor containing 0.7 CoQH₂ molecules per LDL particle before supplementation (Fig. 3A) vs. 2.8 CoQH₂ molecules per LDL particle after 11 days supplementation (Fig. 3B and C). Concentrations of
other (detected) lipid antioxidants were essentially the same in the pre- and post-supplementation LDL, i.e., 12 α-tocopherol molecules/LDL particle. Ascorbate, normally present at variable concentrations in our LDL preparations and which completely inhibits detectable lipid oxidation by aqueous radicals [13], was eliminated by treating the plasma with ascorbate oxidase before LDL isolation [4].

In agreement with our previous observations [4], detectable cholesteryl ester hydroperoxides (CEOOH) and phospholipid hydroperoxides (PLOOH) were formed without delay following addition of AAPH, although initially at very low rates (detection limits ≤ 0.05 μM). Rapid and near quantitative (recovery 92 ± 5%) oxidation of CoQH₂ to CoQ ensued, whereas more than 70% of each urate, α-tocopherol and the carotenoids was still present at the end of the incubation periods. Overall rates of urate consumption were 27%, 22% and 32% per 180 min in the incubations of Fig. 3A–C, respectively, corresponding to ≈ 0.2, 0.2 and 0.3 nM s⁻¹, respectively. Autoxidation of α-tocopherol and urate in the absence of AAPH was negligible. In each case, the rate of lipid oxidation increased dramatically after depletion of most (80–90%) endogenous CoQH₂ in the LDL and this oxidation ‘break point’ appeared unrelated to substantial changes in the α-tocopherol or urate contents of the incubating LDL (Fig. 3).

Interestingly, although the accumulation of LOOH was strongly inhibited by CoQH₂, the oxidation of CoQH₂ accounted for less than half (29–32%) of the radical flux in the initial incubation periods, assuming that each molecule of CoQH₂ scavenges one molecule of ROO⁻ [14]. Peroxide accumulation was negligible during these initial periods so that only a small proportion of the radical flux (< 5% assuming 1 × LOOH/ROO⁻) was reacting with the polyunsaturated lipids in LDL. α-Tocopherol consumption was not measured with sufficient precision to estimate its contribution to radical trapping on a time-point-by-time-point basis but it appears from the present and previous studies that the oxidation of α-tocopherol is slight until CoQH₂ is removed. However, since α-tocopherol is present in higher concentration than the CoQH₂ (Fig. 2G) and since it also has a higher molar trapping capacity (2 vs. 1 × ROO⁻/antioxidant), it may contribute significantly to radical trapping in the early phase of oxidation. Judged by its overall consumption rate, urate might account for ≈ 20–40% (1 × ROO⁻/antioxidant) of the aqueous radical flux, although (as with α-tocopherol) the exact contribution during the ‘lag phase’ is obscured by fact that a small relative loss of urate would correspond to substantial proportion of radical trapping. Thiol groups present in LDL (not measured here) may provide the remaining radical antioxidant protection. Like urate, thiol groups have been shown to lower the rate of detectable lipid oxidation in plasma by intercepting ROO⁻ in the aqueous phase while not interacting readily with lipid radicals [13,15,10].

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![Fig. 3](https://example.com/image3.png)

Fig. 3. Relative susceptibilities towards AAPH-mediated oxidation of non-supplemented vs. supplemented LDL. The non-supplemented LDL (A, 5.8 mg/ml) and supplemented LDL (B, 4.5 mg/ml; C, 4.5 mg/ml) were incubated under air at 37°C with AAPH (1 mM for A and B; 2 mM for C) and time-dependently analysed for antioxidants (broken lines) and lipid hydroperoxides (LOOH, solid lines) as described in Materials and Methods. All of the LDL preparations used were initially free of detectable LOOH. Initial concentrations were for CoQH₂: 1.9 μM (A), 5.7 μM (B), and 5.7 μM (C); and for α-tocopherol (α-Toc): 21 μM (A), 16 μM (B), and 16 μM (C). Symbols: ○, α-Toc; □, CoQH₂; ▲, cholesteryl ester hydroperoxides (CEOOH); ●, phospholipid hydroperoxides (PLOOH).
The effective radical chain length ($\chi = \text{LOOH accumulation rate/radical flux}$) in the linear phase of lipid oxidation after CoQH$_2$ depletion is calculated to be essentially the same for the 'non-supplemented-LDL + 1.0 mM AAPH' (Fig. 3A) and 'supplemented-LDL + 2.0 mM AAPH' (Fig. 3C) incubations, viz. $\chi = 10.0$ and 10.5, respectively. Although the 'supplemented-LDL + 1.0 mM AAPH' (Fig. 3B) combination was not incubated long enough to deplete CoQH$_2$, the LOOH accumulation rate appears fully consistent with the earlier time-point data of the other incubations. The change in the ratio of oxidized core to surface lipids (see CEOOH/PLOOH in Fig. 3) from non-supplemented to supplemented LDL suggests that CoQH$_2$ might be more effective in protecting the core lipids than the surface lipids. In contrast to the above, AAPH (1.0 mM) oxidation of LDL (from the same donor supplemented in vitro with 5 $\mu$M CoQH$_2$ (added in ethanol 0.5%)) led to substantial LOOH accumulation; the coenzyme in its oxidized and reduced forms be-
tween the plasma lipoproteins, and to examine the content and redox status of CoQ in the various classes of circulating lipoproteins and that CoQH$_2$-sup-
plemented LDL is indeed more resistant towards oxidation than the non-supplemented lipoprotein. Both the content and redox status of CoQ in the various plasma lipoproteins were obtained using a rapid isolation method and under conditions which precluded oxidation of the antioxidants. A detailed interpretation of the supplementation data must be qualified, how-
though the small number of participants ($n = 3$) so that some results, while interesting, are considered preliminary rather than definitive.

In the 'preliminary' category is the observed transient increase in plasma [\alpha-tocopherol] around the fourth day of supplementation (Fig. 2B). This would correspond to a substantial increase in the total radical trapping capacity of plasma LDL particles: assuming each molecule of \alpha-tocopherol traps two peroxyl radicals [2] and carotenoids and CoQH$_2$ each trap one [14,18], we estimate that the total radical trapping capacity of LDL particles increased from 25 to a peak of 40 (ROO·/LDL) in the first 4 days of supplementation before falling back to 29 by day 11 (Fig. 2E and F). While the mechanism for the transient increase in [\alpha-tocopherol] in plasma and LDL following dietary supplementation with CoQ is not known at present, the observation is interesting and suggests the importance of carefully analysing antioxidants other than the particular antioxidant being supplemented. In this context it is interesting to note that dietary supplementation of rats with \alpha-tocopherol resulted in substantial increases in [CoQ] in certain tissues [19]. We have not tested whether oral supplementation with \alpha-tocopherol, which results in an increase in LDL in both its vitamin E content and resistance towards oxidation [20], also affects [CoQH$_2$] in LDL.

Our CoQ supplementation data for plasma may be compared with previous reports. In particular, Tomono et al. [16] analysed the plasma pharmacokinetics of a labeled coenzyme Q$_{\text{in}}$ supplement in terms of a multi-
compartment model. Accordingly, CoQ is absorbed at a constant (zero-order) rate in the gastrointestinal tract with an absorption time of 6.2 h per 100 mg, and then distributed sequentially to: (i) a compartment representing chylomicrons and tissues which rapidly absorb the chylomicron-packaged coenzyme; (ii) the liver; and (iii) a compartment representing VLDL and tissues which rapidly absorb the VLDL-packaged coenzyme. In this model, the subsequent break-down of VLDL into HDL and LDL was not considered. Although the temporal similarity between the plasma response to 100 mg and 200 mg doses (cf. Fig. 1A and B) seems at odds with the first assumption of this model (zero-order absorption), the hypothesis that CoQ is returned to the liver and resecreted in VLDL is consistent with the observed peaking and rapid fall-off in TRL-[CoQH$_2$] (Fig. 1B). It would be expected that, after absorption and subsequent liver resecretion ceases at $\approx 8$ h, the CoQH$_2$ in the TRL fraction diminishes rapidly owing to the short life-time of circulating VLDL. The response to long-term CoQ supplemen-
tation predicted by Tomono's model is, however, somewhat larger than that which we found. Based on measured single dose pharmacokinetic parameters, long-
term supplementation using the same protocol as used in this study (viz. $3 \times 100$ mg/day) was estimated to produce a daily mean plasma concentration of labeled coenzyme of 6.5 $\mu$M (corresponding to the increase in total coenzyme in our study) by day 10 and 90% of this level by day 4 [16]. In contrast, we observed a more modest 3 $\mu$M increase.

Although CoQH$_2$ is possibly the most effective lipid antioxidant present in LDL [4], it is only present at relatively low concentrations (i.e., 0.5–1.0 CoQH$_2$ vs. 6–12 \alpha-tocopherol molecules per LDL particle) and so...
we were particularly interested to test the resistance of LDL from supplemented plasma towards radical oxidation. In the event, CoQ supplementation did afford a more ‘radical resistant’ LDL. A 4-fold increase in LDL-[CoQH₂] was reflected in a nearly proportional increase in the total radical dose required to reach the breakpoint in LOOH formation, i.e., on a radical/LDL particle basis, ROO· /LDL = 3 for non-supplemented vs. = 11 for the supplemented LDL (Fig. 3A vs. C). In comparison, the less-than-proportional increase in radical resistance seen for exogenously CoQH₂-supplemented LDL (see Results) shows that in vitro supplementation confers less effective antioxidant protection. Presumably this difference between in vivo and in vitro supplemented LDL data arises from non-uniform incorporation of CoQH₂ in vivo [21], and this may also apply to other lipid-soluble antioxidants.

The correspondence between CoQH₂ content and resistance to radical induced oxidation of the LDL lipids indicates that it is indeed CoQH₂, and not some as yet undetected antioxidant, which confers the (initial) antioxidant protection in the lipid phase. The fact that the radical flux is = 3-fold greater than the consumption of CoQH₂ suggests, however, that additional radical trapping takes place, although probably in the aqueous rather than lipid phase (i.e., by urate and/or thiol groups). A quantitative examination of plasma oxidation [22] has demonstrated that plasma thiol groups are consumed in the initial stages of oxidation, even while ascorbate and CoQH₂ are present.

α-Tocopherol, quantitatively the major antioxidant in LDL lipids and a strong inhibitor of lipid oxidation in bulk solution, does not effectively prevent lipid oxidation in LDL in the absence of CoQH₂, cf. [4] and Results. The mechanism for the ubiquinol dependence of lipid oxidation in LDL is not clear at present, although a simple sparing effect, whereby CoQH₂ merely prevents consumption of α-tocopherol, can immediately be ruled out because the vitamin is present in much (5–20-fold) higher concentration than CoQH₂. One possibility is that CoQH₂ is kinetically superior to α-tocopherol as a lipid antioxidant in LDL. A more interesting possibility is that CoQH₂ reduces the tocopheroyl radical formed by radical attack to prevent it from re-initiating lipid oxidation [23]. We are presently investigating such a role of CoQH₂ in LDL.

The potential in vivo significance of these results is that ubiquinol-enriched LDL is both more slowly oxidized by a given radical flux and can resist a proportionately higher radical flux, for a given time, than non-enriched LDL. The former would thus be expected to be more resistant to biological oxidants generated at the putative site of atherogenie ‘oxidative modification’ or during ischemia/reperfusion. In support of this putative in vivo antioxidant activity of CoQH₂, we have recently discovered that the content of LOOH in the blood plasma of fasting, healthy donors has a strong inverse correlation with the plasma reduct status of the coenzyme but is less well correlated with contents of other detectable lipid antioxidants, including α-tocopherol (Bowry, V.W., Stanley, K.K. and Stocker, R., unpublished data).

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