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Coenzyme Q, oxidative stress and aging

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Abstract

Coenzyme Q (CoQ) has three well-characterized functions in mitochondria, namely (i) transfer of reducing equivalents in the electron transport chain, (ii) generation of superoxide anion radical ($O_2^{\cdot -}$), and (iii) quenching of free radicals. The main purpose of this review is to discuss the effects of CoQ₁₀ intake for relatively prolonged periods on mitochondrial respiratory capacity, indicators of oxidative stress, and life span of animals, in context of the broader issue of whether or not the overall progression of the aging process can be modified by CoQ₁₀ administration. Comparative studies on different mammalian species have indicated that the rate of mitochondrial superoxide anion radical generation is directly correlated with mitochondrial CoQ₉ content and inversely related to amounts of CoQ₁₀, particularly the CoQ₁₀ bound to mitochondrial membrane proteins. Contrary to the historical view, dietary supplementation of mice and rats with CoQ₁₀ has been demonstrated to augment the endogenous CoQ content (CoQ₉ + CoQ₁₀) in mitochondria and homogenates of various tissues, albeit to varying extent. Ingestion of CoQ₁₀ results in the elevation of endogenous CoQ₉, the predominant homologue in mice and rats. In our studies, there was no indication of a discernable effect of CoQ₁₀ intake reflecting enhancement of mitochondrial respiratory activity, antioxidant capacity and pro-oxidant potentiation or prolongation of life span. The possibility that CoQ₁₀ intake affects certain other biological functions by as yet unelucidated mechanisms cannot be ruled out as CoQ has been shown to broadly alter gene expression in mice.

Keywords

Coenzyme Q; aging; mitochondria; oxidative stress; vitamin E; antioxidants; free radicals

1. Introduction

Coenzyme Q (CoQ) or ubiquinone (2,3-dimethoxy-5-methyl-6-multiprenyl-1,4-benzoquinone) molecules are located in the hydrophobic domain of the phospholipid bilayer of cellular membranes (Battino et al., 1990; Lenaz et al., 1999). CoQ is composed of a tyrosine-derived quinone ring, linked to a polyisoprenoid side chain, consisting of 9 or 10 subunits in higher invertebrates and mammals (Ernster and Dallner, 1995). The benzoquinone ring can assume three alternate redox states: the fully oxidized or ubiquinone (Q); the univalently reduced ($1e^- + 1H^+$) ubisemiquinone ($\cdot QH$), a free radical; and the fully reduced ($2e^- + 2H^+$) ubiquinol. The polyisoprenyl chain apparently facilitates the stability of the molecule within

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the hydrophobic lipid bilayer. In addition, the length of the CoQ isoprenoid chain seems to affect the mobility, intermolecular interaction with membrane proteins, and autoxidizability (Matsura et al., 1992; James et al., 2004). The physiological roles of CoQ in biological systems are most well characterized in the inner mitochondrial membrane, where three of its main functions are: (i) carrier of electrons from respiratory complexes I and II to complex III, (ii) generation of superoxide anion radical by autoxidation of ubiquinone and (iii) anti-oxidant quenching of free radicals (Crane and Navas, 1997; James et al., 2004; Turunen et al., 2004). The apparently paradoxical property of mitochondrial CoQ to potentially act both as a pro-oxidant and an antioxidant would seem to suggest that it may also be a modulator of the cellular redox state under physiological and/or pathological conditions, and particularly it may play a role in the aging process.

It is now widely recognized that during aging there is a pro-oxidizing shift in the cellular redox state, accompanied by an accrual of the amounts of oxidatively damaged molecules, which in combination may play a causal role in senescence (Sohal and Weindruch, 1996; Sohal et al., 2002). The main premise of this hypothesis, often referred to as the oxidative stress hypothesis, is that the imbalance between pro-oxidant generation and anti-oxidant defenses, or the level of oxidant load or stress, increases during aging, and mitochondria play a critical role in this homeostatic perturbation. The reason why mitochondria are thought to be implicated is that the rates of mitochondrial O_2^-/H_2O_2 production and oxidative damage to mitochondrial DNA, proteins and lipids increase during aging (Sohal and Sohal, 1991; Sohal et al., 1994 a,b; Sohal and Dubey, 1994). An important consequence of this apparently self-initiated damage is the acceleration of the rate of reactive oxygen species (ROS) generation, a phenomenon first reported in (Sohal and Sohal, 1991; Sohal and Dubey, 1994).

Another major age-related mitochondrial alteration is that ADP-stimulated (state 3) and the maximal (uncoupled) rates of mitochondrial oxygen consumption decline during aging (Ferguson et al., 2005). These twin changes, i.e., elevation of oxidative stress/damage due to enhanced O_2^-/H_2O_2 production, and the decline in mitochondrial ability to synthesize ATP, are thought to progressively attenuate the functional capacity of various physiological systems. CoQ is suspected to be involved in both of these age-related alterations because as an electron carrier, CoQ is a component of the oxidative phosphorylation system, and because CoQ is also an ROS generator and a quencher. The main question though is whether there is a cause-and-effect relationship between age-related changes in mitochondria and the CoQ-related parameters. In this context, the main purpose of this review is to examine whether variations in CoQ content or the relative abundance of its homologues affect mitochondrial function and have an impact on the aging process.

2. Effect of age on CoQ content in different tissues

CoQ content as well as the ratios of Q_9 and Q_{10} vary in different organelles, tissues and species. For instance, lysosomes and Golgi membranes generally contain relatively higher concentrations of CoQ than mitochondrial membranes or microsomes (Dallner and Sindelar, 2000). In mice, the variation in CoQ content among homogenates of different tissues is about 100-fold, with rank order: kidney > heart > skeleton > muscle > brain > liver (Lass et al., 1999a; Lass and Sohal, 2000). Compared to the homogenates, CoQ ($CoQ_9 + CoQ_{10}$) content of mitochondria was greater by six-times in liver, three-times in kidney, four-times in heart and 23-times in the skeletal muscle. CoQ concentrations in mitochondria also varied in different tissues, with heart containing 3.6-, 3.3-, 2.7- and 1.5-times higher amounts than those in the kidney, liver, brain, and skeletal muscle, respectively.

Results of the various studies in the literature on the age-related changes in CoQ levels do not support the existence of a common trend. For instance, Kalen *et al.* (1989) reported an age-

related loss of CoQ content in homogenates of human tissues. Beyer *et al.* (1985) found no age-related changes in CoQ level in homogenates of rat brain and lungs, an increase in the liver, and a decrease in the heart, kidney and skeletal muscles. Battino *et al.* (1995) reported a decline in CoQ content in nonsynaptic mitochondria from mouse brain between 2 and 18 months of age, followed by an increase at 24 months of age.

Studies in this laboratory suggest that age-associated changes in CoQ content are most evident in mitochondria, which also preferentially sequester CoQ, rather than in the homogenate. For instance, in the rat, there were no significant differences in the amounts of CoQ₉ or CoQ₁₀ in the plasma or the tissue homogenates of liver, heart and kidney at 4-, 19-, or 24 months of age (Kamzalov and Sohal, 2004). In contrast, mitochondrial content of CoQ₉, which is the predominant homologue, declined with age in all three tissues. A previous study showed a similar loss in mitochondria of rat skeletal muscle (Lass *et al.*, 1999b). Homogenates of mouse liver, heart, kidney, skeletal muscle and brain also showed no age-related loss in CoQ₉ or CoQ₁₀ content (Sohal *et al.*, 2006). Rather, during the period of 7 to 19 months of age, CoQ₉ content increased in brain and skeletal muscle, respectively, by 20% and 12%, while CoQ₁₀ content increased 33% and 52%. The aforementioned discrepancies between the findings from different laboratories may be due to the specific ages of the sampled animals or the procedure used for extraction and quantification of CoQ, or differences in species/strains/diets.

To summarize, it seems that during aging, decreases in CoQ content may occur in mitochondria of some tissues in certain species, but such losses are selective rather than ubiquitous. It has also been experimentally shown that physiological concentrations of CoQ in mitochondria do not exceed those required for kinetic saturation of NADH-Q-oxidoreductase, suggesting that CoQ is rate limiting in the electron transport chain (Estornell, *et al.*, 1992). Therefore, decreases of CoQ below the physiological levels can potentially affect mitochondrial respiratory function, which may indeed occur under specific pathological conditions.

3. Inter-species variations in mitochondrial CoQ content and superoxide anion radical generation

The variations observed in the amounts of CoQ and ratios of the CoQ homologues among different tissues raise the question whether they carry any physiological significance, particularly whether differential amounts of CoQ₉ or CoQ₁₀ affect mitochondrial functions. This issue was addressed by us by first comparing the concentrations of CoQ homologues in cardiac mitochondria from nine different mammalian species, namely mouse, rat, guinea pig, rabbit, goat, sheep, pig, cow and horse (Lass *et al.*, 1997; Sohal *et al.*, 1999). The total amount of CoQ (CoQ₉ + CoQ₁₀) present in different species varied about 2-fold with the rank order: horse = mouse = cow = sheep = goat > rat > pig = rabbit > guinea pig; however, the ratios of CoQ₁₀:CoQ₉ in different species varied 60-fold. The total CoQ content was not found to be correlated with maximum life span (MLS) of the species. In contrast, CoQ₉ content was inversely and CoQ₁₀ directly correlated with the MLS of the species (Fig. 1). For instance, CoQ₉ concentration was 40 to 60-times greater in mitochondria of shorter-lived species such as mouse or rat compared to the longer-lived horse or cow.

In separate studies involving comparisons of different mammalian species (Sohal *et al.*, 1989; Ku *et al.*, 1993; Sohal *et al.*, 1999), we found that species-specific maximum life span was inversely correlated with mitochondrial rates of O₂^{•-} and H₂O₂ generation (Fig. 2). It was thus of interest to further examine whether CoQ₉ or CoQ₁₀ content or the ratio of the two were also correlated with the rate of mitochondrial O₂^{•-} generation (Lass *et al.*, 1997; Sohal *et al.*, 1999). CoQ₉ content of cardiac mitochondria was found to correlate directly and CoQ₁₀ inversely with the rate of O₂^{•-} generation (Fig. 3).

Such correlations led to the hypothesis that CoQ₉ content of mitochondria might be a determinant of the rate of O₂⁻ generation. This possibility was addressed in CoQ depletion/repletion studies on submitochondrial particles (SMPs) of rat and cow, which differ 16-fold in total CoQ content (Fig. 4). Depletion of CoQ, followed by repletion with different amounts of CoQ₉ or CoQ₁₀, indicated that at relatively lower concentrations, there were no significant differences in O₂⁻ generation between repletions with equal amounts of CoQ₉ or CoQ₁₀ (Lass et al., 1997). However, at repletions with relatively higher concentrations of CoQ₉ or CoQ₁₀, the rates of O₂⁻ generations were greater in CoQ₉- than CoQ₁₀-augmented SMPs. This can be interpreted to suggest that increased CoQ₉ content may lead to relatively higher rates of O₂⁻ generation *in vivo*. Interestingly, an increase in the rate of O₂⁻ generation due to CoQ₉ augmentation of SMPs of rat was an order of magnitude higher than that in cow SMPs, suggesting that structural organization of the inner mitochondrial membrane also plays a determining role in the rate of O₂⁻ production.

To further examine the possibility that binding of CoQ and mitochondrial membrane proteins (presumably the oxidoreductases of the electron transport chain), modulates the rate of O₂⁻ generation, proteins in mitochondrial membranes were isolated as micelles from five different mammalian species that varied in their relative amounts of CoQ₉ and CoQ₁₀ (Lass and Sohal, 1999). It was found that up to 32% of the total mitochondrial CoQ is bound to proteins, the rest presumably belonged to the freely diffusible pool. Notably, the amount of protein-bound CoQ in micelles of mitochondria from heart of different species was found to be inversely related to the rate of mitochondrial O₂⁻ generation (Figure 5). For instance, micelles from cow and pig contained two-fold higher amounts of CoQ than those from rat and mouse. It is worth pointing out that those micelles with relatively high CoQ:protein ratio were derived from species that are longer-lived and have CoQ₁₀-rich mitochondria with relatively low rates of O₂⁻ generation. On the basis of such studies, it can be hypothesized that variations in longevity among different species co-evolved with the increases in the amounts of CoQ₁₀ bound to the mitochondrial proteins.

Altogether, results of the various correlational studies discussed above suggest that variations in the relative amounts of CoQ homologues may be associated with rate of mitochondrial O₂⁻ generation as well as longevity of different species; notwithstanding, such associations do not establish a cause-and-effect relationship. Experimental tests of this idea would require manipulations of the relative amounts of CoQ homologues.

4. Effect of CoQ administration on endogenous CoQ content

CoQ is synthesized endogenously by the mevalonate pathway (Ernster and Dallner, 1995). The historical view about the contribution of the dietary sources to endogenous levels of CoQ (Reahal and Wigglesworth, 1992; Zhang et al., 1995; 1996), reiterated recently (Bentinger et al., 2003), is that although ~6% of the orally administered CoQ permeates the gastrointestinal tract into the blood and is transferred to liver and spleen, CoQ uptake by other tissues such as heart, kidney, brain and skeletal muscle is low or completely absent, unless the endogenous levels have fallen below a critical threshold. More recent studies, however, have reported that this historical perspective was based on administration of relatively low dosages of CoQ for a comparatively short period. It was first shown by Matthews et al. (1998) that CoQ₁₀ intake by 12- or 24-month-old rats increased CoQ content in brain mitochondria and had a neuroprotective effect against 3-nitropropionic acid. Subsequently, a series of studies conducted by us (Lass et al., 1999a,b; Lass and Sohal, 2000; Kwong et al., 2002; Kamzalov et al., 2003; Rebrin et al., 2004) demonstrated that CoQ₁₀ administration via food to young adult mice or rats caused an increase in amounts of both CoQ₉ and CoQ₁₀ homologues in plasma, and in homogenates and mitochondria of liver, heart and skeletal muscle (Fig. 6). In the brain, the increase was of a lesser magnitude and occurred primarily in mitochondria and not the

homogenate. In all the tissues, the amount of CoQ augmentation was greater in mitochondria than in the homogenate, suggesting its preferential sequestration in mitochondria. These studies also indicated that CoQ₁₀ administration enhanced endogenous CoQ₉, by a mechanism that remains to be elucidated. In general, greater augmentations of CoQ (CoQ₉ + CoQ₁₀) could be achieved with increases in the duration of the CoQ₁₀ administration. These augmentations were equivalent to or greater than those achieved by short-term increases in CoQ dosage. Furthermore, when compared with the relatively hydrophobic CoQ powder, a water-miscible CoQ₁₀ formulation (Q-Gel from Tishcon) resulted in more consistent augmentation of endogenous CoQ, particularly in brain (see Kwong et al., 2002; Kamzalov et al., 2003 versus Lass et al., 1999a; Sohal et al., 2006). Notwithstanding, it should be noted that the uptake of CoQ and other lipoidal substances is a complex process dependent upon a number of different factors.

5. Antioxidant roles of CoQ and α -tocopherol in inner mitochondrial membrane

The inner mitochondrial membrane contains CoQ as well as α -tocopherol, both of which have antioxidant properties, thereby raising the issue about their respective roles in quenching the free radicals generated in inner mitochondrial membrane. In solutions, CoQ has been shown to inhibit lipid peroxidation in mitochondrial membranes that have been depleted of α -tocopherol (Mellors and Tappel, 1966; Takayanagi et al., 1980). α -Tocopherol has also been unambiguously demonstrated to be capable of scavenging lipid peroxy radicals, thereby preventing the propagation of chain reactions during lipid peroxidation (McCay, 1985). Notwithstanding, the reactivity of α -tocopherol with peroxy radical, which generates α -tocopheroxy radical, far exceeds that of peroxy radicals with ubiquinol, thereby suggesting that ubiquinol is unlikely to be a direct radical scavenger *in vivo*. Current evidence suggests that ubiquinol and α -tocopherol act in concert to scavenge radicals during autooxidation of mitochondrial membranes (Kagan et al., 1990; Stoyanovsky et al., 1995; Lass and Sohal, 1998; 2000; Sohal, 2004). α -Tocopherol seems to act as a direct scavenger forming tocopheroxy radical, whereas ubiquinol reacts with tocopheroxy radical to regenerate α -tocopherol. Several studies seem to confirm the sparing/regenerative effect of CoQ on α -tocopherol *in vivo* (reviewed in Sohal, 2004). In young adult mice, CoQ₁₀ intake effectively augmented the α -tocopherol concentration in tissue homogenates and mitochondria from liver, heart, and skeletal muscle (Kamzalov et al., 2003). A similar effect was observed in homogenates and mitochondria of rats (Fig. 7).

6. CoQ intake, mitochondrial function and life span in mice

Because CoQ can act as a generator or a quencher of ROS and because it is widely consumed by humans as a dietary supplement motivated us to conduct studies on the effects of long-term intake of CoQ₁₀ on the aging process. Specifically, we examined whether CoQ₁₀ intake affects the level of oxidative stress, mitochondrial respiratory functions, or the survival of the animals (Sohal et al., 2006). Mice were fed diets providing daily supplements of 0, 93, or 371 mg CoQ₁₀/kg body weight, starting at 3.5 months of age. Amounts of CoQ₉ and CoQ₁₀, determined at 7 and 21 months of age, were found to increase in relation to dosage and duration of CoQ₁₀ administration. Augmentations of CoQ were detected in homogenates and mitochondria of liver, heart, kidney, and skeletal muscle, and were evidently maintained throughout life. Different tissues tended to vary in their capacity for CoQ accretion, with liver and skeletal muscle exhibiting the highest elevations, and the brain showing the least. Thus, these studies confirmed our previous observations in young adult mice and rats, firmly refuting the long-held notion that CoQ content of tissues other than plasma, liver or spleen cannot be significantly augmented by dietary administration of CoQ₁₀. Indeed these demonstrations have provided

the necessary rationale for testing the effects of CoQ₁₀ intake on a broad range of parameters associated with mitochondrial functions, oxidative stress, and life span.

Long-term CoQ₁₀ intake, lasting from 3.5 up to 25 months had no effect on activities of the major antioxidant enzymes, such as catalase, glutathione peroxidase and superoxide dismutase in liver, kidney, skeletal muscle or brain. Similarly, long-term CoQ₁₀ intake had no effect on mitochondrial respiratory chain, measured as activities of oxidoreductases such as NADH ferricytochrome *c* reductase (complex I/III) and ferrocytochrome *c* oxidase (complex IV). The rates of oxygen consumption by liver mitochondria, measured as glutamate/malate and succinate supported state-3 respiration, were also not affected by CoQ₁₀ intake. To further determine whether CoQ₁₀ intake affected the level of oxidative stress, rates of O₂⁻ generation were measured in SMPs from heart, kidney and skeletal muscle of 25-month old experimental and control mice. No significant differences were detected between the groups. Levels of protein carbonyls and GSH:GSSG ratios also showed no notable effect of CoQ₁₀ intake. Thus, prolonged CoQ₁₀ intake seemingly failed to modulate mitochondrial respiratory capacity or levels of oxidative stress.

CoQ₁₀ administration, starting at 3.5 months of age, also had no significant effect on the long-term survival of the mice (Fig. 8). Two previous studies on mice and rats in other laboratories, in which CoQ₁₀ was administered at dosages lower than the highest dosage used by us, also reported no effect on life span (Lonnrot et al., 1998; Lee et al., 2004). Results of studies in other species are, however, quite contradictory and species-specific. For instance, different groups have reported that life span of the worm, *C. elegans*, is prolonged by CoQ₁₀ supplementation (Asencio et al., 2003), or, paradoxically, by a deficiency of CoQ in the diet (Larsen and Clarke, 2002) or even by the inability of a mutant strain to synthesize the normal CoQ homologue (Branicky et al., 2002). One explanation of these contradictory findings may be the unusual life history and the mode of adaptation of *C. elegans* to stress. A deficiency of CoQ induces a hypometabolic or a dauer-like state, which in nature facilitates survival under adverse conditions. For instance, the life span of the worm is extended by the intake of antimycin A, an inhibitor of the electron transport chain, which is extremely toxic to most other aerobic species (Dillin et al., 2002). Notwithstanding, the results of studies on the effects of CoQ₁₀ intake on the life span of mammals are in agreement that CoQ₁₀ supplementation has no effect on longevity.

7. CoQ intake and brain function in mice

Concurrently with our studies of long-term intake of CoQ₁₀ on the aging process in mice, we also examined the effect of supplementation of CoQ₁₀ alone, α -tocopherol alone or CoQ₁₀ + α -tocopherol on cognitive and motor functions of 24 month old mice, which had been treated for 13 weeks (McDonald et al., 2005). CoQ₁₀ intake alone increased α -tocopherol concentrations in plasma, liver, heart, and skeletal muscle of these 24-month-old mice, however, in the brain tissue of old mice, the mitochondrial α -tocopherol concentration was augmented only when CoQ₁₀ and α -tocopherol were administered together. This treatment (CoQ₁₀ + α -tocopherol) also partially ameliorated impaired learning of an avoidance problem by these old mice, whereas treatments with CoQ₁₀ alone or α -tocopherol alone were relatively less effective. None of the treatments improved age-related impairment of the mice in tests of motor performance. In a follow-up experiment, much higher doses of CoQ₁₀ administration also failed to improve avoidance performance of the old mice. These studies suggested that intake of α -tocopherol and CoQ₁₀ together has a synergistic effect.

To conclude, although CoQ may act as a pro-oxidant or an antioxidant *in vitro*, it has no notable *in vivo* effects on mitochondrial respiratory functions or levels of oxidative stress. There is also no clear indication of its ability to influence the life span or brain function of mammals,

however, it is conceivable that beneficial effects of CoQ₁₀ intake may occur under certain pathological conditions. It is also worth noting that CoQ₁₀ intake has been shown to broadly affect the pattern of gene expression (Lee et al., 2004; Groneberg et al., 2005), indicated by the abundance of mRNAs, however, the nature of the physiological impact remains to be demonstrated.

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Fig 1.

Relationship between CoQ₉ (A) and CoQ₁₀ (B) content of heart mitochondria from different species and maximum lifespan potential (MLSP) of the species, expressed as log₁₀ units. (Adapted from data in Lass et al., 1997).

Fig 2. Relationship between rate of superoxide anion radical generation by cardiac submitochondrial particles and maximum life span potential (MLSP) of different species, expressed as $\log_{10}$ units. (Adapted from data in Lass et al., 1997).

Fig 3.

Relationship between rates of superoxide anion radical generation by cardiac submitochondrial particles from different species and amounts of CoQ₉ (A) and CoQ₁₀ (B) extracted from heart mitochondria. (From Lass et al., 1997).

Fig 4. Rates of superoxide anion radical generation by CoQ-depleted/repleted rat (A) and bovine (B) heart submitochondrial particles (SMPs). Freeze-dried SMPs were depleted of native CoQ by six repeated extractions with pentane and reconstituted with specific amounts of CoQ homologues, followed by measurements of rates of O₂^{-•} generation. (From Lass et al., 1997).

Fig 5.

Relationship between amounts of CoQ associated with membrane proteins and rate of superoxide anion radical generation by cardiac mitochondria of different mammalian species. Mitochondrial membrane proteins were isolated as deoxycholic acid (DOC) pelletable micelles, and the CoQ₉ and CoQ₁₀ content was determined by HPLC. The CoQ content (CoQ₉ + CoQ₁₀), retained in the mitochondrial DOC micelles in different species, is expressed as percent of the total amount of CoQ present in whole mitochondria and is plotted against the rate of O₂^{•-} generation, reported previously by Lass et al., 1997.

Fig 6. Effect of CoQ₁₀ intake on CoQ₉ (top panels) and CoQ₁₀ (bottom) content in mitochondria from different tissues of young adult mice (left) or rats (right). In studies on mice (Kamzalov et al., 2003), CoQ₁₀ was added to the food yielding daily CoQ intakes of 148 or 654 mg/kg body weight for 11 weeks. Rats were fed an amount equivalent to the low dose (150 mg/kg/d) for 13 weeks prior to tissue collection (Kwong et al., 2002). Values are means $\pm$ SE for 5–8 mice or 6–7 rats; * $p < 0.05$ when compared with the control group (planned individual comparison within one-way ANOVA). The mouse data are from Kamzalov et al., 2003.

Fig 7.

Effect of coenzyme Q₁₀ intake on α -tocopherol concentration in mitochondria from different tissues of young adult mice or rats. In studies on mice (Kamzalov et al., 2003), CoQ₁₀ was added to the food in different amounts yielding daily CoQ intakes of 148 (low) or 654 (high) mg/kg body weight for 11 weeks. Rats consumed an amount equivalent to the low dose (150 mg/kg/d) for 13 weeks prior to tissue collection (Kwong et al., 2002). Values are means $\pm$ SE for 5–8 mice or 6–7 rats; * p<0.05 when compared with the control group (planned individual comparison within one-way ANOVA). Data for mouse are from Kamzalov et al., 2003; α -tocopherol concentrations in rat mitochondria are from previously unpublished data from the study described by Kwong et al., 2002.

Fig 8.

Survival plots for groups of 50 mice fed a control diet or low or high amounts of CoQ₁₀. The low (0.72 mg/g of food) and high (2.81 mg/g) CoQ diets were introduced when the mice were 3.5 months of age and yielded daily CoQ intakes of approximately 93 or 371 mg/kg body weight throughout life. Survivorship, expressed as Kaplan-Meier probability, was not significantly different from the control for the mice with low or high intakes of CoQ ($p > 0.065$, Tarone-Ware). Adapted from Sohal et al., 2006.