Prolonged Intake of Coenzyme Q₁₀ Impairs Cognitive Functions in Mice^{1–3}

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Abstract

Coenzyme Q₁₀ (CoQ₁₀) is widely consumed as a dietary supplement to enhance bioenergetic capacity and to ameliorate the debilitating effects of the aging process or certain pathological conditions. Our main purpose in this study was to determine whether CoQ₁₀ intake does indeed attenuate the age-associated losses in motor, sensory, and cognitive functions or decrease the rate of mortality in mice. Mice were fed a control nonpurified diet or that diet containing 0.68 mg/g (low dosage) or 2.6 mg/g (high dosage) CoQ₁₀, starting at 4 mo of age, and were tested for sensory, motor, and cognitive function at 7, 15, and 25 mo of age. Amounts of the ubiquinol CoQ₉H₂ and CoQ₁₀H₂ measured in a parallel study were augmented in the cerebral cortex but not in any other region of the brain. Intake of the low-CoQ₁₀ diet did not affect age-associated decrements in muscle strength, balance, coordinated running, or learning/memory, whereas intake at the higher amount increased spontaneous activity, worsened the age-related losses in acuity to auditory and shock stimuli, and impaired the spatial learning/memory of old mice. The CoQ₁₀ diets did not affect survivorship of mice through 25 mo of age. Our results suggest that prolonged intake of CoQ₁₀ in low amounts has no discernable impact on cognitive and motor functions whereas intake at higher amounts exacerbates cognitive and sensory impairments encountered in old mice. These findings do not support the notion that CoQ₁₀ is a fitness-enhancing or an “antiaging” substance under normal physiological conditions. J. Nutr. 139: 1926–1932, 2009.

Introduction

Coenzyme Q (CoQ)⁶ or ubiquinone (2,3-dimethoxy-5 methyl-6-multiprenyl-1-4-benzoquinone) is a lipophilic, redox-active molecule located within the phospholipid bilayer of cellular membranes, serving multiple functions (1,2). CoQ is synthesized endogenously by the mevalonate pathway and its concentrations vary considerably in different tissues (3). It is composed of a redox-active quinone head linked to a chain of 9 or 10 isoprene units. In the inner mitochondrial membrane, CoQ transfers electrons from respiratory complexes I and II to complex III of the electron transport chain, with simultaneous extrusion of protons into the intermembrane compartment, thereby creating the transmembrane proton gradient that drives ADP phosphorylation (2,4). Auto-oxidation of semiquinone, a partially reduced form of CoQ, is the primary source of mitochondrial superoxide anion radical production, whereas the fully reduced, ubiquinol form (QH₂) inhibits peroxidation of membrane lipids

by reacting with lipid peroxyl radicals and by reducing tocopheroxyl radicals (5–9).

CoQ has been widely postulated to be directly or secondarily involved in the aging process as well as in pathogenesis of a variety of abnormalities associated with the impairment of mitochondrial bioenergetic function and/or oxidative stress. The rationale for the implication of CoQ in such conditions is that: 1) the rates of mitochondrial superoxide anion radical generation and amounts of oxidative damage to mitochondrial proteins, lipids, and DNA increase with age and are also elevated in several age-associated diseases; 2) the rate of mitochondrial ADP-stimulated, or state 3, respiration tends to decline during aging (10,11); and 3) mitochondrial CoQ content decreases in several tissues with age and in some disease conditions (2).

Nevertheless, the rationale for the therapeutic use of CoQ became available only relatively recently. The historically held view was that, following oral intake, augmentation of endogenous CoQ concentrations occurred only in plasma, liver, and spleen (12–14). In a series of studies, Lass et al. (3,15) and Matthews et al. (16) demonstrated that the then prevalent view, apparently based on the intake of relatively low dosages of CoQ for short periods, was erroneous. Endogenous CoQ concentrations could indeed be significantly enhanced in various tissues as well as their mitochondria, including heart, skeletal muscle, kidney, and brain, by relatively prolonged (~14 wk) intake of CoQ.

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³ Supplemental Figures 1–3 and Tables 1 and 2 are available with the online posting of this paper at jn.nutrition.org.

⁶ Abbreviations used: CoQ, coenzyme Q; MWM, Morris water maze; NIA, National Institute on Aging; QH₂, fully reduced, ubiquinol form of coenzyme Q.

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Results of several studies have suggested that CoQ intake has an ameliorative effect on age-related abnormalities such as hypertension (17) and heart failure (18), as well as neurodegenerative diseases, including Parkinson's and Huntington's diseases (19). CoQ is also widely prescribed for humans to offset the CoQ-depleting effects of statins in control of cholesterol levels (20,21), whereas some others take it for enhancing physical fitness (22). In addition, CoQ₁₀ is widely consumed as a supplement to maintain or improve health.

An increase in the levels of indicators of oxidative stress and the deterioration of mitochondrial bioenergetic capacity are 2 of the most ubiquitous age-related biochemical alterations that occur in various species, whereas losses in cognitive and motor functions are among the most recognized manifestations of functional decline in laboratory animals and humans (23–25). Because CoQ is simultaneously an essential component of the electron transport chain, an antioxidant, and a primary source of superoxide anion radical production, the question arises whether complementary CoQ intake would retard/attenuate the age-related deteriorations in functional capacities, or whether it would exacerbate the age-related increase in the level of oxidative stress and the consequent functional losses that are putatively associated with it. In this context, the present study was undertaken to determine the nature of the effects of long-term intake of CoQ₁₀ on the age-related losses in motor, sensory, and cognitive functions and on the survival of mice.

Materials and Methods

Mice. All the procedures pertaining to animal handling and maintenance adhered to the NIH guidelines and were approved by the University of North Texas Health Science Center Institutional Animal Care and Use Committee. Male C57BL/6 mice ($n = 150$) were obtained from the National Institute on Aging (NIA) at 3.5 mo of age and were subsequently maintained in the vivarium of the University of North Texas Health Science Center. As reported previously (26), this colony of NIA mice tested positively for 1 or more non-C57BL/6 marker(s). Mice were individually housed in clear polycarbonate cages (divided into 2 compartments by a stainless-steel partition) at $23 \pm 1^\circ\text{C}$ under a 12-h-light/12-h-dark cycle starting at 0600. Mice consumed food and water ad libitum. CoQ₉ and CoQ₁₀ concentrations in various regions of the brain were determined in a separate set of 10 male C57BL/6 mice, purchased at 20 mo of age from NIA, and subsequently maintained under the same conditions for 14 wk.

A total of 150 mice were randomly assigned to receive either a control diet (Purina 5001) or the control diet with CoQ₁₀ added in low (0.72 mg/g) or high (2.81 mg/g) amounts (Supplemental Table 1). A certified analysis (Tishcon) indicated total CoQ₁₀ concentrations of 0.68 and 2.6 mg/g in the low and high CoQ diets, respectively. Body weights were recorded monthly and survivorship was monitored daily for all mice in the long-term study. Food intake was measured in a subset ($n = 8$ –12) of each treatment group after 1 or 20 mo of receiving the diets.

To determine whether administration of exogenous CoQ₁₀ could indeed cause the augmentation of endogenous CoQ levels in the brain, 20-mo-old mice were gavaged daily with 123 mg CoQ₁₀/kg or the vehicle (soybean oil) with a volume of 0.1 mL for 14 wk. They were then killed by carbon dioxide asphyxiation and the brain was dissected into 6 separate regions (cerebral cortex, hippocampus, striatum, midbrain-diencephalon, cerebellum, and brain stem) and stored at -80°C .

Extraction and quantification of endogenous CoQ. Brain samples were homogenized in 10 volumes (wt:v) of isolation buffer (0.32 mol/L sucrose, 1 mmol/L EDTA, 10 mmol/L Tris, 20% SDS, pH 7.4) centrifuged for 5 min at $700 \times g$ at 4°C to sediment unbroken cells and cell debris; the resulting supernatant was used for the determination of CoQ homologs, as previously described (15).

Behavioral test battery. Mice were subjected to a series of behavioral tests at 7, 15, and 25 mo of age (i.e. after 3, 11, or 21 mo of CoQ₁₀ intake). Performance of mice on these tests has been shown to decline as a function of age in several previous reports, which also describe the methodology in detail (24,27).

Motor functions. Spontaneous forward locomotion and rearing (standing) movements of the mice were monitored using a Digiscan apparatus (Omnitech Electronics, model RXYZCM-16) during a 16-min session, as described previously. Reflexive musculoskeletal responses of the mice were also measured, including the ability to initiate walking, turn in a dead-end alley, exhibit negative geotaxis, grip a horizontal wire, and walk across a narrow bridge. The mice were administered each of these tests during 4 consecutive daily sessions. Finally, motor learning and maximum running performance of each mouse was measured over the course of 7–12 training sessions using an accelerating rotorod.

Spatial learning and memory. Ability of the mice to learn and remember the location of a hidden platform was measured using a Morris water maze (MWM) test as described previously. Competence of the mice to locate the platform was measured in a series of 8 initial training sessions (acquisition) and in 2 additional sessions (retention) conducted after a 2-d hiatus. The platform location remained in a fixed site during the acquisition and retention test sessions but was moved to a different place during 4 additional sessions to assess cognitive flexibility (reversal).

Sensory acuity. The musculoskeletal startle reflex to auditory (90–140 dB) or shock (0.02–0.64 mA) stimuli of various intensities was determined as described previously (24) using a standard testing system (SA Lab, San Diego Instruments). The amplitude of the startle reflex was defined as the peak force of response to each auditory or shock intensity.

Statistical analysis. The data were subjected to 2-way ANOVA, with age and treatment (diet) as between-groups factors. Planned individual comparisons of young to old control groups, and between age-matched treatment and control groups, were made using single degree-of-freedom F tests in which the denominator was the error for the overall analysis. Data on CoQ amounts in different regions of the brain were subjected to 2-way analysis with treatment and region as the factors. Body weight, MWM, and motor learning data were subjected to a 3-way analysis with session (MWM or motor learning) or age (body weight) as a within-subjects (repeated measures) factor. For the analysis of the effect of CoQ intake on longevity, Kaplan-Meier survival distributions were calculated based on exact failure (dead or moribund) or right-censored (lost to follow-up) data for all 150 mice in the study. We used log-rank χ^2 statistics (Tarone-Ware) to compare mortality among the 3 groups. Pearson correlation coefficients were calculated to determine the relationship between spontaneous forward locomotion and MWM performance in the 25-mo mice. The α level was set at 0.05 for all analyses.

Results

Effect of CoQ₁₀ intake on endogenous levels of CoQ₉ and CoQ₁₀ in brain. The oxidized form of CoQ, ubiquinone (Q₉ and Q₁₀), was ~10-fold more abundant than the reduced form, ubiquinol (Q₉H₂ and Q₁₀H₂). Concentrations of both homologs, CoQ₉ and CoQ₁₀, greatly varied in different regions of the brain (all $P < 0.001$) (Fig. 1A–D). Ubiquinol concentration decreased gradually from the forebrain to the hindbrain, with the rank order: cortex > hippocampus $\cong$ striatum > midbrain-diencephalon > cerebellum > brainstem (Fig. 2). The pattern of ubiquinone distribution did not exhibit a forebrain-to-hindbrain concentration gradient and had the rank order: cortex $\cong$ hippocampus $\cong$ cerebellum > brainstem > striatum $\cong$ midbrain (Fig. 1B,D).

FIGURE 1 Effect of CoQ₁₀ intake in mice on endogenous CoQ₉H₂ (A), CoQ₉ (B), CoQ₁₀H₂ (C), and CoQ₁₀ (D) in different regions of the brain. Values are mean $\pm$ SEM, $n = 3$ –5. Abbreviations are: CTX, cerebral cortex; HP, hippocampus; ST, striatum; MB-D, midbrain-diencephalon; CB, cerebellum; BR, brain stem. *Different from control within the same brain region, $P < 0.05$.

Intake of CoQ₁₀ resulted in the augmentation of Q₉H₂ plus Q₁₀H₂ content in the cortex by ~22% ($P < 0.034$) but had no such effect in any other region of the brain. In contrast, CoQ₁₀ administration did not significantly affect Q₉ or Q₁₀ amounts in any part of the brain. Analysis of the data indicated that CoQ₁₀ intake led to a treatment $\times$ region interaction for Q₁₀H₂ ($P = 0.035$), whereas for Q₉H₂, the interaction approached significance ($P = 0.054$).

FIGURE 2 Concentration gradient of CoQH₂ in the untreated mouse brain (sagittal section at 1.8 mm lateral to the midline). The bar graph represents the relative concentration of total CoQH₂ in each dissected brain region relative to the cerebral cortex. Labels in the bar graph represent the dissected regions (some encompassing multiple structures) as shaded in the diagram. CTX (cortex); ST (striatum); VS (ventral striatum); CP (caudate putamen); HP (hippocampus); MB-D (midbrain-diencephalon); MB (midbrain); TH (thalamus); SN (substantia nigra); GP (globus pallidus); BF (basal forebrain); HY (hypothalamus); AM (amygdala); fi (fornix); st (stria terminalis); int (internal capsule); CB (cerebellum); BR (brain stem); P (pons); MY (medulla).

Body weight, food intake, and survivorship. Neither the low- nor the high-CoQ₁₀ diet had a significant effect on the body weight of the mice (Fig. 3A). Regardless of the amount of CoQ₁₀ consumed, body weights increased by 39%, reaching a plateau between 15 and 20 mo of age. The effects of treatment and the treatment $\times$ age interaction were not significant ($P > 0.417$).

Analysis of survivorship data, expressed as Kaplan-Meier probability (Fig. 3B), indicated that neither of the 2 dosages of CoQ₁₀ affected survival in mice ($P > 0.565$; Tarone-Ware). Mortality in the groups used for functional tests was negligible at 7 or 15 mo of age but reached 25–40% at 25 mo.

Neither age nor CoQ₁₀ intake affected food consumption ($P > 0.12$), determined after the mice had consumed the 3 diets for 1 and 20 mo (Supplemental Table 2). The 1- and 20-mo groups were pooled to estimate mean daily CoQ₁₀ intakes of 106 or 352 mg/kg body weight for mice receiving the low- or high-CoQ₁₀ diets.

Motor functions. Mice exhibited a 26–50% decline in spontaneous forward locomotion and rearing as a function of age (Fig. 4A,B). The control and the 2 CoQ₁₀ diet groups had similar levels of locomotion and rearing at 7 mo; however, by 25 mo, the high-CoQ₁₀ group was more active than the control or the low-CoQ₁₀ group ($P < 0.042$). The analysis of rearing yielded a main effect of treatment ($P = 0.044$), whereas the main effect of age was significant for both variables ($P < 0.001$).

The initiation of walking and negative geotaxis were not affected by age in the control mice, whereas the delay to turn in the dead-end alley increased with age, specifically between 7 and 15 mo (Supplemental Fig. 1A). Although individual comparisons suggested the low-CoQ₁₀ diet decreased the delay to turning in the dead-end alley at 15 mo of age ($P = 0.038$), analysis revealed neither a main effect of CoQ₁₀ treatment nor an age $\times$ treatment interaction ($P > 0.346$).

Regardless of the treatment, latencies to tread or fall from the wire, or to fall from the bridge, were decreased with age by 50–75%, most notably between 7 and 15 mo (Supplemental Fig. 1B). Neither low- nor high-CoQ₁₀ diets affected the performance at any age. There was no main effect of treatment and no

FIGURE 3 Effect of CoQ₁₀ intake at low and high concentrations on mean $\pm$ SEM body weight (A) and survivorship (B) of mice ($n = 50$). Arrows indicate the approximate ages when different subsets ($n = 11$ – 22) of the diet groups were tested for functional performance (and lost to follow-up).

interaction of age with treatment for any of the measures ($P > 0.398$).

The control as well as the experimental mice had incremental improvement in running performance over the first 7 training sessions (Supplemental Fig. 2A), albeit the magnitude of improvement diminished as a function of age. Furthermore, the plateau level of performance reached at the end of training also decreased steadily with age (Supplemental Fig. 2B). CoQ₁₀ intake did not affect the level of performance, as indicated by a lack of effects of treatment and its interactions with age and training session ($P > 0.155$).

Spatial learning and memory. The length of the path taken to reach the hidden platform was determined to assess the efficiency with which the mice located the platform, independently of their speed of swimming. All groups increased in efficiency over the course of the acquisition (learning) phase, maintained this level of performance during the retention phase,

FIGURE 4 Effect of CoQ₁₀ intake on spontaneous forward locomotion (A) and rearing (standing on the hindlimbs) behavior (B). Values are mean $\pm$ SEM, $n = 10$ – 21 . *Different from 7-mo group of the same treatment, $P < 0.05$. #Different from control group of the same age, $P < 0.05$.

and learned to locate the platform in its new position during the reversal phase (Fig. 5). Analysis of the data confirmed the effect of testing session on path length for the acquisition and reversal phases ($P < 0.001$) and the lack of an effect for the retention phase ($P = 0.557$).

Although the low-CoQ₁₀ diet had no apparent effect on the performance of mice in this test, the high-CoQ₁₀ diet rendered them 46% less efficient than the controls during the first session and 109% less efficient on the 8th session. There was a main effect of treatment for the acquisition phase ($P = 0.017$) but not for the retention and reversal phases ($P > 0.098$). There was no interaction of treatment with testing sessions within any of the testing phases ($P > 0.385$). Spatial bias for the platform location increased with training in all groups (Supplemental Fig. 3), as indicated in performance on 4 probe trials during acquisition ($P = 0.003$). Neither of the CoQ₁₀-containing diets affected the probe trial performance ($P > 0.428$). Swimming speed remained relatively steady and unaffected by CoQ intake (data not shown) and data analysis revealed no main effect of treatment or interactions of the treatment with testing session ($P > 0.321$). Forward locomotion in the motor activity test was positively correlated with MWM impairment measured as the mean of sessions 1–8 ($r = 0.547$; $P = 0.035$).

Sensory acuity. Based on sound intensity-response curves, the auditory startle responses were analyzed separately for low intensity sounds (leading to submaximal responses) (Fig. 6A) compared with high intensity sounds yielding maximal responses (Fig. 6B). Control mice had an age-related 75% decline in responses to low sound intensity and a 50% decrease in the responses to high intensities. The low-CoQ₁₀ diet did not affect responses within either range of intensity; however, the high-CoQ₁₀ diet decreased the response to low intensity stimuli by 50% at 15 mo of age ($P = 0.022$).

The shock startle responses were also analyzed according to low or high shock intensity (Fig. 6C,D). During 15–25 mo of age, the control mice exhibited a 77% decrease in responses to shocks of low intensity but no decline in responses to those of high intensity. Compared with the controls, the high-CoQ₁₀ diet decreased the responses to high shock intensities by 75–87% at 15 mo of age but had no effect at 25 mo. The low-CoQ₁₀ diet had no apparent effect on the response to low shock intensity at

FIGURE 5 Effect of CoQ₁₀ intake in 25-mo-old mice on their efficiency in locating a hidden platform as a function of training sessions within separate phases of the MWM test (acquisition, retention, and reversal). Values are mean $\pm$ SEM, $n = 9-15$. #Different from control group, $P < 0.05$.

15 mo, but the response to high shock intensity was 59% lower than controls at 25 mo of age. Analysis revealed an interaction between age and treatment for the high shock intensities ($P = 0.018$), but showed no main effect of treatment or its interaction with age for the response to low intensity shocks ($P > 0.134$). A measure of reaction time derived from the startle data (24) was not affected by treatment ($P > 0.098$; data not shown).

Discussion

The main findings of this study were as follows: 1) the endogenous CoQ content greatly varied in different regions of the brain, exhibiting a declining concentration gradient from the cerebral cortex to the hindbrain; 2) administration of exogenous CoQ₁₀ elevated the level of endogenous ubiquinol (Q₉H₂+Q₁₀H₂) in the cortex, but not in any other brain region; 3) intake of CoQ₁₀ in low (106 mg/kg body weight daily) or high amounts

(352 mg/kg) did not affect the mortality of mice; 4) the low-CoQ₁₀ diet had no detectable ameliorative effect on aging-associated attenuations in motor and cognitive fitness; however, high CoQ₁₀ intake adversely affected some of these functions.

The present study differs from a previous one by this group (26) in that the CoQ concentrations were determined here in different regions of the brain separately as ubiquinones, Q₉ and Q₁₀, and ubiquinol, Q₉H₂ and Q₁₀H₂, rather than as total CoQ (Q+QH₂) in the nondissected whole brain. The present approach permitted us to detect that administration of exogenous CoQ augments CoQH₂ in the cerebral cortex only, as also reported by Matthews et al. (16). Unlike the results in our previous study, the current investigation did not address the accumulation of CoQ following long-term intake. However, the regional effect obtained here would seem to account for the previous observation of minimal augmentation of endogenous CoQ content when measured in the nondissected whole brain.

It is unclear why exogenous CoQ augments CoQH₂ only in the cerebral cortex and why there is a virtually 2-fold variation in the concentration of CoQH₂ in different regions of the brain. Concentrations of CoQH₂ rise progressively from the caudal to the rostral end of the brain, with the highest amounts in the telencephalic structures, such as cortex, hippocampus, and striatum, and lowest in the brainstem (Fig. 1). Glutathione distribution also exhibits a similar pattern, being 2-fold higher in the telencephalic structures relative to the brainstem (28). Higher glutathione amounts were correlated with relatively elevated levels of oxidative stress, indicated by the glutathione: glutathione disulfide ratio, glutathione redox potential, and the concentrations of glutathione-protein mixed disulfides. Such data suggest that a redox imbalance may exist in the brain cortex, whereas a higher degree of regulation occurs in the more caudal structures.

Age-associated declines in psychomotor performance, thought to be a manifestation of a variety of neural, vascular, and musculoskeletal dysfunctions, have been widely documented in animals as well as humans (23-25,29). In the present

FIGURE 6 Effect of CoQ₁₀ intake on the startle reflex to submaximal (A) and maximal (B) auditory stimuli or low (C) and high (D) shock stimuli as a function of age. Values are mean $\pm$ SEM, $n = 11-22$. Note that different ordinate scales are shown in C and D. *Different from 15-mo group of the same treatment, $P < 0.05$. #Different from control group of the same age, $P < 0.05$.

study, the performance of control mice in standard tests of psychomotor functions, such as balance (bridge-walking), coordinated running (rotorod), reaction time, muscle strength (wire suspension), reflexive ability, and spontaneous locomotion (walking and rearing), was also declined as a function of age by magnitudes similar to those reported previously (24,30,31). The results were similar for mice maintained on diets containing lower amounts of CoQ₁₀, suggesting that chronic intake did not lead to fitness-enhancing or antiaging effects for a variety of psychomotor functions.

The ability of mice and rats to perform in the MWM test is generally thought to require competent hippocampal and cortical functions that undergo moderate age-associated decline (32–35). The low-CoQ₁₀ diet had no discernable effect on the performance in the MWM test; however, mice maintained on the high-CoQ₁₀ diet had impaired performance involving both a difficulty in learning as well as an overall decrease in navigational efficiency. However, the magnitude of the deleterious effects did not reach the levels in mouse models of Alzheimer's disease (36) or following hippocampal lesions (37), although it was more severe than the mild age-related cognitive impairment detectable in mice at this age.

The high-CoQ₁₀ diet did not affect swimming speed, suggesting that a motor impairment did not readily account for the MWM performance deficit; nevertheless, an effect on the arousal level or visual function could not be ruled out. Indeed, the high-CoQ₁₀ diet led to an increased activity level at this age, an effect that was found to be predictive of poor MWM performance. Thus, the activity level of mice in the high-CoQ₁₀ group could be hypothesized to impair their ability to pay attention, thereby leading to poorer cognitive performance than the controls. This interpretation accords with the results of a previous study, which showed that administration of a relatively high dosage of CoQ₁₀ (500 mg/kg daily for 14 wk), worsened the performance in a different learning task (active avoidance) (38).

The high-CoQ₁₀ diet also had aggravating effects on the age-related losses in the musculoskeletal reflex responses to auditory and shock stimuli. The decrease in responses to auditory stimuli may be particularly important, because it could be associated with hearing loss, which is known to occur in the aged C57BL/6 and other mouse strains (30,39,40). Hearing loss, detected by a decreased startle response or by attenuation of auditory-evoked brainstem response, has been widely studied in mice as a model of human auditory presbycusis (41). On the other hand, the finding that shock startle responses of the CoQ₁₀-treated mice were also diminished may alternatively suggest that the deleterious effects of CoQ involve the motor, rather than the sensory component of the startle reflex.

Based on the human:mouse body surface area ratio of 12.3, the human dose equivalent for the low-CoQ₁₀ diet administered to mice in this study would be ~500 mg/d CoQ₁₀, whereas the high-CoQ₁₀ diet would be ~1700 mg/d CoQ₁₀ (42). The lower dosage represents the upper limit of daily consumption suggested for the treatment of mitochondrial disorders, statin-induced CoQ depletion, hypercholesterolemia, and congestive heart failure (17,18,20,43) and for enhancing exercise tolerance (18). Dosages of 1500–2500 mg have been used in clinical trials for the treatment of neurological diseases (19) and even daily intake of up to 3000 mg for relatively short periods has been reported to have no toxic effects (44,45). Notwithstanding these results, the present results suggest that prolonged intake of relatively high amounts of CoQ may indeed be deleterious.

The mechanisms underlying the deleterious effects of CoQ₁₀ intake in relatively high amounts are presently unclear. It is conceivable that CoQ administration over prolonged periods may lead to either an excessively pro-oxidative or a reductive condition that impairs redox-dependent signaling cascades, thought to be critical components in memory formation and retrieval (46–48). In a previous study, we reported that the same high-CoQ₁₀ diet had little or no effect on oxidative damage and did not modify the glutathione redox state in the whole brain (26). Furthermore, even though dietary intake of CoQ has been demonstrated to enhance the endogenous levels of CoQ in skeletal muscles, peripheral organs, and the cerebral cortex of the brain, no significant effect has been demonstrated on a variety of parameters linked to mitochondrial bioenergetics (3,26). Thus, it is unclear whether the mechanism underlying the effect of CoQ₁₀ in these studies involves a modification of oxidative stress or bioenergetic function.

In summary, our present findings accord with those reported previously in that CoQ₁₀ administration during adult life does not extend the life span of rodents (26,49,50). Although prolonged CoQ₁₀ intake in low amounts did not have a discernable effect on cognitive and motor functions, intake at higher amounts exacerbated some of the cognitive and sensory impairments encountered in aged mice. Thus, regardless of whether CoQ₁₀ ultimately proves to be ameliorative in specific disease conditions involving oxidative stress and/or mitochondrial dysfunctions, the current findings tend to controvert the view that CoQ plays a direct or significant role in the mammalian aging process and is a credible antiaging intervention.

Acknowledgments

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