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Behavioral Improvement after Chronic Administration of Coenzyme Q10 in P301S Transgenic Mice

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Abstract

Coenzyme Q10 is a key component of the electron transport chain which plays an essential role in ATP production and also has antioxidant effects. Neuroprotective effects of coenzyme Q10 have been reported in both *in vitro* and *in vivo* models of neurodegenerative diseases. However, its effects have not been studied in cells or in animals with tau induced pathology. In this report, we administered coenzyme Q10 to transgenic mice with the P301S tau mutation, which causes fronto-temporal dementia in man. These mice develop tau hyperphosphorylation and neurofibrillary tangles in the brain. Coenzyme Q10 improved survival and behavioral deficits in the P301S mice. There was a modest reduction in phosphorylated tau in the cortex of P301S mice. We also examined the effects of coenzyme Q10 treatment on the electron transport chain enzymes, the mitochondrial antioxidant enzymes, and the tricarboxylic acid cycle. There was a significant increase in complex I activity and protein levels, and a reduction in lipid peroxidation. Our data show that coenzyme Q10 significantly improved behavioral deficits and survival in transgenic mice with the P301S tau mutation, upregulated key enzymes of the electron transport chain, and reduced oxidative stress.

Keywords

Coenzyme Q10; mitochondria; tauopathy; transgenic mice

INTRODUCTION

Mitochondria play an essential role in the production of energy within the cell. In the central nervous system, mitochondria are of utmost importance due the high energy demand of synaptic activity. Energy is generated through oxidative phosphorylation in the form of adenosine triphosphate (ATP). In Alzheimer's disease (AD), there are impairments of both the electron transport chain and the tricarboxylic acid cycle enzymes [1], leading to energy defects [2].

Coenzyme Q10, also called ubiquinone, is a component of the electron transport chain and is located in the inner membrane of mitochondria where it functions as an electron carrier between respiratory chain complexes [3, 4]. Interestingly, coenzyme Q10 has antioxidant effects which are seen in models of neurodegenerative diseases [5–8]. Coenzyme Q10 exerts beneficial effects in both the behavioral impairments and the neuropathology seen in

transgenic mouse models of amyotrophic lateral sclerosis [9], Huntington's disease [10–12], and AD [13–15], and against the neuronal loss produced by MPTP, malonate, and 3-nitropropionic acid [12, 16–18]. However, the effects of coenzyme Q10 have not been investigated in disease models in which tau pathology plays an important role. This is of potential interest since both *in vitro* and *in vivo* models of tauopathy are associated with mitochondrial dysfunction. In immortalized cortical neurons, expression of truncated tau at Asp-421 mimics caspase 3 cleavage (T4C3) and induces toxicity relative to full length tau isoform (T4) [19]. It also increased mitochondrial fragmentation, mitochondrial membrane damage, diminished calcium buffering capacity, and oxidative stress [19]. The expression of truncated tau with amyloid- β enhanced the stationary mitochondrial population, loss of mitochondrial membrane potential, and oxidative stress *in vitro* [20]. *In vivo*, David and colleagues showed that P301L transgenic mice had reduced complex V levels, impaired mitochondrial respiration and ATP synthesis, and elevated reactive oxygen species (ROS) production [21]. In the triple transgenic mice with both amyloid- β protein precursor (A β PP) and presenilin 2 (PS2) mutations and P301L tau mutations, there were synergistic effects in impairing oxidative phosphorylation [22]. It was shown that deregulation of complex I was tau dependent whereas deregulation of complex IV was amyloid- β dependent, and synergistic effects on oxidative phosphorylation, synthesis of ATP, and ROS were seen in triple transgenic mice at 12 months of age [22].

In the present report, we examined the effects of coenzyme Q10 treatment on tau pathology in transgenic mice with the P301S tau mutation which causes fronto-temporal dementia in humans. These mice develop progressive tau hyperphosphorylation and neurofibrillary tangles [23]. The P301S tau mice were fed a coenzyme Q10 diet from 1 to 10 months of age. We found that coenzyme Q10 improved survival, without significantly affecting levels of tau hyperphosphorylation in the brains of P301S mice. It also reduced hyperactivity and disinhibition. In addition, coenzyme Q10 decreased significantly levels of malondialdehyde, a marker of lipid peroxidation. We investigated its mechanism of action by examining mitochondrial electron transport and tricarboxylic acid cycle enzymes and observed that administration of coenzyme Q10 increased both the protein level and activity of complex I.

MATERIALS AND METHODS

Animals and treatments

Male P301S transgenic and female wild-type mice were obtained from Jackson Laboratory (Bar Harbor, ME, USA) and bred to generate all experimental groups. P301S mice were fed control or 0.5% coenzyme Q10 diet (Kaneka, Pasadena, TX, USA). Wild-type littermates were fed control diet. The chow was pelleted by Purina-Mills (Richmond, IN, USA). The treatment was given from 1 month to 10 months of age. All experiments were approved by the Weill Cornell Medical College Institutional Animal Care and Use Committee.

Behavior

At 5 and 7 months of age, we assessed locomotor activity, exploration, and anxiety in the openfield as previously described [24]. Briefly, mice were placed in the apparatus for a single trial of 5 min. Total distance traveled, rearing frequency, and time spent in the center were recorded using a video tracking system (Ethovision 3.1, Noldus Technology, Attleborough, MA, USA).

Immunohistochemistry

At 10 months of age, one cohort of mice was deeply anesthetized with sodium pentobarbital and transcardially perfused with ice cold 0.9% sodium chloride and 4% paraformaldehyde.

Brains were removed and post-fixed in 4% paraformaldehyde and gradient sucrose and stored in cryoprotectant for immunohistochemical studies.

Sections were cut at 50 μ m thickness and stained with AT8 mouse monoclonal anti-human tau pSer202/Thr205 (1 : 500, Thermo Fisher Scientific, Rockford, IL, USA). Immunolabeling was detected by the streptavidin-horse radish peroxidase method and visualized after DAB (diaminobenzidine) incubation for 30 s (Vector, Burlingame, CA, USA). Sections were viewed on a Nikon Eclipse E600 microscope, and digital images were captured using Stereo Investigator 4.35 (Microbrightfield, Burlington, VT, USA).

Quantification was done using five 50 μ m serial, non-adjacent sections per animal (300 μ m apart, from bregma -1.34 through bregma -2.84). The percentage area occupied by AT8 immunoreactivity was measured.

Mitochondria characterization

Sample preparation—Another cohort of mice was euthanized by decapitation and brains were dissected at 10 months of age. Cortex samples (~30–55 mg) were stored frozen at -80°C until assaying. Before assays, tissue samples were thawed on ice and homogenized with Dounce-type 2 ml homogenizer (glass vessel/glass pestle). The homogenate was centrifuged at $1,000\text{ g} \times 5\text{ min}$ to get rid of nuclear fraction and cell debris; the resulting supernatant was centrifuged at $14,000\text{ g} \times 5\text{ min}$. The pellet was collected and centrifuged again at $14,000\text{ g} \times 5\text{ min}$; the final pellet obtained in this step was resuspended in 20 mM HEPES (pH 7.8) and used for all assays.

Immunoblot analysis—mitochondria-enriched fraction—The protein lysates containing equal amounts of protein were separated by SDS-PAGE, electroblotted onto a nitrocellulose membrane (BioRad, Hercules, CA, USA), and immunoreacted with an appropriate primary antibody (see below), followed by HRP-conjugated secondary antibodies (Kierkegaard Perry Labs Inc., Gaithersburg, MD, USA). Immunoreactive proteins were visualized by incubating blots in chemiluminescence substrate (Pierce, Rockford, IL, USA). Quantitative analysis was performed using NIH “ImageJ” software. Statistical analysis was performed using ratios of the densitometric value of each band normalized to β -actin as loading control.

Assays—All samples were assayed for the following: complex I activity (NADH:CoQ reductase, rotenone-sensitive [25]), complex I subunit expression (immunoblotting with anti-complex I subunit NDUFB8 1 : 1,000, Invitrogen, Carlsbad, CA, USA), complex III subunits expression (immunoblotting with anti-Complex III Core 2 subunit UQCR2/QCR2 1 : 1,000, Invitrogen, Carlsbad, CA, USA), complex IV subunit expression (immunoblotting with anti-complex IV MT-CO1 subunit 1 : 1,000, Invitrogen, Carlsbad, CA, USA), ATPase subunit expression (immunoblotting with anti-ATPase ATP5A1 subunit 1 : 1,000, Invitrogen, Carlsbad, CA, USA), cytochrome C content by quantitative ELISA (“Rat/Mouse Cytochrome c Quantikine ELISA Kit”, R&D Systems, Minneapolis, MN, USA), succinate dehydrogenase activity (succinate:CoQ:DCIP reductase, TTFA-sensitive [26]), citrate synthase activity [27], aconitase activity (“Aconitase Assay Kit”, Cayman Chemical, MI, USA), glutathione reductase activity (“Glutathione Reductase Assay Kit”, Cayman Chemical, Ann Arbor, MI, USA), superoxide dismutase activity (“Superoxide Dismutase Assay Kit”, Cayman Chemical, Ann Arbor, MI, USA). All activities and content values were normalized by protein content (BCA protein assay, Thermo Scientific, FL, USA).

High performance liquid chromatography (HPLC)

Malondialdehyde levels—The HPLC determination of MDA was carried out by a method modified from a previous report by Agarwal and Chase [28]. Fresh tissues were homogenized in 40% ethanol solution. 50 μ l of sample homogenate or MDA standard were prepared in 40% ethanol. 50 μ l of 0.05% butylated hydroxytoluene (BHT), 400 μ l of 0.44 M H₃PO₄, and 100 μ l of 0.42 mM 2-thiobarbituric acid (TBA) were added to each. Samples were then vortexed, heated for 1 h at 100°C, and immediately cooled with iced water to stop the derivative reaction. MDA-TBA derivative was extracted by adding 250 μ l n-butanol, followed by vortexing and centrifugation. 50 μ l of n-butanol extract was used for the HPLC assay. The HPLC mobile phase used acetonitrile buffer (20 : 80, v/v, buffer 50 mM KH₂PO₄, pH 6.8). The column was an ESA 150 $\times$ 3 mm C18 column with particle size of 3 μ m (ESA, Inc., Bedford, MA, USA). Fluorescence detectors were set at an excitation wavelength of 515 nm and emission wavelength of 553 nm. MDA was eluted in 2 min. Data were normalized by protein content (Biorad Protein Assay Kit, Hercules, CA, USA).

Coenzyme Q10 levels—Tissues were added to ice-cold 2-propanol 80%. Samples were briefly sonicated, vortexed, and centrifuged at 14000 rpm $\times$ 20 min twice at 4°C. Supernatant (50 μ l) was taken to inject for HPLC analysis. Briefly, samples and CoQ10 standards were eluted through a 4.6 $\times$ 100 mm C18 column (ESA, Inc. Chelmsford, MA, USA) in an isocratic model with a mobile phase prepared with the following recipe: 40 ml of 1 M ammonium acetate stock buffer (pH to 4.4), 400 ml 1-propanol, and 1,560 ml methanol. The eluting rate was 0.8 ml/min, and the running time was 20 min. Electrochemical detector (ESA, Inc. Chelmsford, MA, USA) was set at +650 mV for pre-column cell and analytical cells E1 at -700 mV and E2 at +600 mV. Protein concentrations of tissue homogenates were measured using the Bio-Rad kit (Bio-Rad Laboratories, Hercules, CA, USA).

Oxidized and reduced glutathione levels—Tissues were homogenized and centrifuged in chilled 0.1 M perchloric acid. Supernatants were used to measure the reduced (GSH) and oxidized (GSSG) forms of glutathione by HPLC. Briefly, 15 μ l of supernatant was eluted through a 4.6 $\times$ 150 mm C18 column (ESA, Inc Chelmsford, MA, USA) with a mobile phase containing 50 mM LiH₂PO₄, 1.0 mM 1-octanesulfonic acid and 1.5% (v/v) methanol and detected by a 2-channel Coulochem III electrochemical detector (ESA, Inc. Chelmsford, MA, USA). Guard cell potential was set at 950 mV with channel 1 potential at 500 mV for GSH detection and channel 2 potential at 880 mV for GSSG detection. Concentrations of GSH and GSSG are expressed as nmol per milligram protein. The protein concentrations of tissue homogenates were measured using the Bio-Rad kit (Bio-Rad Laboratories, Hercules, CA, USA).

Statistical analysis

When only 2 groups were involved in the study, two-tailed unpaired *t*-tests were used to process the data. ANOVA was used to compare the 3 groups. After the ANOVA, post-hoc Fisher's PLSD test was used for further comparison between groups. (Statview 5.0.1, SAS Institute Inc., Cary, NC, USA).

RESULTS

Levels of coenzyme Q10 in P301S mice

After treatment with a coenzyme Q10 supplemented diet, we measured levels of coenzyme Q10 in the liver and brain of P301S mice. Levels of coenzyme Q10 were elevated in both liver and brains after dietary supplementation (data not presented).

Administration of coenzyme Q10 improved survival and behavior in P301S mice without affecting tau pathology

We examined survival with 5 mice per group (Fig. 1). By 400 days of age, 4 P301S mice fed control diet died. However, by the same age, only two P301S mice fed the coenzyme Q10 diet died. The cumulative survival curve is presented in Fig. 1A using the Kaplan-Meier analysis. As shown, coenzyme Q10 significantly improved survival in the P301S mice. At 5 and 7 months of age, the P301S transgenic mice fed a control diet had increased locomotor activity and anxiety in openfield testing as compared to their wild-type littermates (Fig. 1B–D). Administration of coenzyme Q10 significantly reduced the hyperactivity and disinhibition in P301S mice (Fig. 1B–D).

At 10 months of age, levels of tau phosphorylation were assessed in the cortex and the hippocampus of P301S mice by examining immunostaining with the AT8 antibody (Fig. 2). Coenzyme Q10 treatment reduced the percent area covered by AT8 immunoreactivity in the cortex (Fig. 2A), but the effect was not statistically significant and there was no effect in the hippocampus (Fig. 2B) of P301S mice.

Effects of coenzyme Q10 on the antioxidant system and oxidative stress

Coenzyme Q10 is known to have antioxidant properties in brain, since in its reduced form it can scavenge free radicals and other oxidants [29]. To determine whether it has other indirect antioxidant effects, we examined its effects on mitochondrial enzymes which are involved in the scavenging of ROS. We measured the activities of glutathione reductase (GR), isocitrate dehydrogenase (ICD2, which is a NADPH-linked enzyme that supplies NADPH for GR to reduce oxidized glutathione), and superoxide dismutase (SOD) (Fig. 3A). Additionally, we assessed levels of both oxidized and reduced glutathione (Fig. 3B). No differences were observed in these enzymes or in glutathione concentrations after coenzyme Q10 treatment in the P301S mice. We also examined the levels of malondialdehyde, a marker of lipid peroxidation, and found that it was significantly reduced after coenzyme Q10 treatment in the cortex of P301S mice (Fig. 3C).

Effects of coenzyme Q10 on the tricarboxylic acid cycle and the electron transport chain

We studied the effects of coenzyme Q10 on the tricarboxylic acid cycle enzymes, another possible mitochondrial target. We measured the enzymatic activities of succinate dehydrogenase (SDH), aconitase (ACO), and citrate synthase (CS) in cortical tissue of P301S mice (Fig. 4A). P301S mice treated with coenzyme Q10 diet did not show any significant differences in these enzyme activities relative to littermates treated with control diet (Fig. 4A).

More importantly, we assessed the enzymes of the mitochondrial electron transport chain by measuring the enzymatic activity of complex I and protein levels of cytochrome c, ATPase, complex III (CIII), complex IV (COX) and complex I (CI) in the cortex of P301S mice. There was a significant increase of CI activity (Fig. 5A) and protein levels (Fig. 5C) in the P301S mice which received the coenzyme Q10 supplemented diet, relative to P301S littermates on unsupplemented diets. Levels of cytochrome c were also modestly elevated after treatment with coenzyme Q10 (Fig. 5B). These data did not reach significance due to inherent variability of the ELISA method.

DISCUSSION

There is a large body of evidence demonstrating the importance of mitochondria in the pathogenesis of neurodegenerative diseases including those with tau pathology such as fronto-temporal dementia (FTD), progressive supranuclear palsy (PSP), and Alzheimer's

disease (AD). Components of both the electron transport chain and the tricarboxylic acid cycle are impaired in AD [1], which contributes to energy defects [2]. In addition, oxidative stress is increased in FTD [30, 31], PSP [32–34], and AD brains [35]. Previous work showed that oxidative stress caused by a reduction in manganese superoxide dismutase (MnSOD) results in increased numbers of phosphorylated tau immunoreactive neurofibrillary tangles [36]. In addition, vitamin E was shown to reduce tau pathology in the P301S transgenic mice [37]. We showed that increased expression of MnSOD attenuated numbers of amyloid plaques, amyloid burden, amyloid- β 1-42 levels and impaired performance on the Morris water maze test [38]. Similarly another group showed that increased MnSOD attenuated both numbers of amyloid plaques and free radicals [39]. In the triple transgenic mice, there was a synergistic effect of both amyloid- β and tau on oxidative phosphorylation, ATP synthesis, and production of ROS [22]. Considering the high demands for energy in the brain, several groups have studied the therapeutic effects of compounds which improve energy metabolism in the treatment of FTD, PSP, and AD.

Because coenzyme Q10 plays a role in mitochondrial function, has antioxidant effects and is neuroprotective [5–8], it is an interesting therapeutic agent for the treatment of neurodegenerative diseases such as FTD, PSP, and AD. The effects of coenzyme Q10 on the amyloid protein have been studied in transgenic AD mice. Administration of coenzyme Q10 reduced the amyloid burden, intracellular amyloid accumulation [14, 15], and delayed age-induced brain atrophy [40]. We showed that administration of coenzyme Q10 in the diet to Tg19959 mice, which have two mutations in the A β PP gene, significantly reduced oxidative damage to proteins, the numbers of amyloid plaques, amyloid plaque burden, amyloid- β 1-42 levels, and it improved performance on the Morris water maze test [13]. A recent report showed that in addition to increased oxidative stress, levels of coenzyme Q10 were reduced in transgenic AD mice expressing both A β PP and tau mutations [41]. However, it is not known whether coenzyme Q10 can affect tau induced pathology.

Several reports indicated that both *in vitro* and *in vivo* models of tauopathy showed increased oxidative stress and impaired activity of mitochondrial electron transport enzymes and mitochondrial function [19, 21]. PSP is a neurodegenerative disease with impaired eye movements, motor deficits, and a subcortical dementia which are associated with the presence of phosphorylated tau immunoreactive neurofibrillary tangles in the basal ganglia and brainstem. A recent Phase II clinical trial on patients with PSP using coenzyme Q10 over 6 weeks showed improvement in brain energy metabolism and cognition [42]. To address the question of the long term effects of coenzyme Q10 on tau induced pathology, we fed P301S mice with coenzyme Q10 from 1 to 10 months of age. We and others previously showed that after oral administration of coenzyme Q10, total coenzyme Q10 levels were elevated in the brains of treated mice or rats [9, 43]. To ensure that the drug was delivered to both the peripheral tissues and the central nervous system of P301S mice, we measured levels of coenzyme Q10 in both the liver and brain, and found that levels were increased the coenzyme Q10 treatment. In addition, we found that coenzyme Q10 increased the survival rate of the P301S mice as compared to a control group treated with an unsupplemented diet. Similar data were reported in normal mice [44], as well as in transgenic mouse models of Huntington's disease and the MPTP model of Parkinson's disease [12]. To further study the effects of coenzyme Q10 on disease pathogenesis, we assessed locomotor activity and anxiety in openfield testing at 5 and 7 months of age. The P301S mice showed increased activity and anxiety. These deficits were reduced after treatment with coenzyme Q10. Tau hyperphosphorylation is another hallmark of tauopathy. Brains of P301S mice were immunostained with AT8 antibody to visualize and quantify tau hyperphosphorylation in the cerebral cortex and the hippocampus at 10 months of age. In our P301S mice, we have previously observed a significant increase in tau pathology at 10 months of age. No AT8 positive immunostaining was found in wild-type littermates [45]. We found that coenzyme

Q10 treatment showed a trend towards decreasing phosphorylated tau in the cerebral cortex but it did not reach statistical significance. The relatively modest protective effects observed may be attributed to the relatively low dose of coenzyme Q10 that we utilized. In a dose-response study by Smith and colleagues in R6/2 mice, it was shown that higher doses increased the efficacy of the treatment [11], and we also saw improved effects against MPTP toxicity with higher doses [17]. In these studies, chronic coenzyme Q10 treatment was neuroprotective against MPTP induced dopamine depletion, loss of tyrosine hydroxylase neurons and α -synuclein inclusions in the substantia nigra [17]. Similar beneficial effects were seen in models of Huntington's disease [12]. In both R6/2 mice and 3-NP treated rats, coenzyme Q10 treatment reduced striatal pathology and improved survival and motor function. These beneficial effects were enhanced with the use of combined coenzyme Q10 and creatine [12]. To further explore the role of coenzyme Q10 *in vivo*, additional studies with more animals and/or different mouse models of tauopathy would be worthwhile.

To understand the mechanism of action of coenzyme Q10, we studied its effects on mitochondrial enzymes of the antioxidant system, the tricarboxylic acid cycle, and the electron transport chain. We observed that P301S mice did not differ from wild-type mice, making effects of treatment difficult to evaluate. However, coenzyme Q10 could possibly alter their activities by sparing other metabolic intermediates, such as NADH or NADPH.

After administration of coenzyme Q10, we did not observe any enzymatic differences in the antioxidant system, such as glutathione reductase, isocitrate dehydrogenase, and superoxide dismutase. However, we found that levels of malondialdehyde were decreased after treatment with coenzyme Q10. These data are consistent with those of by Yang and colleagues, in which coenzyme Q10 reduced lipid peroxidation and DNA oxidative damage in the striatum of 3-NP treated rats [12]. In the enzymes of the tricarboxylic acid cycle, there was no change in activity of succinate dehydrogenase, citrate synthase, or aconitase in P301S brains with or without coenzyme Q10 treatment.

Considering that coenzyme Q10 is a component of the electron transport chain that acts as an electron carrier from complex I and complex II to complex III, we assessed the activity and levels of these enzymes. Complex I activity and protein levels were elevated after coenzyme Q10 administration. Levels of cytochrome c were also increased. The reduction of oxidative stress in P301S mice may be a consequence of these mitochondrial enzyme changes, but coenzyme Q10 can also directly scavenge free radicals [29]. David and colleagues suggested that increased ROS levels in P301 L transgenic mice may be a direct consequence of the reduction of complex I activity [21]. Thus, it is possible that the increased activity of complex I produced by coenzyme Q10 has lead to a reduction of oxidative stress.

In conclusion, coenzyme Q10 had neuroprotective effects and improved survival and behavioral deficits in P301S mice. These effects may be related to its beneficial effects on mitochondrial enzymes of the electron transport chain. To our knowledge, this is the first work that shows an effect of chronic exogenous administration of coenzyme Q10 on ameliorating tau induced pathology.

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Fig. 1.

Administration of coenzyme Q10 improved survival and behavior in P301S mice. Cumulative survival curve (A) of P301S mice fed control and coenzyme Q10 (CoQ) diet. Coenzyme Q10 improved survival of P301S mice ($n = 5$). Ambulation (B), vertical movements (C), and anxiety (D) in the openfield for wild-type (Wt) and P301S mice (Tg) treated with control (Control) and coenzyme Q10 (CoQ) at 5 and 7 months of age. There was an increase in distance traveled, vertical movements, and time spent in the center in P301S mice as compared to wild-type littermates (Fisher PLSD, $n = 12-20$). Administration of coenzyme Q10 rescued this phenotype ($n = 12-18$). $p < 0.05$.

Fig. 2.

Administration of coenzyme Q10 modestly reduced tau pathology in the cortex of P301S mice. AT8 staining in the cortex (A) and the hippocampus (C) of P301S mice (Tg) fed control and coenzyme Q10 (CoQ) diet. AT8 immunoreactivity expressed as percent area in the cortex (B) and the hippocampus (D) of P301S mice (Tg) fed control and coenzyme Q10 (CoQ) diet. Coenzyme Q10 did not affect tau phosphorylation in the hippocampus of P301S mice. However, there was a trend toward a decrease of percent area covered by AT8 immunoreactivity in the cortex of P301S mice ($n = 3-4$).

Fig. 3.

Effects of coenzyme Q10 on the antioxidant system and oxidative stress. A) Enzymatic activity of glutathione reductase (GR), isocitrate dehydrogenase (ICD), and superoxide dismutase (SOD) in the cortex of P301S mice fed with control, coenzyme Q10 (CoQ) diet. B) Level of oxidized (GSSG) and reduced glutathione (GSH) in brains of P301S mice fed with control and coenzyme Q10 (CoQ) diet. The antioxidant system was not affected by coenzyme Q10 administration in P301S mice ($n = 8-12$). C) Level of malondialdehyde in brains of P301S mice fed with control and coenzyme Q10 (CoQ) diet. Administration of coenzyme Q10 reduced malondialdehyde level in P301S mice ($n = 4-8$). $p < 0.05$.

Fig. 4.

Effects of coenzyme Q10 on the tricarboxylic acid cycle. Enzymatic activity of succinate dehydrogenase (SDH), aconitase (ACO), and citrate synthase ($CS \times 0.1$) in the cortex of P301S mice fed with control and coenzyme Q10 (CoQ) diet. No differences were observed in tricarboxylic acid cycle enzymes after treatment with coenzyme Q10 ($n = 3-6$).

Fig. 5. Effects of coenzyme Q10 on the electron transport chain. Activity of complex I (A), levels of cytochrome c (B), ATPase (C), complex III (CIII) (C), complex IV (COX) (C) and complex I (CI) (C) in the cortex of P301S mice fed control and coenzyme Q10 (CoQ) diet. There was an increase in complex I activity and level in P301S mice after coenzyme Q10 treatment ($n = 3-6$). $p < 0.05$.