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# Coenzyme Q10 and cognition in atorvastatin treated dogs

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ABSTRACT

Statins have been suggested to protect against Alzheimer's disease (AD). Recently, however, we reported that aged dogs that underwent chronic statin treatment exhibited cognitive deficits compared with age matched controls. In human studies, blood levels of Coenzyme Q10 (CoQ10) decrease with statin use. CoQ10 is important for proper mitochondrial function and is a powerful antioxidant, two important factors for cognitive health in aging. Thus, the current study tested the hypothesis that CoQ10 levels in the serum and/or parietal cortex are decreased in statin treated dogs and are associated with poorer cognition. Six aged beagles (>8 years) were administered 80 mg/day of atorvastatin for 14.5 months and compared with placebo-treated animals. As predicted, serum CoQ10 was significantly lower in statin-treated dogs. Parietal cortex CoQ10 was not different between the two groups. However, poorer cognition was correlated with lower parietal cortex CoQ10. This study in dogs suggests that serum CoQ10 is reduced with atorvastatin treatment. CoQ10 levels in brain may BE linked to impaired cognition in response to atorvastatin, in agreement with previous reports that statins may have a negative impact on cognition in the elderly.



Alzheimer's disease (AD) is the most common cause of dementia in the elderly, affecting an estimated 5.5 million people in the United States. This number is expected to rise as the average age of the population increases. AD is pathologically characterized by senile plaques formed from beta-amyloid (Aβ) peptides and neurofibrillary tangles (NFTs) formed from hyper-phosphorylated tau [1,13]. Inhibiting Aβ production is one possible means of preventing the development of AD. HMG-CoA reductase inhibitors (statins) prescribed to lower plasma cholesterol can modify Aβ levels. High intracellular cholesterol levels may influence the amyloid precursor protein (APP) to increase the production of Aβ. Therefore, the reduction of cholesterol through statins may reduce Aβ production [36]. Previous cell culture and rodent studies have found that statins improve cognitive function and reduce the production of Aβ [5,15,31].

Statin use has been associated with reduced risk of AD in human epidemiological studies [4,12]. Li and colleagues reported an association between statin treatment and decreased AD-related neuropathological changes [17]. However, recent randomized controlled trials to determine if statin use prevented AD found that statins have no benefit in preventing AD when compared with controls, although statin therapy as a treatment for AD showed promise [19]. It is clear that the discussion of whether statin use is a possible treatment for AD remains controversial.

Aged dogs are a useful model for exploring chronic statin treatment to prevent AD. Dogs naturally develop human sequence Aβ deposits, vascular pathology and cognitive impairment [8]. Additionally, dogs were used to establish the efficacy and safety of statins, due to their similarity with humans with respect to responsiveness, drug tolerance and metabolism [24]. The efficacy and safety of most statins on the market were established in dogs given chronic, physiologically relevant doses for over 2 years [7]. A recent pilot study conducted in our lab used the dog model of AD to examine whether aged animals treated with atorvastatin show reduced neuropathology and cognitive benefits. Results from this study demonstrated that the statin-treated dogs showed deficits in a task that measures executive function [24]. However, no neu-

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ropathological differences existed between the two groups that accounted for impaired cognition. Results from the canine study were consistent with previous reports in hypercholesterolemic aged individuals treated with statins, who showed decreased cognitive performance when compared to a placebo group [22,23]. These results prompted us to investigate other possible mechanisms that may lead to cognitive decline with statin treatment.

One mechanism of particular interest is the depletion of Coenzyme Q10 (CoQ10) with statin use. CoQ10 is a mitochondrial electron transporter vital for ATP production and a powerful mitochondrial and cellular antioxidant found in all cells [11]. CoQ10 is a potent gene regulator, involved in the expression of hundreds of genes, including those involved in optimal mitochondrial function and inflammatory processes [30]. HMG-CoA reductase is a key enzyme in CoQ10 biosynthesis. Inhibition of HMG-CoA reductase by statins is associated with lower circulating levels of CoQ10 in rodents [37], canines [29] and humans [28]. CoQ10 deficiency results in decreased mitochondrial activity and mitochondrial degradation and increased reactive oxygen species (ROS) and inflammation [34]. CoQ10 levels tend to naturally decline with age and may play a role in both AD-related mitochondrial dysfunction and inflammation [35]. Further, aged canines show impaired mitochondrial function and may be particularly vulnerable to reduced CoQ10 [10].

Twelve beagles ranging in age from 8.9 to 13.2 years were obtained from either the Lovelace Respiratory Research Institute (Albuquerque, NM) or from Harlan Laboratories (Indianapolis, IN). Based on our previous work, dogs of this age show cognitive decline and significant amounts of brain Aβ peptides [8]. All animals had documented dates of birth, comprehensive medical histories and a veterinary examination ensuring that the animal was in good health prior to the start of the study. At the end of the study, all but one control animal had received treatment for 14.5 months and ranged in age from 10.1 to 14.6 years. All research was conducted in accordance with approved IACUC protocols.

At baseline animals were ranked by cognitive test scores and placed into equivalent groups with 2 males and 4 females per group. These groups were randomly designated as either the placebo-treated control group or the atorvastatin-treated group. One dog in the control group was euthanized prior to collecting reversal learning error scores.

Atorvastatin (Atorvastatin Calcium, also known as Lipitor®, 40 mg tablets) and placebo tablets were kindly provided by Pfizer Inc. (New York, NY). Treated animals received 80 mg per day (2 40 mg tablets) and control animals received 2 placebo tablets per day. Atorvastatin was chosen for this study because long term studies using an 80 mg/day dose in dogs did not result in adverse events such as cataracts [27] and this is the highest dose typically used in humans with hypercholesterolemia.

Cognitive tests were used to assess learning and memory. A detailed description of cognitive testing has been described previously [24]. For the current study, scores from a size reversal learning task, a measure of executive function, was used. This task was administered after ~6 months of treatment and resulted in impaired reversal learning in treated dogs. Animals were simultaneously presented with two objects that differed only in size [9]. Once animals were proficient at choosing either the larger or smaller object, the reward contingencies were reversed, requiring animals to select the object that was previously negative. Error scores were used for data analyses.

Blood samples were collected in 10 cc red top tubes, centrifuged, aliquoted and frozen at −80 °C. For the current study, blood collected 62 days prior to the end of the study was used for CoQ10 measurement.

Animals were sedated by subcutaneous injection with 0.2-mg/kg acepromazine 20 min prior to induction of general anesthesia. General anesthesia was induced by inhalation with 5% isoflurane. While maintained under anesthesia, dogs were exsanguinated by cardiac puncture. Within 15 min of death, the brain was removed from the skull and bisected midsagitally. The right hemisphere was coronally sectioned (~1 cm) and flash frozen at −80 °C. The dissection procedure was completed within 20 min, yielding 35–45 min post mortem interval. For the current study, the coronal section containing the parietal cortex was used for CoQ10 assays and a 50 mg piece of cortex was selected.

CoQ10 was extracted from both serum and parietal cortex samples as previously described [21], with minor modifications. Briefly, 1 mL of serum from each control and atorvastatin treated dog was mixed with 1 mL of ethanol containing 0.1 mM butylatedhydroxytoluene (BHT) and extracted with 3 mL of hexane. For parietal cortex samples, brain tissues from control and atorvastatin treated dogs were homogenized in lysis buffer (pH 7.4) containing Sucrose 320 mM, Tris–HCl (pH 8.8) 9.9 mM, $MgCl_2$ 0.098 mM, EDTA 0.076 mM, proteinase inhibitors leupeptin (0.5 mg/mL), pepstatin (0.7 μg/mL), aprotinin (0.5 mg/mL) and PMSF (40 μg/mL) and phosphatase inhibitor cocktail (Sigma–Aldrich, St. Louis, MO). 1 mL of homogenate was mixed with 1 mL of methanol and extracted with 3 mL of hexane. Each sample was centrifuged at 4000 × *g* for 10 min. The hexane phase was evaporated to dryness under nitrogen, residues were dissolved in 25 μL of ethanol, and 20 μL were analyzed by HPLC.

The HPLC measures of CoQ10 were conducted as previously described by Mosca et al. [21]. Briefly, the HPLC system consists of a Waters 616 quaternary pump equipped with a Waters 996 Diode array detector. The samples were eluted through a Hypersil GOLD column (C18, 4.6 cm × 25 cm, 5 μm particle size) with a guard column (10 mm) of the same material matrix (Thermo Scientific, Waltham, MA). The elution was performed at a flow rate of 1 mL/min with a gradient consisting of a mixture of Solution A (methanol:water 80:20, v/v) and Solution B (ethanol:isopropanol 95:5, v/v). The initial conditions were 39% Solution A and 61% Solution B. After 16 min, the mobile phase was changed linearly over 2 min to 100% Solution B. After 10 min of 100% Solution B, the system was reversed linearly over 2 min to the initial conditions. The absorbance was monitored at 275 nm. CoQ10 concentrations were calculated by reference to a standard curve of CoQ10 (0.39–50 μM) in ethanol. By this method, a linear fit ($r^2 = 0.99$) was obtained.

CoQ10 levels in serum and brain were compared across groups using independent *t*-tests. Pearson correlations were used to test the association between brain CoQ10 and either size discrimination or reversal learning error scores. All statistics were conducted using SPSS Statistics 18 (IBM; Armonk, NY).

Previous studies using this cohort of aged dogs indicated that chronic statin treatment increased size reversal learning error scores, a sign of cognitive dysfunction [24]. Overall, the goal of the current study was to determine if (a) CoQ10 decreased in serum and brain in atorvastatin treated dogs and; (b) whether decreases in CoQ10 were associated with the cognitive deficits observed previously in statin treated dogs.

We were interested in determining if CoQ10 concentrations are reduced in parietal cortex following chronic treatment with atorvastatin, given that decreased blood concentrations of CoQ10 are a major side effect of statin use in human clinical studies. However, it remains unclear whether statins decrease brain tissue concentrations of CoQ10 and what role CoQ10 may have in brain function. Here we measured CoQ10 concentration in serum to demonstrate reduction of blood CoQ10 in these dogs. We measured CoQ10 concentration in parietal cortex to examine whether brain CoQ10 is reduced with statin treatment, as seen in blood levels. As expected, total serum CoQ10 was significantly reduced in statin treated dogs compared with controls $t(9) = 3.66$, $p = 0.005$ (Fig. 1a). In contrast,

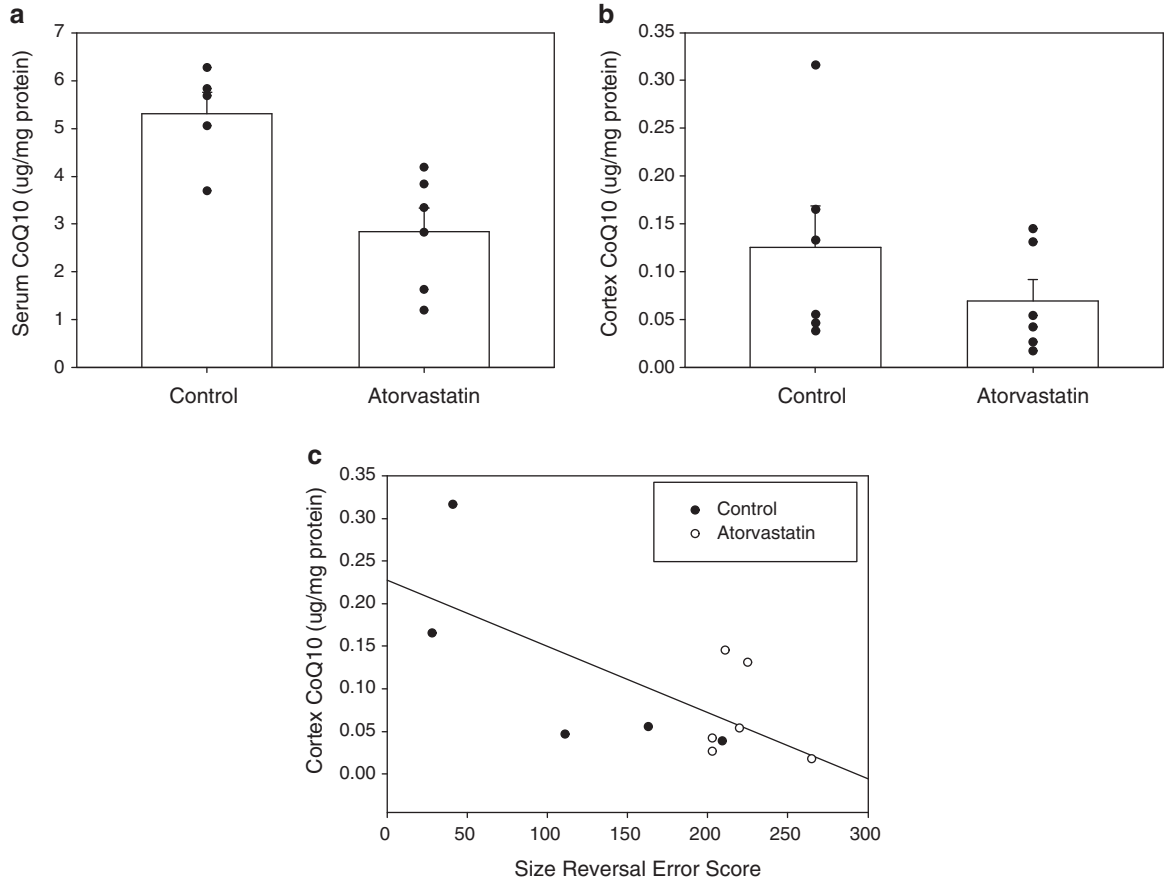


**Fig. 1.** CoQ10 in statin treated and control aged dogs. (a) Serum CoQ10 concentration ($y$-axis) is decreased in atorvastatin treated dogs. (b) Parietal cortex CoQ10 concentration ($y$-axis) does not differ between groups. (c) Reversal learning error scores ($x$-axis) was inversely correlated with parietal cortex CoQ10 ($y$-axis).

parietal cortex CoQ10 was not significantly lower in statin treated dogs $t(10) = 1.15$, $p = 0.276$ (Fig. 1b). We then correlated parietal cortex and serum CoQ10 levels. Interestingly, serum CoQ10 levels were not associated with parietal cortex levels of CoQ10 ($r^2 = -0.010$, $p = 0.976$).

We hypothesized that brain and serum CoQ10 was associated with poorer reversal learning error scores. Reversal learning error scores were inversely correlated with parietal cortex CoQ10 ($r^2 = -0.68$, $p = 0.02$) (Fig. 1c), but not serum CoQ10 ($r^2 = -0.325$ $p = 0.359$). Thus, lower levels of CoQ10 in the parietal cortex, but not serum, are associated with deficits in reversal learning ability.

Dogs develop Aβ pathology and cognitive deficits with age, similar to humans [8]. Dogs also offer additional information compared with mouse models, given that dog studies utilize chronic doses of statins (over 2 year periods) in doses that are physiologically relevant to those of human [7]. These doses can be administered without the upregulation of HMG-CoA typically observed in rodents [6]. Dogs in this study were given a chronic dose of 80 mg per day, the highest dose given to humans with hypercholesterolemia. This dose is ~6–10 mg/kg in a 6–12 kg dog, compared to ~1 mg/kg in humans. Although the dose was much higher in mg/kg compared to human doses, it was chosen for the initial study parameters to determine whether atorvastatin leads to beneficial changes in the brain of aged dogs with Aβ.

In human clinical studies, plasma levels of CoQ10 decline following statin use [28]. CoQ10 deficits have been linked to inflammation, increased ROS and mitochondrial dysfunction, all of which may impair brain function [33]. Therefore, the aims of the current study were to determine if atorvastatin treatment reduced serum or brain CoQ10 levels and whether CoQ10 was associated with cognitive function. Here we used aged dogs chronically treated with atorvastatin or aged matched controls.

We first examined if CoQ10 was depleted with statin treatment. Although previous studies have reported lower CoQ10 levels in blood in humans following statin treatment, little is known about CoQ10 levels in brain tissue. Statins are prescribed more often in older individuals [18], when CoQ10 levels are naturally declining [35]. Statin treatment in dogs [29] and humans [28] lead to decreased blood levels of CoQ10 and we have also shown similar results in the current study. Interestingly, the results of the current study suggest that atorvastatin treatment does not lead to depletion of CoQ10 in the parietal cortex, and there is no correlation between serum and parietal cortex CoQ10 levels. We next examined whether parietal cortex or serum CoQ10 levels alone are associated with cognitive performance on the reversal learning task [24]. The parietal cortex was used because it is vulnerable to Aβ neuropathology in aged dogs and is a component of the cortical circuit involved with reversal learning [3]. We concluded that lower parietal cortex, but not serum, CoQ10 concentration is associated with poorer reversal learning. Taken together, our data suggest that brain CoQ10 may be linked to cognitive status in aged dogs.

Supplementation with CoQ10 may be beneficial in the aging population, at risk for Alzheimer's disease. CoQ10 supplements are safe for human consumption in high doses and has already shown potential as a neuroprotectant [34]. CoQ10 treatment of human neuroblastoma cells protect against Aβ toxicity, inhibits formation and extension of Aβ fibrils and destabilizes pre-formed Aβ fibrils [25]. Further, CoQ10 supplementation in AD transgenic mice attenuates brain atrophy [16], decreases production of Aβ [38] and protects against both plaque formation and memory loss [34]. Fur-

ther studies are needed to determine whether oral doses of CoQ10 increase CoQ10 levels in the cortex. Previous studies have shown improvement in circulating levels of CoQ10 following supplementation in humans [2,20,32] and dogs [14,26,39], but it is not clear whether CoQ10 levels in brain tissue are also improved. Additionally, it is unclear whether a combination of CoQ10 supplementation and statin treatment would improve cognitive function in domains sensitive to statin treatment. As this may be a concern for human clinical trials, future studies using a larger sample size and a more lipophilic statin should consider further investigating the importance of concurrent statin treatment and CoQ10 supplementation.

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