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Coenzyme Q_{10} as a Possible Treatment for Neurodegenerative Diseases

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Coenzyme Q_{10} (CoQ_{10}) is an essential cofactor of the electron transport gene as well as an important antioxidant, which is particularly effective within mitochondria. A number of prior studies have shown that it can exert efficacy in treating patients with known mitochondrial disorders. We investigated the potential usefulness of coenzyme Q_{10} in animal models of Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD). It has been demonstrated that CoQ_{10} can protect against striatal lesions produced by the mitochondrial toxins malonate and 3-nitropropionic acid. These toxins have been utilized to model the striatal pathology, which occurs in HD. It also protects against 1-methyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity in mice. CoQ_{10} significantly extended survival in a transgenic mouse model of ALS. CoQ_{10} can significantly extend survival, delay motor deficits and delay weight loss and attenuate the development of striatal atrophy in a transgenic mouse model of HD. In this mouse model, it showed additive efficacy when combined with the *N*-methyl-D-aspartate (NMDA) receptor antagonist, remacemide. CoQ_{10} is presently being studied as a potential treatment for early PD as well as in combination with remacemide as a potential treatment for HD.

Keywords: Amyotrophic lateral sclerosis; Parkinson's; Huntington's; Free radicals

INTRODUCTION

There is increasing interest in the potential usefulness of coenzyme Q_{10} (CoQ_{10}) to treat both mitochondrial disorders as well as neurodegenerative diseases such as Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). CoQ_{10} serves as important cofactor of the electron transport chain where it accepts electrons from complexes I to II.[1,2] It is initially reduced to the semiubiquinone radical and then transfers electrons one at a time to complex III of the electron transport chain. CoQ_{10} which is also known as ubiquinone, serves as an important antioxidant in both mitochondria and lipid membranes.[1,3] Recent evidence suggests that at least part of its antioxidant effects are mediated through interactions with α-tocopherol.[4]

The importance of CoQ_{10} for central nervous system function is corroborated by children, in whom a marked CoQ_{10} deficiency was documented. An initial report was of two sisters with encephalopathy, proximal weakness, myoglobinuria and lactic acidosis.[5] A further case report was that of a 35 year old woman who developed proximal weakness, premature exertional fatigue, myoglobinuria and complex-partial seizures.[6] She was documented to have decreased complex I–III and II–III activities of the electron transport chain, as well as reduced muscle CoQ_{10} content. Another case was that of a four year old boy who presented with progressive muscle weakness, seizures, cerebellar ataxia and elevated CSF lactate concentrations.[7] A muscle biopsy showed decreased complex I–II and II–III activities as well as reduced mitochondrial CoQ_{10}

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content. This patient did not improve with CoQ_{10} supplementation. A recent report documented two siblings in whom there was a severe encephalomyopathy as well as renal failure. The patients developed nystagmus, visual loss, sensorineural deafness, progressive ataxia, dystonia with amyotrophy and lower extremity spasticity.[8] Both patients developed nephrotic syndrome followed by renal failure. The patients were found to have widespread CoQ_{10} deficiency, with decreases in CoQ_{10} dependent respiratory chain activities. There was clinical improvement with oral ubidecarenone therapy.

There are a number of reports of both clinical and biochemical improvement following treatment with CoQ_{10} in patients with known mitochondrial disorders.[9–12] The most success appears to have been with patients with mitochondrial encephalopathy lactic acidosis and strokes (MELAS). The results in patients with other mitochondrial disorders have been less consistent.[13] A study using phosphorus magnetic resonance spectroscopy showed improved energy metabolism in both the brain and muscle, in six patients with mitochondrial disorders with CoQ_{10} treatment.[14] A clear clinical improvement however, was only seen in one patient with Leber's optic atrophy. Two patients with MELAS improved based on oxygen consumption as assessed by noninvasive tissue oximetry.[15] A 32 year old man who had bilateral visual loss developed choreic movements associated with hypointense lesions in the subthalamic nucleus on MRI.[16] Treatment with CoQ_{10} at 250 mg/d resulted in recovery of the movement disorder, normalization of the lactate/pyruvate ratio and disappearance of the MRI lesions 3 years later.

A number of recent studies also showed improvement in patients with mitochondrial disorders after treatment with the CoQ_{10} analog idebenone. Idebenone protects against excitotoxic cell death in cultured cortical neurons.[17] Treatment of a 36 year old man with MELAS with idebenone produced improved oxygen extraction without increasing cerebral blood flow as assessed by PET.[18] Another patient with Leber's optic atrophy developed spastic paraparesis with white matter lesions on MRI.[19] The patient was assessed using phosphorus MRS both before and following administration and withdrawal of idebenone. The patient showed reversal of paraparesis with idebenone, which was correlated, with normalization of serum lactate and brain and muscle phosphorus MRS. It has also been shown that Friedrich's ataxia is caused by a deficiency of frataxin, which regulates mitochondrial iron content. In three patients treated with idebenone there was a significant decrease in left ventricular mass.[20] This has led to a larger ongoing clinical trial.

The antioxidant effects of CoQ_{10} are maintained by the enzyme DT diaphorase which keeps CoQ_{10} in a reduced state promoting its antioxidant function.[21] CoQ_{10} protects against glutamate toxicity in cultured cerebellar neurons and against degeneration of neurons produced by mumps and sendai virus.[22,23]

ANTIOXIDANT PROPERTIES AND EFFECTS OF COQ_{10} SUPPLEMENTATION

A number of studies have shown that oral administration of CoQ_{10} can produce protection in experimental models of cerebral ischemia or against mitochondrial toxins.[24–28] A contentious issue however, is whether CoQ_{10} administration increases either muscle or brain concentrations.[29,30] In young rats α-tocopherol supplementation produced increases in tissue levels in the plasma, liver, kidney, muscle and brain, however CoQ_{10} supplementation increased CoQ_{10} levels only in plasma and liver.[30] In another study oral administration of CoQ_{10} and α-tocopherol alone or together increased serum levels, and CoQ_{10} increased mitochondrial levels of both CoQ_{10} and α-tocopherol, consistent with a sparing effect of α-tocopherol.[31] In this study, CoQ_{10} increased mitochondrial CoQ_{10} levels in liver and kidney, but not in brain or skeletal muscle. Similar findings were found in another study.[32] We also found no alteration in muscle and brain after oral loading in young (1–2 month old) rats.[27] It has been suggested that it is only possible to increase CoQ_{10} levels in muscle and brain when there is a deficiency.[2]

There is evidence for a decrease in CoQ_{10} levels with aging in both human and rat tissues. This could be a consequence of either decreased synthesis or increased oxidative damage. In rats, there is a significant decrease in brain CoQ_{10} levels as early as five months of age.[33,34] Decreases with aging in man have also been documented.[35] We therefore examined whether feeding CoQ_{10} for 2 months could increase brain CoQ_{10} levels in 12 month old Sprague–Dawley rats.[27] Oral administration of CoQ_{10} produced significant 30–40% increases of both the oxidized and reduced forms of CoQ_9 and CoQ_{10} restoring concentrations to those seen in young animals. An increase of approximately 10% was seen following supplementation in Fischer 344 rats, which may reflect strain differences. We also found that CoQ_{10} supplementation increased mitochondrial levels in the cerebral cortex of 12 month old Sprague–Dawley rats. There was also a nonsignificant trend towards an increase in α-tocopherol, consistent with the α-tocopherol sparing effect reported in other studies.[31,32]

CoQ_{10} is recognized to be an important antioxidant in the inner mitochondrial membrane, where it can scavenge radicals directly.[36] A direct reaction of ubiquinol with nitric oxide has also been documen-

ted.[37] There is substantial evidence that ubiquinol may act in a concerted antioxidant activity with α-tocopherol, reducing α-tocopheroxyl radical to α-tocopherol.[38–41] In rat liver mitochondrial CoQ_9 levels are oxidized prior to the onset of massive lipid peroxidation and the subsequent depletion of α-tocopherol.[3] In rat mitochondria supplementation with succinate results in a reduction of CoQ to ubiquinol and this preserves α-tocopherol concentrations during antioxidation.[4] In the absence of succinate CoQ is oxidized, and mitochondria are depleted of α-tocopherol, which correlates with autooxidation. This suggests that α-tocopherol, is the direct radical scavenger and ubiquinol acts to regenerate α-tocopherol. Another interaction is between dihydrolipoic acid and CoQ.[42] Dihydrolipoic acid reduces ubiquinone to ubiquinol by the transfer of a pair of electrons, thereby, increasing the antioxidant capacity of CoQ in biomembranes. Lipoic acid was shown to maintain a normal ratio of reduced to oxidized CoQ following MPTP administration *in vivo*.[43]

The effects of oral supplementation with CoQ or α-tocopherol on the rate of mitochondrial superoxide radical ($O_2^{\cdot}$) generation have been examined in skeletal muscle, liver and kidney of 24 month old mice.[4] In this study, the administration of α-tocopherol (200 mg/kg/d) produced a seven-fold increase in mitochondrial content, while CoQ_{10} administration increased both total CoQ content and α-tocopherol by about five-fold. In these mice the rate of $O_2^{\cdot}$ generation from submitochondrial particles was inversely related to α-tocopherol content, but unrelated to CoQ content. This study, therefore, provides *in vivo* evidence that the antioxidant effects of CoQ are at least in part mediated by its ability to reduce the α-tocopheroxyl radical. Another potential mechanism is by interactions with uncoupling proteins. CoQ has been shown to be an obligatory cofactor for uncoupling protein function.[44,45] It has been hypothesized that uncoupling proteins may regulate the ATP level, the NAD/NADH ratio and reduce superoxide production in mitochondria.[46] CoQ_{10} supplementation of human lymphocytes *in vitro* decreases oxidative DNA damage.[47]

NEUROPROTECTIVE EFFECTS IN ANIMALS

A number of studies have examined the ability of CoQ_{10} to exert neuroprotective effects in the central nervous system. Experimental ischemia can be produced by intracerebroventricular administration of the potent vasoconstrictor endothelin.[28] Administration of CoQ_{10} at a dose of 10 mg/kg i.p. resulted in a significant attenuation of ATP and glutathione depletion, and diminished neuronal injury in the hippocampus.[28]

We carried out a number of studies of the protective effects of CoQ_{10} against lesions produced by mitochondrial toxins. We initially showed that oral administration of CoQ_{10} produced dose-dependent neuroprotective effects against striatal lesions produced with the mitochondrial toxin malonate.[24] We also found that CoQ_{10} exerted additive neuroprotective effects when administered with MK-801, an *N*-methyl-D-aspartate receptor antagonist.[48] The administration of CoQ_{10} attenuated both malonate-induced lesions as well as depletions of ATP and increases in lactate concentrations. We also found that CoQ_{10} administration attenuated striatal lesions produced by aminooxyacetic acid.[26] We had previously shown that this compound again acts as a mitochondrial toxin by blocking the malate–aspartate shunt. We investigated the role of CoQ_{10} in MPTP toxicity. We demonstrated significant protection against depletions of dopamine as well as depletion of tyrosine hydroxylase immunostained neurons produced by MPTP in 24 month old mice.[25] We examined whether CoQ_{10} can exert neuroprotective effects against systemic administration of 3-nitropropionic acid.[27] This is an irreversible inhibitor of succinate dehydrogenase, which produces selective striatal lesions in both rats and primates, which closely resemble those, found in HD.[49,50] The striatal lesions are characterized by sparing of NADPH diaphorase neurons, which are also spared in HD postmortem tissue. In primates the toxin produced a choreiform movement disorder and frontal type deficits, which resemble those found in HD patients. The lesions are accompanied by focal increases in lactate confined to the basal ganglia. The lesions are attenuated by antioxidants. The pathogenesis of the lesions appears to involve both impaired energy metabolism as well as oxidative stress. We found that oral administration of CoQ_{10} for one week prior to coadministration with 3-nitropropionic acid resulted in a significant 90% neuroprotection against the 3-nitropropionic acid induced lesions.[27] Oral supplementation with CoQ_{10} also significantly attenuated reductions in reduced CoQ_9 and reduced CoQ_{10} following 3-nitropropionic acid administration in the same animals.

We also recently examined whether CoQ_{10} supplementation could exert neuroprotective effects of transgenic mouse model of familial ALS. A major advance in the understanding of ALS was the finding that a subset of families with autosomal dominant inherited ALS harbors point mutations of the enzyme superoxide dismutase. Overexpression of the mutant enzyme in transgenic mice leads to motor neuron degeneration whereas overexpression of wild-type human SOD does not.[51] An early pathologic finding in these mice is mitochondrial

swelling and vacuolization, which correlates with the subsequent onset of rapid loss of motor neurons.[52] We found that oral administration of CoQ_{10} starting at 70 days of age in these mice significantly increased the life span of these mice.[27]

Similarly, in HD a major advance has been the development of transgenic mouse models. Transgenic mice expressing exon 1 of the human HD gene with an expanded CAG repeat developed a progressive neurological disorder.[53] At approximately 6 weeks of age, the R6/2 mice develop loss of brain and body weight and at 9–11 weeks, they develop an irregular gait, abrupt shuttering stereotypic movements, resting tremors and epileptic seizures. The brains of the R6/2 mice, show progressive striatal atrophy as well as neuronal intranuclear inclusions that are immunopositive for both huntingtin and ubiquitin.

We previously examined the effects of creatine in these mice.[54] Creatine can increase brain levels of phosphocreatine, thus compensating for an energetic defect. We found that creatine exerted significant neuroprotective effects in the HD transgenic mice. We have also recently examined the effects of CoQ either alone or in combination with the NMDA antagonist remacemide (Ferrante *et al.*, unpublished data). These compounds were administered in a diet starting at 21 days of age. We administered CoQ at a dose of 0.02% in the diet. Remacemide was administered at a dose of 0.007% in the diet. Diets were made in pelleted mouse chow. The calculated dose for CoQ_{10} was 400 mg/kg/d and remacemide at 14 mg/kg/d. We found that the mean survival in the CoQ_{10} treated R6/2 mice increased by 14.5%, the percentage increase in survival using remacemide in the diet was 15.5%, and the combined treatment using both CoQ_{10} and remacemide increased survival by 32%. This increase was more than twice that observed using either compound alone, consistent with additive neuroprotective effects. We also found that administration of either CoQ_{10} or remacemide significantly delayed the development of motor deficits, weight loss, cerebral atrophy and neuronal inclusions. Once again, the combination of CoQ_{10} and remacemide was more efficacious than either compound alone. We also studied the effects of these compounds using magnetic resonance spectroscopy. We found that administration of CoQ_{10} with remacemide significantly attenuated decreased in *N*-acetylaspartate concentrations (Andreassen, Ferrante, Jenkins and Beal, unpublished data).

EFFECTS OF COQ_{10} SUPPLEMENTATION IN PATIENTS WITH NEURODEGENERATION

We and others have previously examined a number of aspects of CoQ_{10} in patients with neurodegenerative diseases. We investigated CoQ_{10} levels in mitochondria isolated with platelets of PD patients.[55] We found significant reductions in CoQ_{10} levels, which directly correlated with decreases in complex I activity, Oral administration of CoQ_{10} to the PD patients was well tolerated and resulted in dose-dependent significant increases in plasma CoQ_{10} levels. We also carried out clinical studies of the effects of CoQ_{10} on elevated striatal and occipital cortex lactate concentrations in HD patients.[56] Our initial studies demonstrated that there was significant increase in lactate concentrations in both basal ganglia as well as numerous areas of cerebral cortex in HD. We administered CoQ_{10} a dose of 360 mg/d to these patients for one or two months. We obtained a baseline lactate concentration both prior to during and following discontinuation of CoQ_{10} therapy. CoQ_{10} therapy led to a 37% reduction in occipital cortex lactate concentrations, which was reversed following discontinuation of therapy indicating a therapeutic effect of CoQ_{10}. A tolerability study of CoQ_{10} in HD patients showed that there were minimal adverse effects in doses of 600–1200 mg/d.[57] This has led to a full-scale clinical trial examining the effects of CoQ_{10} with or without the NMDA receptor antagonist remacemide. This is being carried out by the Huntington's Study Group. The trial encompasses 340 patients treated for 30 months. They are randomized to CoQ_{10} at 600 mg/d, remacemide or the combination of 2×2 factorial design. Administration of CoQ_{10} to HD patients does not produce short term improvement which removes this potential confounding effects from its evaluation for neuroprotection.[57]

Other data had shown that serum CoQ_{10} levels are unaltered in patients with AD and ALS.[58,59] Studies showed that the reduced CoQ_{10} to oxidized CoQ_{10} ratio was significantly reduced in PD patients platelets.[60] Serum levels of CoQ_{10} in PD patients however are unaltered.[61] Presently a clinical trial at 600 mg/d is being carried out in early PD patients by the Parkinson's Disease Study Group.

CONCLUSIONS

We demonstrated that CoQ_{10} administration can increase brain concentrations in mature and older animals. It can also increase brain mitochondrial concentrations. There is substantial evidence that it can act in concert with α-tocopherol as an antioxidant within mitochondria. CoQ_{10} administration has been demonstrated to be efficacious in experimental models of cerebral ischemia. It is also efficacious against lesions produced by the mitochondrial toxins malonate, 3-nitropropionic acid and MPTP. CoQ_{10} has been shown to extend survival in a

transgenic mouse model of ALS. We have recently found that CoQ_{10} both by itself as well as in combination with the NMDA antagonist remacemide exerts significant neuroprotective effects in a transgenic mouse model of HD. CoQ_{10} is presently being tested in clinical trials to determine whether it has efficacy in both HD and PD and a trial in ALS is being planned. The findings discussed suggest that CoQ_{10} administration may prove be an useful treatment to slow the progress of neurodegenerative diseases.

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