Review

Coenzyme $Q_{10}$: a progress towards the treatment of neurodegenerative disease

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SUMMARY

Coenzyme $Q_{10}$ ($Q_{10}$, or ubiquinone) is an electron carrier of the mitochondrial respiratory chain (electron transport chain) with antioxidant properties. In view of the involvement of $Q_{10}$ in oxidative phosphorylation and cellular antioxidant protection a deficiency in this quinone would be expected to contribute to disease pathophysiology by causing a failure in energy metabolism and antioxidant status. Indeed, a deficit in $Q_{10}$ status has been determined in a number of neuromuscular and neurodegenerative disorders. Primary disorders of $Q_{10}$ biosynthesis are potentially treatable conditions and therefore a high degree of clinical awareness about this condition is essential. A secondary loss of $Q_{10}$ status following HMG-CoA reductase inhibitor (statins) treatment has been implicated in the pathophysiology of the myotoxicity associated with this pharmacotherapy. $Q_{10}$ and its analogue, idebenone, have been widely used in the treatment of neurodegenerative and neuromuscular disorders. These compounds could potentially play a role in the treatment of mitochondrial disorders, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, Friedreich’s ataxia, and other conditions which have been linked to mitochondrial dysfunction. This article reviews the physiological roles of $Q_{10}$, as well as the rationale and the role in clinical practice of $Q_{10}$ supplementation in different neurological diseases, from primary $Q_{10}$ deficiency to neurodegenerative disorders. These will help in future for treatment of patients suffering from neurodegenerative disease.

Key words: Coenzyme $Q_{10}$; Antioxidant; Ageing; Oxidative stress; Neurodegenerative diseases

INTRODUCTION

Over the past decade, interest in the roles of nutritional supplements in neurodegenerative disease has intensified. One of these supplements, coenzyme $Q_{10}$ ($Q_{10}$), is an essential cofactor involved in mitochondrial oxidative phosphorylation as well as a potent antioxidant. Strong evidence has now emerged supporting the role of oxidative stress and defective energy metabolism in the pathogenesis of many neurodegenerative disorders, such as Parkinson’s disease (PD), Huntington’s disease (HD), and Alzheimer disease (AD). There is, therefore, a robust scientific rationale for testing...
Peeyush kumar et al. received a Nobel Prize for his hypothesis about the role of coenzyme Q₁₀ and the transfer of energy in the mitochondria.

Meat, poultry and fish are the richest sources of CoQ₁₀ and the daily intake of these foods provides between 2 to 20 mg, which does not significantly increase the levels of CoQ₁₀ in blood and tissues. Small amounts are found in cereals, soybeans, nuts and vegetables, particularly spinach and broccoli (Kitano et al., 2006; Mason et al., 2005). The absorption of CoQ₁₀ from the diet (or supplements) occurs in the small intestine and is influenced by the presence of food and beverages. It is better absorbed in the presence of foods rich in lipids. After being absorbed, the CoQ₁₀ is transported to the liver where it is incorporated into lipoproteins and concentrated in tissues (Mason et al., 2005).

CoQ₁₀ is produced from tyrosine in all cells of the body, but especially in the heart, liver, kidney and pancreas, where it begins its essential role in intracellular energy production. As all cellular activities depend on energy, CoQ₁₀ is essential for the health of all organs and tissues (Ernster et al., 1995). Several cofactors are involved in its synthesis, including vitamin B₂, vitamin B₆, folic acid, vitamin B₁₂, niacin, panthotenic acid and vitamin C. The concentration of CoQ₁₀ in human tissues reaches its peak at the age of twenty years, after which it progressively decreases. Because CoQ₁₀ is not classified as a vitamin or mineral, no dietary reference value or established daily recommended levels are available. However, some signs and symptoms are associated with a lack of CoQ₁₀ such as congestive heart failure, ischemic heart disease, cardiomyopathy, hypertension, hyperthyroidism and breast cancer (Quinzii et al., 2007). However, it is unclear whether the lack of CoQ₁₀ contributes to the development of these diseases or is caused by the diseases. The deficiency may occur as a result of low ingestion or inadequate production caused by aging or due to deficiency of the nutrients needed for its synthesis. Genetic or acquired defects in its synthesis or metabolism, and interactions with CoQ₁₀...
medications such as β-blockers, hydrochlorothiazide, methyldopa, statin and tricyclic antidepressants may also reduce levels of CoQ10 (Quinzii et al., 2007).

**CLINICAL ASPECTS OF COENZYME Q10**

The fundamental role of CoQ10 in mitochondrial bioenergetics and its well-acknowledged antioxidant properties constitute the basis for its clinical applications, although some of its effects may be related to a gene induction mechanism. Studies have found that among CoQ10’s benefits is a beneficial effect regarding migraine headaches. (Rozen et al., 2002; Sandor et al., 2005). One research study concluded that coenzyme Q10 has the potential in hypertensive patients to lower systolic blood pressure and diastolic blood pressure without significant side-effects. (Rosenfeldt et al., 2007).

Longer lifespans were noted in rats and roundworms following CoQ10 supplementation (Coles et al., 1996; Ishii et al., 2004; Quiles et al., 2004). CoQ10 benefits in rats were also shown in a 2002 study to include the reduction of radiation damage in the blood. (Koryagin et al., 2002). A 2010 study noted CoQ10’s role in improving circulatory system function, as well as CoQ10’s role in mitigating headache symptoms. (Littarru et al., 2010). In a 2010 Swedish study, mice treated with CoQ10 showed a significantly prolonged swim times, suggesting that CoQ10 improves physical endurance, as well as has an anti-fatigue effect. (Fu et al., 2010). A 2010 Italian study found that there was a deficit in CoQ10 status in a number of neuromuscular and neurodegenerative disorders. (Mancuso et al., 2010). In a 2009 study out of Belgium, major depression was found to be accompanied by a lowered antioxidant status. Accordingly, plasma CoQ10 was significantly lower in depressed patients than in normal controls. The study concluded that lower CoQ10 plays a role in the pathophysiology of depression and stated that it is suggested that depressed patients may benefit from CoQ10 supplementation. (Maes et al., 2009). CoQ10’s potential neuro-protective effects were found in studies of toxicity of nerve cells and neurodegenerative disorders. (Spindler et al., 2009). A Japanese study suggested that CoQ10 protected the skin against oxidative stress and enhanced the production of components of the epidermal basement membrane. (Muta-Takada et al., 2009). In one study, heart failure patients used 50 to 150 milligrams of CoQ10 daily for three months. Following this period, 80 percent of the subjects were found to have some type of improvement. (Langsjoen et al., 1993). The results of a 2010 study where subjects used CoQ10 supplementation showed some performance enhancing effects (Gokbel et al., 2010).

**IMPORTANCE FOR HEALTH**

**Energy Production**

It is well established that CoQ10 is essential for cellular energy conversion and ATP production in all cells of the body. Therefore it plays a crucial physiological role in maintaining good health. ATP is a high energy phosphate substance necessary to fuel all cellular functions. The major part of ATP production occurs in the inner membrane of mitochondria, where CoQ10 is located as a vital electron and proton carrier in the mitochondrial electron transport. CoQ10 supports ATP synthesis in the mitochondrial inner membrane and stabilises cell membranes, thus preserving cellular integrity and function (Dutton et al., 2000; Crane et al., 2001).

**Energy And Sporting Activity**

CoQ10 is reported to be effective in sporting activity by improving the physical work capacity (especially, in aerobic exercise) through activation of energy supply and favourable effects on lipid metabolism, and also through its anti-oxidative muscle-protective action.

**Antioxidant Function**

It is well established that CoQ10 acts in its reduced
form (ubiquinol) as an antioxidant. Ubiquinol represents more than 80% of the total CoQ$_{10}$ pool in human plasma and is an important antioxidant in plasma lipoproteins. Ubiquinol inhibits protein and lipid oxidation in cell membranes, and it prevents the initiation of lipid peroxidation, oxidative injury to DNA and other molecules (Crane et al., 2001; Thomas et al., 2000). CoQ$_{10}$ acts as an antioxidant through several mechanisms which essentially fall into two categories: direct reaction with free radicals and regeneration of the active form of vitamin E by reducing the alphatocopheryl radical (Quinn et al., 1999; Arroyo et al., 2000). Peroxidation of plasma lipoproteins, namely LDL, is known to play an important role in the formation of foam cells and in the development of the atherosclerotic process. Studies in the last decade have demonstrated that the content of CoQ$_{10}$ in human LDL affords some protection against the oxidative modifications of LDL themselves, thereby lowering their atherogenic potency (Stocker et al., 1991). Studies on isolated serum lipoproteins point out that CoQ$_{10}$ is the most reactive antioxidant in these particles and protects them from oxidative damage.

CoQ$_{10}$ As Anti-Aging

The property of CoQ$_{10}$ to act both as a pro-oxidant and an antioxidant suggests that it may also be a modulator of cellular redox state under physiological or pathological conditions, and particularly, could play a role in the aging process (Sohal et al., 2007). During aging, pro-oxidant changes in cellular redox status take place, with a consequent increase of oxidative damage in molecules (Sohal et al., 2004). This hypothesis refers to the imbalance between the generation of pro-oxidant and antioxidant defense, and the level of oxidative stress that increases during aging; the mitochondria play a critical role in this homeostatic disturbance (Sohal et al., 1994). The elevation of the stress or oxidative damage due to increased production of O$_2^·$/H$_2$O$_2$ and the decline in mitochondrial ability to synthesize ATP, reduces the functional capacity of several physiological systems (Sohal et al., 2007). There is a hypothesis that CoQ$_{10}$ is involved in these age-related changes because it is a carrier of electrons and is, therefore, involved in the oxidative phosphorylation system as a generator and sequester of reactive oxygen species (ROS).

The results of several studies in the literature on age-related changes in levels of CoQ$_{10}$ do not support the existence of a common trend. Kalen, Appelkvist and Dallner (1989) reported loss in CoQ$_{10}$ content (related to age) in human tissue homogenates. (Beyer et al., 1985) studied age-related changes in the levels of CoQ$_{10}$ in several tissues and found no differences in homogenates of brain and lung of rats. However, there was an increase in the liver and a decrease in heart, kidney and skeletal muscles. The differences between the studies may be due to age of animals or the procedures used for extraction and quantification of CoQ$_{10}$ or, differences between species, lines or diets. (Matthews et al., 1998a) showed that the intake of CoQ$_{10}$ by rats with twelve or twenty-four months of age increased its content in brain mitochondria and had a neuroprotective effect against acid 3-nitropropionic (3-NPA). Several studies in young rats have shown that administration of CoQ$_{10}$ by feeding caused an increase in the quantity of CoQ$_{10}$ in plasma and homogenates and mitochondria of liver, heart and skeletal muscle (Kwong et al., 2002; Kamzalov et al., 2003; Rebrin et al., 2004).

Heart And Cardiovascular Health

Coenzyme Q$_{10}$ helps to maintain a healthy cardiovascular system. There is evidence of CoQ$_{10}$ deficiency in hypertension, heart failure and in statin-treated hypercholesterolemic individuals.

Blood pressure

Blood pressure is a well-established biomarker for heart health. A meta-analysis of 12 clinical trials of CoQ$_{10}$ for hypertension has shown that CoQ$_{10}$ is effective in lowering systolic blood pressure by up
to 17 mm Hg and diastolic blood pressure by up to 10 mm Hg without significant adverse events (Rosenfeldt et al., 2007).

**Heart function**

There is substantial evidence that heart function is improved by the supplementation of CoQ<sub>10</sub> (Langsjoen et al., 1999; Baggio et al., 1994). A meta-analysis of the use of CoQ<sub>10</sub> (60 - 200 mg/day) in randomised clinical trials in people with congestive heart failure showed a significant and clinically relevant improvement in various parameters of heart function (Soja et al., 1997). A comprehensive review of the use of CoQ<sub>10</sub> (50-200 mg/day for 1-12 months) in cardiovascular indications showed that the adjuvant supplementation with CoQ<sub>10</sub> in people with chronic heart failure should be recommended (Tran et al., 2001).

**Statins**

Statins (HMG Co-A reductase inhibitors; cholesterol lowering drugs) may decrease body CoQ<sub>10</sub> levels below the threshold that is required for numerous cellular processes. The depletion of CoQ<sub>10</sub> is dose related and could be particularly important in the elderly where CoQ<sub>10</sub> levels are generally low, but also in those with pre-existing heart failure. Statin-induced CoQ<sub>10</sub> deficiency is completely preventable with supplemental CoQ<sub>10</sub> with no adverse impact on the cholesterol lowering or the anti-inflammatory properties of the statin drugs (Langsjoen et al., 2003).

**COENZYME Q<sub>10</sub> AND NEURODEGENERATIVE DISORDERS**

The brain needs high energy and oxygen consumption (Floyd et al., 1999). As a result, it is also replete with readily oxidized amino acids and unsaturated fatty acids, with the easy production of free radicals (Murata et al., 2008). This makes the brain vulnerable to oxidative damage, and several recent articles suggest that oxidative stress plays a major role in the onset of neurodegenerative diseases related to aging.

The key role of CoQ<sub>10</sub> in oxidative phosphorylation emphasizes its importance in the metabolism of neurons, given the constant and high energy demand of these cells. The nervous system is exposed to oxidative stress, and this may emphasize the role of CoQ<sub>10</sub> in the central nervous system (Littarru et al., 2006). From clinical and pre-clinical studies, it is clear that oxidative stress and its consequences - oxidative damage in lipids, proteins, nucleic acids, may be the cause, or at least a contributory factor, of a large number of neurodegenerative diseases (Coyle et al., 1993; Beal et al., 2005). The neurodegenerative diseases include common and debilitating disorders, and are characterized by progressive and irreversible loss of neurons in specific regions of the brain. The most common neurodegenerative disorders are Parkinson’s disease and Huntington’s disease, where the loss of neurons in the basal ganglia structures results in changes in the control of movement; Alzheimer’s disease, in which the loss of neurons in the hippocampus and the cortex leads to deficiency in memory and cognitive capacity; and amyotrophic lateral sclerosis, in which muscle weakness results from the degeneration of motor, bulbar and cortical neurons (Littarru et al., 2006).

In several animal models of neurodegenerative diseases including amyotrophic lateral sclerosis, Huntington’s disease and Parkinson’s disease, CoQ<sub>10</sub> has a beneficial effect, reducing the progression of disease (Shults et al., 2002; Kwong et al., 2002; Ferrante et al., 2002; Somayajulu et al., 2005). (Beal et al., 1994) injected malonic acid in striatum of laboratory animals, and found that this procedure induced depletion of ATP and an increase in lactic acid. The administration of CoQ<sub>10</sub> in animals was able to mitigate the depletion of ATP induced by malonate while minimizing the increase in concentrations of lactate. Beal and Matthews also examined whether CoQ<sub>10</sub> can exert antioxidant effects in brain tissue. They demonstrated that oral supplementation with CoQ<sub>10</sub> (200 mg/kg/day) for
one month significantly protected against the increase in the 2,5-dihydroxybenzoic acid (DHBA) induced by malonate. The DHBA is a biochemical marker for the generation of potent oxidative species such as hydroxyl radicals. These data indicate that experimentally-induced lesion, as well as the changes caused by oxidative stress, can be neutralized by oral administration of CoQ10 in animals. It is well known that the administration of CoQ10 in young rats leads to a significant increase of CoQ10 in plasma and the liver (Zhang et al., 1995; Beal et al., 1997). (Beal et al., 1999) found no increased concentrations of CoQ10 in the brain of young animals supplemented with CoQ10 and this could be due to saturation of the membrane by CoQ10 in animals of this age. Furthermore, we know that aging in rats and humans leads to a decrease of CoQ10 in several tissues, including the brain (Beyer et al., 1985; Kallen et al., 1989). Indeed, (Matthews et al., 1998) conducted a study with supplementation of CoQ10 in twelve-month-old rats and showed an increase in CoQ9 and CoQ10 in cerebral cortex. The extent of the increase (30 - 40%) almost restored the levels to those found in young animals.

**Parkinson’s disease**

First described by James Parkinson in 1817, Parkinson’s disease (PD) is a progressive neurological disorder characterized clinically by tremor, muscle rigidity, slowness and lack of movement and a disability of postural balance that leads to changes in gait and fall. It is one of the most common neurological conditions the cause of which remains unknown. The prevalence of PD is approximately 0.3% of the population and of these, 1% is over 60 years of age. The incidence rate is 150 - 200 per 100,000 persons per year, although this is increasing (de Lau et al., 2006).

The main histopathological feature of PD is the selective loss of dopaminergic neurons of the substantia nigra in the central nervous system (Dawson et al., 2003). The tyrosine hydroxylase, a key enzyme for the synthesis of dopamine, is also deficient. From a biochemical point of view it is known that the activity of mitochondrial complex I is selectively reduced in the substantia nigra of PD patients (Parker et al., 1998; Schapira et al., 1990). This defect can cause a “leakage” of electrons from mitochondria, leading to an accumulation of ROS (Reactive Oxygen-Derived Species) that damages proteins, lipids and nucleic acids (Jenner et al., 2003). Interestingly, this enzyme activity is reduced in platelets of patients with PD (Benecko et al., 1993). The brain of PD patients also shows evidence of impaired proteasomal function, a defect those results in increased oxidative stress and decreased removal of damaged polypeptides oxide (McNaught et al., 2003; Halliwel et al., 2002; Farout et al., 2006).

Mitochondrial dysfunction and oxidative stress are considered important in the pathogenesis of PD. The initial hypothesis that the deficiency in mitochondrial complex I may be involved in the etiology of PD came from the discovery that the complex I mitochondrial inhibitor MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) causes a syndrome indistinguishable from PD and selective loss of dopaminergic cells in the substantia nigra (Langston et al., 1983).

The known position of CoQ10 in the respiratory chain, where it acts as electron acceptors for complexes I and II/III, led the researchers at the University of California, San Diego, to check the level of CoQ10 in the mitochondria of platelets isolated from patients with PD. The level of CoQ10 mitochondrial in these patients (141.8 ng/mg protein ± 11.3) was lower than in controls (216.3 ± 12.7). This difference was highly significant, and in addition, there was a significant correlation between concentrations of CoQ10 and the activities of complex I and complex II/III. It is important to emphasize that the platelets reflect certain biochemical processes that occur in the brain (Shults et al., 1999; Sohmiya et al., 2004) had observed some years before, a deficiency of CoQ10 in the plasma of PD patients. In order to ascertain whether the treatment with CoQ10 could benefit patients with PD, (Shults
et al., 1999) first investigated whether oral administration of CoQ\textsubscript{10} might be beneficial in a laboratory model of PD. MPTP is a chemical agent selectively toxic to dopaminergic neurons and the first to be impaired in PD. A group of one-year-old rats were treated with CoQ\textsubscript{10} (200 mg/kg per day) and also received MPTP. The levels of dopamine in the striatum were significantly higher (37\%) in the group of rats treated with CoQ\textsubscript{10} and MPTP, compared to the group treated only with MPTP. Based on these observations, a preliminary study was conducted in fifteen PD patients supplemented with CoQ\textsubscript{10} for a month. The complex I citrate synthase in mitochondria isolated from platelets of patients after treatment with CoQ\textsubscript{10} was higher than the corresponding activity before treatment, and similar to the activity found in the control group.

All these observations in laboratory animals and patients led to a study with a larger number of patients (80) to verify if CoQ\textsubscript{10} could slow the progression of PD. This study reported that the intake of 1200 mg per day of CoQ\textsubscript{10} for sixteen months was associated with 44\% less functional decline in PD patients, including in daily activities (Shults et al., 2002). Another study in twenty-eight patients with PD also showed moderate improvement in symptoms with daily oral administration of 360 mg of CoQ\textsubscript{10} (Muller et al., 2003). While these data are promising, they need to be confirmed in larger clinical trials before the use of CoQ\textsubscript{10} can be recommended for PD, but support the idea that high levels of CoQ\textsubscript{10} could yield therapeutic benefits.

Alzheimer’s disease

Alzheimer’s disease (AD) is a degenerative disease of the brain and the most common cause of dementia in the elderly, affecting approximately 200 million people worldwide and causing cognitive disabilities with gradual onset (Evans et al., 1989; Hebert et al., 2001). In general, the first clinical aspect is memory deficiency, where remote memories are preserved relatively well in the course of the disease. The patient’s degree of alertness or lucidity is not affected until the disease is very advanced (Francis et al., 1999). The pathophysiology of AD is complex and includes a defect in β-amyloid protein metabolism (Aβ), irregularities in neurotransmission, and the involvement of inflammatory, oxidative and hormonal pathways (Cutler et al., 2001).

Oxidative stress, an imbalance between the formation of free radicals and the antioxidant system, plays a critical role in the pathogenesis of AD (Gary et al., 2005; Butterfield et al., 2004; Kawamoto et al., 2005) conducted a study involving oxidative stress and AD, and found that patients with AD compared with elderly controls, showed an increase in the production of TBARS (thiobarbituric acid reactive substances), as well as in the activities of NOS (nitric oxide synthase), SOD (superoxide dismutase) and Na/K-ATPase. However, no change was found in the basal content of cGMP (cyclic guanosine monophosphate). Thus, they concluded that there is a break in the modulation of systemic oxidative stress during aging, and that this disruption is more pronounced. As oxidative damage is involved in the etiology of neurologic complications, treatment with antioxidants has been used as a therapeutic approach in several types of neurodegenerative diseases, including AD (Ahmad et al., 2005; Ansari et al., 2004).

It has been shown that CoQ\textsubscript{10} improves cognitive functions, regulates mitochondrial functions and facilitates the synthesis of ATP (McDonald et al., 2005). CoQ\textsubscript{10} significantly attenuates the depletion of ATP and malonate-induced increases of lactate in brain mitochondria of rats (Beal et al., 1994). Supplementation of CoQ\textsubscript{10} in rats increased the endogenous content of CoQ\textsubscript{10} in the brain and provided antioxidant protection against free radical generation (Soderberg et al., 1992; Lenaz et al., 1999; Kwong et al., 2002; Rauscher et al., 2001; Somayajulu et al., 2005) found increased levels of CoQ\textsubscript{10} in most brain regions of patients with Alzheimer’s disease. A recent study by (Bustus et al., 2000) found no significant difference in plasma levels of CoQ\textsubscript{10} in
patients with Alzheimer’s disease and controls. According to (Isharat et al., 2006), CoQ10 supplementation improves learning and memory deficits by possibly inhibiting oxidative stress, and also improves levels of ATP, being an important therapy in the treatment of AD. Promising preliminary evidence from studies in humans suggests that supplementation with CoQ10 may reduce, but not cure, dementia in individuals with AD. Additional well-designed studies are needed to confirm these results before a recommendation can be made.

**Huntington’s disease**

Huntington’s disease (HD) is an inherited neurodegenerative disorder. It was given the name of the physician George Huntington, who described it in 1872. In 1993 the gene causing the disease was identified (Browne et al., 1999). Huntington’s disease is an autosomal dominant phenotype, with the gene called IT15 responsible for the disease, located at the short arm of chromosome 4. The mutant gene is constituted by abnormal repetitions of the sequence of nucleotides cytosine, adenosine and guanine (CAG), responsible for encoding glutamine (Beal et al., 1995). The number of CAG repetitions is considered normal up to thirty, while in HD the number of repetitions is usually greater than thirty-six. It has been observed that the larger the number of repetitions of the trinucleotide CAG, the earlier the manifestation of the disease (Goldberg et al., 1994). The mechanism by which mutations of this gene causes HD remains undefined, although evidence of animal models and clinical trials indicate a role of oxidative stress and impaired mitochondrial function (Kasparov et al., 2006). The gene defect may cause a slight reduction in the capacity of energy metabolism, leading to neuronal degeneration, primarily in the striatum and then in other regions of the brain (Jenkins et al., 1998). The impaired energy production leads to increased intracellular calcium and generation of free radicals, however the exact mechanism for the decreased capacity of energy in HD is unclear. Clinically, this disease is characterized by psychiatric and behavioral disorders, cognitive dysfunction (thinking, hearing, memory) and progressive dementia. The prevalence of HD is of 3-7 per 100,000, and the annual incidence is 0.2 - 0.7 per 100,000 (Cardoso et al., 2006). The symptoms of the disease may appear at any stage of life, but in most cases, disease onset typically occurs between forty and fifty years of age with average survival of fifteen to twenty years (Duyao et al., 1993).

Patients with HD have elevated levels of lactate in the brain. The measurement of lactate production in the brains of HD patients done by H-MRS (Proton (H') Magnetic Resonance Spectroscopy) has revealed that creatine, cyclocreatine, CoQ10 and nicotinamide - compounds that increase energy metabolism - could exert neuroprotective effects in this disease (Koroshetz et al., 1997; Matthews et al., 1998a; Beal et al., 1999b). CoQ10 has been shown effective in reducing the damage produced by toxins that inhibit complex II, preventing the depletion of ATP and increases in lactate (Beal et al., 1994; Matthews et al., 1998b). CoQ10 also prolonged survival while delaying the onset of motor impairment in a HD model in transgenic mice (Ferrante et al., 2002). The neuropathological and clinical symptoms of HD can be simulated in animal models, with the systemic administration of 3-nitropropionic acid (3-NP). (Kasparov et al., 2006) studied the activity of creatine kinase (CK) and mitochondrial respiratory chain function in the brain of aged rats administered with 3-NP, with and without prior application of antioxidants CoQ10 + Vitamin E. They found that the content of CoQ10 in tissues decreased in rats that received 3-NP. Antioxidants CoQ10 + Vitamin E were effective in preventing the decrease of CoQ10 content in brain tissue, but failed to prevent the decline in function of the respiratory chain.

Pre-treatment with α-tocopherol caused no neuroprotective effect in an animal model of HD (Beal et al., 1988), and treatment with high doses of α-tocopherol was effective only in patients in early
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stages of the disease (Peyser et al., 1995). Moreover, pre-treatment with CoQ10 exerted neuroprotective effects in a variety of animal models of HD and the oral administration of CoQ10 significantly reduced the elevated levels of lactate in patients with HD (Beal et al., 1999). Levels of CoQ10 in the serum of HD patients were significantly lower than in both healthy controls and patients with HD treated with CoQ10 (Andrich et al., 2004). A six-month pilot test assessed the tolerability of CoQ10 (Feigin et al., 1996). Ten subjects with symptomatic HD received 600 mg of CoQ10 per day, in three doses. The individuals were assessed three times: before the administration of CoQ10 and after three and six months of treatment, using the Scale for the Assessment of Huntington’s disease, the HD Functional Capacity Scale, and neuropsychological tests. All subjects completed the study, with some mild adverse effects including heartburn, fatigue, headache, and increased involuntary movements. When the results of motor and functional scales obtained before the administration of CoQ10 and after six months were compared, no significant effect was observed. However, this study was small and unable to detect such effects.

As mentioned previously, HD patients have high levels of lactate in the brain. The administration of 360 mg/d of CoQ10 for two to eight weeks was associated with decreased levels of lactate in the occipital cortex in fifteen out of eighteen subjects (Koroshetz et al., 1997). Following interruption of administration of CoQ10, levels returned to baseline values, indicating that these effects were due to CoQ10. These results regarding the ability of CoQ10 to change the levels of cortical lactate support the therapeutic potential of CoQ10 for HD treatment.

Amyotrophic lateral sclerosis
Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by degeneration of motor neurons in the spinal cord, brainstem and motor cortex, resulting in progressive muscle weakness and atrophy, observed as loss of muscle mass with progressive difficulty in performing movements, and loss of muscle strength. The incidence of ALS is approximately one to two cases per 100,000 per year, with onset typically at around the age of sixty years, with survival of three to five years (Rowland et al., 2001; Sorenson et al., 2002).

ALS can occur in sporadic or familial form, which corresponds to only ten percent of cases. The possible involvement of free radicals in the etiology of ALS is suggested by the discovery that mutations in the gene encoding the antioxidant enzyme superoxide dismutase Cu/Zn (SOD1) are associated with familial ALS (Rosen et al., 1993). In both cases (sporadic or familial), although the etiology of ALS is not well known, several recent studies suggest an increase in oxidative damage (Bogdanov et al., 2000; Beal et al., 1997; Ferrante et al., 1997). According to (Murata et al., 2008), mitochondrial oxidative damage contributes to the pathogenesis of sporadic ALS. The concentrations of oxidized and reduced CoQ10 in the cerebrospinal fluid were measured by high performance liquid chromatography in thirty patients with ALS and seventeen controls without neurological diseases. The percentage of oxidized CoQ10 in the cerebrospinal fluid of patients with ALS was significantly higher than in controls. High levels of oxidized CoQ10 in plasma were found in patients with sporadic ALS, consistent with oxidative stress (Sohmiya et al., 2005). Given the evidence of mitochondrial dysfunction and oxidative stress in the pathogenesis of ALS,
CoQ₁₀ has been studied as a possible therapeutic approach (Galpern et al., 2007). The development of non-toxic drugs to block the oxidative injury may interrupt the process of disease at an early stage.

Studies using animal models of ALS have suggested that CoQ₁₀ may be effective in dealing with this problem. In a transgenic mice model with a SOD1 mutation, supplementation with 200 mg/kg of CoQ₁₀ increased survival, suggesting a potential therapeutic role of CoQ₁₀ in patients (Matthews et al., 1998). Recently, a systematic review of candidate therapeutic agents for ALS was conducted, and CoQ₁₀ has been identified as one of twenty agents prioritized for research in clinical trials (Traynor et al., 2006).

**SAFETY OF COENZYME Q₁₀**

According to a study published in 2009, CoQ₁₀ is very well tolerated with minimal adverse effects. (Spindler et al., 2009). A 2009 report concluded that the published reports concerning safety studies indicate that CoQ₁₀ has low toxicity and does not induce serious adverse effects in humans. Overall, these data from preclinical and clinical studies indicate that CoQ₁₀ is highly safe for use as a dietary supplement. (Hidaka et al., 2008)

According to Karl Folkers, Ph.D., director of the Institute for Biochemical Research at the University of Texas, CoQ₁₀ is safe and has no negative side effects, though it may decrease the need for other heart medicines.

**CONCLUSION**

There is an urgent need to identify agents that will provide neuroprotection and slow disease progression in neurodegenerative diseases that have an enormous collective impact on our society. Detailed and extensive pre-clinical studies have strongly supported CoQ₁₀ as such a potential agent. This review outlines results from clinical trials that are encouraging, but have not yet clearly demonstrated its effect. One issue that the studies raise is the barrier to translating promising animal studies into human neurodegenerative disease. Improvements in animal models and development of relevant biomarkers to track disease progression and identify presymptomatic patients are ways in which this barrier is currently being addressed. It is also possible that response to CoQ₁₀ may vary not only among different neurodegenerative diseases but also among subtypes of these diseases. Small sample sizes make it difficult to perform any meaningful regression analyses of the existing trials to stratify response by subtype. Future studies that will hopefully have larger sample sizes should aim to assess responses within subgroups of neurodegenerative diseases, defined either by phenotype, end phenotype, or genotype. Finally, the therapeutic range of CoQ₁₀ in neurodegenerative disease may be much higher than the doses that have been studied, especially given that the central nervous system bioavailability of oral CoQ₁₀ in humans is unknown.

**REFERENCES**


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251-262.
Beal MF. (1999b) Coenzyme Q10 administration and its potential for treatment of neurodegenerative diseases. Biofactors. 9, 261-266.


Mason P. (2005) Potential uses for coenzyme Q<sub>10</sub>


Peyser CE, Folstein M, Chase GA, Starkstein S, Brandt...


Stocker R, Pollicino C, Gay CA. (1991) Neither plasma coenzyme concentration, nor its decline during pravastatin therapy, is linked to recurrent cardiovascular disease events: A prospective case-control study from the LIPID study.