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Review

Coenzyme Q_{10} and its effects in the treatment of neurodegenerative diseases

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According to clinical and pre-clinical studies, oxidative stress and its consequences may be the cause or, at least, a contributing factor, to a large number of neurodegenerative diseases. These diseases include common and debilitating disorders, characterized by progressive and irreversible loss of neurons in specific regions of the brain. The most common neurodegenerative diseases are Parkinson's disease, Huntington's disease, Alzheimer's disease and amyotrophic lateral sclerosis. Coenzyme Q_{10} (CoQ_{10}) has been extensively studied since its discovery in 1957. It is a component of the electron transportation chain and participates in aerobic cellular respiration, generating energy in the form of adenosine triphosphate (ATP). The property of CoQ_{10} to act as an antioxidant or a pro-oxidant, suggests that it also plays an important role in the modulation of redox cellular status under physiological and pathological conditions, also performing a role in the ageing process. In several animal models of neurodegenerative diseases, CoQ_{10} has shown beneficial effects in reducing disease progression. However, further studies are needed to assess the outcome and effectiveness of CoQ_{10} before exposing patients to unnecessary health risks at significant costs.

Uniterms: Coenzyme Q_{10}. Antioxidant. Oxidative stress. Neurodegenerative diseases.

De acordo com estudos clínicos e pré-clínicos, o estresse oxidativo e suas conseqüências podem ser a causa, ou, no mínimo, o fator que contribui para grande número de doenças degenerativas. Estas doenças incluem problemas comuns e debilitantes, caracterizados por perda progressiva e irreversível de neurônios em regiões específicas do cérebro. As doenças degenerativas mais comuns são doença de Parkinson, de Hutington, de Alzheimer e esclerose amiotrófica lateral. A Coenzima Q_{10} (CoQ_{10}) tem sido intensamente estudada desde sua descoberta, em 1957. É um componente da cadeia de transporte eletrônico e participa da respiração aeróbica celular, gerando energia na forma de trifosfato de adenosina (ATP). A propriedade da CoQ_{10} de atuar como antioxidante ou pró-oxidante sugere papel importante na modulação do estado redox celular sob condições fisiológicas e patológicas, desempenhando, também, papel no processo de envelhecimento. Em vários modelos animais de doenças neurodegenerativas, a CoQ_{10} mostrou efeitos benéficos na redução do curso da doença. Entretanto, há necessidade de estudos adicionais para avaliar o efeito e a eficácia da CoQ_{10} antes de expor os pacientes a riscos de saúde desnecessários e de alto custo.

Unitermos: Coenzima Q_{10}. Antioxidante. Estresse oxidativo. Doenças neurodegenerativas.

INTRODUCTION

The Coenzyme Q_{10} (2,3-dimethoxy-5-methyl-6-decaprenil-1,4-benzoquinone) is a liposoluble substance also known as CoQ_{10}, vitamin Q_{10}, ubidecarenone or ubiquinone (Figure 1) (Bonakdar, Guarneri, 2005 ; Schoepp, 1999; Pepping, 1999). It can be obtained from the diet or supplements, but is also produced endogenously. It is found mainly in the mitochondria, the cellular organelles for energy production.

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Meat, poultry and fish are the richest sources of CoQ_{10}, and the daily intake of these foods provides between 2 to 20 mg, which does not significantly increase the levels of CoQ_{10} in blood and tissues. Small amounts are found in cereals, soybeans, nuts and vegetables, particularly spinach and broccoli (Kitano *et al.*, 2006, Mason, 2005). The absorption of CoQ_{10} 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 CoQ_{10} is transported to the liver where it is incorporated into lipoproteins and concentrated in tissues (Mason, 2005).

CoQ_{10} 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, CoQ_{10} is essential for the health of all organs and tissues (Ernster, Dallner, 1995). Several cofactors are involved in its synthesis, including vitamin B2, vitamin B6, folic acid, vitamin B12, niacin, panthotenic acid and vitamin C (Figure 2). The concentration of CoQ_{10} in human tissues reaches its peak at the age of twenty years, after which it progressively decreases.

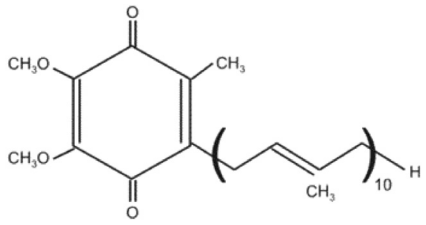

FIGURE 1 - Structure of coenzyme Q_{10} (2,3-dimethoxy-5-methyl-6-decaprenil-1,4-benzoquinone). Source: Shinde, Patil, Tendokar, 2005.

CoQ_{10} can be found in most living organisms, and since its discovery in 1957 by Crane *et al.* and the identification of its chemical structure by Folkers *et al.* in 1958, it has been extensively studied for its key role in cellular energy production – it is involved in the transport of electrons and protons and in the synthesis of ATP in the mitochondrial membrane - and acts as an antioxidant scavenger of free radicals (Kitano *et al.* , 2006; Shinde, Patil, Tendolkar, 2005, Hughes *et al.*, 2002, Nohl *et al.*, 2001).

Because CoQ_{10} 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 CoQ_{10}, such as congestive heart failure, ischemic heart disease, cardiomyopathy, hypertension, hyperthyroidism and breast cancer (Quinzii, DiMauro, Hirano, 2007[a]). However, it is unclear whether the lack of CoQ_{10} 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 medications such as beta-blockers, hydrochlorothiazide, methyldopa, statin and tricyclic antidepressants may also reduce levels of CoQ_{10} (Quinzii, Hirano, DiMauro, 2007b).

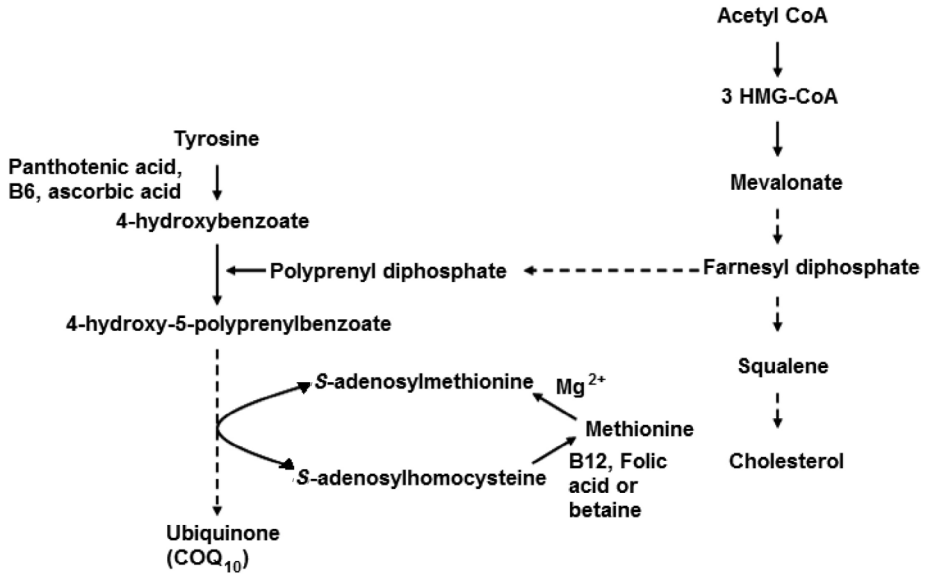

FIGURE 2 - Synthesis of coenzyme Q_{10}. Human cells synthesize CoQ_{10} from the amino acid tyrosine, through eight steps which require adequate levels of vitamins such as folic acid, niacin, riboflavin and pyridoxine. A deficiency in any of these nutrients results in CoQ_{10} deficiency (adapted from Shinde, Patil, Tendokar, 2005).

Coenzyme Q_{10} and 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, Forster, 2007). During aging, pro-oxidant changes in cellular redox status take place, with a consequent increase of oxidative damage in molecules (Sohal, Mockett, Orr, 2002). 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, Dubey, 1994). The elevation of the stress or oxidative damage due to increased production of $O_2^{\cdot-}/H_2O_2$, and the decline in mitochondrial ability to synthesize ATP, reduces the functional capacity of several physiological systems (Sohal, Forster, 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, Sohal, 2004).

Antioxidant role of Coenzyme Q_{10}

The mitochondrial inner membrane contains CoQ_{10} and α-tocopherol, both possessing antioxidant properties. This raises questions on their respective roles in the sequestration of free radicals generated in the mitochondrial inner membrane. In solution, CoQ_{10} has been shown to inhibit lipid peroxidation in mitochondrial membrane depleted of α-tocopherol (Mellors, Tappell, 1966; Takayanagi *et al.*, 1980). Current evidence suggests that α-tocopherol and ubiquinol act in combination to scavenge free radicals during auto oxidation of mitochondrial membrane (Stoyanovsky *et al.*, 1995; Lass, Sohal, 1998; Sohal, 2004). The reduced form of CoQ_{10} is able to scavenge free radicals that can cause damage to DNA, proteins and lipids, as well as causing cardiovascular disease, and neurodegenerative diseases such as Alzheimer and Parkinson.

The intake of CoQ_{10} in the long term over a period spanning 3.5 to 25 months, had no effect on activities of main antioxidant enzymes such as catalase, glutathione peroxidase and superoxide dismutase in the liver, kidney, skeletal muscle or brain (Sohal, Forster, 2007).

The endogenous antioxidants are important to maintain the normal activities of cells and systems of the body. However, when exposed to alcohol, drugs, trauma, cold, infections, toxins, radiation, diet low in nutrients, or vigorous physical activity, the endogenous antioxidant defense cannot neutralize the oxidative stress, requiring supplementation of antioxidants from the diet (Kaliora, Dedoussis, Schmidt, 2006).

The mitochondrion is where most free radicals are produced in the cell. A small percentage of mitochondrial oxygen consumption results in the production of hydrogen peroxide (Somayajulu *et al.*, 2005). Reactive oxygen species produced as subproducts of the mitochondrial electron transport chain are suppressed by antioxidants and converted into non-toxic compounds by enzyme scavengers of free radicals (Beal, 1999a; Sanders *et al.*, 1993). However, accumulation of free radicals in tissues can result in dysfunction and cell death. Excessive cell death is a feature of many neurological disorders including stroke, ischemia, Parkinson's and Alzheimer's diseases.

Previous studies have indicated that neuronal cells are highly sensitive to reactive oxygen species such as free radicals (Kim, Won, Gwag, 2002). There is a hypothesis that mitochondrial dysfunction and the consequent production of ROS can induce the neuronal cell death that occurs in neurodegenerative diseases (Somayajulu *et al.*, 2005; Kitazawa, Ananth, Kanthasamy, 2003; Christen, 2000; Behl, 1999; Piantadosi, Zhang , 1996; Coyle, Puttafarcken, 1993). Somayajulu *et al.* (2005) demonstrated that CoQ_{10} protects the cells from apoptosis, both morphologically and biochemically. The first evidence that CoQ_{10} can exert neuroprotective effects in the central nervous system *in vivo* was reported in 1994 by Beal *et al.*

Coenzyme Q_{10} and the Central Nervous System

The brain needs high energy and oxygen consumption (Floyd, 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, Ohtsuki, Terayama, 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_{10} 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_{10} in the central nervous system (Littarru, 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, Puttfarken, 1993; Beal, 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, 2006).

In several animal models of neurodegenerative diseases including amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease, CoQ_{10} 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_{10} in animals was able to mitigate the depletion of ATP induced by malonate while minimizing the increase in concentrations of lactate.

Beal and Matthews (1997a) also examined whether CoQ_{10} can exert antioxidant effects in brain tissue. They demonstrated that oral supplementation with CoQ_{10} (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 CoQ_{10} in animals. It is well known that the administration of CoQ_{10} in young rats leads to a significant increase of CoQ_{10} in plasma and the liver (Beal, Matthews, 1997a, Zhang *et al.*, 1995).

Beal *et al.* (1999a) found no increased concentrations of CoQ_{10} in the brain of young animals supplemented with CoQ_{10} and this could be due to saturation of the membrane by CoQ_{10} in animals of this age. Furthermore, we know that aging in rats and humans leads to a decrease of CoQ_{10} in several tissues, including the brain (Kallen, Appelkvist, Dallner, 1989; Beyer *et al.*, 1985). Indeed, Matthews *et al.* (1998a) conducted a study with supplementation of CoQ_{10} in twelve-month-old rats and showed an increase in CoQ_9 and CoQ_{10} 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, Breteler, 2006).

The main histopathological feature of PD is the selective loss of dopaminergic neurons of the substantia nigra in the central nervous system (Dawson, Dawson, 2003; Cookson, 2005). 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, Boyson, Parks, 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, 2003). Interestingly, this enzyme activity is reduced in platelets of patients with PD (Benecko, Strumper, Weiss, 1993). The brain of PD patients also shows evidence of impaired proteasomal function, a defect that results in increased oxidative stress and decreased removal of

damaged polypeptides oxide (McNaught, Olanow, 2003; Halliwell, 2002; Farout, Friguet, 2006; Pope, Gomes, Rockwell, 2007).

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 CoQ_{10} 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 CoQ_{10} in the mitochondria of platelets isolated from patients with PD. The level of CoQ_{10} 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 CoQ_{10} 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, Haas, Beal, 1999). Sohmiya *et al.* (2004) had observed some years before, a deficiency of CoQ_{10} in the plasma of PD patients.

In order to ascertain whether the treatment with CoQ_{10} could benefit patients with PD, Shults *et al.* (1999) first investigated whether oral administration of CoQ_{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_{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_{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_{10} for a month. The complex I / citrate synthase in mitochondria isolated from platelets of patients after treatment with CoQ_{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_{10} could slow the progression of PD. This study reported that the intake of 1200 mg per day of CoQ_{10} for sixteen months was associated with 44% less functional decline in PD patients, including in daily activities (Shults, 2002). Another study in twenty-eight patients with PD also showed moderate improvement in symptoms with daily oral administration of 360 mg of CoQ_{10} (Muller *et al.*, 2003). While these data are promising, they need to be confirmed in larger clinical trials before the use of CoQ_{10} can be recommended for PD, but support the idea that high levels of CoQ_{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, Sramek, 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, Hsueh-Meei, 2005; Butterfield, 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_{10} improves cognitive functions, regulates mitochondrial functions and facilitates the synthesis of ATP (McDonald, Sohal, Forster, 2005). CoQ_{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_{10} in rats increased the endogenous content of CoQ_{10} in the brain and provided antioxidant protection against free radical generation (Kwong *et al.*, 2002; Lenaz *et al.*,

1999; Rauscher, Sanders, Watkins, 2001; Somayajulu *et al.*, 2005).

Söderberg *et al.* (1992) found increased levels of CoQ_{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_{10} in patients with Alzheimer's disease and controls. According to Isharat *et al.* (2006), CoQ_{10} 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 CoQ_{10} 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, Ferranti, Beal, 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, 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 number of repetitions of the trinucleotide CAG, the earlier the manifestation of the disease (Goldberg, Telenius, Hayden, 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, CoQ_{10} and nicotinamide - compounds that increase energy metabolism - could exert neuroprotective effects in this disease (Koroshetz *et al.*, 1997; Matthews *et al.*, 1998b; Beal, 1999b).

CoQ_{10} 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.*, 1998a). CoQ_{10} 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 CoQ_{10} + Vitamin E. They found that the content of CoQ_{10} in tissues decreased in rats that received 3-NP. Antioxidants CoQ_{10} + Vitamin E were effective in preventing the decrease of CoQ_{10} 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 stages of the disease (Peyser *et al.*, 1995). Moreover, pre-treatment with CoQ_{10} exerted neuroprotective effects in a variety of animal models of HD and the oral administration of CoQ_{10} significantly reduced the elevated levels of lactate in patients with HD (Beal, 1999b). Levels of CoQ_{10} in the serum of HD patients were significantly lower than in both healthy controls and patients with HD treated with CoQ_{10} (Andrich *et al.*, 2004).

A six-month pilot test assessed the tolerability of CoQ_{10} (Feigin *et al.*, 1996). Ten subjects with symptomatic HD received 600 mg of CoQ_{10} per day, in three doses. The individuals were assessed three times: before the administration of CoQ_{10}; 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 CoQ_{10} 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 CoQ_{10} 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 CoQ_{10}, levels returned to baseline values, indicating that these effects were due to CoQ_{10}. These results regarding the ability of CoQ_{10} to change the levels of cortical lactate support the therapeutic potential of CoQ_{10} 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, Shneider, 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.*, 1997b; Ferrante *et al.*, 1997).

According to Murata, Ohtsuki and Terayama (2008), mitochondrial oxidative damage contributes to the pathogenesis of sporadic ALS. The concentrations of oxidized and reduced CoQ_{10} 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 CoQ_{10} in the cerebrospinal fluid of patients with ALS was significantly higher than in controls.

High levels of oxidized CoQ_{10} 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, CoQ_{10} has been studied as a possible therapeutic approach (Galpern, Cudkowicz, 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 CoQ_{10} may be effective in dealing with this problem. In a transgenic mice model with a SOD1 mutation, supplementation with 200 mg/kg of CoQ_{10} increased survival, suggesting a potential therapeutic role of CoQ_{10} in patients (Matthews *et al.*, 1998a). Recently, a systematic review of candidate therapeutic agents for ALS was conducted, and CoQ_{10} has been identified as one of twenty agents prioritized for research in clinical trials (Traynor *et al.*, 2006).

CONCLUSION

While data from pilot studies are encouraging, it is important to note that the results of these studies are not conclusive and more studies are needed before CoQ_{10} can be recommended as effective to patients, without exposing them to unnecessary risks and significant costs.

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