The Emerging Role of Coenzyme Q-10 in Aging, Neurodegeneration, Cardiovascular Disease, Cancer and Diabetes Mellitus

Muralikrishnan Dhanasekaran¹ and Jun Ren²,*

¹Scott and White Clinic and the Texas A&M University System Health Science Center, Temple, TX 76504; ²Division of Pharmaceutical Sciences & Center for Cardiovascular Research and Alternative Medicine, University of Wyoming, Laramie, WY 82071, USA

Abstract: Coenzyme Q (ubiquinone, 2-methyl-5,6-dimethoxy-1,4-benzoquinone), soluble natural fat-soluble vitamin, is crucial to optimal biological function. The coenzyme Q molecule has amphiphatic (biphasic) properties due to the hydrophilic benzoquinone ring and the lipophilic poly isoprenoid side-chain. The nomenclature of coenzyme Q-n is based on the amount of isoprenoid units attached to 6-position on the benzoquinone ring. It was demonstrated that coenzyme Q, in addition to its role in electron transport and proton transfer in mitochondrial and bacterial respiration, acts in its reduced form (ubiquinol) as an antioxidant. Coenzyme Q-10 functions as a lipid antioxidant regulating membrane fluidity, recycling radical forms of vitamin C and E, and protecting membrane phospholipids against peroxidation. The antioxidant property, high degree of hydrophobicity and universal occurrence in biological system, suggest an important role for ubiquinone and ubiquinol in cellular defense against oxidative damage. Coenzyme Q-10 is a ubiquitous and endogenous lipid-soluble antioxidant found in all organisms. Neurodegenerative disorders, cancer, cardiovascular diseases and diabetes mellitus and especially aging and Alzheimer's disease exhibit altered levels of ubiquinone or ubiquinol, indicating their likely crucial role in the pathogenesis and cellular mechanisms of these ailments. This review is geared to discuss the biological effect of coenzyme Q with an emphasis on its impact in initiation, progression, treatment and prevention of neurodegenerative, cardiovascular and carcinogenic diseases.

Key Words: aging, antioxidant, cancer, cardiovascular disease, coenzyme Q-10, diabetes, fatigue, neurodegenerative disorders.

INTRODUCTION

Coenzyme Q or ubiquinone is ubiquitous in nature and is widely distributed in plants, animals and microorganisms. Coenzyme Q homologs are classified based on their isoprenoid units (Q-n). The number, Q-n, refers to the amount of isoprenoid units attached to the 6-position on the benzoquinone ring of the coenzyme Q moiety. Coenzyme Q-10 was first isolated from beef hearts (Crane et al., 1957) and its chemical structure was identified in 1958 (Shunk et al., 1958). The naturally occurring coenzymes, depending on the source, differ from one another in their chemical structures in configuration of the isoprenoid side chain of ubiquinone and plastoquinone (the plant form) (Saitoh et al., 1992) as well as the number of isoprenoid units. Coenzyme Q-n is synthesized in the body mainly using 4-hydroxybenzoate and the polypropenyl chains. The primary role of coenzyme Q-10 is to facilitate electron transfer between redox components of electron transport chain in order to create a proton gradient across the inner mitochondrial membrane, thereby facilitating ATP formation (Fernandez-Ayala et al., 2003). Additional biological functions of coenzyme Q-10 encompass maintenance of membrane fluidity, recycling of radical forms of vitamin C and E (Beyer et al., 1985, Villalta et al., 1995, Malachir et al., 2005, Siemeninuk and Skrzydlewska, 2005) and most importantly, antioxidant protection against membrane lipid peroxidation (Al-Thakafy et al., 2005, Bliznakov, 1999, Somayajulu et al., 2005). Coenzyme Q-10 is the only endogenously occurring lipid-soluble antioxidant among all coenzymes ubiquitously synthesized (Ernst and Dallner, 1995, Battino et al., 2003, Molyneux, et al., 2005). Coenzyme Q-10 is the predominant form in humans, while coenzyme Q-9 is predominant in rodents.

The content of coenzyme Q differs drastically in organelles or sub-cellular fractions of cells. However, a significant amount of coenzyme Q has been found in mitochondria, which functions in concert with other enzymes involved in cellular respiration and ATP generation (Marubayashi et al., 1982). Coenzymes or ubiquinones, which are ubiquitous in nature are found in certain mammalian species with variations in interspecies concentrations. In mice, the levels of coenzyme Q-9 and coenzyme Q-10 are ~ 3 ng/mg and ~ 10 ng/mg, respectively in the brain. More specifically, there are concentration variations of coenzyme Q-9 and coenzyme Q-10 in brain, heart, liver, kidney, plasma/serum and skin (Naini et al., 2003). In addition, intracellular organelles such as lysosomes, endoplasmic reticulum, nucleus, the Golgi apparatus, cytosol and mitochondria also display different coenzyme concentrations (Ramassarma, 1985). Coenzyme Q-10 is currently obtainable as an over-the-counter dietary supplement in the United States and in several other countries. Coenzyme Q-10 has an enviable therapeutic safety profile for oral usage. Oral administration has been shown to increase coenzyme Q-10 concentration in serum and various organs (Zita et al., 2003). Hence, there is no need for special phar-
maceutical delivery system. Use of coenzyme Q-10 is considered as a form of alternative therapy and the modern health care profession has embraced the use of coenzyme Q-10 in various disease conditions including a series of cardiovascular and neurological disorders. Coenzyme Q-10 is quantified using high performance liquid chromatography (HPLC) connected with an ultraviolet detector. Coenzyme Q-10 can be extracted from various samples using hexane and methanol (25% and 75% respectively for the mobile phase in HPLC). Coenzyme Q10 is separated on C-18 Hypersil-ODS silica based column with a length of 125 mm and diameter of 3 mm. The flow rate is 0.3 ml/min and the UV-detection is performed at 275 nm (Albano et al., 2002).

This review will focus on literature dealing with neurodegenerative and cardiovascular etiology associated with alteration of coenzyme Q-10, predominantly those published during the last five years. The goal is to enrich the understanding of the complex interactions among coenzyme Q-10, redox status and bodily function, which should help to better understand the pathogenesis of certain neurodegenerative, cardiovascular and carcinogenic disorders so that optimal therapeutic application of coenzyme Q-10 may be achieved for individuals with the above mentioned health problems.

COENZYME Q-10 IN AGING AND NEURODEGENERATIVE DISORDERS

Aging

As an irreversible physiological process affecting all living organisms, aging is a rather complex physiological phenomenon with several theories being elaborated to help understand its origin. Among such theories, the “evolutionary theory of aging” envisions that human longevity is at the cost of impaired reproductive success (Westendorp and Kirkwood, 1998). An advanced vision of this theory, namely “antagonistic pleiotropy theory of aging” favors genes conferring short-term benefits at the expense of quality of later life (Bowen and Atwood, 2004). The “free radical theory of aging”, which favors accumulation of oxidant insult leading to ultimate senescence (Harman, 1956), paved the way to the modern “mitochondrial theory of aging” (Alexeyev et al., 2004), or the newly revised concept of “mitochondrial-lysosomal axis theory of aging” (Brunk and Terman, 2002: Terman, et al., 2004). Age-related increases in oxidative stress could account for aging-induced organ damage. The ‘mitochondrial theory of aging’, has gained convincing support on the concept of accumulation of somatic mutations of mitochondrial DNA that may lead to loss of mitochondrial function. Alterations of coenzyme Q-10 in relation to mitochondrial function with aging have been carefully studied in both human and rodents. It was speculated that aging-related increases in mitochondrial oxidative stress may be due to the depletion of coenzymes and vitamin E (Vercel et al., 1988: Miles et al., 2004). It was recently accepted that coenzymes in their reduced form, ubiquinol, may act as antioxidants. The antioxidant property of ubiquinol in conjunction with its high degree of lipophilicity and ever present occurrence in biological membranes suggests a likelihood of vital function in the cellular defense against oxidative stress. Ubiquinol acts as an antioxidant, preventing the initiation and propagation of lipid peroxidation in biological membranes and in serum low-density lipoprotein. The antioxidant activity of ubiquinol is independent as compared to the effect of vitamin E. Vitamin E acts as a chain-breaking antioxidant, inhibiting the propagation of lipid peroxidation. In addition, ubiquinol can significantly prolong the effect of vitamin E by recycling the vitamin from the tocopherol radical. Ubiquinol is synthesized de novo only. The amount of coenzyme Q decreases in various tissues with aging (Battino et al., 1995. Beal and Matthews, 1997), which increases the vulnerability towards injury caused by oxidative stress. Several studies have clearly shown an age-related decline of coenzyme Q-10 in both human and rodents (Pignatti et al., 1980, Lonroen et al., 1995). similar to the decline of vitamin E. Mitochondria obtained from heart, kidney and liver show an age-related decline in the levels of coenzyme Q and -tocopherol (Kamatzov, Sohal, 2004). Coenzymes are the mandatory components of both the respiratory chain and uncoupling proteins (UCP), both of which are essential to delay the aging process (Villalba et al., 1995). The fact that mitochondrial function, to which coenzyme Q-10 is heavily associated, determines that longevity was substantiated by an RNA interference study of mitochondrial respiration. Silencing of the mitochondrial respiratory chain was found to significantly modify the adult life span (Rodriguez-Agullera et al., 2005). The incorporation of exogenous coenzyme Q also affects the aging process in nematodes by reducing formation of reactive oxygen species. It was reported that animals supplemented on coenzyme Q may reach a significantly longer mean life span (11.7% higher), a significantly higher maximum life span (24% higher) and increased learning capacity than non-supplemented animals, suggesting that a long-term supplementation with a small dosage of coenzyme Q-10 may represent a good anti-aging therapy (Ishii et al., 2004. Quiles et al., 2004, McDonald et al., 2005). Such a beneficial role of coenzyme Q-10 is speculated to be related to its pivotal effects on levels of flavoproteins and cytochromes in mitochondrial respiratory chain (Battino, 2001, Quiles et al., 2004). In addition, coenzyme Q-10 may protect DNA from oxidative damage, although the precise mechanism still needs full validation (Quiles et al., 2004). Anti-aging therapies based on coenzyme Q-10 are currently being used to alleviate the symptoms of aging. Further study is warranted as to how the aging process may induce a decreased capacity of adequate coenzyme Q-10 levels. It is documented that point mutations in the insulin signaling cascade and/or caloric restriction may effectively slow down the aging process (Tatar et al., 2003). Coenzyme Q-10 has been shown to affect the insulin signaling cascade (McCart, 2000) and thus insulin signaling-related aging process. On the contrary, no link between coenzyme Q-10 and caloric intake has been documented. Both coenzyme Q-10 and caloric restriction inhibit age-related alterations in gene expression involved in the extracellular matrix, cellular structure and protein turnover. However, unlike caloric restriction, coenzyme Q-10 does not prevent age-related transcriptional alterations associated with energy metabolism (Lee et al., 2004), indicating that coenzyme Q-10 intervention is not as effective as caloric restriction in inhibiting the aging process.

Alzheimer’s Disease

Alzheimer’s disease is the foremost age-related neurodegenerative disorder prevalent in the United States and rest of
the world. The prevalence of developing Alzheimer's disease has significantly increased recently and is expected to double every 5 years, due to the lengthened overall life span. Deposition of the β-amyloid peptide into plaques in the brain parenchyma and cerebral blood vessel walls is one of the distinguishing neuropathological features of Alzheimer's disease. β-Amyloid peptide production and deposition have been hypothesized to begin the cascade of events that result in the neurodegenerative changes responsible for the memory loss and behavioral changes associated with Alzheimer's disease (Näslund et al., 2000). Reduction in β-amyloid deposition and/or destabilization of preformed β-amyloid peptide in the brain is now considered the most effective therapeutic approach for the treatment of Alzheimer's disease. Coenzyme Q-10 has shown to inhibit the in vitro formation of the β-amyloid peptide (Ono et al., 2005). Oxidative stress and mitochondrial dysfunctions are implicated in the pathophysiology of the disease. Coenzyme Q-10 has been found to be significantly increased in most regions of the brain in patients with Alzheimer's disease (Edlund et al., 1992, 1994, de Bustos et al., 2000). A reduction in serum ubiquinone deficiency related mitochondrial dysfunction could contribute to the etiology and pathology of Alzheimer's disease (Kurup and Kunap, 2003). Decreased mRNA expression of NADH dehydrogenase-4 and NADH dehydrogenase-13 was found in the hippocampus and inferior parietal lobe of the brains of patients with Alzheimer's disease. This decrease of NADH dehydrogenase-4 gene expression may cause the inhibition of ubiquinone oxidoreductase activity (Aksenov et al., 1999). Several reports suggest that the coenzyme Q-10 deficiency may be related to increased risk of Alzheimer's disease or vascular dementia. Combinations of antioxidants (vitamins E, vitamin C and ubiquinone) may serve as an effective therapy for Alzheimer's disease (Grundman et al., 2002, Beal, 2004, Bragin et al., 2005).

Amyotrophic Lateral Sclerosis

In the United States, amyotrophic lateral sclerosis is called Lou Gehrig's disease, after the Yankees baseball player who died of it in 1941. In Britain and rest of the world, amyotrophic lateral sclerosis is called motor neuron disease, in reference to the cells that are lost in this disorder. This is a disease involving nervous system controlling voluntary muscle movement. Amyotrophic lateral sclerosis is a progressive neurodegenerative disorder for which no cure or effective treatment presently exists. Various types of drugs have been tested; most of which are based on different hypotheses of mechanisms for neuronal death, including oxidative damage, loss of trophic factors, glutamate-mediated excitotoxicity, and chronic inflammation. The discovery that a small percentage of amyotrophic lateral sclerosis cases are familial and involve mutation in a superoxide dismutase gene led to the development of transgenic mouse models widely used for drug testing. Mutations in vascular endothelial growth factor gene and oxidative stress also appear to be involved in the etiology of this disease. Patients suffering from amyotrophic lateral sclerosis have a significantly increased amount of oxidized coenzyme Q-10 in the plasma, suggesting systemic oxidative stress in the pathogenesis of this disease (Sohmya et al., 2005). An ample amount of evidence shows that bioenergetic dysfunction plays either a primary or secondary role in the etiology of cell death in neurodegeneration. Drugs that ameliorate bioenergetic defects are useful in therapy. Creatine and coenzyme Q-10, which increase muscle and brain phosphocreatine concentrations, may inhibit the activation of the mitochondrial permeability transition and protect against neuronal degeneration (Strong and Pattee, 2000, Tamepolsky and Beal, 2001). Similarly, in animal models of amyotrophic lateral sclerosis, coenzyme Q-10 significantly decreased striatal lesions produced by systemic administration of 3-nitropropionic acid and significantly increased the life span in a transgenic mouse model of familial amyotrophic lateral sclerosis. These studies provide further evidence that coenzyme Q-10 can exert neuroprotective effects in amyotrophic lateral sclerosis and might be useful in the treatment of neurodegenerative diseases (Matthews et al., 1998).

Fatigue

It is one of the most widespread but not clearly understood symptom in humans. Fatigue is the seventh most common symptom in primary health care (Kroenke et al., 1988). Fatigue is defined physiologically as the inability to maintain the expected power output. It is most often chronic and at times severe in intensity. Fatigue is very often identified as central or peripheral in nature. Chronic fatigue in elderly people causes functional dependence, which may lead to interruption of treatment, decline in quality of life and expensive home care (Tralongo et al., 2003). There is evidence that mitochondrial dysfunction and oxidative stress are directly related to fatigue in humans (Schulte-Mattler et al., 2003; Finsterer, 2004). Mitochondrial injuries are considered the main link between cellular stress signals activated during acute and chronic injury leading to the death of cells. Mitochondrial dysfunction can lead to the initiation of cell death processes that are believed to contribute to cell death in aging and neurodegenerative disorders. Similarly, mitochondrial mutations cause excessive metabolic muscle fatigue (Schulte-Mattler et al., 2003). Complex-I is a crucial member of the mitochondrial respiratory chain that is necessary for the synthesis of ATP. Defects in mitochondrial complex I activity are also found in fatigue (Tiso and Mendel, 2002). Nicotinamide adenine dinucleotide and another cofactor similar to coenzyme Q-10 is known to resist fatigue and to have beneficial effects in the treatment of fatigue (Forsyth et al., 1999; Logan et al., 2003; Lands et al., 1999, Santaella et al., 2004). The administration of coenzyme Q-10 to heart transplant candidates led to a significant improvement in functional status, clinical symptoms, and quality of life (Berman et al., 2004). Thus, enhancement of mitochondrial functions with coenzyme Q-10 may be an important mechanism by which fatigue can be reduced (Werbach, 2000).

Friedreich's Ataxia

Friedreich's ataxia is caused by a pronounced lack of frataxin, a mitochondrial protein. Several reports suggest that continuous oxidative damage resulting from hampered superoxide dismutase signaling participates in the mitochondrial deficiency and ultimately the neuronal and cardiac cell death. Mitochondrial abnormalities are linked to neurodegenerative diseases through a variety of different pathways, including free-radical generation, impaired calcium buffering
and the mitochondrial permeability transition. This results in apoptotic and necrotic cell death. Current studies have shown increased mitochondrial iron content, which appears to be linked to increased free-radical generation in Friedreich's ataxia (Beal et al., 1999b). Hence, the current therapeutic trials for Friedreich's ataxia rely on antioxidative treatment with coenzyme Q-10 or its short-chain variant idibenone (Beal et al., 1999a; Cooper and Schapira, 2003; Schols et al., 2004; Hart et al., 2005; Seznec et al., 2005; Quinizi et al., 2005; Aure et al., 2004). Lack of frataxin homologs in yeast and mice also leads to increased sensitivity to oxidative stress, depletion of proteins with iron-sulfur clusters such as respiratory chain complexes I-III and aconitase, and to iron accumulation in mitochondria. Alternative strategies aiming at an enhancement of frataxin by stem cell transplantation, gene transfer or frataxin supplementation are also currently under research. Additionally, more efficient biomarkers are needed to monitor treatment effects. Interestingly, idibenone, a coenzyme Q-10 analog profoundly reduced cardiac mass in patients with Friedreich's ataxia (Tarnopolsky and Beal, 2001).

Huntington's Disease

Huntington's disease is a progressive, prototypical, and genetic neurodegenerative disease characterized by selective loss of neurons in the basal ganglia. Bioenergetic defects, oxidative stress and excitotoxicity play an important role in the pathogenesis of Huntington's disease. Huntington's disease patients have a significant reduction in NADH:ubiquinone oxidoreductase (complex I) activity without any changes in the other electron transport chain activities. Huntington's disease may be caused by a mutation in one of the nuclear coded subunits of NADH:ubiquinone oxidoreductase (Parker et al., 1990). Coenzyme Q-10 enhances mitochondrial complex I activity and may therefore provide a therapeutic benefit in Huntington's disease (Parker et al., 1990; Feigin et al., 1996, Huntington Study group, 2001; Beal and Shults, 2003; Andrich et al., 2004, Steele et al., 2004, Walker and Raymond, 2004). The tolerability of coenzyme Q-10 (600 to 1,200 mg per day) suggests it to be a good candidate for evaluation in long-term clinical trials designed to slow down the progression of Huntington's disease. Oral administration of coenzyme Q-10 significantly reduces concentrations of lactate assessed by using magnetic resonance spectroscopy in the occipital cortex, cortex and striatum of Huntington's disease patients, which are typically increased in Huntington's disease patients as compared to non-diseased patients. This may be due to the increased coenzyme Q-10 concentrations in brain mitochondria leading to neuroprotective effects in animal models of Huntington's disease and ALS (Matthews et al., 1998).

Parkinson's Disease

Parkinson's disease is the second most prevalent age-related neurodegenerative disease in the United States today. The recent focus on Parkinson's disease research is the development of neuroprotective therapies to retard the progression of the disease. Parkinson's disease occurs due to the degeneration of dopaminergic neurons in the striatum. Recent studies have shown reduced complex I activity of the electron transport chain in the brain and platelets of patients with Parkinson's disease. The reduced complex I activity may be due to environmental or genetic factors. These factors play a crucial role in the neurodegeneration of Parkinson's disease by generating reactive oxygen species and increasing the risk of neuronal susceptibility to mitochondrial toxins. (Dabbeni-Sala et al., 2001; Ebadi et al., 1996, Swerdlow et al., 2001; Moon et al., 2005). The mitochondrial electron transport enzyme, complex I, is encoded by both mitochondrial DNA and nuclear DNA (Somayajulu et al., 2005). There are substantial evidences to show that mitochondria are a major source of free radicals within the cell. Several agents are available that can modulate cellular energy metabolism and may exert antioxidant effects. These effects appear to be produced both at the iron-sulfur clusters of complex I as well as the ubiquinone site. Therapeutic drugs that have shown to be beneficial in animal models of Parkinson's disease include creatine, coenzyme Q-10, Ginkgo biloba, nicotinamide, and acetyl-L-carnitine. Coenzyme Q-10 is also effective in animal models and has shown promising effects both in clinical trials of patients with Parkinson's disease, as well as in clinical trials in Huntington's disease and Friedreich's ataxia (Beal, 2003a, Sharma et al., 2004). The level of coenzyme Q-10 is found to be significantly lower in mitochondria from parkinsonian patients than in mitochondria from age and sex-matched control subjects (Shults et al., 1997, 1998, 2002). Platelet coenzyme Q-10 was non-significantly decreased by levodopa treatment but selegiline treatment partially restored coenzyme Q-10 redox ratios (Gott et al., 2000, Jimenez-Jimenez et al., 2000). MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine) is a specific dopaminergic toxin that induces neurotoxicity in the nigrostriatal tract of humans and rodents. MPTP causes enhanced hydroperoxides/coenzyme Q-10 molar ratios due to the depletion of coenzyme Q-10 and the concomitant increase in hydroperoxides (Battino et al., 1996). Coenzyme Q-10 has shown to protect against MPTP-induced toxicity in mice (Matthews et al., 1998). Coenzyme Q-10 also protects against striatal lesions produced by both malonate and 3-nitropropionic acid. Coenzyme Q-10 has shown to extend the duration of survival in a transgenic mouse model of amyotrophic lateral sclerosis (Beal, 1999a). Coenzyme Q-10 has shown to possess significant therapeutic effects in the treatment of Parkinson's disease (Strijkstra et al., 1997, Ogawa et al., 2002, Koller and Cersosimo, 2004). In another study, oral administration of coenzyme Q-10 caused a substantial increase in the plasma coenzyme Q-10 level. Coenzyme Q-10 was well tolerated orally and no adverse effect was seen (Ulm, 2004). A trend towards an increase in complex I activity in the subjects treated with coenzyme Q-10 was observed (Shults et al., 1998). This data suggests that coenzyme Q-10 may play a role in cellular dysfunction found in Parkinson's disease and may be a potential protective agent for parkinsonian patients (Shults et al., 1999). There is also evidence for increased numbers of activated microglia in both Parkinson's disease postmortem issues as well as in animal models of Parkinson's disease. Impaired mitochondrial function and activated microglia may both contribute to oxidative damage in Parkinson's disease. A number of therapies targeting inflammation and mitochondrial dysfunction are efficacious in the MPTP model of Parkinson's disease. Of these, coenzyme Q-10 appears to be particularly promising based on the results of a recent phase II clinical trial in
which it significantly slowed the progression of Parkinson's disease (Beal, 2003b). Coenzyme Q-10 provides a significant symptomatic benefit on Parkinson's disease symptoms and a significantly better improvement of PMT (fluorescence-mediated tomographic technique) performance compared with placebo (Muller et al., 2003). Thus, coenzyme Q-10 is a safe and well tolerated drug for the therapeutic treatment of Parkinson's disease and a significant rise in its levels were seen in parkinsonian patients (Sohmiya et al., 2004).

Table 1 summarizes the significant role of enzyme Q-10 in aging and neurodegenerative diseases.

**COENZYME Q-10 AND CARDIOVASCULAR DISEASES**

**Cardiomyopathy**

Cardiomyopathy is a heart muscle disease, which occurs due to the impaired contractility and dilation of the ventricles. Cardiomyopathy includes the contractile cardiomyocytes and the autonomic innervation of the heart. Cardiomyopathy augments the risk for abrupt cardiac mortality. The mitochondrial respiratory chain in cardiomyocytes directly controls the cardiac metabolism. In humans, coenzyme Q-10 is significantly deficient in myocardial tissue (Littarru et al., 1972; Folkers et al., 1982; Nawarskas, 2005). It is well accepted that this disease is caused by a decrease in cellular bioenergetic activity that is secondary to myocarditis and oxidative phosphorylation. A small group of patients has shown familial inheritance of cardiomyopathy resulting in the identification of specific genomic loci and gene defects. However, little evidence is available pointing to a single gene in the initiation and progression of cardiomyopathy. It was demonstrated that environmental factors such as viral or genetic defects can increase the vulnerability of this disease (Poller et al., 2005). Coenzyme Q-10 has shown significant improvement in cardiomyopathy (Langsjoen 1985, 1998, Permanetter et al., 1992, Jones et al., 2004; Conklin, 2005, Lulani et al., 2005, Rosenfeldt et al., 2005).

**Hypertension**

Hypertension is a condition in which the blood pressure is persistently higher than normal. People with hypertension are at risk for heart attack, stroke or kidney failure. Oxidative and nitrosative stress are observed in hypertension (Rosenfeldt et al., 2003). Elevated oxidative and nitrosative stress within the arterial wall leads to augmented blood pressure and vascular dysfunction. The maintenance of increased blood pressure could be chiefly due to contraction of the arterial wall. Contraction or relaxation of the arterial wall is dependent upon bioenergetics, which also supplies the energy for biosynthesis of angiotensin II, renin, aldosterone, and the energy for sodium and potassium transport. It appears that coenzyme Q-10 is decreased during therapy with beta blockers, gemfibrozil, and anidriamycin (Kish et al., 1975). Coenzyme Q-10 deficiency has also been observed in patients with congestive heart failure, angina pectoris, coronary artery disease, cardiomyopathy, hypertension, mitral valve prolapse and following coronary revascularization. The current therapies for hypertension are based on blood pressure reduction associated with the implementation of certain lifestyle modifications. Coenzyme Q-10, fish oil, garlic, vitamin C, and L-arginine are currently being used for the therapeutic treatment of hypertension (Langsjoen et al., 1994; Wilburn et al., 2004). The clinical benefits of coenzyme Q-10 are mainly due to its ability to improve energy production, antioxidant activity, and membrane stabilizing properties. Hypertensive patients treated with coenzyme Q-10 showed significant reductions in systolic and diastolic pressures. However, the treatment did not affect cardiac out-

<table>
<thead>
<tr>
<th></th>
<th>Effects of coenzyme Q-10</th>
<th>Possible cellular mechanisms involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>Increased longevity (Ishii et al., 2004, McDonald et al., 2005)</td>
<td>Enhanced mitochondrial functions (Battino, 2001)</td>
</tr>
<tr>
<td></td>
<td>Delayed aging process (Quiles et al., 2004); (Quiles et al., 2004)</td>
<td>Affect insulin signaling cascade (McCarty, 2000)</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>Increased the mitochondrial substrates and cofactors</td>
<td>Enhancement of ubiquinone oxidoreductase activity</td>
</tr>
<tr>
<td></td>
<td>Enhanced antioxidant defense system</td>
<td>Scavenged reactive oxygen species (Beal, 2004)</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Ameliorated bio-energetic defects</td>
<td>Increased muscle and brain phosphocreatine</td>
</tr>
<tr>
<td></td>
<td>Protected against neuronal degeneration (Tarnopolsky and Beal, 2001)</td>
<td>(Strong and Patte, 2000)</td>
</tr>
<tr>
<td></td>
<td>Extended the duration of survival in animal models (Beal, 1999a)</td>
<td>Inhibited activation of mitochondrial permeability transition</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Enhances mitochondrial functions</td>
<td>Increased mitochondrial complex-I activity</td>
</tr>
<tr>
<td></td>
<td>Improves quality of life (Berman et al., 2004)</td>
<td>Reduced generation of free radicals</td>
</tr>
<tr>
<td>Friedreich's ataxia</td>
<td>Decreased cardiac mass (Tarnopolsky and Beal, 2001)</td>
<td></td>
</tr>
<tr>
<td>Huntington's disease</td>
<td>Provided therapeutic benefit and neuroprotective effects (Matthews et al., 1998)</td>
<td>Enhanced mitochondrial complex-I activity (Parker et al., 1990, Huntington Study group, 2001)</td>
</tr>
<tr>
<td></td>
<td>Reduced lactate in brain</td>
<td>Reduced lactate in brain</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Provided symptomatic and therapeutic benefit (Beal 2003b, Muller et al., 2003, Sohmiya et al., 2004)</td>
<td>Enhanced mitochondrial complex-I activity</td>
</tr>
<tr>
<td></td>
<td>Increase in the plasma coenzyme Q-10 level</td>
<td></td>
</tr>
</tbody>
</table>
puts or stroke volumes (Folkers et al., 1981). A clinical benefit from administration of coenzyme Q-10 to patients with essential hypertension could be based upon correcting a deficiency in bioenergetics, and points to possible combination treatments with a form of coenzyme Q-10 and anti-hypertensive drugs (Yamagami et al., 1975). Its efficacy is associated with a decrease in total peripheral resistance, and appears to reflect a direct impact of coenzyme Q-10 on the vascular wall. A reasonable interpretation of these findings is that coenzyme Q-10 acts as an antagonist of vascular superoxide anion, either by scavenging it or suppressing its synthesis. Moreover, once superoxide is formed, it readily reacts with nitric oxide to produce peroxynitrite, which is toxic to endothelial cells and smooth muscle cells causing vascular dysfunction (Chung et al., 2000, Guzik et al., 2002, Koppenol et al., 1992). Coenzyme Q-10 can quench the toxic properties of peroxynitrite and may inhibit nitrosative damage to proteins and lipids (Schopfer et al., 2000, Hodgson and Watts, 2003). By improving the efficiency of shuttle mechanisms that transfer high-energy electrons from the cytoplasm to the mitochondrial respiratory chain, coenzyme Q-10 may decrease cytoplasmic NADH levels and thereby diminish the reductive power that drives superoxide synthesis in endothelium and vascular smooth muscle (McCarty 1999). Coenzyme Q-10 has been administered to patients having essential hypertension. In these patients, the systemic and diastolic pressures were reduced, the specific activity of coenzyme Q-10 was increased and the deficiency of coenzyme Q-10 activity was negated. These effects of coenzyme Q-10 administration are presumably due to improved bioenergetics through correction of a deficiency of endogenous coenzyme Q-10 (Yamagami et al., 1976, Drzewoski et al., 1981, Sarter, 2002, Li et al., 2005).

Ischemic Damages

Ischemia is a condition in which blood flow (and thus oxygen) is restricted to a part of the body. Coenzyme Q-10 is involved in the synthesis of ATP and, hence, is useful in preventing cellular damage during ischemia-reperfusion injury. Coenzyme Q-10 synthesis is known to decrease during ischemia (Sugawara et al., 1990). NADH: ubiquinone oxidoreductase of heart mitochondria is known to induce superoxide radicals (Vinogradov et al., 2005). Administration of α-tochocopherol and coenzyme Q-10 has shown to increase the survival rate by nearly 50% of the rats subjected to ischemia and coenzyme inhibitors have shown to induce cardiac toxicity (Combs et al., 1976, Nakamura et al., 1982, 1984, Okamoto et al., 1983). These results indicate that α-tocopherol and coenzyme Q-10 have a protective effect on ischemic damage to the rat kidney, demonstrated by an increase in ATP re-synthesis after re-flow following ischemia and by the maintenance of a lower serum creatinine level (Takemaki et al., 1981, Nakamura et al., 1982, Fujikawa et al., 1983). The protective effect of coenzyme Q-10 on the ischemic and reperfused myocardium was also investigated in the isolated rat heart preparation. Rats were treated with coenzyme Q-10 intraperitoneally, and the recovery of cardiac power by coenzyme Q-10 was significantly better than the control. Creatine phosphokinase release during reperfusion was significantly reduced by coenzyme Q-10. Tissue lactate content in ischemia was significantly lower in the coenzyme Q-10 pretreated group. These results suggest that pretreatment with coenzyme Q-10 is effective for reducing ischemic injury caused by acute cross clamping (Tominaga et al., 1983). Coenzyme Q-10 has shown to protect myocardial and arterial smooth muscle cell function via antioxidant mechanisms such as scavenging reactive oxygen species (Whitman et al., 1997). Pretreatment with coenzyme Q-10 results in an improved tolerance to myocardial reperfusion injury due to decreases in the oxidative stress after an ischemic insult, supporting the pivotal role of coenzyme Q-10 in cardiovascular diseases (Table 2).

**COENZYME Q-10 AND CANCER**

Cancer is one of the leading causes of death in the United States, second only to cardiovascular disease. Cancer is diagnosed in over one million people a year. Low blood levels of coenzyme Q-10 have been found in patients with myeloma, and cancers of the breast, lung, prostate, pancreas, colon, kidney, brain and neck (Folkers et al., 1981, 1993). Patients with malignant tumors exhibited characteristic and highly significant changes in the serum patterns of immuno-

<table>
<thead>
<tr>
<th>Effects of Coenzyme Q-10</th>
<th>Possible cellular mechanisms involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>Augmented cellular bioenergetic activity</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Improved energy production Membrane stabilizing properties Quenched toxic properties of peroxynitrite Inhibits nitrosative damage Schopfer et al., 2000, Hodgson and Watts, 2003</td>
</tr>
<tr>
<td>Ischemic damages</td>
<td>Increase in ATP re-synthesis Maintained a lower serum creatinine level Takemaki et al., 1981, Nakamura et al., 1982, Fujikawa et al., 1983 Decreased lactate content</td>
</tr>
</tbody>
</table>
globulin-G subclasses, which consist of decreased immunoglobulin G1 and increased immunoglobulin G2 (Felsner et al., 2000). Interest in coenzyme Q-10 as a potential treatment for cancer began in 1961, when a deficiency was noted in the blood of cancer patients. There is a plethora of anecdotal evidence where claims have been made for the beneficial effects of coenzyme Q-10 in patients with cancer (Shekelle et al., 2003, For激one, 2004, Perumal et al., 2005). Studies have shown that when patients with regressing tumors were treated with coenzyme Q-10, levels of tumor necrosis factors- were reduced to below the detection threshold (Hodges et al., 1999). In addition, levels of immunoglobulin-G significantly increased when patients were administered with coenzyme Q-10. However, further in-depth studies are required to confirm the therapeutic role of coenzyme Q-10 in cancer.

COENZYME Q-10 AND DIABETES MELLITUS

Diabetes is a multifactorial disorder that leads to deleterious effects in many organ systems within the body, potentially as a result of enhanced oxidative stress. Accumulating evidences suggest that oxidative stress plays an important role in the pathogenesis of diabetes mellitus (Baynes, 1999, Thorpe, 1999). Although the mechanism behind the enhanced oxidative stress associated with diabetes is not well understood, impaired balance between pro-oxidants such as free radicals, reactive oxygen species and antioxidants such as superoxide dismutase and catalase is speculated to play a role in the cellular damage in diabetes (Rosen et al., 2001, Schroder et al., 2005). Under normal conditions, mitochondrial respiration generates reactive oxygen species that will be efficiently scavenged by various antioxidant defense mechanisms. However, in diabetes, this scavenging mechanism is believed to be impaired resulting in cellular dysfunction (Chen et al., 2001). A previous study using the streptozotocin-induced rat model of diabetes revealed alteration of coenzyme Q-10 in the liver and kidney (Wold et al., 2003). Insulin-like growth factor 1 (IGF-1) has been considered as an "essential surviving factor" and its level has been shown to be compromised in diabetes. Administration of IGF-1 to the above rat model of diabetes prevented the alteration of coenzyme Q-10. Exogenous coenzyme Q-10 administration has shown to increase myocardial coenzyme Q-10 content and improve myocardial relaxation in streptozotocin-administered diabetic rats (Serizawa et al., 1988). Coenzyme Q-10 administration to diabetic patients was effective in relieving symptoms in the legs, fatigue, and residual urine in the bladder (Suzuki et al., 1995).

One of the key mechanisms coenzyme Q-10 offers to protect against diabetes is through "recoupling" of endothelial NOS. Increased oxidative stress in diabetes may trigger diabetic complications by reducing the bio-availability of nitric oxide (NO). This is believed to be mediated through uncoupling of eNOS due to presence of redox imbalance and oxidation of tetrahydrobiopterin (BH4) – a key cofactor for eNOS (Esberg and Ren, 2003). In mitochondria, increased redox potential uncouples oxidative phosphorylation leading to inhibition of electron transport and increased electron transfer to oxygen to form superoxide anion and ONOO-.

Coenzyme Q10 (CoQ), a potent antioxidant and a critical intermediate of the electron transport chain, may improve mitochondrial and endothelial dysfunction by 'recoupling' eNOS and mitochondrial oxidative phosphorylation (Chew and Watts, 2004, Oda et al., 1985). Coenzyme Q10 acts by blocking the endothelial dysfunction by activating endothelial nitric oxide synthase and mitochondrial oxidative phosphorylation. Coenzyme Q10 may also act synergistically with anti-atherogenic agents. such as fibrates and statins, to improve endotheliopathy in diabetes. Arteriopathy is the main complication of diabetes mellitus (type 2) and this is due to endothelial dysfunction. Fenofibrate and coenzyme Q-10 have shown to enhance endothelial function by regulating dyslipidemia and oxidative stress (Playford et al., 2003). Thus, coenzyme Q10 supplementation has shown to alleviate the symptoms of diabetes mellitus in animals and humans. Coenzyme Q10 treatments in humans are generally consistent in decreasing blood pressure in hypertensive individuals (Hodgson and Watts, 2003). Similarly, in type 2 diabetic patients with endothelial dysfunction, coenzyme Q10 and fenofibrate had a synergistic action.

COENZYME Q-10 DEFICIENCY AND THERAPY IN OTHER DISEASES:

There are several other diseases like anemia (Niklowitz et al., 2004, Ohnishi et al., 2004), arteriosclerosis (Chapizde

---

**Table 3. Effects of Coenzyme Q-10 in Cancer, Diabetes and Other Disease and the Possible Cellular Mechanisms Involved in its Protective Effect**

<table>
<thead>
<tr>
<th></th>
<th>Effects of coenzyme Q-10</th>
<th>Possible cellular mechanisms involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Inhibited dense cell formation (Ohnishi, et al., 2000)</td>
<td>Protected the cell membrane against reactive oxygen species damage</td>
</tr>
<tr>
<td>Artherosclerosis</td>
<td>Prevented further development of atherosclerosis in native coronary arteries (Chapizde et al., 2005)</td>
<td>Decreased oxidative stress and reduces platelet aggregation</td>
</tr>
<tr>
<td>Cancer</td>
<td>Decreased tumor necrosis factors-α (Hodges et al., 1999)</td>
<td>Decreased tumor necrosis factors-α (Hodges et al., 1999)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Relieved symptoms in the legs, fatigue, and residual urine in the bladder (Suzuki et al., 1995)</td>
<td>Improved myocardial relaxation (Serizawa et al., 1988)</td>
</tr>
<tr>
<td>Stroke</td>
<td>Improved lactic acidosis (Berbel-Garcia et al., 2004)</td>
<td>Enhanced mitochondrial function</td>
</tr>
</tbody>
</table>
et al., 2005, Kuettner et al., 2005, Wang et al., 2004, Yalcin et al., 2004, Singh et al., 2003), asthma (Konno and Yamaguchi et al., 1990, Gazdik et al., 2002a, Gazdik et al., 2002b), visual dysfunctions (Chario et al., 1999, Huang et al., 2002, Feher et al., 2003, Feher et al., 2005), and stroke (Shinkai et al., 2000. Berbel-Garcia et al., 2004), which are related to coenzyme Q-10 deficiency and hence, currently, coenzyme Q-10 is being used as an alternative therapy or adjuvant for the treatment of these disorders (Table 3).

CONCLUSION

Coenzyme Q-10 is intrinsic to human tissues and is considered as a vitamin, according to the basic science of nutrition. Coenzyme Q-10 plays a significant role in the respiratory process, involved in the mechanism of blood coagulation and controls the membrane fluidity and oxidative stress (Fig 1). Hence deficiency of coenzyme Q-10 may be related to various cardiovascular and neurological diseases. Thus, these deficits are currently overcome by therapeutically treating with coenzyme Q-10 (Fig. 2).

Fig. (1). Various cellular functions of coenzyme Q-10.
1. Coenzyme enhances the mitochondrial functions and increases ATP production;
2. Scavenges reactive oxygen species and renders protection to the cells;
3. Protects against DNA damage and has anti-apoptotic effects;
4. Enhances the antioxidant enzyme activities and modulates the activities of growth factors;
5. Inhibits the peroxidation of lipids and protects the cell membrane.
Fig. (2). Effect of coenzyme Q-10 in the various organs.

REFERENCES


