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## Therapeutic role of coenzyme Q<sub>10</sub> in Parkinson's disease

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### Abstract

Mitochondrial dysfunction has been well established to occur in Parkinson's disease (PD) and appears to play a role in the pathogenesis of the disorder. A key component of the mitochondrial electron transport chain (ETC) is coenzyme Q<sub>10</sub>, which not only serves as the electron acceptor for complexes I and II of the ETC but is also an antioxidant. In addition to being crucial to the bioenergetics of the cell, mitochondria play a central role in apoptotic cell death through a number of mechanisms, and coenzyme Q<sub>10</sub> can affect certain of these processes. Levels of coenzyme Q<sub>10</sub> have been reported to be decreased in blood and platelet mitochondria from PD patients. A number of preclinical studies in vitro and in vivo models of PD have demonstrated that coenzyme Q<sub>10</sub> can protect the nigrostriatal dopaminergic system. A phase II trial of coenzyme Q<sub>10</sub> in patients with early, untreated PD demonstrated a positive trend for coenzyme Q<sub>10</sub> to slow progressive disability that occurs in PD.

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**Keywords:** Coenzyme Q<sub>10</sub>; Parkinson's disease; Mitochondria; Neuroprotection; Apoptosis

**Abbreviations:** AIF, apoptosis-inducing factor; ATP, adenosine 5' triphosphate; *C. elegans*, *Caenorhabditis elegans*; CoA, coenzyme A; ETC, electron transport chain; FADH<sub>2</sub>, flavin adenine dinucleotide; IAP, inhibitors of apoptosis proteins; MOMP, mitochondrial outer membrane permeabilization; MPP<sup>+</sup>, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; NADH, nicotinamide adenine dinucleotide; PD, Parkinson's disease; PTP, permeability transition pore; ROS, reactive oxygen species; SOD2, superoxide dismutase 2 or manganese superoxide dismutase;  $\Delta\Psi_m$ , transmembrane potential; TH-IR, tyrosine hydroxylase immunoreactive; UCP, uncoupling proteins; UPDRS, Unified Parkinson Disease Rating Scale

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## 1. Introduction

The study of the role of coenzyme Q<sub>10</sub> in Parkinson's disease (PD) began with the discovery that 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), which can cause Parkinsonism in humans (Langston et al., 1983), nonhuman primates (Langston et al., 1984), and mice (Heikkila et al., 1984), acts through the inhibition of complex I of the mitochondrial electron transport chain (ETC; Singer et al., 1987; Przedborski et al., 2000; Greenamyre et al., 2001). These discoveries stimulated the evaluation of mitochondrial function in tissue from PD patients. At approximately the same time, Schapira et al. (1989, 1990) and Parker et al. (1989) studied mitochondrial function in the brain and platelets of parkinsonian patients, respectively. Schapira et al. (1990) reported a significant decrease in complex I activity in the substantia nigra of Parkinsonian patients compared with age-matched control subjects and individuals who had multiple system atrophy. This finding has been replicated by Janetzky et al. (1994). Parker et al. (1989) reported a significant decrease in complex I activity in platelets from PD patients. Other groups have also reported a reduction of complex I activity in platelets, muscle, and lymphocytes (Bindoff et al., 1991; Shoffner et al., 1991; Krige et al., 1992; Nakagawa-Hattori et al., 1992; Yoshino et al., 1992; Barroso et al., 1993; Benecke et al., 1993; Cardellach et al., 1993; Blin et al., 1994). Not all groups have found the reduction in mitochondrial activity (Anderson et al., 1993; DiDonato et al., 1993; Martin et al., 1996), perhaps because of differences in the techniques used. Following the initial reports of Schapira et al. (1989, 1990) and Parker et al. (1981) the question remained whether the reduction in complex I activity was part of the pathogenic process underlying PD or was due to the drugs used to treat PD or the debilitation accompanying a chronic disease, such as PD.

If impaired complex I function plays a role in the pathogenesis of PD, then reduced complex I activity should be present early in the course of the illness, before patients are significantly disabled by PD and require medication. We conducted a study of PD subjects with early untreated disease and 2 control groups: age/gender-matched, healthy control subjects and healthy spouses, who served as controls for the home environment (Haas et al., 1995). Mitochondrial function was assayed in mitochondria isolated from platelets. We found significantly reduced complex I activity in the parkinsonian subjects compared with both control groups and significantly reduced the activity of complex II/III in the parkinsonian subjects compared with the age/

gender-matched control subjects. No significant difference was found among the 3 groups in the activities of complex IV and citrate synthase. In a second part of the study, the PD patients were treated with carbidopa/levodopa (25/100 mg, 3 times/day) for 1 month and had a second assay of platelet mitochondrial function; they were then treated with carbidopa/levodopa and selegiline (5 mg, twice/day) for a second month, and had a third assay of platelet mitochondrial function (Shults et al., 1995). No significant differences were noted across the 3 assays in complexes I, II/III and IV, and citrate synthase. These studies provided strong evidence that mitochondrial dysfunction occurs early in the course of PD and plays a pathogenetic role in at least some cases of the disease.

The etiology of the mitochondrial dysfunction is uncertain. Exogenous toxins, such as MPTP, or endogenous toxins, such as reactive oxygen species (ROS), could contribute to the impaired function. Genetic abnormalities, both nuclear and mitochondrial, could be involved. Valente et al. (2004) recently reported that a rare, familial form of PD is associated with mutations in the gene for PINK1, which is a protein located in the mitochondrion. Two groups utilized cybrid cells in which the native mitochondrial DNA was replaced with mitochondria from PD patients and reported that the cybrids had defects in complex I activity (Swerdlow et al., 1996; Gu et al., 1998). However, mitochondrial disorders typically have a maternal pattern of inheritance because mitochondria and mitochondrial DNA are inherited from the mother, and PD does not usually have a pattern of maternal transmission. Parker and his colleagues have recently reported that PD patients have low frequency, amino acid changing, heteroplasmic mutations in a narrow region of ND5, a mitochondrial gene encoding a complex I subunit, in brain tissue (Smigrodzki et al., 2004; Parker & Parks, 2005). The etiology of mutations in mitochondrial genes in PD and their possible contribution to the development of the disorder will require further study.

## 2. Mitochondria and bioenergetics and oxidative stress

Mitochondria are composed of an outer membrane, an intermembrane space, an inner membrane, and a matrix (Fig. 1). Pyruvate, which is generated largely by glycolysis in the cytosol, is metabolized to acetyl coenzyme A (CoA) on the inner membrane. Acetyl CoA, which is also a product of fatty acid oxidation, is in turn metabolized via the citric acid cycle to CO<sub>2</sub> and high-energy electrons, which are

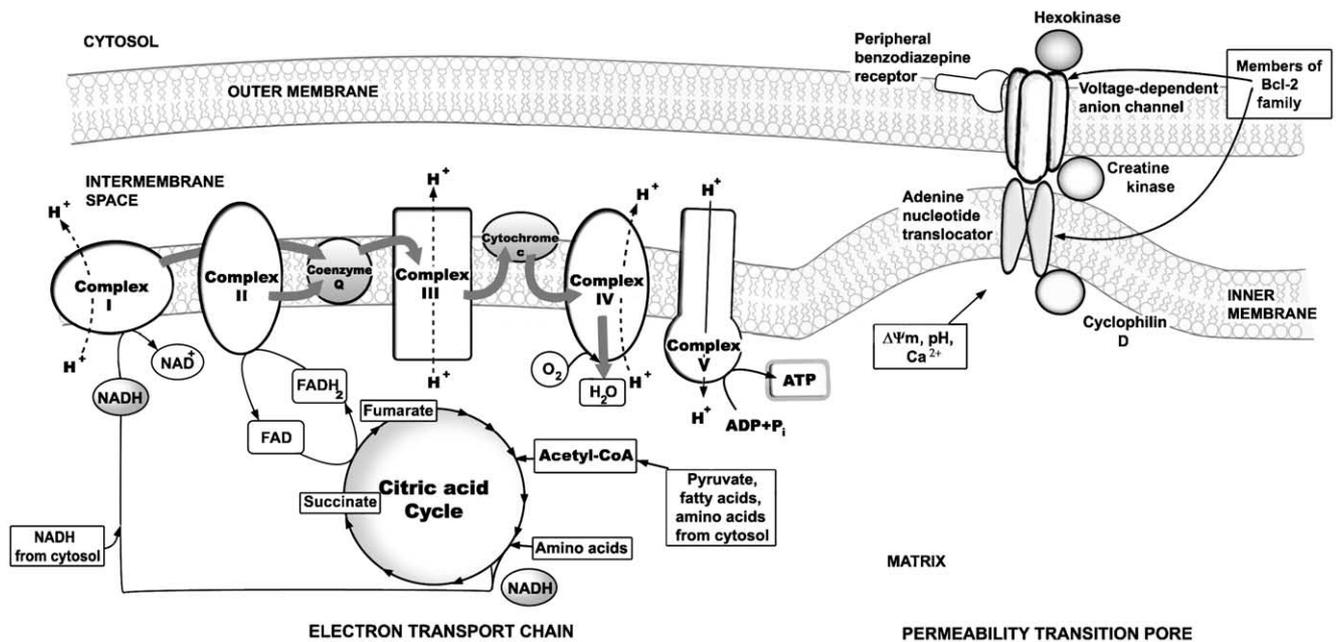


Fig. 1. Diagram of the electron transport chain (ETC) and the permeability transition pore (PTP). Coenzyme Q<sub>10</sub>, which is the electron acceptor for complexes I and II, plays a central role in the ETC. Its presence in the mitochondria inner membrane also positions it to affect the PTP.

carried by the activated carrier molecules nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH<sub>2</sub>). The high-energy electrons are transferred into the ETC, which is located in the inner membrane, by NADH to complex I (NADH:ubiquinone oxidoreductase) and succinate via FADH<sub>2</sub> to complex II (succinate:ubiquinone oxidoreductase). The ETC is composed of 5 complexes: complex I, complex II, complex III (ubiquinol:cytochrome *c* oxidoreductase), complex IV (cytochrome *c* oxidase), and complex V (H<sup>+</sup>-translocating adenosine 5' triphosphate (ATP) synthase). The transport of electrons down the ETC is energetically favorable, and the energy released is used by complexes I, III, and IV to transport protons from the matrix to the intermembrane space. The transport of protons creates a proton and electrochemical gradient across the inner membrane. The energy stored in the electrochemical proton gradient is used to drive complex V to form ATP.

The transport of high-energy electrons through the ETC can also be a source not only of ATP but also of ROS, as the high-energy electrons can react with O<sub>2</sub> to form superoxide (Halliwell, 2001). It has been estimated that up to 2% of the O<sub>2</sub> consumed by healthy mitochondria is converted to superoxide, and this amount is higher in damaged and aged mitochondria. Manganese superoxide dismutase (SOD2) in the matrix converts the superoxide to hydrogen peroxide, and hydrogen peroxide is typically detoxified by glutathione peroxidase, thioredoxin, and catalase. However, in the presence of transition metals, hydrogen peroxide can be converted by the Fenton reaction to the highly reactive hydroxyl radical. The production of ROS can damage components of the mitochondria, including the mitochondrial DNA, lipids, and protein.

ROS can damage proteins, lipids, and nucleic acids, and methods have been developed to measure the amount of oxidative damage to each of these cellular components. Protein carbonyls reflect oxidative damage (Dalle-Donne et al., 2003), and widespread increases in protein carbonyls in postmortem PD brains have been reported (Alam et al., 1997a). Lipid oxidation is reflected by increased levels of malondialdehyde and cholesterol lipid hydroperoxides (Jenner, 2003), and both malondialdehyde (Dexter et al., 1989) and cholesterol lipid hydroperoxides (Dexter et al., 1994) have been found to be increased in parkinsonian brains. Oxidative damage to DNA is reflected in the amount of 8-hydroxy-2-deoxy-guanosine and 8-hydroxy-guanine, and increased levels have been reported in the brains (Sanchez-Ramos et al., 1994; Alam et al., 1997b) and cerebrospinal fluid and serum (Kikuchi et al., 2002).

In addition to the direct action of oxygen-free radicals on proteins, superoxide can react with nitric oxide to form peroxynitrite, which can result in the nitration of proteins (Ischiropoulos & Beckman, 2003), and nitration of Lewy bodies has been reported in parkinsonian brains (Giasson et al., 2000).

### 3. Mitochondria and apoptosis

In addition to its role in the bioenergetics of the cell or perhaps because of its central position in the energetics of the cell, the mitochondrion has evolved to play a central role in apoptosis or programmed cell death. The mitochondrion has been described as a receiver/integrator

organelle (Goldenthal & Marín-García, 2004). Surprisingly, a role for mitochondria in cell death was not recognized until ~10 years ago (Jacobson et al., 1993; Zamzami et al., 1995a).

The processes leading to death of the nigral dopaminergic neurons in PD are not fully understood. Evidence has accumulated to suggest that apoptosis is involved in this process, but this remains somewhat controversial (Kingsbury et al., 1998; Andersen, 2001). Apoptosis is defined on morphological grounds, and the characteristics of apoptosis include chromatin condensation, nuclear fragmentation, condensation of cell contents with formation of small membrane-bound vesicles, which are phagocytosed by nearby cells without accompanying inflammation (Nijhawan et al., 2000; Zimmermann et al., 2001). Mitochondria influence apoptosis at a number of levels: (1) maintenance of ATP levels, (2) maintenance of the mitochondrial membrane potential, and (3) release of proapoptotic factors.

Apoptosis can be triggered through both external and internal pathways (Reed, 2002; Mattson & Kroemer, 2003; Green & Kroemer, 2004). The external pathways are activated through the ligation of death receptors, such as tumor necrosis factor receptor-1, and act through the activation of cysteine aspartyl-specific proteases (caspases). The internal pathway, which appears to be the major pathway for apoptosis in vertebrate cells, works through the mitochondria and the pivotal event in the process is the mitochondrial outer membrane permeabilization (MOMP) and release of proapoptotic factors. The proapoptotic factors released can either be caspase dependent, such as cytochrome *c*, or caspase independent, such as nucleases (e.g., endonuclease G), nuclease activators [e.g., apoptosis-inducing factor (AIF)], sequesterers of inhibitors of apoptosis proteins (IAPs; Smac/DIABLO) or serine proteases (e.g., Omi/HtrA2, which also interact with IAPs; van Gurp et al., 2003).

MOMP can occur by mechanisms that involve either the outer membrane only or involve the inner membrane also (Green & Kroemer, 2004). Mechanisms that act through the outer membrane only involve members of the Bcl-2 family of apoptosis regulating proteins acting directly on the outer membrane. Members of the Bcl-2 family serve as proapoptotic or antiapoptotic factors (Tsujimoto, 2003; van Gurp et al., 2003; Green & Kroemer, 2004) and typically act through the mitochondria. The proapoptotic members of the Bcl-2 family are classified into 2 groups: multidomain members, for example, Bax and Bak, and BH3-only members, for example, Bad, Bid, and Bim (Tsujimoto, 2003). Apoptotic signals can cause Bax and Bak to form complexes in the mitochondrial outer membrane and release of cytochrome *c* and other proapoptotic molecules. The BH3-only members of the Bcl-2 family serve as monitors of cellular integrity — Bad for growth factor withdrawal, Bid for external pathway signals and Bim for cytoskeletal integrity. The BH3-only proteins can stimulate Bax and Bak to form multimer complexes in the mitochondrial

membrane or can interfere with antiapoptotic members of the Bcl-2 family.

Proapoptotic factors can also be released by mechanisms that involve both the outer and inner membranes through the formation of the mitochondrial permeability transition pore (PTP). The molecules comprising the PTP are not fully defined, but it is thought to be composed of the outer membrane voltage-dependent anion channel, the inner membrane adenine nucleotide translocase, the mitochondrial (peripheral) benzodiazepine receptor, and cyclophilin D (Ly et al., 2003; Fig. 1). There is some evidence that hexokinase, creatine kinase, and members of the Bcl-2 family, both proapoptotic and antiapoptotic members, can interact with the PTP (Le Bras et al., 2005). The permeability transition is a sudden increase in the permeability of the mitochondrial membrane to solutes with a mass of less than 1.5 kD. The opening of the PTP leads to entry of  $K^+$ ,  $Mg^{+2}$ , and  $Ca^{+2}$  and water, which results in the swelling of the matrix, rupture of the outer membrane, and leakage of the proteins, including the proapoptotic proteins. Inhibitors of the PTP, such as the cyclophilin D inhibitor cyclosporin A, and the adenine nucleotide translocase inhibitor bongkrekic acid, block apoptosis in certain models of apoptosis, thus supporting the involvement of the PTP in apoptosis in some systems. PTP pore opening is controlled by the transmembrane potential ( $\Delta\Psi_m$ ; the probability of opening increasing with decreasing  $\Delta\Psi_m$ ) and the pH of the matrix (the probability of opening decreasing with acidification of the matrix if the pH drops below 7.0). Elevated cytosolic  $Ca^{2+}$  also favors PTP opening. A number of models of PTP opening have been proposed. In the PTP-induced mitochondrial swelling model, there is rapid depolarization of the mitochondria, swelling, and rupture of the outer membrane with the release of proapoptotic molecules. However, the PTP opening can be transient or “flickering of the pore” (Green & Kroemer, 2004).

The role of reduction in  $\Delta\Psi_m$  in release of cytochrome *c* and other proapoptotic molecules from the mitochondria is not fully defined. In certain models of apoptosis, cells with lowered  $\Delta\Psi_m$  appear destined for apoptosis (Zamzami et al., 1995b; Kroemer, 2003). Although cells with disrupted  $\Delta\Psi_m$  appear to be doomed to cell death, in certain models of apoptosis, the reduction in  $\Delta\Psi_m$  occurs late and may be a subsequent event (Ly et al., 2003). Thus, the dissipation of  $\Delta\Psi_m$  cannot be considered as a prerequisite for apoptosis, and in some instances, dissipation of  $\Delta\Psi_m$  may serve to amplify the apoptotic signaling.

The evidence reviewed above indicates that the central role of mitochondria in cellular bioenergetics positions them as monitors of the cell viability, and mitochondria can initiate or amplify proapoptotic signals in the cell. Coenzyme  $Q_{10}$  could affect the apoptotic process through a number of mechanisms, such as interference with mitochondrial depolarization (Walter et al., 2000; Papucci et al., 2003), production of and protection against ROS (Sandhu et

al., 2003; Ishii et al., 2004), which can trigger release of proapoptotic molecules (Madesh & Hajnoczky, 2001), interference with production of ceramide (Navas et al., 2002), and mitochondrial uncoupling proteins (UCP).

Papucci et al. (2003) studied the effects of coenzyme Q<sub>10</sub> in models of apoptosis that are independent of ROS - treatment of keratocytes with antimycin A, C<sub>2</sub> ceramide, and serum starvation. They showed that coenzyme Q<sub>10</sub>, but not alpha-tocopherol, reduced apoptotic cell death in these models. The mechanism of action of coenzyme Q<sub>10</sub> appeared to be through the inhibition of mitochondrial depolarization and the reduction of the subsequent release of cytochrome *c* and activation of caspase 9.

Coenzyme Q<sub>10</sub> has been shown to reduce the production of ROS in *Caenorhabditis elegans*. Ishii et al. (2004) reported that coenzyme Q<sub>10</sub> extended the life span of wild-type *C. elegans* and recovered the life-shortening effects and supernumerary apoptosis in the *mev-1* mutant, which encodes for cytochrome *b* — a large subunit of complex II. Ishii et al. found that coenzyme Q<sub>10</sub> (but not alpha-tocopherol) reduced the generation of superoxide, strikingly in the *mev-1* mutants, when the *C. elegans* were exposed to the complex II stimulant succinate.

Navas et al. (2002) studied the effects of coenzyme Q<sub>10</sub> leukemic cells deprived of serum, which causes a mild oxidative stress and production of ceramide. Ceramide is a mediator of cellular stress responses and can activate caspases. Navas et al. reported that treatment of the serum deprived cells with coenzyme Q<sub>10</sub> resulted in reduced apoptotic cell death and reduced activation of caspase 3. The mechanism appeared to be through the inhibition of neutral sphingomyelinase, which has been related to the release of ceramide in apoptosis.

Coenzyme Q has been shown to be an obligatory cofactor for UCP1, 2, and 3 (Echtay et al., 2000, 2001), reportedly through a contribution to the formation of superoxide (Echtay et al., 2002). UCP2 has been shown to protect cells through a number of mechanisms (Horvath et al., 2003; Mattiasson et al., 2003; Paradis et al., 2003) — partial reduction in the  $\Delta\Psi_m$  (although not to the levels associated with classic PTP) with a resultant reduction of the influx of calcium that occurs often in cell injury (Teshima et al., 2003), reduction in ROS production (Nègre-Salvayre et al., 1997; Arsenijevic et al., 2000; Teshima et al., 2003), and increase in transport of ROS to the cytosol (Mattiasson et al., 2003), where they could stimulate the production of antiapoptotic molecules, such as SOD2 and Bcl2.

#### 4. Coenzyme Q<sub>10</sub> and Parkinson's disease

Coenzyme Q<sub>10</sub> (ubiquinone) is composed of a quinone ring and a 10 isoprene unit tail, and it is distributed in all membranes throughout the cell (Crane, 2001). It acts as the electron acceptor for complexes I and II of the mitochondrial electron transport chain and is also an antioxidant. In

the mitochondria, NADH and succinate dehydrogenase keep coenzyme Q<sub>10</sub> partly reduced, while in the plasma and endomembranes, a number of enzyme systems can reduce it to the quinol form. Its presence in the cell membranes positions it well to serve as an antioxidant. The antioxidant effect of coenzyme Q<sub>10</sub> may be due to its ability to work in concert with alpha-tocopherol and reduce oxidized tocopherol and regenerate the reduced, antioxidant form (Noack et al., 1994; Lass & Sohal, 1998). In addition to its roles in mitochondrial function and as an antioxidant, recent studies have indicated that coenzyme Q<sub>10</sub> functions in aspects of the oxidation/reduction control of signal transmission in cells.

The role of coenzyme Q<sub>10</sub> as the electron acceptor for both complexes I and II prompted us to measure its levels in the mitochondria isolated in the study of described above (Haas et al., 1995), in which mitochondrial function was evaluated in PD patients with early untreated disease. We found a significantly reduced level of coenzyme Q<sub>10</sub> in the mitochondria from PD subjects compared with age/gender-matched control subjects (Shults et al., 1997).

Reduced levels of coenzyme Q<sub>10</sub> in blood had been reported in PD by a number of investigators. Matsubara et al. (1991) reported that the serum level of coenzyme Q<sub>10</sub> in parkinsonian patients was significantly lower than that in patients with stroke, who were of similar age. This group had previously found in patients without neurological disease a higher level of coenzyme Q<sub>10</sub> (Yamagami et al., 1981) than that found in the PD patients (Matsubara et al., 1991). Similarly, Molina et al. (2002) reported that the serum level of coenzyme Q<sub>10</sub>, but not the coenzyme Q<sub>10</sub>/cholesterol ratio, was reduced in patients with Lewy body disease. However, Jiménez-Jiménez et al. (2000) did not find a reduction in the serum level in PD. Recently, Sohmiya et al. (2004) reported not only a significant reduction in plasma coenzyme Q<sub>10</sub> in PD patients, but also a significant increase in the percentage that oxidized coenzyme Q<sub>10</sub> comprised of total coenzyme Q<sub>10</sub>, which was interpreted as evidence of oxidative stress.

Levels of coenzyme Q<sub>10</sub> from various tissues, including the brain, decline in humans with aging (Edlund et al., 1992). The reasons for this decline and the contribution that the decline may have to diseases that occur more commonly in the elderly remain uncertain. Battino et al. (1995) reported that in rats the levels of coenzyme Q<sub>9</sub> and coenzyme Q<sub>10</sub> tend to be higher in 2- and 6-month-old animals than in 12- and 18-month-old animals. In a more recent study in mice, Lass et al. (1999) reported that levels of coenzyme Q did not decline from ages 6 months to 12 months.

#### 5. Preclinical studies of coenzyme Q<sub>10</sub> in models of Parkinson's disease

A number of studies have been carried out in in vitro models of PD. A number of groups have demonstrated in in

vitro models of PD that coenzyme Q<sub>10</sub> can protect against 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>), which is the active metabolite of MPTP (Akaneya et al., 1995; Gille et al., 2004), rotenone (Menke et al., 2003; Sherer et al., 2003), and 1-Benzyl-1,2,3,4-tetrahydroisoquinol (Shavali et al., 2004).

The reduced levels of coenzyme Q<sub>10</sub> in blood and platelet mitochondria suggested that, perhaps, supplemental coenzyme Q<sub>10</sub> might be useful in the treatment of PD, as the discovery of the dopamine deficit led to the development of levodopa as a treatment for PD. Beal and members of his laboratory had earlier pioneered the study of coenzyme Q<sub>10</sub> in animal models of PD and other neurological disorders, including Huntington's disease (Beal, 1994) and amyotrophic lateral sclerosis (Matthews et al., 1998). Schulz et al. (1995) observed that treatment of mice with coenzyme Q<sub>10</sub> and nicotinamide attenuated the effects of low doses of MPTP in young mice. Coenzyme Q<sub>10</sub> alone reduced the loss of striatal dopamine in the young, MPTP-treated mice, but the effect was not statistically significant. We hypothesized that young mice might not be the most appropriate animals to study the effects of coenzyme Q<sub>10</sub> in a model of PD for 2 reasons. First, as mentioned above, levels of coenzyme Q<sub>10</sub> in the brain decline after middle age in humans. Second, the greatest risk factor for PD is age. We speculated that a more appropriate model would be MPTP-treated, aged mice, and carried out a study of the effects of coenzyme Q<sub>10</sub> in MPTP-treated, 1-year-old mice (Beal et al., 1998). Four groups of 1-year-old, male C57BL/6 mice received either a standard diet or a diet supplemented with coenzyme Q<sub>10</sub> (200 mg/kg/day) for 5 weeks. After 4 weeks, 1 group that had received the standard diet and 1 group that had received the coenzyme Q<sub>10</sub> supplemented diet were treated with MPTP. The 4 groups continued on their assigned diets for an additional week prior to sacrifice. Striatal dopamine concentrations were reduced in both groups treated with MPTP, but they were significantly higher (37%) in the group treated with coenzyme Q<sub>10</sub> and MPTP than in the group treated with a standard diet and MPTP. The density of tyrosine hydroxylase immunoreactive (TH-IR) fibers in the caudal striatum was reduced in both MPTP-treated groups, but the density of TH-IR fibers was significantly (62%) greater in the group treated with coenzyme Q<sub>10</sub> and MPTP than in the group treated with standard diet and MPTP. The striatal level of dopamine and density of TH-IR fibers were not significantly different in animals receiving coenzyme Q<sub>10</sub>-supplemented diet from those in the group treated with standard diet alone. Beal's group subsequently showed that oral coenzyme Q<sub>10</sub> increased the mitochondrial content of coenzyme Q<sub>10</sub> in the cortex in 12-month-old rats (Matthews et al., 1998).

Horvath et al. (2003) reported that in monkeys, 10 days of oral supplementation with coenzyme Q<sub>10</sub> (15–22 mg/kg, a dosage range similar to that used in the phase II trial in

patients with PD, see Section 7.2) prior to treatment with MPTP significantly attenuated the loss of nigral dopaminergic neurons. Horvath et al. presented data to support the premise that the mechanism of action of coenzyme Q<sub>10</sub> was through the activation of UCP2. Another plausible mechanism is through the inhibition of the mitochondrial PTP, as Walter et al. (2000) have shown coenzyme Q<sub>10</sub> to do.

Finally, coenzyme Q<sub>10</sub> could interfere with the actions of endogenous or exogenous complex I inhibitors. Degali Esposti (1998) has classified complex I inhibitors into 3 types, which all interfere with the cycling of coenzyme Q<sub>10</sub> in complex I. It is conceivable that supplemental coenzyme Q<sub>10</sub> could overcome the effects of complex I inhibitors, such as rotenone.

## 6. Effects of coenzyme Q<sub>10</sub> on life span

Because of the chronic nature of PD and the anticipation that patients might take coenzyme Q<sub>10</sub> for extended periods, the limited information on the effects of coenzyme Q<sub>10</sub> on life span should be discussed. Manipulations of amounts of coenzyme Q<sub>9</sub> and coenzyme Q<sub>10</sub> in the diets of the nematode *C. elegans* (the predominate form of coenzyme Q in *C. elegans* is coenzyme Q<sub>9</sub>) have given different results. Larsen and Clarke (2002) reported that growing wild-type as well as *clk-1*, *daf-2*, and *daf-12* mutants on bacterial strains lacking coenzyme Q extended the life spans of the nematodes. However, Ishii et al. (2004) reported that coenzyme Q<sub>10</sub> extended the life span of wild-type *C. elegans* and recovered the life shortening effects and supernumerary apoptosis in the *mev-1* mutant. One obvious difference between the 2 studies is that Larsen and Clarke (2002) depleted the diet of coenzyme Q<sub>8</sub>, which can be metabolized to coenzyme Q<sub>9</sub>, while Ishii et al. increased the amount of coenzyme Q<sub>10</sub>. Ishii et al. hypothesized that ROS production may decrease as the rate of respiration is limited by the availability of coenzyme Q, but the ability to scavenge ROS may increase proportionately with increasing levels of coenzyme Q. Reassuring is the report of Lönnrot et al. (1998) that supplementation of the diets of C57/B17 mice and Sprague–Dawley rats with coenzyme Q<sub>10</sub> (10 mg/kg/day) did not significantly affect the life span.

Kieburtz and colleagues in The Huntington Study Group (2001) carried out a trial in which 347 patients with early Huntington's disease were randomized to receive either coenzyme Q<sub>10</sub> (600 mg/day), remacemide (600 mg/day), coenzyme Q<sub>10</sub>, and remacemide, or placebo, and were followed every 4 to 5 months for a total of 30 months; 174 patients received coenzyme Q<sub>10</sub>. Coenzyme Q<sub>10</sub> was well tolerated; only stomach "upset" was reported more commonly in the coenzyme Q<sub>10</sub>-treated group. In a phase II study of high dosages of coenzyme Q<sub>10</sub> in patients with PD (Shults et al., 2002; see Section 7.2), it was well tolerated, with no deaths in the study.

## 7. Trials of coenzyme Q<sub>10</sub> in Parkinson's disease patients

### 7.1. Trials in Parkinson's disease patients on medication for Parkinson's disease

In anticipation for a phase II trial (see below), an open-label trial was conducted of what was then considered high dosages of coenzyme Q<sub>10</sub> (400, 600, and 800 mg/day) for 1 month in PD patients, who were on symptomatic drugs for PD, for example, levodopa, dopaminergic agonists, to ascertain the safety, tolerability, and plasma levels of coenzyme Q<sub>10</sub> achieved with these dosages (Shults et al., 1998). Coenzyme Q<sub>10</sub> was well tolerated; minor, impersistent changes in the urinalysis were noted in 2 subjects at the dosage of 800 mg/day, but these changes were not found in the subsequent larger study. Review of videotapes of the motor portion of the Unified Parkinson Disease Rating Scale (UPDRS) at the baseline and last visit by an assessor unaware of the timing of the examination showed no significant effect of treatment with coenzyme Q<sub>10</sub>. A similar lack of effect on UPDRS score was found in a later study of higher dosages of coenzyme Q<sub>10</sub> in PD patients on symptomatic medications (see Section 7.2).

There was a stepwise increase in plasma level with increasing dosage of coenzyme Q<sub>10</sub>. Timing of blood sampling in relation to the last dose of coenzyme Q<sub>10</sub> is important in determining the steady state level of coenzyme Q<sub>10</sub>. A number of studies have evaluated the pharmacokinetics of coenzyme Q<sub>10</sub> in humans (Lucker et al., 1984; Tomono et al., 1986; Okamoto et al., 1989; Bogentoft et al., 1991; Mohr et al., 1992). A single oral dose of coenzyme Q<sub>10</sub> is followed by 2 peaks in the serum level. The first peak occurs ~5 to 6 hr after the oral dose, and the second, much smaller peak occurs ~24 hr after the oral dose. The explanation for the second peak remains somewhat controversial, but uptake by the liver and subsequent resecretion has been proposed. The absorption of coenzyme Q<sub>10</sub>, which is extremely lipophilic, is improved by the inclusion of lipid in the formulation and by taking it with food. The elimination half-life has been estimated to be between 33 and 50 hr. In this study and the subsequent studies (Shults et al., 2002, 2004), each subject's last dose of coenzyme Q<sub>10</sub> was at bedtime the night before their clinic visit the following day.

Müller et al. (2003) conducted a placebo controlled, double-blinded trial of coenzyme Q<sub>10</sub> (180 mg, 2 times/day) versus placebo in 28 subjects (14 in each treatment arm). The subjects were all on symptomatic treatment for PD (levodopa, dopaminergic agonist, and selegiline), and the dosages of these medications were not changed during the course of the 4-week study. The groups were matched for age and gender, but not for the severity of PD, as measured by the UPDRS. The subjects were assessed with the UPDRS and the Farnsworth-Munsell 100 Hue test, which is an assessment of color discrimination, at the initial and final visits. Müller et al. found that comparison of the UPDRS

score at the final visit to that at the initial visit was significantly different in the coenzyme Q<sub>10</sub>-treated group but in not the placebo-treated group. However, neither the comparison of the UPDRS scores at the final visit between the 2 groups nor the comparison of the change in the UPDRS scores from the initial to final visits between the 2 groups was reported. The score on the Farnsworth-Munsell 100 Hue test improved significantly in both treatment groups, but more so in the group treated with coenzyme Q<sub>10</sub>.

In a Letter-to-the-Editor, Drs. Horstink and van Engelen (2003) reported their study of 12 PD patients who received coenzyme Q<sub>10</sub> 1000 mg/day for 3 months and then 1500 mg/day for an additional 3 months, in which they reported a "quite minor" clinical improvement. It is unclear that their data demonstrate a symptomatic effect of coenzyme Q<sub>10</sub> for a number of reasons. First, the study was open label. Second, the study lacked a placebo control group; a placebo effect in studies in PD is well recognized (Goetz et al., 2002). Third, their analysis of the variables revealed that "none improved when analyzed using multicomparisons techniques".

The studies to date have not convincingly shown a significant improvement with coenzyme Q<sub>10</sub> in PD patients who are already on symptomatic medications, such as levodopa. Larger trials are needed to evaluate this possibility.

### 7.2. Trials in Parkinson's disease patients with early disease not requiring medication

The studies described above made it plausible that coenzyme Q<sub>10</sub> could slow the progression of PD, thus, planning such a clinical trial of coenzyme Q<sub>10</sub> in PD was undertaken. A major challenge in developing a proposal to study the ability of coenzyme Q<sub>10</sub> to affect the course of PD was the identification of an efficient trial design. We first canvassed a number of the leading researchers in clinical trials in PD and were convinced that studies to assess the ability of an intervention to affect the course of PD would give the most clear-cut results if they were carried out in patients with early disease, who did not yet need treatment with "symptomatic" drugs, such as levodopa. Fortunately, Dr. David Oakes of the University of Rochester had analyzed the data from the DATATOP study (Parkinson Study Group, 1993), which used time until disability requiring levodopa treatment as the primary outcome measure, and determined that a more efficient endpoint would be the change in total UPDRS score from baseline visit to the month 9 visit or the visit at which the subject was considered to need levodopa. This design has been given the nickname "Oakes I".

We conducted a phase II trial comparing placebo and 3 dosages of coenzyme Q<sub>10</sub> (300, 600, and 1200 mg/day) in a prospective, randomized, double-blind study with ~20 subjects in each group, and the study began in 1998 (Shults et al., 2002). All subjects also received vitamin E (alpha-

tocopherol) at a dosage of 1200 IU/day. The DATATOP study had previously shown that alpha-tocopherol at a dosage of 2000 IU/day did not affect the progression of PD (Parkinson Study Group, 1993). Because the study was a phase II study, it was powered to determine whether there was a trend toward a reduction of the progressive worsening of PD, and the prespecified criterion for a positive trend was  $P < 0.1$ . The official name of the study was “Effects of Coenzyme Q<sub>10</sub> in Early Parkinson’s Disease,” which was given the nickname “QE2” for “Coenzyme Q<sub>10</sub> Evaluation 2”.

The subjects were evaluated with the UPDRS at the screening, baseline, and months 1, 4, 8, 12, and 16 visits and followed until the subjects had developed disability requiring treatment with levodopa or for a maximum of 16 months. The study found that the high dosages of coenzyme Q<sub>10</sub> were safe and well tolerated. The primary response variable was the change in the total score on the UPDRS at baseline compared with that at the last visit. The adjusted mean total UPDRS changes were the following: placebo, +11.99; 300 mg/day, +8.81; 600 mg/day, +10.82; and 1200 mg/day, +6.69 (+ indicates worsening). The  $P$  value for the primary analysis, test for a linear trend between dosage, and the mean change in the total UPDRS score was 0.09, which met the prespecified criterion for a positive trend for the trial. A prespecified, secondary analysis was a comparison of each treatment group to the placebo group, and the difference between the 1200 mg/day and placebo groups was significant ( $P = 0.04$ , uncorrected for multiple comparisons). In addition, the Schwab and England Scale, which measures independence, as evaluated by the clinician, showed significant benefit for those receiving coenzyme Q<sub>10</sub> ( $P = 0.04$ ). Dr. Haas measured the mitochondrial activity of complexes I–III in mitochondria isolated from platelets, employing an assay that depended on the endogenous coenzyme Q<sub>10</sub>, and found significantly greater activity in subjects receiving coenzyme Q<sub>10</sub> ( $P = 0.04$ ). Although these results are tremendously encouraging, we have stressed that it would be inappropriate for PD patients to begin to take high dosages of coenzyme Q<sub>10</sub> until a larger phase III trial confirms the benefit demonstrated in the phase II study.

Because the highest dosage studied was the most effective, it is important that any phase III study evaluate a higher dosage of coenzyme Q<sub>10</sub> as well as the 1200 mg/day dosage. The most appropriate higher dosage of coenzyme Q<sub>10</sub> could be limited by a number of factors including safety, tolerability, and blood levels achieved with increasing dosages. We studied the safety and tolerability of high dosages of coenzyme Q<sub>10</sub> in 17 patients with Parkinson’s disease (PD), who were receiving symptomatic medication for PD, in an open-label study (Shults et al., 2004). The subjects received an escalating dosage of coenzyme Q<sub>10</sub> — 1200, 1800, 2400, and 3000 mg/day, with a stable dosage of vitamin E (alpha-tocopherol) 1200 IU/day. The plasma level of coenzyme Q<sub>10</sub> was measured at

each dosage. Thirteen of the subjects achieved the maximal dosage, and adverse events were typically considered to be unrelated to coenzyme Q<sub>10</sub>. The plasma level reached a plateau at the 2400 mg/day dosage and did not increase further at the 3000 mg/day dosage. A review of videotapes of the motor portion of the UPDRS at baseline and last visit by an assessor unaware of the timing of the examination showed no significant effect of treatment with coenzyme Q<sub>10</sub>. The data suggest that, in future studies of coenzyme Q<sub>10</sub> in PD, a dosage of 2400 mg/day (with vitamin E/alpha-tocopherol 1200 IU/day) is an appropriate highest dosage to be studied.

### 7.3. Ongoing trials

The NET-PD program of the National Institute of Neurological Disorders and Stroke is conducting a trial of coenzyme Q<sub>10</sub> at a dosage of 2400 mg/day in patients with early, untreated PD to assess the effect on the progression of disability as measured by the UPDRS. The study is using a variation of the “Oakes 1” trial design, but it was devised to look for futility (that the drug does not achieve a prespecified effect on the change in UPDRS score based on historical data), thus, will not provide information on efficacy but will provide useful data on the appropriateness of studying coenzyme Q<sub>10</sub> at this dosage in a phase III trial. The study should be completed in 2005 (Dr. Karl Kieburtz, personal communication).

The PARK study is being conducted in Germany to assess the symptomatic effects in PD patients who are Hoehn and Yahr scale 2–3 and on a stable dose of symptomatic medication, such as levodopa. The subjects will receive placebo or coenzyme Q<sub>10</sub> at a dosage of 100 mg, 3 times/day. The primary outcome measure is the UPDRS score. The study should be completed in 2005 (Dr. Jürgen Koch, personal communication).

### 7.4. Future trials

The encouraging results of the phase II study prompted us to plan a phase III study of coenzyme Q<sub>10</sub> in patients with early PD (nicknamed the QE3 study). The study, which hopefully will begin in 2005, will compare placebo and 2 dosages of coenzyme Q<sub>10</sub> (1200 and 2400 mg/day), as was done in the QE2 study, but with 200 subjects in each treatment arm. The QE3 study should answer many of the questions regarding the short- and longer term effects of coenzyme Q<sub>10</sub> in PD.

## 8. Conclusion

Mitochondria play central roles in the bioenergetics of the cell and apoptotic cell death, and mitochondrial dysfunction appears to play a role in the pathogenesis of PD. The central position of coenzyme Q<sub>10</sub> in the ETC and

its antioxidant capability position it well to intervene in a number of mechanisms involved in cell death. Preclinical studies have established its ability to reduce damage to the nigrostriatal dopaminergic system in models of PD, and a phase II clinical trial demonstrated a positive trend for coenzyme Q<sub>10</sub> to slow the progressive disability that occurs in PD. A larger study, which will hopefully begin in 2005, should better define the short- and longer term effects of coenzyme Q<sub>10</sub> in PD.

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Dr. Shults is listed as co-inventor in a pending patent application for the use of coenzyme Q<sub>10</sub> in neurodegenerative diseases. The application is jointly owned by Enzymatic Therapy, Inc. and The Regents of the University of California.

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