Organelles in focus

Coenzyme Q_{10} as a therapy for mitochondrial disease

Q1 I.P. Hargreaves *

Neurometabolic Unit, National Hosptal, London, UK

ABSTRACT

Treatment of mitochondrial respiratory chain (MRC) disorders is extremely difficult, however, coenzyme Q_{10} (CoQ$_{10}$) and its synthetic analogues are the only agents which have shown some therapeutic benefit to patients. CoQ$_{10}$ serves as an electron carrier in the MRC as well as functioning as a potent lipid soluble antioxidant. CoQ$_{10}$ supplementation is fundamental to the treatment of patients with primary defects in the CoQ$_{10}$ biosynthetic pathway. The efficacy of CoQ$_{10}$ and its analogues in the treatment of patients with MRC disorders not associated with a CoQ$_{10}$ deficiency indicates their ability to restore electron flow in the MRC and/or increase mitochondrial antioxidant capacity may also be important contributory factors to their therapeutic potential.

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1. Introduction

The mitochondrial respiratory chain (MRC; Fig. 1) is located in the inner mitochondrial membrane and consists of five enzyme complexes: complex I (NADH:ubiquinone reductase; EC 1.6.5.3); complex II (succinate: ubiquinone reductase; EC 1.3.5.1); complex III (ubiquinol: cytochrome c reductase; EC 1.10.2.2) complex IV (cytochrome c oxidase; EC 1.9.3.1) and complex V (ATP synthase; EC 3.6.3.14; Land et al., 2004; Rahman and Hanna, 2009). However, the paradigm of the MRC as discrete enzymes present in the inner mitochondrial membrane has been superceded and the MRC enzymes are now thought to be associated as supercomplexes within the inner mitochondrial membrane existing as aggregates of complexes I, III, and IV, complexes I and III, and complexes III and IV as well as in their free enzyme forms (Lapuente-Brun et al., 2013a,b). The major function of the MRC is to synthesise ATP via the process of oxidative phosphorylation which is essential for cellular function. Disorders of the MRC constitute a heterogeneous group of multisystemic diseases that develop as the result of mutations in nuclear or mitochondrial DNA (Rahman and Hanna, 2009). Once believed to be extremely rare, inherited disorders of the MRC are now thought to represent one of the more commoner groups of metabolic disease with a birth prevalence of 1 in 5000 (Haas et al., 2007). Treatment for MRC disorders is notoriously difficult and can be woefully inadequate and there is no overall consensus on the treatment of these disorders (Dimauro et al., 2004).

To date coenzyme Q_{10} (CoQ$_{10}$; Fig. 2) and its analogues are the only agents which have proven to have some therapeutic potential (Geromel et al., 2002; Mahoney et al., 2002) in the treatment of MRC disorders by their ability to restore electron flow in the MRC chain, provide electrons to the chain and increase mitochondrial antioxidant capacity.

CoQ$_{10}$ is the predominant form of ubiquinone in humans where it serves as an electron carrier in the MRC (Ernster and Dallner, 1995a,b). A study by Benard et al. (2006) however has indicated that **Q3** not all mitochondrial CoQ$_{10}$ is required for its MRC function. There appears to be two distinct pools of CoQ$_{10}$ in the inner mitochondrial membrane, one pool is protein bound and the other is free of such associations (Lass and Sohal, 1999). Although the exact function of **Q4** these CoQ$_{10}$ pools is uncertain, given that approximately 30% of mitochondrial CoQ$_{10}$ has been reported to be protein bound (Lass and Sohal, 1999) and that in *Caerorhabditis elegans* a reduction of mitochondrial CoQ$_{10}$ content by 60–70% of original did not decrease MRC activity (Asencio et al., 2003) this may suggest that the protein bound CoQ$_{10}$ pool may be principally involved in oxidative phosphorylation. The free CoQ$_{10}$ pool may consequently be required for other functions including: serving as a potent lipid soluble antioxidant (Bentinger et al., 2007); regulation of the permeability transition pore opening and maintenance of body temperature via its role as a cofactor for the mitochondrial uncoupling proteins (Lopez-Martin et al., 2007). CoQ$_{10}$ also functions as an antioxidant in other cellular membranes and lipoproteins (Ernster and Forsmark-Andree, 1993). In addition it is also involved in other cell functions, these include: DNA replication and repair through its role in pyrimidine synthesis and the regulation of the physicochemical properties of cellular membranes (Lopez-Martin et al., 2007;

Q2 * Tel.: +44 203 44 83844.
E-mail address: iain.hargreaves@uclh.nhs.uk
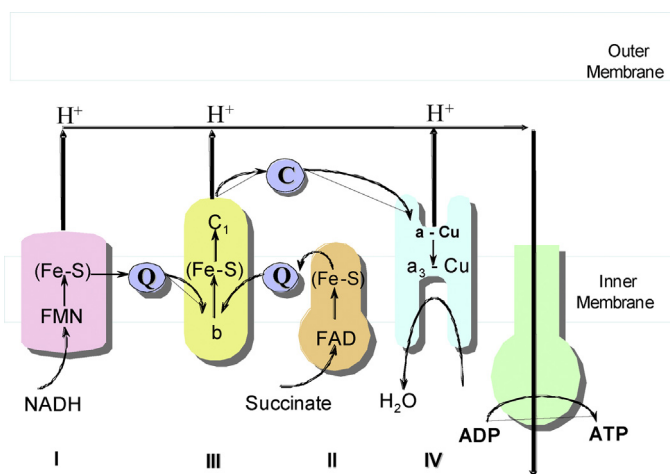
Fig. 1. A diagram showing the structure of mitochondrial respiratory chain. CoQ_{10} is denoted as Q and cytochrome c as C.

Turunen et al., 2004). In humans CoQ_{10} is present in most tissues of the body, the highest levels being found in the heart, kidney, liver and muscle, 114, 67, 55 and 40 $\mu g/g$ wet weight of tissue, respectively. In contrast, the lowest levels are found in the lungs and colon, 8 and 11 $\mu g/g$ wet weight of tissue, respectively (Turunen et al., 2004). It is uncertain as yet whether the differences in tissue CoQ_{10} status reflect disparities in tissue specific synthesis or variations in the level of mitochondrial enrichment as the mitochondria is the major site of CoQ_{10} synthesis within the cell (Turunen et al., 2004). CoQ_{10} present in tissues is mostly in its fully reduced, ubiquinol form apart from the brain and lungs were CoQ_{10} predominates (67% and 65% of total, respectively) which may reflect the higher level of oxidative stress in these tissues (Aberg et al., 1992). Animal studies have indicated that there may be some decrease in the mitochondrial CoQ_{10} status of some tissues in certain species with age although this has not been reported in human studies (Sohal and Forster, 2007). Although no studies have so far assessed the effect of CoQ_{10} supplementation on ageing in humans, a study in rats has reported an attenuation of both the age related decrease in plasma total antioxidant capacity as well as the increase in DNA damage in lymphocytes following life-long CoQ_{10} supplementation (Quiles et al., 2005).

Disorders of CoQ_{10} biosynthesis can respond markedly to CoQ_{10} supplementation if treatment is started early, although responses may vary between patients (Emmanuele et al., 2012). CoQ_{10} has low toxicity and does not induce any serious side effects in humans at a dosage up to 1.2 g/day (Hidaka et al., 2008). Furthermore, CoQ_{10} has been reported to be safe and well tolerated at doses as high as 3000 mg/day although further studies are required before the possibility of adverse side effects can be excluded at this dosage. Although CoQ_{10} therapy may be relatively free of side effects, there are concerns that CoQ_{10} may reduce the efficacy of warfarin (Landbo and Almdal, 1998), although a study by Engelsen et al., 2003 observed no influence of CoQ_{10} on the clinical effect of warfarin.

The therapeutic potential of CoQ_{10} in the treatment of MRC disorders that are not the result of a defect in CoQ_{10} biosynthesis would indicate the possibility of a secondary CoQ_{10} deficiency associated with these diseases. In deed, evidence of a deficit in CoQ_{10} status has been reported in a variety of MRC disorders most recently in mitochondrial DNA depletion syndrome which will be discussed in this review. The ability of CoQ_{10} and its analogues (generically known as quinones) to demonstrate clinical/biochemical improvements in patients with MRC disorders that are not associated with a CoQ_{10} deficiency suggests that their therapeutic potential may

not purely result from a replenishment of the endogenous quinone pool. The therapeutic efficacy of quinones has been reported to rely on both their ability to restore electron flow in the MRC and increase mitochondrial antioxidant capacity and this will be discussed in the following review (Geromel et al., 2002).

1.1. Disorders of CoQ_{10} biosynthesis and their treatment

The first patients to be reported with a suspected defect in CoQ_{10} biosynthesis were two sisters born to unrelated parents who presented with recurrent rhabdomyolysis, associated with seizures and mental retardation (Ogasahara et al., 1989). The muscle CoQ_{10} status of these patients was approximately 3.7% of mean control values indicating a primary defect in CoQ_{10} biosynthesis although to date no genetic diagnosis has been reported. Since this time 149 patients have been described and CoQ_{10} deficiency appears to have a particularly heterogeneous clinical presentation. However, there appears to be five distinct clinical phenotypes: encephalomyopathy; severe infantile multisystemic disease; nephropathy; cerebellar ataxia and isolated myopathy (Emmanuele et al., 2012). In most cases the family history suggests an autosomal recessive mode of inheritance and the reader is referred to the review by Rahman et al. (2012) which discusses the genetics of coenzyme Q_{10} deficiency in detail.

In view of its hydrophobicity and large molecular weight, only a small fraction (less than 5%) of orally administered CoQ_{10} reaches the plasma (Bhagavan and Chopra, 2007). Therefore, high doses and long term administration of exogenous CoQ_{10} may be required to elicit clinical improvement in patients with a CoQ_{10} deficiency (Quinzii et al., 2007). It has been recommended that CoQ_{10} supplementation with oral doses of 12,000–3000 mg/day for adults and up to 30 mg/kg/day for children should be administered to patients (Emmanuele et al., 2012; Rahman et al., 2012). It is recommended that solubilised formulations of CoQ_{10} rather than powder based CoQ_{10} are used therapeutically as the former have superior bioavailability as indicated by their enhanced plasma response (Bhagavan and Chopra, 2007). At present the level of plasma CoQ_{10} that may have therapeutic potential is uncertain. In a study by Langsjoen and Langsjoen, 1998 a blood concentration of approximately 4.1 μM was required before any therapeutic benefit was reported in patients with congestive heart failure. No studies to date have assessed this parameter in patients with CoQ_{10} deficiency although a study by Lopez et al. (2010) reported an improvement in bioenergetic status as indicated by increased ATP/ADP ratio and normalisation of cellular oxidative stress in CoQ_{10} deficient fibroblasts following 7 days of treatment with 5 μM CoQ_{10}. However, it has been suggested that blood mononuclear cells (BNC) may represent a more appropriate surrogate than plasma for the assessment of endogenous CoQ_{10} status (Duncan et al., 2005). This was indicated by the significant ($p < 0.02$) correlation between skeletal muscle and BNC CoQ_{10} status in 12 patients with no evidence of a MRC disorder. In contrast, no correlation was observed between plasma and skeletal muscle CoQ_{10} status (Duncan et al., 2005). The close relationship between skeletal muscle and BNC CoQ_{10} status was also reported by Land et al. (2007) in a cohort of 22 patients with no evidence of an MRC disorder. The possibility arises however that there may be tissue specific isoenzymes in the CoQ_{10} biosynthetic pathway and therefore, although the CoQ_{10} status of BNC may represent that of skeletal muscle it may not be an appropriate surrogate for other tissues (Ogasahara et al., 1989). Therefore, the establishment of therapeutic ranges of BNC CoQ_{10} status may have more clinical utility.

Whilst the muscle symptoms associated with CoQ_{10} deficiency have been reported to improve in most cases upon CoQ_{10} supplementation, neurological symptoms appear to be only partially ameliorated (Emmanuele et al., 2012). In patients with the
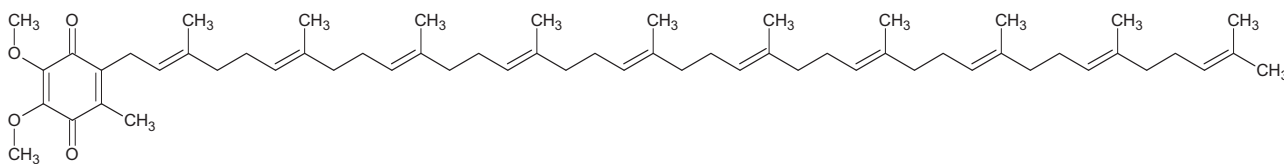
Fig. 2. The structure of coenzyme Q_{10}.

encephalomyopathic and myopathic clinical phenotypes muscle symptoms were reported to improve following CoQ_{10} supplementation. In contrast, only 49% of patients with the cerebellar ataxic phenotype have been reported to demonstrate improvement/stabilisation in their ataxic symptoms following CoQ_{10} supplementation (Emmanuele et al., 2012). At present the reasons for the refractory nature of the neurological symptoms associated with CoQ_{10} deficiency to CoQ_{10} supplementation remain to be elucidated. However they may include; poor transfer of CoQ_{10} across the blood–brain barrier (BBB), irreversible structural and/or biochemical neuronal dysfunction (Duberley et al., 2013). To date no studies have assessed the transport of CoQ_{10} across the human blood brain barrier (BBB) or assessed whether a BBB CoQ_{10} deficiency may impede transport of CoQ_{10} into the central nervous system. Animal studies however have indicated a certain degree of CoQ_{10} transport across the BBB. In a study by Mathews et al. (1998) a 30% increase in cerebral cortex CoQ_{10} and coenzyme Q_9 (CoQ_9; predominant ubiquinone species in rat) was reported following oral supplementation of 12 month old Sprague-Dawley rats with CoQ_{10} (200 mg/kg) for 2 months. In addition, Smith et al., 2006 reported significant ($p < 0.01$) increases in brain levels of CoQ_{10} and CoQ_9 following supplementation with high dose (1000–5000 mg/kg) CoQ_{10} in a mouse model of Huntington's disease. However, it is uncertain from these studies whether the degree of cerebral uptake of CoQ_{10} would be sufficient to replenish cellular levels of this quinone in a CoQ_{10} deficiency state.

Patients who develop renal disease as the result of a CoQ_{10} deficiency respond well to CoQ_{10} supplementation if treatment is started at an early stage of the disease. Following the development of renal dysfunction in a 12 month old female, CoQ_{10} supplementation (30 mg/kg/day) resulted in progressive recovery of renal function and a reduced level of proteinuria following 20 days of treatment. The patient had normal renal function following 50 months of CoQ_{10} supplementation (Montini et al., 2008a). Heeringa et al., 2011 also reported a dramatic improvement in renal function in 2 patients with a CoQ_{10} deficiency as the result of a *COQ6* mutation.

Whilst CoQ_{10} deficiency is commonly associated with inborn errors of metabolism (Emmanuele et al., 2012) it has also been postulated to occur as a result of statin (HMG-CoA reductase inhibitors) therapy (Hargreaves et al., 2005a,b). A number of studies have reported a decrease in plasma/serum CoQ_{10} status following statin therapy (Hargreaves et al., 2005a,b) however, few studies have assessed the effect of statin treatment upon skeletal muscle CoQ_{10} status. A decrease in CoQ_{10} level and MRC complex I, II–III and IV activities has been reported in skeletal muscle of hypercholesterolemia patients following simvastatin treatment (80 mg/day) for 8 weeks (Päivä et al., 2005). However, the decrease in MRC activities and CoQ_{10} status reported in the study by Päivä et al. (2005) was thought to reflect a decrease in mitochondrial volume/enrichment rather than a statin induced inhibition of CoQ_{10} biosynthesis and enzyme activity. Although the aetiology of the myopathic side effects associated with statin therapy is as yet unknown, a deficit in CoQ_{10} status may be a contributory factor although this has yet to be confirmed (Hargreaves et al., 2005a,b). At the present time there is an ongoing clinical trial to assess the effect of CoQ_{10} supplementation on the extent and intensity of muscle pain during statin therapy (Parker et al., 2013).

In contrast to patients with disorders of CoQ_{10} biosynthesis the efficacy of CoQ_{10} treatment in other MRC disorders is less consistent as highlighted in the following section.

1.2. CoQ_{10} treatment of MRC disorders

In 1985 Ogashara and colleagues reported an improvement in lactate/pyruvate metabolism, cardiac function and eye movement in a patient with Kearns-Sayre syndrome (mitochondrial myopathy which usually presents before age of twenty) following CoQ_{10} supplementation. Since this time a number of studies have assessed the therapeutic potential of CoQ_{10} in the treatment of MRC disorders with varying clinical outcomes. Improvement in: neurological function (Bresolin et al., 1988; Nishikawa et al., 1989); tremor and ataxia (Zierz et al., 1989); exercise intolerance, cramps and muscle stiffness (Sacconi et al., 2010) as well as a minor positive effect on cycle exercise capacity (Glover et al., 2010) have been reported in patients with MRC disorders following CoQ_{10} supplementation. Interestingly, CoQ_{10} monotherapy has been reported to maintain serum calcium levels in the normal range in two patients with Kearns–Sayre Syndrome and hypoparathyroidism. It was speculated that CoQ_{10} therapy restored the capacity of proximal tubule mitochondria to produce the active form of vitamin D (Papadimitriou et al., 1996). However, the most consistent finding of clinical studies is a CoQ_{10} treatment induced progressive reduction in serum lactate and pyruvate levels following exercise (Ogasahara et al., 1986; Goda et al., 1987; Bresolin et al., 1990; Bendahan et al., 1992; Fadic and Johns, 1996; Chan et al., 1998; Abe et al., 1999; Glover et al., 2010). In vivo studies of brain and muscle energy metabolism by phosphorous magnetic resonance spectroscopy have indicated that the CoQ_{10} treatment of patient with mitochondrial cytopathies improves mitochondrial respiration in both these tissues (Barbiroli et al., 1999). Improvement in respiratory function was reported in a patient with Kearns-Sayre/chronic external ophthalmoplegia plus syndrome (Shoffner et al., 1989). Since the patient had virtually no detectable MRC complex I activity, the rational for this treatment was that reducing equivalents could be introduced into the MRC by oxidation of succinate by Complex II and the subsequent transfer to complex III by CoQ_{10} thus bypassing impaired complex I. In contrast, some studies have failed to demonstrate any tangible biochemical or clinical benefit following CoQ_{10} supplementation (Matthews et al., 1993). The failure to elicit clinical and/or biochemical improvement in response to CoQ_{10} supplementation in patients with MRC disorders may be the result of the duration of the treatment or the dosage of CoQ_{10} employed. At present there is no overall consensus on the appropriate therapeutic dose of CoQ_{10} to administer to patients with MRC disorders. It has been reported that doses as high as 30 mg/kg/day may be required to ameliorate neuromuscular and renal dysfunction in the cases of primary CoQ_{10} deficiency (Montini et al., 2008b) and this level of CoQ_{10} supplementation may be appropriate for patients with primary MRC disorders. It has been suggested that patients who show positive therapeutic effects (responders) to CoQ_{10} supplementation may be restricted to

MRC disorder patients with an underlying CoQ_{10} deficiency (Zierz et al., 1989; Chan et al., 1998). This is illustrated by the study of Sacconi et al. (2010) which observed some clinical benefit of CoQ_{10} supplementation in 7 out of 8 MRC disorder patients with a confirmed muscle CoQ_{10} deficiency. In contrast, only 1 out of 15 MRC disorder patients with 'normal' muscle CoQ_{10} status showed some clinical improvement following supplementation. At present there are large scale double blind, randomised clinical trials in progress to assess the efficacy of CoQ_{10} supplementation in the treatment of MRC disorders (Hassani et al., 2010; Stacpole et al., 2012). The results of these studies may confirm or refute the therapeutic efficacy of CoQ_{10} in the treatment of MRC disorders.

1.3. CoQ_{10} deficiency in MRC disorders

The therapeutic potential of CoQ_{10} in the treatment of MRC disorders may indicate an underlying CoQ_{10} deficiency associated with these disorders and indeed a number of studies have reported evidence a deficit in CoQ_{10} status in patients with various mitochondrial diseases. Bresolin et al. (1988) described 3 patients, two with ophthalmoplegia and one with Kearns-Sayre syndrome with markedly decreased serum CoQ_{10} levels. Unfortunately, in this study no assessment of skeletal muscle CoQ_{10} status was undertaken in view of the possibility that serum/plasma CoQ_{10} status may not reflect cellular levels (Hargreaves, 2003). Decreased muscle and serum CoQ_{10} status was determined in a patient with Kearns-Sayre syndrome who showed significant clinical improvement following CoQ_{10} supplementation (Zierz et al., 1989). In a study by Matsuoka et al. (1991) a decreased muscle mitochondrial CoQ_{10} status was reported in 25 patients with mitochondrial encephalomyopathies mostly as the result of mitochondrial DNA mutations. The determination of a decreased muscle CoQ_{10} status in six patients from a group of thirteen with low MRC complex I + III (NADH:Ubiquinone reductase; EC 1.6.5.3 + 1.10.2.2) and complex II-III (succinate: cytochrome reductase; EC 1.3.5.1 + 1.10.2.2) activities has highlighted the diagnostic value of a reduction in these enzyme activities in the detection of CoQ_{10} deficiency (Montero et al., 2005). This study also reported a mild muscle CoQ_{10} deficiency in one patient from a group of nine with a definitive diagnosis of mitochondrial disease. In a study by Miles et al. (2008) the mean muscle CoQ_{10} status of 12 patients with a probable MRC defect (defined as one or more MRC complexes with activities $\leq 30\%$ respective control mean value) was found to be 165.2 nmol/mg (control mean: 214.9 nmol/mg), an approximate 23% decrease compared to control levels. However, one patient in this group was found to have a markedly decreased muscle CoQ_{10} status (37.1 nmol/mg) compared to the reference interval, 107–317 nmol/mg. Furthermore, since no difference in the CoQ_{10} redox (reduced: oxidised) ratio was observed between the control and MRC defective patients the authors concluded that the assessment of these parameters may be unnecessary in the diagnostic algorithm. In a multicentre study 28 from a total 76 patients suffering from a wide spectrum of mitochondrial diseases were found to have a decreased level of muscle Q_{10} compared to control levels (Sacconi et al., 2010). Nine of these patients harboured pathogenic mutations in mitochondrial DNA indicating the deficit in CoQ_{10} status was a secondary phenomena. Interestingly, a severe CoQ_{10} deficiency ($\leq 20\%$ of control mean vales) was detected in two of the nine patients with pathogenic mitochondrial DNA mutations. A recent study by Montero et al. (2013) has reported evidence of muscle CoQ_{10} deficiency in association with mitochondrial depletion syndrome (MDS). Six of the fourteen patients with diagnosed MDS had a decreased muscle CoQ_{10} status which ranged from 4 to 82 nmol/g (reference interval: 121–451 nmol/g). The cause of CoQ_{10} deficiency is MDS is uncertain however, it may result as a secondary consequence of the disease pathophysiology or from increased degradation of the quinone (Sacconi et al., 2010). In view of the essential cofactor role of CoQ_{10} in pyrimidine synthesis, the possibility arises that a deficit in CoQ_{10} status may contribute to the loss of mitochondrial DNA in MDS (Lopez-Martin et al., 2007).

Proliferation of mitochondria has been reported in muscle tissue of patients with MRC disorders (Ogasahara et al., 1986; Dimauro et al., 2004). Therefore, since approximately 50% of cellular CoQ_{10} is present within the mitochondrial (Ernster and Dallner, 1995a,b) expressing CoQ_{10} levels in relation to either mitochondrial protein or a mitochondrial marker enzyme, citrate synthase has been suggested in order to reveal evidence of a CoQ_{10} deficiency (Ogasahara et al., 1986; Montero et al., 2008). In the studies by Montero et al. (2005) and Sacconi et al. (2010) no details were reported to clarify whether the decrease in muscle CoQ_{10} status of the MRC disorder patients was distinct from that of an overall reduction in the mitochondrial enrichment of the tissue. Therefore, in these studies the possibility that the reported decrease in muscle CoQ_{10} status reflects an overall reduction in mitochondrial enrichment of the tissue cannot be excluded. In three patients with Kearns-Sayre Syndrome muscle CoQ_{10} was found to be reduced only when the concentration was expressed per mitochondrial protein (Ogasahara et al., 1985). In an assessment of the muscle CoQ_{10} status of eight patients aged 8 patients aged 0.2–14 years with biochemical evidence of multiple MRC enzyme deficiencies (decreased complex I, II–III and IV activities compared to reference intervals; no genetic diagnosis to date) the author found that although the muscle CoQ_{10} status was within the reference interval (Table 1), expressing CoQ_{10} status as a ratio to citrate synthase activity revealed clear evidence of a CoQ_{10} deficiency (Table 1).

1.4. CoQ_{10} analogues and their utility in the treatment of MRC disorders

In addition to CoQ_{10}, the short chain synthetic analogue of this quinone, idebenone (Fig. 3) has also been used in the treatment of patients MRC dysfunction. Orally administered CoQ_{10} has been reported to have some limited mitochondrial uptake (Kwong et al., 2002). In contrast however, idebenone is readily taken up by cells even those with a normal CoQ_{10} concentration and is able to cross the blood brain barrier (Geromel et al., 2002; Kerr, 2013).

Table 1
Comparison of the muscle coenzyme Q10 (CoQ10) status of control and patients with multiple MRC enzyme deficiencies. Results expressed as mean ± SEM × 103.

	Control	MRC deficient patients
CoQ_{10} (pmol/mg)	140–580 pmol/mg	144.7 ± 19.0
CoQ_{10}/CS (10^{-3} min)	2.27 ± 0.11	$0.95 \pm 0.12^{**}$

The multiple MRC deficient group consisted of 8 patient with combined MRC complex I (0.071 ± 0.007; mean ± SEM, ref. interval: 0.104–0.268), II–III (0.027 ± 0.006; mean ± SEM, ref. interval: 0.040–0.204) and IV (0.008 ± 0.001; mean ± SEM, ref. interval: 0.014–0.034) deficiencies.
Control group: 20 patients with no evidence of an MRC deficiency. Aged 0.6–18 years; mean ± SEM: 5.6 ± 1 years.
MRC enzymes activities expressed as a ratio to citrate synthase (CS) activity to account for mitochondrial enrichment (Duberley et al., 2013).
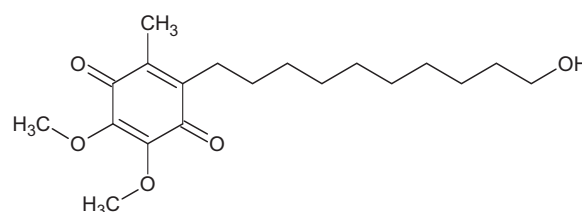** $p < 0.001$.

Fig. 3. The structure of Idebenone.

Idebenone has been recommended as a potential treatment for Leber's hereditary optic neuropathy (LHON). LHON is an inherited mitochondrial disease that causes rapid bilateral visual loss and life long legal blindness (Kirkman et al., 2009). The findings of both a randomised placebo controlled trial (Klopstock et al., 2011) and a retrospective analysis of 103 patients have reported the efficacy of idebenone in protecting and facilitating the recover of visual acuity in LHON. Idebenone has also recently been reported to prevent loss of colour vision in LHON (Guenther et al., 2012). Idebenone has also demonstrated some therapeutic efficacy in the treatment of MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes; Ikejiri et al., 1996) and Leigh syndrome (subacute nectrotising encephalomyeolopathy; Haginoya et al., 2009).

LHON is associated in most patients with mutations in mitochondrial DNA affecting complex I of the MRC resulting in an impairment of enzyme activity and a subsequent deficit in ATP levels in addition to increased oxidative stress (Guenther et al., 2012). The therapeutic efficacy of idebenone in the treatment of LHON in addition to its antioxidant capacity may be its ability to mediate electron flow from the cytosol directly to complex III of the MRC therefore bypassing complex I (Haefeli et al., 2011). Idebenone is a good substrate for cytosolic NQO1 (NAD(P)H dehydrogenase, quinone 1) which catalyses electron transfer from cytosolic NAD(P)H to idebenone which then passes them to complex III therefore enhancing oxidative phosphorylation (Haefeli et al., 2011). In vitro studies using human cybrid cells have indicated that idebenone may cause mitochondrial membrane depolarisation and that only in its reduced state is it able to restore mitochondrial membrane potential in MRC complex I deficient cells (Giorgio et al., 2012). Furthermore, in an animal study using liver submitochondrial particles, idebenone treatment was reported to inhibit the activity of MRC complex I, but increase the activity of complex II (Briere et al., 2004). Therefore, in addition to its therapeutic capacity idebenone may also have the potential to induced MRC dysfunction. However, idebenone is converted into its metabolites, QS-10, QS-6 and QS-4 within minutes of administration to patients and no idebenone is detectable within plasma after 1 h (Bodmer et al., 2009). Therefore, the therapeutic potential of this quinone may not be attributable to idebenone itself but one of its longer lasting metabolites (Giorgio et al., 2012). Whereas CoQ_{10} treatment can result in clinical improvement in patients with defects in CoQ_{10} biosynthesis, idebenone therapy has not proved efficacious. Indeed clinical deterioration has been reported in CoQ_{10} deficient patients following treatment with idebenone (Aure et al., 2004; Rotig et al., 2007). These clinical findings are supported by the study of Lopez et al. (2010) which showed that idebenone treatment was unable to correct defective mitochondrial energy metabolism in CoQ_{10} deficient fibroblasts.

An 31P-NMR study by Argov et al. (1986) reported improvement in both clinical presentation and muscle bioenergetic status (at rest) of a patient with mitochondrial myopathy due to an MRC complex III deficiency following treatment with the quinone vitamin K3 and vitamin C. The reasons for the therapeutic efficacy of this treatment are uncertain however it is hypothesised that treatment with vitamins K3 and C bypassed the deficiency at complex III possibly reducing cytochrome c directly and therefore enhancing oxidative phosphorylation. The antioxidant potential of these two vitamins may also have been contributory factors to the amelioration of symptoms.

In the mitochondria MitoQ is reduced to its active antioxidant quinol form by MRC complex II (James et al., 2005). However, since MitoQ is not oxidised by MRC complex III it cannot function as an electron carrier in the MRC (James et al., 2005). Furthermore, in vitro studies have indicated that at concentrations greater or equal to 150 nM, MitoQ may cause uncoupling of the MRC resulting in a decrease in mitochondrial ATP synthesis possibly as a
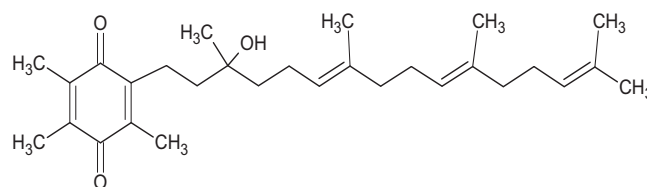

Fig. 4. The structure of EPI-743.

consequence of the pro-oxidant capacity of MitoQ (Fink et al., 2012). In view of these bioenergetic limitations, the therapeutic potential of MitoQ has not been evaluated in patients with primary MRC disorders, although mitoQ has shown some efficacy in the treatment of diseases that involve mitochondrial oxidative damage such as chronic hepatitis C (Smith and Murphy, 2010).

The synthetic quinone, EPI-743 (Fig. 4) may represent a new drug in the treatment MRC disorders. EPI-743 was initially used to treat 14 patients (1 adult, 13 children) with a variety of genetically confirmed mitochondrial disease in a study by Enns et al. (2012). Following ninety days of treatment with EPI-743, eleven patients showed clinical improvement with three showing partial relapse of symptoms. In a subsequent study, EPI-743 was reported to improve both neurological and neuromuscular function in genetically defined Leigh syndrome (Martinelli et al., 2012). EPI-743 has also been demonstrated to reverse disease progression and restore visual loss in LHON (Sadun et al., 2012).

Although the precise mechanism by which EPI-743 elicits its therapeutic effect is uncertain it is thought to involve its ability to increase cellular reduced glutathione (GSH) status. Decreased levels of GSH have been reported in patients with MRC disorders and may be a contributory factor to disease pathophysiology (Hargreaves et al., 2005a,b). In a study by Pastore et al., 2013 lymphocyte GSH status was found to be severely decreased in ten children with Leigh syndrome. Following six months of treatment with EPI-743 lymphocyte GSH status significantly increased to within control levels. However, serum lactate levels remained unchanged and elevated in patients indicating that EPI-743 may not have an effect on mitochondrial energy metabolism. Due to its redox potential, EPI-743 is thought to be able to facilitate the transfer of reducing equivalents between NQO1 and glutathione reductase enhancing the restoration of cellular GSH status (Martinelli et al., 2012). Glutathione reductase is also capable of reducing CoQ_{10} to ubiquinol, albeit the effect of EPI-743 treatment upon the redox state of CoQ_{10} has so far not been investigated (Bjornstedt et al., 2004). Although a deficit in both the GSH (Hargreaves et al., 2005a,b) and CoQ_{10} (Miles et al., 2008) status of patients with primary MRC disorders has been reported studies have yet to evaluate the direct relationship between tissue glutathione (both redox state and total levels) and CoQ_{10} status. However, long term CoQ_{10} supplementation of mice lasting up to 25 months has no effect on the mitochondrial GSH: GSSG (oxidised glutathione) compared to controls in heart, kidney and skeletal muscle (Sohal and Forster, 2007).

2. Conclusion

In addition to patients with disorders of CoQ_{10} biosynthesis, CoQ_{10} therapy has shown some efficacy in the treatment of patients with MRC deficiencies although to a lesser degree. Since mitochondrial disease patients with a secondary CoQ_{10} deficiency may be more responsive to CoQ_{10} therapy than those with 'normal' CoQ_{10} levels it has been recommended that the CoQ_{10} status is determined in the muscle samples from all patients with suspected mitochondrial disorders (Rahman et al., 2011). However, there appears to be no overall consensus on the appropriate surrogate to assess CoQ_{10}

status in patients following supplementation or indeed the level of CoQ_{10} which may be of therapeutic value. Although idebenone has shown some efficacy in the treatment of patients with MRC complex I deficiency (Klopstock et al., 2011), there is a paucity of data available on the appropriate quinone to select for the treatment of patients with other MRC enzyme deficiencies. Dual treatment may also be a consideration utilising the ability of particular quinones to restore electron flow in the MRC and/or increase mitochondrial antioxidant capacity. At present time there is no clear biochemical phenotype-quinone treatment correlation in MRC disease and this information will be critical to develop therapeutic strategies for the treatment of these disorders.

Uncited references

Bentinger et al. (2003), Carelli et al. (2011), Cocheme et al. (2007) and Ferrante et al. (2005).

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