The International Journal of Biochemistry & Cell Biology 49 (2014) 105–111

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Organelles in focus

Coenzyme Q_{10} as a therapy for mitochondrial disease

I.P. Hargreaves*

Neurometabolic Unit, National Hospital, London, UK

ARTICLE INFO

Article history:
Received 21 November 2013
Received in revised form 14 January 2014
Accepted 26 January 2014
Available online 2 February 2014

Keywords:
Coenzyme Q10
Mitochondrial respiratory chain
Idebenone
EPI-743
Oxidative stress

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.

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 However, the paradigm of the MRC as discrete enzymes present in the inner mitochondrial membrane has been superceded and the MRC enzymes are now thought to be associated as supercomplexes within the inner mitochondrial membrane existing as aggregates of complexes I, III, and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., 2013). 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 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 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; Turunen et al., 2004). In humans CoQ_{10} is present in most tissues of

* Tel.: +44 203 44 83844.
E-mail address: iain.hargreaves@uclh.nhs.uk

1357-2725/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.biocel.2014.01.020

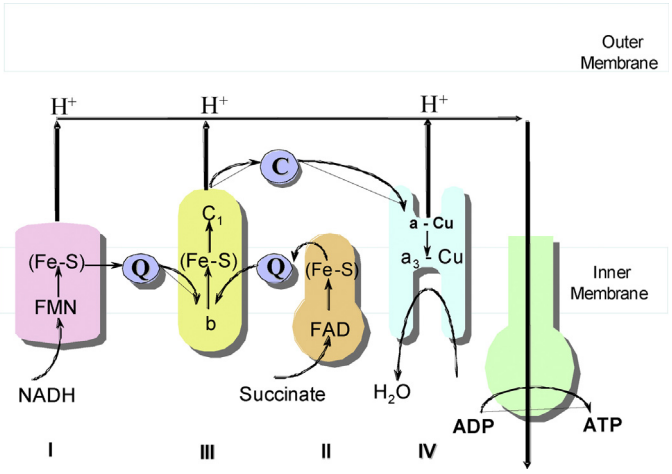

Fig. 1. A diagram showing the structure of mitochondrial respiratory chain. CoQ_{10} is denoted as Q and cytochrome c as C.

the body, the highest levels being found in the heart, kidney, liver and muscle, 114, 67, 55 and 40 μg/g wet weight of tissue, respectively. In contrast, the lowest levels are found in the lungs and colon, 8 and 11 μg/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 dosoge 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