

## MINIREVIEW

# Function of Coenzyme Q in the Cell: Some Biochemical and Physiological Properties

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### Summary

Coenzyme Q (CoQ), a lipophilic substituted benzoquinone, is well known as a redox component of the mitochondrial and many bacterial respiratory chains. However, additional locations and roles have been recently discovered. CoQ is described as a redox component of extramitochondrial electron transport chains and it is a powerful antioxidant and a membrane stabilizer. Increasing evidence for the beneficial clinical effects of CoQ administration in senescence or in different disorders (e.g. cerebrovascular, muscular, neurogenic) may be explained by the multiple roles of CoQ in cells.

### Key words

Coenzyme Q – Mitochondrial respiratory chain – Inner cell membranes – Antioxidant effect – Therapeutic effect

### Introduction

Mammalian metabolism involves many different enzyme-catalyzed reactions which need or release energy. The energy needed for anabolic pathways is in the form of chemical energy of ATP and is provided by its dephosphorylation. ATP (the principal carrier of energy for life) is produced during the process of oxidative phosphorylation in the mitochondrial respiratory chain. The pairs of electrons derived from the intermediates of Krebs cycle and other metabolic pathways are carried by a respiratory chain. This mitochondrial transport chain possesses electron-carriers and prosthetic groups of enzymes with increasing redox potentials where the ultimate electron acceptor is molecular oxygen. An essential role in the respiratory chain is played by coenzyme Q (CoQ) which is also called ubiquinone. The standard redox potential of oxidized and reduced CoQ couple is approximately 0.1 V. In comparison with other respiratory carriers in the inner mitochondrial

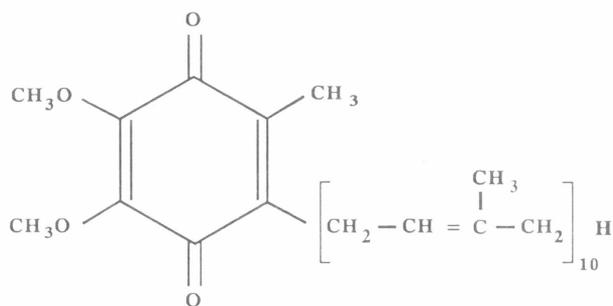
membrane, the content of CoQ exceeds the other redox components by about tenfold.

In our short review we have attempted to show certain discussed roles of CoQ (for more extensive reviews see Lenaz 1985, Lenaz *et al.* 1990a, 1994a). Better knowledge of ubiquinone functions at molecular level is required for fully understanding its physiological role, its requirements in pathological states and its reliable therapeutic use.

### Occurrence of CoQ

CoQ or ubiquinone, is present in most aerobic microorganisms, all animal and plant organs and tissues but in variable amounts (Battino *et al.* 1990, Elmberger *et al.* 1987, Ramasarma 1985). The number of isoprene units in CoQ depends on the species: in mammalian tissues it is frequently designated as CoQ<sub>10</sub>, referring to the number of isoprene units in its side chain (Fig. 1). The rat is a notable exception, with

CoQ<sub>9</sub> (it has only nine isoprene units in its side chain) as the major homologue and only a small quantity of CoQ<sub>10</sub> is present in subcellular membranes (Ramasarma 1985).



**Fig. 1**  
Chemical structure of coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>).

In addition, CoQ is present in the bile and in the blood, where it is bound almost exclusively to the plasma lipoproteins of low and very low density (Ernster 1993). On the contrary, CoQ is not present in a number of organisms including gram-positive bacteria, at least one species of photosynthetic bacterium, and some fungi. It is also not present in methanogenic bacteria (Beyer 1990).

### Localization in the membrane

A great effort has been made to understand the localization and orientation of CoQ in the lipid bilayer. The isoprenoid tail gives an exceedingly hydrophobic nature to the CoQ molecule and this enables it to diffuse rapidly inside the hydrocarbon phase of the membrane phospholipid bilayer (Lenaz *et al.* 1987).

Linear dichroism studies in model bilayer vesicles support the concept that the CoQ molecule is located in the lipid bilayer in a dynamic state. The quinone ring and the first couple of isoprene units oscillate between two limiting positions. One position is with the quinone ring in the bilayer midplane parallel to the membrane surfaces and the other with the quinone ring parallel to the lipid chain near the polar lipid heads. In both positions most of the long isoprene hydrophobic chain lies in the lipid bilayer midplane (Lenaz *et al.* 1992, Samori *et al.* 1992).

### Role of CoQ in mitochondria

Three different possibilities are described where the CoQ molecule acts in the respiratory chain:

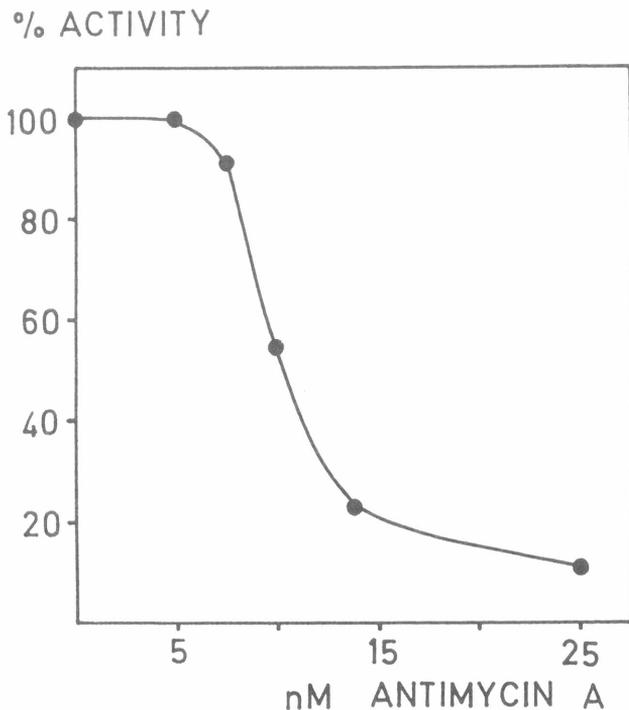
1) It has been established that CoQ (in its oxidized or reduced form) behaves kinetically as a mobile homogeneous pool which carries electrons

between flavoprotein dehydrogenases, i.e. NADH CoQ reductase (Complex I) and succinate CoQ reductase (Complex II) and the bc<sub>1</sub> complex (Complex III) in the inner mitochondrial membrane (Kröger and Klingenberg 1973). In spite of the excess of CoQ in comparison with the other electron carriers, it was shown that its concentration is not saturating for NADH oxidation (Estornell *et al.* 1992). Cottingham and Ragan (1980) found that electron transfer between glycerol-3-phosphate dehydrogenase and Complex III also obeys a pool behaviour in a system reconstituted from partially purified glycerol-3-phosphate dehydrogenase from the pig brain and isolated Complex III in the presence of excess CoQ. Our experiments performed on glycerol-3-phosphate dehydrogenase of mitochondrial membranes *in situ* support this idea and eliminate the possibility of a direct connection of glycerol-3-phosphate dehydrogenase with Complex III through specific CoQ molecules (Rauchová *et al.* 1992). In order to demonstrate a pool behaviour between glycerol-3-phosphate dehydrogenase and the bc<sub>1</sub> complex, we performed titration curves of glycerol-3-phosphate cytochrome c oxidoreductase activity with the bc<sub>1</sub> complex inhibitors, antimycin A and myxothiazol. As the glycerol-3-phosphate dehydrogenase cannot fully saturate the respiratory chain and the enzyme itself is not affected by these inhibitors, we obtained inhibition curves of sigmoidal shape with a lag in which the enzyme activity is not inhibited by either inhibitor. The lag phase is proportional to the excess of the bc<sub>1</sub> complex over glycerol-3-phosphate dehydrogenase (Fig. 2). In the case of ubiquinol cytochrome c reductase the inhibitory curves of antimycin A and myxothiazol have a linear shape because the inhibitor acts directly on the enzyme molecule (Rauchová *et al.* 1992).

2) Protein-bound CoQ has also been suggested as a fixed coenzymatic form of ubiquinol cytochrome c reductase or other ubiquinone-containing segments of the respiratory chain (King *et al.* 1985, Yu and Yu 1981). Spin-label electron paramagnetic resonance and differential scanning calorimetry studies revealed that Complexes II and III may function as a fixed supercomplex with CoQ as a required component in a 1:1 stoichiometry between the enzymes (Gwak *et al.* 1986) which is in contrast to the pool concept.

3) In addition, an aliquot of protein-bound CoQ is involved in H<sup>+</sup> translocation in the "Q-cycle" (Mitchell 1976, 1990) where the cytochrome bc<sub>1</sub> complex transfers electrons from ubiquinol to cytochrome c and links this electron transfer to translocation of protons across the membrane in which the bc<sub>1</sub> complex resides (Trumpower 1990). Protein-bound CoQ has also been involved in H<sup>+</sup> translocation by Complex I in the form of a dual-CoQ-gated H<sup>+</sup> pump (Degli Esposti and Ghelli 1994).

It was found that diets containing different types of lipid supplementation induce a different CoQ content and lipid composition in rat liver mitochondria (Huertas *et al.* 1991a, 1992). Positive correlation between the CoQ content and Complexes III and IV shows coordination in the assembly of the respiratory chain as a whole (Huertas *et al.* 1991b).



**Fig. 2**  
Inhibition of glycerol-3-phosphate cytochrome c oxidoreductase by antimycin A in the presence of 10 mM glycerol-3-phosphate. The enzyme was measured in hamster brown adipose tissue mitochondria (0.05 mg prot./ml) spectrophotometrically at 550 nm in a reaction medium containing 100 mM K-phosphate buffer (pH 7.6), 1 mM KCN, 50  $\mu$ M cytochrome c as described earlier (Rauchová *et al.* 1993).

#### Extramitochondrial locations of CoQ in the cell

Besides the well established redox activity of CoQ in the mitochondrial respiratory chain, it has been demonstrated in recent years that CoQ is also localized in other internal membranes, as in the Golgi apparatus, the endoplasmic reticulum, lysosomes, the outer membrane of mitochondria and the plasma membrane (Ernster 1993). This finding has been examined by many investigators (Appelkvist *et al.* 1991, Battino *et al.*

1990, Rauchová *et al.* 1994). Kalén *et al.* (1990) found that CoQ is synthesized in the endoplasmic reticulum-Golgi system of the rat liver and subsequently distributed to various cell membrane destinations. We examined the cellular distribution of CoQ in the rat skeletal muscle and liver tissue. We found that, in skeletal muscle, 65 % of the CoQ resides in mitochondrial membranes, whereas in the liver it was only 32 % (Table 1). The relatively high content of CoQ in skeletal muscle mitochondria may be accounted for by the relatively high aerobic metabolism and the high ratio of mitochondria to Golgi membranes in skeletal muscles as compared with the liver (Rauchová *et al.* 1994).

**Table 1**  
Distribution of CoQ in rat skeletal muscle and liver cells

Tissue fraction	Skeletal muscle	Liver
Low speed sediment (%)	25 $\pm$ 5	41 $\pm$ 3
Mitochondria (%)	65 $\pm$ 4	32 $\pm$ 7
Post mitochondrial supernatant (%)	10 $\pm$ 1	27 $\pm$ 6
Content of CoQ in homogenate (nmoles CoQ/g tissue)	33.5 $\pm$ 4.4	141 $\pm$ 14
Content of CoQ in mitochondria (nmoles CoQ/mg prot.)	3.87 $\pm$ 0.25	1.7 $\pm$ 0.4

*Coenzyme Q was extracted from skeletal muscle and liver by two different methods. Method 1 is essentially as described by Kröger (1978). It requires repeated extraction of an aqueous suspension with a hydrocarbon/methanol mixture as the extraction solvent. Method 2 (a modified procedure of Burton *et al.* 1985) involves a combination of sodium dodecyl sulphate (SDS), absolute ethanol and n-heptane as the solvent. Both methods yield comparable values for the CoQ content.*

Recently, it has been recognized that CoQ in the cell plasma membrane and endomembranes represents a redox component of extramitochondrial electron transfer chains involved in yet undefined aspects of signal transduction, although the position and mechanism of action of the quinone are to be defined (Crane *et al.* 1993).

## Antioxidant effect of CoQ

A good deal of evidence exists in support of the contention that CoQ acts as a powerful antioxidant (Beyer 1990, Ernster and Forsmark-Andrée 1993), but some pro-oxidant effects were also found (Cadenas *et al.* 1977, Ksenzenko *et al.* 1983). Packer *et al.* (1991) summarized several findings supporting an antioxidant hypothesis of CoQ actions in membranes: 1. reduced CoQ is an effective scavenger of lipid radicals and an inhibitor of lipid peroxidation, 2. mitochondrial membranes with depleted levels of CoQ are more sensitive to oxidation damage than control membranes or membranes with exogenous CoQ addition, 3. exogenously administered CoQ has proved to be beneficial towards some pathological alterations correlating with the occurrence of lipid peroxidation, 4. CoQ is present not only in the mitochondrial inner membrane but also in other membranes.

There is a significant relation of the antioxidant activity of CoQ and vitamin E. Kagan and Packer (1993) suggested that the important action of CoQ is its ability to recycle and regenerate tocopherols which are the key elements in antioxidant protection.

Experiments with hepatocytes treated with low doses of adriamycin showed that CoQ is able to preserve and potentiate the normal cellular defenses against the oxidative stress induced by adriamycin in rat hepatocytes (Cavazzoni *et al.* 1994, Lenaz *et al.* 1994b).

Reduced CoQ was also found to protect very effectively human low-density lipoproteins (LDL), which are generally implicated in the pathogenesis of atherosclerosis, against lipid peroxidation (Stocker *et al.* 1991, Ingold *et al.* 1993).

## Membrane-stabilizing function of CoQ

The CoQ molecule also has membrane-stabilizing functions (Fato *et al.* 1984, Lenaz and Parenti Castelli 1984). Extraction of endogenous CoQ from mitochondria significantly decreases the fluidity in the membrane core, whereas reincorporation of CoQ to original levels restores fluidity (Fato *et al.* 1984). This fluidizing effect of physiological CoQ concentrations suggests that it may be involved in the maintenance of optimal membrane fluidity which is important for optimal physiological functions of receptors, carriers and membrane-bound enzymes.

## Possible implications of CoQ in senescence

A decrease of the CoQ concentration in postmitotic tissues was described in senescent rats and humans (Kalén *et al.* 1989, Appelkvist *et al.* 1991), although other studies obtained in isolated mitochondria, did not reveal major changes in rat tissues during aging (Lenaz *et al.* 1994b). CoQ is easily

synthesized in animals (Kalén *et al.* 1987), but the beneficial effect of CoQ administration is considered to be important in retarding the aging process. Miquel and Fleming (1986) postulated the "free radicals hypothesis", where free radicals play a key role in starting the chain of age-related disorganization. Mitochondrial DNA (mtDNA) synthesis is easily damaged by reactive oxygen species because mtDNA lacks histone protection and excision repair (Miquel 1991). Inactivation or mutation of mtDNA, which encodes the synthesis of several hydrophobic proteins of the inner mitochondrial membrane, is expected to cause an irreversible decline in the bioenergetic ability of mitochondria. Therefore, the level of antioxidants in the cell may be important, at least in part, to prevent or retard free radical damage. It is expected that exogenous CoQ administration may prove beneficial in senescence (Lenaz *et al.* 1994b).

## Possible therapeutic applications of CoQ

All the above mentioned properties of CoQ are of both biochemical and biomedical interest. The bioenergetic role seems sufficient to explain at least some of the clinical effects. As CoQ concentration is not physiologically saturating, any condition causing a decrease of CoQ content could also decrease the rate of electron transfer and enhance the damages induced by free-radical attack, with possible subsequent severe pathological effects. Moreover, a CoQ decrease could cause a chain of events leading to further CoQ loss by free radical attack (Lenaz *et al.* 1990b).

Over the past decade, many reports have been published on CoQ deficiency and clinical efficiency of the administration of exogenous CoQ. A number of studies were undertaken to examine the CoQ distribution in tissues after both oral and parenteral short- or long-term administrations (Alessandri *et al.* 1988, Reahal and Wrigglesworth 1992, Scalori *et al.* 1988, Scalori *et al.* 1990). Studies on rats showed that CoQ passes from the plasma into tissues within a few hours after intravenous or oral CoQ administration (Alessandri *et al.* 1988, Scalori *et al.* 1988). After a two-week period of oral administration, CoQ is incorporated into the soluble fraction of liver cells, whereas intraperitoneally administered CoQ is incorporated into the liver and spleen. There were no significant changes in mitochondrial CoQ levels following a two-week period of administration (Reahal and Wrigglesworth 1992). This finding agrees with the lack of mitochondrial uptake of CoQ<sub>10</sub> after liver perfusion in the rat, in spite of the high incorporation into the lysosomal fraction (Genova *et al.* 1994). It seems that the employed vehicles may also account for the differences seen after oral or parenteral CoQ administrations (Scalori *et al.* 1990).

The first clinical trial with CoQ was conducted by Japanese investigators (Yamamura 1985). Patients

with congestive heart failure or coronary insufficiency received CoQ intravenously in a dose of 50 mg/day. Nowadays, the clinical action of CoQ is an established fact although higher doses are usually required. Certain beneficial effects of CoQ were found not only in the above cardiovascular disorders but also in hypertension, cerebrovascular disorders, muscular dystrophies, neurogenic atrophies, periodontal diseases, etc. (Folkers *et al.* 1991, 1993, Folkers and Yamamura 1977, 1981, 1984, 1986, Littarru *et al.* 1994, Yamamura *et al.* 1980). Administration of exogenous CoQ has also been postulated to have an important role in the treatment of patients with the acquired immunodeficiency syndrome (Langsjoen *et al.* 1991) because CoQ levels in whole blood were found to be severely depressed in these patients.

The molecular mechanisms by which the therapeutic effects are exerted are not completely elucidated. This incomplete recognition appears to be due to the multiplicity of roles that the CoQ molecule fulfills in mammalian cells.

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