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Review

Biochemical Functions of Coenzyme Q_{10}

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Key words: energy coupling, antioxidant, transmembrane signaling, gene expression

Coenzyme Q is well defined as a crucial component of the oxidative phosphorylation process in mitochondria which converts the energy in carbohydrates and fatty acids into ATP to drive cellular machinery and synthesis. New roles for coenzyme Q in other cellular functions are only becoming recognized. The new aspects have developed from the recognition that coenzyme Q can undergo oxidation/reduction reactions in other cell membranes such as lysosomes, Golgi or plasma membranes. In mitochondria and lysosomes, coenzyme Q undergoes reduction/oxidation cycles during which it transfers protons across the membrane to form a proton gradient. The presence of high concentrations of quinol in all membranes provides a basis for antioxidant action either by direct reaction with radicals or by regeneration of tocopherol and ascorbate. Evidence for a function in redox control of cell signaling and gene expression is developing from studies on coenzyme Q stimulation of cell growth, inhibition of apoptosis, control of thiol groups, formation of hydrogen peroxide and control of membrane channels. Deficiency of coenzyme Q has been described based on failure of biosynthesis caused by gene mutation, inhibition of biosynthesis by HMG coA reductase inhibitors (statins) or for unknown reasons in ageing and cancer. Correction of deficiency requires supplementation with higher levels of coenzyme Q than are available in the diet.

Key teaching points:

- Coenzyme Q is needed for energy conversion.
- Coenzyme Q is an essential antioxidant.
- Coenzyme Q regenerates other antioxidants.
- Coenzyme Q stimulates cell growth and inhibits cell death.
- Decreased biosynthesis may cause deficiency.

INTRODUCTION

The point to emphasize is that coenzyme Q has several biochemical functions [1]. The well recognized functions are in mitochondrial energy coupling and its action as a primary regenerating antioxidant. Less well established functions include oxidant action in the generation of signals and control of cellular redox state. By participation in transmembrane electron transport coenzyme Q can carry reducing equivalents to the inside of vesicles or to the outside of cells. There is also evidence for a role in proton gradient formation in endomembranes and at the plasma membrane. In addition, there is evidence that coenzyme Q can take part in control of membrane structure and phospholipid status [2,3].

Coenzyme Q is 2,3-dimethoxy,5-methyl, 6-polyisoprene parabenzoquinone. The coenzyme Q_{10} found in humans has a polyisoprene chain containing 10 isoprene units (5 carbons each) or a total of 50 carbons. The all *trans* polyisosoprene ensures an affinity for the interior of cell membranes. The two methoxy groups contribute to the specificity in enzyme action as may the methyl group. The fully substituted quinone ring does not allow addition reactions with thiol groups in the cell such as glutathione, thioredoxin or thioctic acid. The functional group is the quinone ring. By reduction of the quinone to quinol a carrier of protons and electrons is produced [4].

Coenzyme Q is distributed in all membranes throughout the cell [5]. In mitochondria there are well defined protein binding sites on the enzymes involved in coenzyme Q oxidation reduction

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[6]. Enzymes in other membranes can be expected to have specific coenzyme Q binding sites, but these have not been defined. In addition there is coenzyme Q floating in the phospholipid bilayer of the membranes. The free form may float with the all *trans* polyisoprene chain extended in a long linear structure with the methyl groups intercalated in the fatty acid chains of the lipid. There is also evidence that in some cases the polyisoprenoid chain may be folded into a shorter, thicker structure. It is thought that the isoprenoid chain may help to stabilize the lipid bilayer [2]. The quinone head group can be either the oxidized (quinone) or reduced (quinol) form. In most membranes enzymes have been defined which can reduce the quinone and oxidize the quinol. The percent in quinol form in various membranes and serum ranges from 30% to 90%, depending on the metabolic state of the cell [7]. The quinol (hydroquinone) is more hydrophilic, so the head group can lie closer to the surface of the membrane. The change of position with oxidation/reduction may modify structural or enzymatic properties in the membrane. For example, the redox state may control activity of phospholipases in the membrane [3].

Genetic mutation, ageing, cancer and statin type drugs can cause a decrease of coenzyme Q in serum or tissue (Table 1). The precise membranes in all cells which have less are not known, but deficiency can be observed in mitochondria of some cells but not in others. The amount of coenzyme Q in the diet is not sufficient to increase serum coenzyme Q significantly. Significant increase of coenzyme Q in serum requires supplementation with about 100 mg/day.

ENERGY COUPLING

Coenzyme Q is an essential part of the cellular machinery used to produce ATP which provides the energy for muscle contraction and other vital cellular functions. The major part of ATP production occurs in the inner membrane of mitochondria, where coenzyme Q is found. The coenzyme Q has a unique function since it transfers electrons from the primary substrates to the oxidase system at the same time that it transfers protons to the outside of the mitochondrial membrane. This transfer results in a proton gradient across the membrane. As the protons return to the interior through the enzymatic machinery for making ATP, they drive the formation of ATP. The coenzyme Q is bound to the oriented enzymatic protein complexes. It is oxidized and releases protons to the outside and picks up electrons and protons on the inside of the mitochondrial membrane [8, 9].

Table 1. Coenzyme Q Deficiency in Humans

Basis	Tissue Analysis	% Decrease from Control	Ref
Genetic	Lymphocytes	—	[49]
Age***	Myocardium	72%	[50]
Age*	Heart	58%	[63]
Age*	Pancreas	83%	[63]
Age*	Adrenal	50%	[63]
Age*	Liver	17%	[63]
Age*	Kidney	45%	[63]
Age**	Skin epidermis	75%	[21]
Genetic	Skin fibroblasts	90%	[49]
Pravastatin[0]	Serum	20%	[64]
Lovastain[0]	Serum	29%	[64]
Simvastatin[0]	Serum	26%	[65]
Cancer (pancreas)	Serum	30%	[66]
Diabetic (NIDDM)	Serum	65%	[67]

* Change from age 19–21 to age 77–81.

** Change from age 30 to age 80.

*** Change from avg. age 58 ± 1.7 to 76 ± 6.8.

[0] HMG CoA reductase inhibitors of isoprene synthesis.

There are two protein complexes in the membrane where electrons and protons are transferred through coenzyme Q. The first is the primary reductase where coenzyme Q is reduced by NADH (complex I). During the reduction process four protons are transported across the membrane for every coenzyme Q reduced [8 (Fig. 1)]. The details of this process are still unclear, but it has been proposed that coenzyme Q is reduced and reoxidized in the complex twice before electrons are transferred to a second loosely bound coenzyme Q to form quinol which can travel through the lipid in the membrane to a second complex where the quinol is oxidized again (complex III) with transfer of protons across the membrane [9 (Fig. 2)]. The details of quinol binding and oxidation at the binding site in this complex are well known. As in complex I, there is a cyclic oxidation-reduction-reoxidation with the oxidation and proton release step always on the outside so that protons are released in the right direction. Again the oxidation-reduction cycle allows for four protons to cross the membrane for each quinol oxidation cycle. The quinone cycle thus doubles the efficiency of the coenzyme Q in building up the proton charge across the membrane which allows twice as much ATP production than a simple one step oxidation of quinol. After the cycle is completed the oxidized quinone migrates through the membrane to be rereduced at complex I.

A simpler form of energy conversion based on coenzyme Q reduction-oxidation is found in lysosomes [10]. In this case the

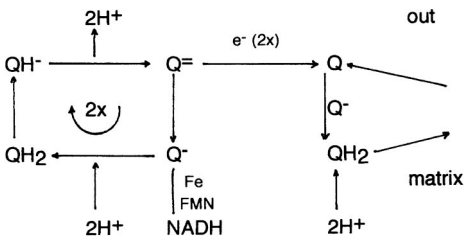

Fig. 1. Reductive Q cycle. Scheme proposed [8] for reduction and proton transfer through the tightly bound coenzyme Q in complex I. Partial oxidation of quinol allows recycling of the quinone to carry more protons across the membrane than electrons transferred to the losely bound coenzyme Q which travels in the lipid bilayer to be oxidized in complex III.

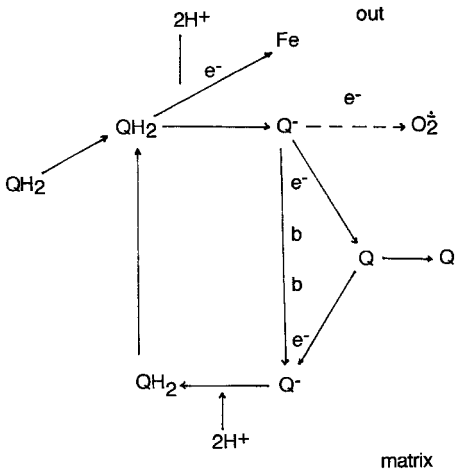

Fig. 2. Oxidative Q cycle. Scheme proposed [9] for partial oxidation of the quinol to provide electrons from the semiquinone for rereduction of quinone to quinol with uptake of protons for transfer across the membrane.

quinol transfers a proton across the lysosomal membrane to acidify the inside which involves energy input to work against a proton gradient. No ATP can be formed since the lysosomal membrane does not have a proton driven ATP synthetase. The acidification of the lysosome activates hydrolytic enzymes for digestion of cellular debris. In other words, coenzyme Q energizes cell house cleaning. The details of the enzymes and possible Q binding sites in the lysosomal membrane are not known. The enzyme complex in the membrane involves reduction of coenzyme Q by NADH in the cytoplasm and reoxidation of the quinol by oxygen.

Another site where coenzyme Q may be involved in vesicle acidification is in pinocytotic endosomes which engulf iron and transferrin bound to transferrin receptors and carry it into the cell. There is a redox system in the membranes of these vesicles which can acidify their interior [11]. Reduction of transferrin-bound iron in an acid environment releases the iron for uptake into the cytoplasm. The possible role of coenzyme Q in iron reduction and proton transfer in these membranes has not been established.

Another role for coenzyme Q in proton movement is indicated at the plasma membrane. In this situation coenzyme Q is involved in activation of Na+/H+ exchange across the membrane carried out by the Na+/H+ antiport. The energy for this process is based on a high concentration of Na+ outside the cell which exchanges for protons in the cell. The Na+ is then pumped out of the cell by the Na+/K+ ATPase which obtains energy from ATP. During this ATP action excess Na+ is released so the cell develops an inside negative membrane potential which is important for many cellular functions and transport action [12]. Coenzyme Q is involved in a plasma membrane electron transport system by which NADH in the cytoplasm transfers electrons through coenzyme Q to electron acceptors such as iron or oxygen outside the cell. When this system is activated, the proton release through the H+/Na+ antiport is greatly increased. When the system is inhibited by inhibitory coenzyme Q analogs, the antiport is inhibited. As a result of activation of the antiport, the interior of the cell becomes more alkaline. The mechanism by which the coenzyme Q dependent electron transport activates the antiport is not known [13].

If the Na+/H+ antiport is inhibited by amiloride, the transplasma membrane electron transport is accompanied by a slow release of protons equivalent to two protons released per quinol oxidized. This proton release indicates that the reduction oxidation of the coenzyme Q in the membrane is organized as in the lysosomes. In contrast, the proton release by activation of the antiport is more that ten times greater than the electron transport driven proton transfer.

ANTIOXIDANT FUNCTIONS

Coenzyme Q is well located in membranes in close proximity to the unsaturated lipid chains to act as a primary scavenger of free radicals. The amount of CoQ in many membranes is from three to 30 times the tocopherol content [14] (also see Table 2)]. Since much of the coenzyme Q in cell membranes is in the quinol form [15], it can be a very effective antioxidant [16]. Even more important is the presence of enzymes in all membranes which can reduce any coenzyme Q quinone radical generated by reaction with lipid or oxygen radicals. At least three enzymes are known which can keep the coenzyme Q reduced in plasma and endomembranes [1]. These enzymes are (1) NADH cytochrome b5 reductase [17], (2) NADH/NADPH oxidoreductase (DT diaphorase [17]), (3) NADPH coenzyme Q reductase [18]. In mitochondria the NADH and succinate dehydrogenases can keep coenzyme Q partly reduced. Reductases 1 and 3 in endomembranes can be especially important by one electron transfer to rereduce any semiquinone generated by reaction of quinol with a radical. The DT diaphorase is unique since it can directly reduce, by 2 electron transfer, any quinone formed without intermediate formation of the semiquinone. Under conditions of oxidative stress induced by nutritional lack of selenium and α-tocopherol, the coenzyme Q in membranes is greatly increased. The amount of DT diaphorase attached to

Table 2. Coenzyme Q in Cell Membranes and Relation to α-Tocopherol

Rat Liver Membranes	CoQ/αtoc mol/mol	CoQ μg/mg protein
Mitochondria (cristae)	35	1.9
Plasma membrane	21	0.7
Peroxisomes	3	0.3
Lysosomes	3	1.9
Golgi membranes	1	2.6
Endoplasmic reticulum	1	0.2

Data based on [5,14].

membranes where it can reduce coenzyme Q is also remarkably increased [19]. Similar decrease in α-tocopherol induced by peroxisomal proliferator is accompanied by a large increase in coenzyme Q [14].

A direct demonstration of the effectiveness of coenzyme Q as an antioxidant can be shown with coenzyme Q deficient yeast. A yeast mutant deficient in coenzyme Q synthesis shows more lipid peroxide formation than normal yeast [20]. Another direct demonstration of elimination of free radicals is shown by coenzyme Q treatment of skin in older persons. Luminescence from free radicals is eliminated when a skin cream containing coenzyme Q is applied [21].

In addition to direct antioxidant radical scavenging, the quinol can rescue tocopheryl radicals produced by reaction with lipid or oxygen radicals by direct reduction back to tocopherol [22]. Without coenzyme Q in a membrane, regeneration of tocopherol is very slow. The regeneration of tocopherol can also be observed in low density lipoprotein where a small amount of coenzyme Q protects a larger amount of tocopherol. This function is presumably favored by the high percent of quinol present in blood [23, 24].

There is some evidence that the coenzyme Q dependent electron transport across the plasma membrane can be used to regenerate ascorbate outside the cell from ascorbate radical (monodehydroascorbate [25]). Ascorbate inside the cell can be regenerated by a glutathione based system. Regeneration outside requires electron transfer through the plasma membrane, some of which depends on the presence of coenzyme Q in the membrane.

CELL SIGNALING AND GENE EXPRESSION

Coenzyme Q can participate in several aspects of oxidation/reduction control of signal origin and transmission in cells. The autooxidation of the semiquinone formed in various membranes during electron transport activity can be a primary basis for generation of H_2O_2 [1,26]. The H_2O_2 in turn activates transcription factors such as NF_KB to induce gene expression [27]. Peroxide can also be involved in calcium signaling in cardiac muscle [28]. It is also possible that reactive oxygen species generation may lead to suppression of other genes. The quinone can also participate in oxidation of thiol groups on growth factor receptors or membrane ion channels. An example is ryanodine receptor controlled Ca++ release which may also be related to oxygen sensing [29,30]. On the other hand, reduction of disulfide bonds by the quinol would require energy driven reverse electron transport since the redox potential of coenzyme Q is higher (+100 mV) than the thiol-disulfide couple (−320 mV). A proton gradient driven electron transport as seen in reduction of NAD by succinate in mitochondria would drive this disulfide reduction by the quinol. Control of the redox state of protein disulfide isomerase at the cell surface by the quinol oxidase or the quinone reductase has been discussed [31].

Formation of the coenzyme Q semiquinone in complex III of mitochondria has long been cited as a primary source of superoxide and subsequently hydrogen peroxide in cells [32]. This source is controlled by the redox state or degree of energy coupling in the mitochondria [26]. Similar control applies to H_2O_2 production at the succinate dehydrogenase (complex II) or NADH dehydrogenase (complex I) sites for reduction/oxidation of coenzyme Q [26 (Fig. 3)]. It is expected that binding of the semiquinone in these complexes would decrease autooxidation, but any condition which disturbs the equilibrium between quinone and binding protein to allow quinone exposure may encourage peroxide production [33].

Since coenzyme Q is not restricted to mitochondria and the coenzyme Q in other membranes undergoes oxidoreduction [10,34,35], there is probably potential for peroxide generation in all membranes. Certainly lysosome, Golgi and plasma membranes are candidates. Plasma membranes do generate peroxide during oxidation of NADH [36].

Although there are enzymes which can reduce coenzyme Q in all endomembranes and in plasma membrane, the presence of binding sites which can protect the semiquinone from autooxidation and prevent subsequent peroxide production are unknown. Furthermore, enzymes for oxidation of quinol in plasma membrane have been identified. A cell surface NADH oxidase and a transplasma membrane NADH oxidase have been observed [37]. The surface oxidase also acts as a coenzyme Q quinol oxidase [38] and shows evidence for superoxide generation [37]. The quinol oxidase portion of the transmembrane oxidase has not been isolated but it appears to require non-heme iron since it is reversibly inhibited by impermeable iron chelators [39]. The transmembrane NADH oxidase requires coenzyme Q [35]. A second transplasma membrane NAD(P)H oxidase has been defined which is homologous with

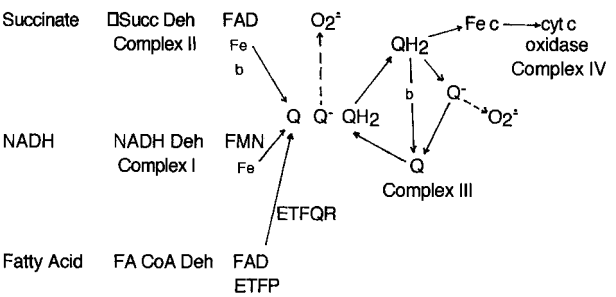

Fig. 3. Sites for semiquinone formation in the redox complexes of mitochondria. Complex I, II and III generate semiquinone which takes part in normal electron transfer. If semiquinone accumulates because of inhibitors, excess substrate or excess proton accumulation, the semiquinone can be autooxidized to produce superoxide [26]. Semiquinone formation in fatty acid oxidation (FA) would probably be associated with the electron transfer flavoprotein (ETFP) coenzyme Q oxidoreductase ETFQR [70]. Glycerol-3-phosphate dehydrogenase also reacts with coenzyme Q (not shown [71]).

the superoxide generating NADPH oxidase found in neutrophil plasma membrane [40, 41]. This oxidase uses cytochrome b558 to produce superoxide and is characteristic of transformed and tumor cells. The coenzyme Q dependent transmembrane enzyme has been defined in rat liver and heart cells and appears to be a normal component in all animal cells [13]. The extent to which it can be activated to produce superoxide has not been defined. Possible evidence that superoxide production induced by phorbol myristate acetate depends on coenzyme Q is suggested by retinoic acid inhibition in Balb 3T3 cells [42]. Retinoic acid does not inhibit transformed Balb 3T3 cells. Loss of retinoic acid response suggests that the b558 oxidase predominates over the coenzyme Q system in some transformed cells [1].

At this point we do not know which plasma membrane electron transport system is responsible for superoxide and peroxide formation at the cell surface of different types of cells (Fig. 4). The inhibition of transplasma membrane electron transport in transformed cells by antitumor drugs but not in untransformed cells suggests that the b_{558} (Mox 1) enzyme is activated in these cells as it is in the ras mutant cells [1,43,44]. On the other hand retinoic acid appears to be a specific inhibitor for the system in nontransformed cells which presumably is the coenzyme Q dependent system [44] since the transmembrane enzyme in normal liver cells is largely dependent on coenzyme Q [35].

The effect of the plasma membrane electron transport on cell proliferation is probably not exclusively related to generation of H_2O_2. This is seen in the effect of ferricyanide as an external electron acceptor on the expression of c-myc and c-fos genes in C3H 10T1/2 cells [45]. Since ferricyanide will destroy any peroxide produced at the cell surface, its growth effect may be based on alteration of the cytosolic redox state by oxidation of NADH [46]. The basis for inhibition of apoptosis by coenzyme Q remains to be established. The effect may be based on redox control or on membrane structure control and modification of phospholipid as in the inhibition of ceramide formation [17, 47]. The role of coenzyme Q in signal transduction, gene expression and membrane channels is therefore a new area in need of further study. There is ample evidence that it is involved in significant control functions.

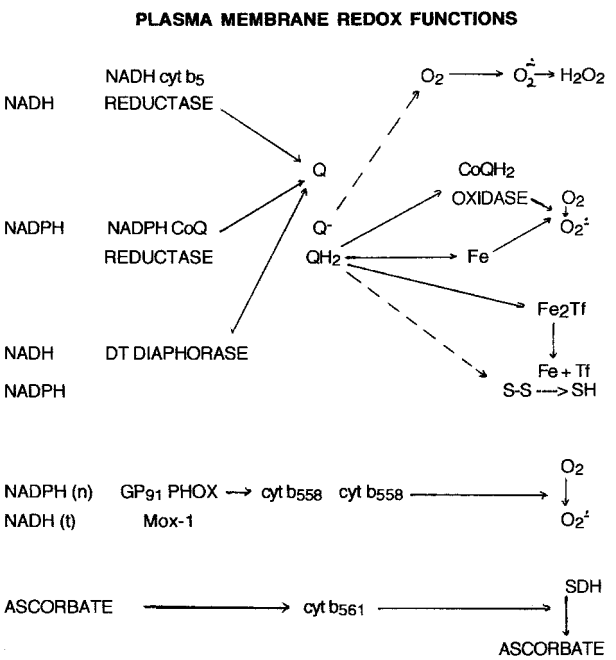

Fig. 4. Plasma membrane redox functions. Two types of transplasma membrane electron transfer are known. One type uses coenzyme Q as a transmembrane electron carrier [72]; the other uses a low redox potential cytochrome b558 complex. This enzyme is analogous to the peroxide generating GP91 phox of neutrophils (n [40, 41]) and may be characteristic of transformed cells (t [73]). In addition, cytosolic ascorbate can reduce external semidehydroascorbate through a cytochrome b561 in some cells. Three different NAD(P)H dehydrogenases (reductases) on the plasma membrane can reduce coenzyme Q [17, 18]. Two different enzymes are indicated for oxidation of the Q quinol. One is a coenzyme Q oxidase at the outer surface which can oxidize quinol at the outer surface with production of superoxide [37]. The other is an external site sensitive to iron chelators [39]. It can be expected that autooxidation of the iron in neutral pH will produce superoxide [74]. It is not known which system is responsible for diferric transferrin reduction at the cell surface [75]. The recycling of the iron on the tranferrin through reoxidation by oxygen could also produce superoxide since diferric transferrin stimulates NADH oxidation by plasma membrane. The peroxide produced by either of these oxidase systems can then feed back into the cell to activate gene transcription [27], SH-S-S controlled calcium channels [28, 76] or inhibit phosphotyrosine phosphatase [77]. The mechanism of control of the Na+/H+ antiport is not known. Tf is transferrin. The mechanism for redox control of the Na+/H+ antiport [12] or Ca++ activated K+ channels is not known [78]. Gene transcription regulated by the hemopexin system is controlled by surface copper reduction dependent on coenzyme Q [79,80].

DEFICIENCY

In normal healthy individuals coenzyme Q is synthesized in all cells from tyrosine (or phenylalanine) and mevalonate [48]. Only four cases are reported with genetic based failure of synthesis [49]. Low levels of coenzyme Q are found in disease or ageing [21,50,51,52]. It is not clear how the distribution of coenzyme Q in tissue is controlled. In tissues with unimpaired synthetic capacity, it appears that coenzyme Q in each membrane reaches a saturation level [53]. Thus supplementation with coenzyme Q does not increase tissue levels above normal (except in liver and spleen). This is especially true in young, healthy animals. In older animals with decreased coenzyme Q, in some tissue, supplemental coenzyme Q can restore normal levels [50,53,54]. In addition to decrease in biosynthesis, other factors may affect levels or function of coenzyme Q. These include increase in degradation [55] or changes in membrane lipids to impede quinone movement [56]. Changes of coenzyme Q in different tissues and cell membranes with ageing seem to vary. For example, ageing rats decrease coenzyme Q

Table 3. Coenzyme Q in the Diet

Food		CoQ_{10} Content μg/g	Daily Portion g/day	CoQ_{10} Intake mg/day
Meat	Pork heart	203	120	24
	Chicken leg	17	120	2.0
	Beef heart	41	120	4.8
	Beef liver	19	120	2.3
	Lamb leg	2.9	120	3.5
	Frog leg	5	120	0.6
Fish	Herring	27	26	0.7
	Trout	11	100	1.1
Vegetable	Cauliflower	0.6	200	0.12
	Spinach	2.3	200	0.46
	Potato	.24	200	0.05
Fruit	Orange	2.2	200	0.44

Data based on [68,69].

selectively in skeletal muscle mitochondria [57] but increase coenzyme Q in mitochondria from brain [58]. Changes in other membranes with ageing need to be determined in relation to loss of function or antioxidant capability.

Nutritional replenishment of coenzyme Q requires a higher level than is available in most food (Table 3). The normal level in blood is around 1 μg/mL [51,59,60]. To increase the concentration significantly requires at least 100 mg/day which can increase the level in blood to around 2 μg/mL or more. An increase to 2 μg/mL in blood can be therapeutic for various conditions [61]; this may indicate that a high blood level is needed to get coenzyme Q into deficient tissues. Even with large amounts of heart or herring in the diet, it would be difficult to supply 100 mg/day.

CONCLUSION

The important point to consider is that coenzyme Q is not just an agent for energy transduction in mitochondria. It is a functional element in all cell membranes. Part of this wider function is based on its antioxidant action with unique capacity for regeneration of redox capacity and a unique location deep in membrane structure. In addition there is growing evidence for a role in control of cell functions and growth. Gene activation or suppression may be based on peroxide production or control of thiol redox state. Other signal functions may involve control of membrane channels, structure and lipid stability.

Biosynthesis in mitochondria and endoplasmic reticulum provides sufficient coenzyme Q for normal individuals. It is not clear if two separate sites of synthesis are involved and how they are controlled [5,62]. Evidence for deficiency is based on genetic failure, age, disease or drugs which inhibit synthesis.

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