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Regulatory Aspects of Coenzyme Q Metabolism

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A number of factors are involved in the regulation of the amount and distribution of coenzyme Q in cells and tissues. These factors modify preferentially the biosynthetic mechanism in order to keep up an optimal tissue concentration of the lipid. The amount of substrate provided by the mevalonate pathway is able to both up- and down-regulate the velocity of synthesis. At the translation level, regulation occurs by receptor-mediated ligand binding and appears most clearly upon treatment with hormones and peroxisomal inducers. There are a number of pathophysiological conditions when these mechanisms of regulation are modified and explain the decreased coenzyme Q tissue concentrations. It is of considerable interest to establish appropriate physiological, hormonal and drug-mediated conditions in order to counteract disturbed cellular functions caused by coenzyme Q deficiency.

Keywords: Coenzyme Q; Mevalonate pathway; Hormones; Peroxisomes; Cancer; Aging

Abbreviations: CoQ, Coenzyme Q; FPP, Farnesyl pyrophosphate; HMG-CoA, 3-Hydroxyl-3-methylglutaryl coenzyme A; PPARα, Peroxisome proliferator-activated receptor α; RXR, Retinoid X receptor; DHEA, Dehydroepiandrosterone; DEHP, Di-(2-ethylhexyl)phthalate; PPRE, Peroxisome proliferator responsive element

INTRODUCTION

Phospholipids dominate the lipid composition in all biological membranes due to their inherent ability to spontaneously form membrane bilayers. While the mevalonate pathway lipids cholesterol, dolichol and coenzyme Q (CoQ) cannot form lipid bilayers by themselves, they have profound effects on the physico-chemical properties of membranes. They are obligatory components in practically all membranes and influence membrane stability, fluidity and permeability to a large extent. Beside its role as a membrane structural component CoQ has two major functions. It serves as redox component in the mitochondrial and plasma membrane electron transport and it is an important endogenously synthesized lipid soluble antioxidant. Obviously, the concentration in organs and membranes is dependent on the functional requirements and exhibits great variations not only in different tissues but also within the same organ and among membranes of the individual cell.[1] Like other polyisoprenoid lipids, CoQ is localized in the central hydrophobic portion of the lipid bilayer. Consequently, this lipid cannot increase freely within membranes due to the destabilization as well as to the physical limits of the bilayer.

CoQ has a high turnover in all tissues so far studied and the $T_{1/2}$ varies between 50 and 125 h depending on the tissue. Even in brain where cholesterol and dolichol exhibit a half-life of several months, CoQ has a half-life of 80 h. Interestingly, while in most tissues the large majority of CoQ is in reduced form, only 20% of the lipid is reduced in brain. To be able to function as an antioxidant, CoQ must be in the reduced form. The large proportion of oxidized CoQ in the brain could therefore be a reflection of the high oxygen consumption in this tissue causing an increased demand of antioxidants.

Studies on the breakdown of CoQ have been very limited although this process may be as important as

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the biosynthesis for the regulation of the tissue concentration of this lipid. The products formed during breakdown of endogenous CoQ have not been characterized yet and it is not known which type of breakdown products can be present in various conditions. The CoQ biosynthesis have been investigated in great detail in bacteria and yeast, however, in mammalian tissues only a few genes have been identified and none of the enzymes has been characterized on a protein level.[2,3] All cells synthesize their own CoQ in order to fulfill intracellular requirements but virtually nothing is known about the intracellular redistribution of this lipid to the different subcellular compartments. Limited amounts of CoQ are discharged from the liver and present in lipoproteins but no redistribution among tissues has been observed as with cholesterol.

From the multitude of CoQ functions and its different concentrations in subcellular compartments, it is evident that the cellular regulation of CoQ must be very complex. In this paper, we have selected to discuss the metabolic, pharmacological and dietary factors that interfere with the uptake and biosynthesis of CoQ and contribute to the increase of this lipid in various organs. The metabolism of CoQ is regulated on a complex manner, and consequently, we can only discuss selected, recent events in this field.

SUBSTRATE DEPENDENT REGULATION OF CoQ SYNTHESIS

The initial part of the mevalonate pathway is a sequence of reactions that forms farnesyl-PP (FPP) from acetyl-CoA (Fig. 1). FPP is the last common substrate for the biosynthesis of several end products including CoQ.[4] In addition to HMG-CoA reductase, the branch point enzymes after FPP synthase, e.g. squalene synthase for cholesterol, *cis*-prenyltransferase for dolichol and *trans*-prenyltransferase for CoQ are the main regulatory enzymes in the biosynthesis of these lipids. According to the "flux diversion hypothesis" the branch point enzymes have different affinities for FPP and consequently, a change in the FPP pool will have different effects on the rate of biosynthesis of each lipid.[5] Thus, squalene synthase has a poor affinity for FPP in opposite to the other branch point enzymes and a decrease in substrate concentration will therefore selectively affect cholesterol biosynthesis. This principle forms the basis for the treatment of hypercholesterolemic patients with HMG-CoA reductase inhibitors.[6] Treatment with these inhibitors was expected to decrease cholesterol biosynthesis while leaving enough FPP to saturate *trans*-prenyltransferase for CoQ biosynthesis. However, both rodent and human studies have

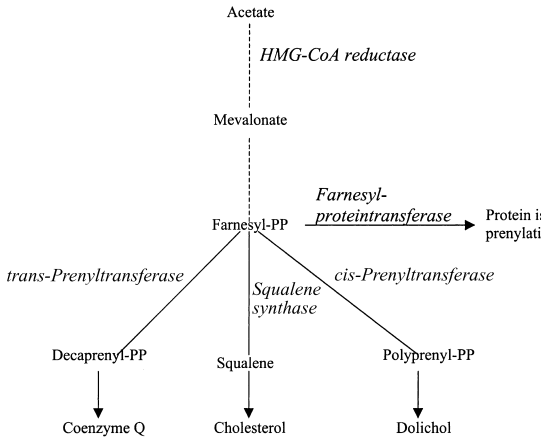

FIGURE 1 Schematic representation of the mevalonate pathway and its rate-limiting enzymes.

demonstrated a partial inhibition of CoQ synthesis in several organs upon treatment with these inhibitors (Fig. 2).[7] On the basis of these findings it was advantageous to develop drugs that would inhibit cholesterol biosynthesis after the branch point. Squalestatin-1 is a competitive inhibitor of squalene synthase and was thought to circumvent the negative effects of HMG-CoA inhibitors.[8] Nevertheless, the almost complete inhibition of cholesterol biosynthesis resulted in a greatly elevated FPP pool with the concomitant production of several farnesol metabolites. Furthermore, in experiments on both tissue culture cells and rats the inhibitor efficiently increased the biosynthesis and concentration of CoQ.[9,10] The above findings indicate that the *trans*-prenyltransferase activity is influenced by the initial part of the mevalonate pathway leading to FPP. Considering the fact that HMG-CoA reductase activity exhibits large diurnal variation, it is tempting to speculate that the biosynthesis of CoQ will vary at least to some extent during day and night.

The pool question is however more complex as the enzyme FPP synthase is present in cytosol, microsomes, mitochondria and peroxisomes.[11] In assays of plant and rat liver microsomal *trans*-prenyltransferase, only geranyl-PP can be used as the starting allylic compound.[12] This suggests that the microsomal FPP synthase is necessary for the conversion of geranyl-PP to FPP and that the cytosolic FPP pool is not available for the biosynthetic process.

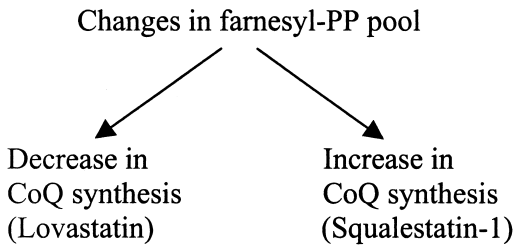

FIGURE 2 Modification of the FPP pool.

Recent studies indicate that the dephosphorylated FPP, farnesol, could be an important factor in lipid regulatory mechanisms.[13] The alcohol exerts effects on several metabolic reactions, transduction mechanisms and also causes apoptosis. It is unclear if it is the alcohol itself or one of its possible metabolites, such as dicarboxylated, hydroxylated or esterified form, i.e. the active substance. It will be an important task to isolate and characterize the various metabolites and investigate their influence on anabolic and catabolic lipid reactions. The possibility that a farnesoid X receptor exists has been raised, but the exact nature of the farnesol-derived ligand has been difficult to establish.[14] This receptor could be of great importance not only for the regulation of the initial part of the mevalonate pathway but also for the regulation of CoQ biosynthesis.

COLD ADAPTATION AND HORMONAL EFFECTS

During aging, the CoQ content in tissues is decreased which could be a potential risk for metabolic disturbances.[15] For this reason it is of interest to study different chemical and physical agents that increase the biosynthesis of this lipid. Cold adaptation induces thermogenesis and peroxisomal β-oxidation of fatty acids in brown adipose tissue.[16] Exposure to cold also increases CoQ concentration in all cellular membranes of liver and kidney.[17] Inhibition of thyroxin production with thiouracil inhibits this up-regulation. The increase is substantial and also occurs in peroxisome proliferator activated receptor α (PPARα)-null mice (Fig. 3). Accordingly, this mechanism involves the thyroid receptor but not PPARα. This is also evident from the fact that cold adaptation does not influence peroxisomal β-oxidation of fatty acids in liver. Interestingly, vitamin A (retinol) deficiency results in an increase in CoQ synthesis and both PPARα and thyroid hormone receptor are dependent on the retinoid X receptor (RXR) to form heterodimers that bind to appropriate response elements at the gene level. The exact nature of how these signal transduction mechanisms ultimately affect CoQ biosynthesis is however unclear.

Beside thyroxin, growth hormone, cortisone and dehydroepiandrosterone (DHEA) increase rat liver CoQ synthesis (Fig. 4). There are several possibilities to explain the effects of hormones on CoQ biosynthesis. They may exert a direct action on the promoters of the genes involved in CoQ biosynthesis. It is also possible that the metabolic changes induced by these hormones result in the production of unknown mediators that control CoQ biosynthesis. In the case of DHEA, this steroid lacks a known receptor but is a ligand to PPARα. This compound may however be of physiological importance since it decreases with age in the same way as CoQ.

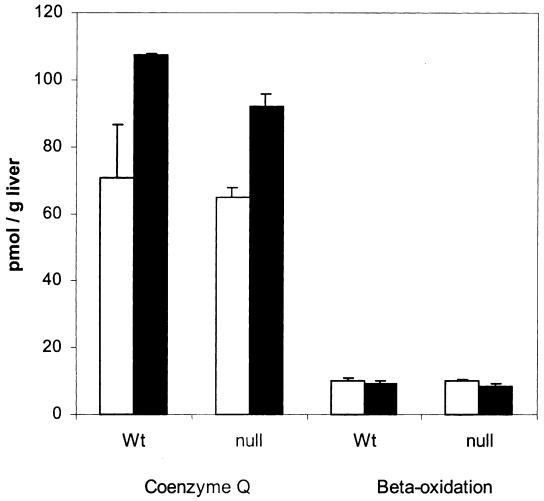

FIGURE 3 Coenzyme Q and β-oxidation activity after cold adaptation. Mice were kept at 4°C for 3 weeks. Liver homogenates were used to measure coenzyme Q content and lauryl-CoA oxidation. Wt = wild type; null = PPARα-null. Empty column = mice kept at 20°C; filled column = mice kept at 4°C.

PEROXISOMAL INDUCTION

A number of substances, mainly drugs developed or used for treatment of hyperlipidemia, are known to induce peroxisomes and to increase peroxisomal fatty acid oxidation 20–40 fold. The peroxisomal induction is also accompanied by an increase of CoQ amount in most tissues.[18] Mice treated with di-(2-ethylhexyl)phthalate (DEHP) display an increased CoQ concentration in the liver while dolichol and cholesterol amounts are unchanged (Table I). There appears to be a correlation between the potency of

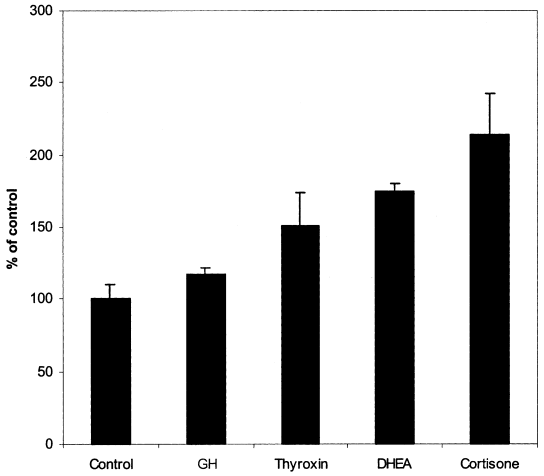

FIGURE 4 Effect of hormones on coenzyme Q content of rat liver. Rats were treated with growth hormone (GH), 0.8 IU, thyroxin 40 μg and cortisone 40 μg IU, by daily i.p. injections for 7 days. DHEA was administered in the diet (0.6%) for 3 weeks. Coenzyme Q content was measured in liver homogenate.

TABLE I Amount of mevalonate pathway lipids in mouse liver after 2% DEHP treatment

	Coenzyme Q (nmol/g tissue)	Dolichol (nmol/g tissue)	Cholesterol (μmol/g tissue)
Wild-type			
None	72.9 ± 3.7	17.3 ± 1.2	1.8 ± 0.1
2% DEHP	109.9 ± 7.7	15.1 ± 1.3	1.7 ± 0.1
PPARα-null			
None	70.6 ± 8.2	16.3 ± 1.5	1.7 ± 0.1
2% DEHP	68.5 ± 8.2	15.4 ± 0.9	1.6 ± 0.1

Mice were treated with 2% DEPH in the diet for 3 weeks. The lipids were separated and quantitated by reversed phase HPLC. Data taken from Ref. [20].

different peroxisomal proliferators and the increase of the lipid amount. Subcellular fractionation demonstrated that the increase in lipid concentration was not restricted to mitochondria but was present in all membranes. Incorporation studies with the precursor [^{3}H]mevalonate revealed an increased synthesis and an unchanged breakdown rate.

Peroxisomal induction is mediated by PPARα, which forms a heterodimer with RXR. The receptor complex is targeted to the promoter region of the appropriate gene and interacts with the peroxisome proliferator response element (PPRE).[19] Almost all genes with this response element are closely associated with lipid metabolism and not necessarily with peroxisomes. In Table I experiments with PPARα-null mice are described. In comparison with the wild type mice the amount of CoQ, dolichol and cholesterol are unchanged. Upon dietary administration of DEHP CoQ increased in the wild type mice but not in the null mice.[20] Thus, induction of CoQ with peroxisomal inducing agents requires the participation of this nuclear receptor.

Peroxisomal proliferation is associated with oxidative stress and the induction of acyl-CoA oxidase results in increased production of hydrogen peroxide. Consequently, sufficient catalase activity is required to remove hydrogen peroxide in order to counteract oxidative damage. Since catalase is not induced to any large extent with peroxisomal inducers, it was proposed that catalase activity is not sufficient and that the increased hydrogen peroxide levels cause DNA damage leading to non-genotoxic carcinogenesis. From this scenario it is reasonable to expect the cell to adapt by increasing its antioxidant CoQ. Treating mice with the catalase inhibitor aminotriazole tested this possible mechanism. After 3 weeks treatment a large part of the catalase activity in the liver was inhibited both in wild type and in PPARα-null mice (Fig. 5). In spite of the elevation of the intracellular hydrogen peroxide concentration by this treatment, no increase of CoQ was found either in wild type or in PPARα-null mice. Thus, the elevation of CoQ upon peroxisomal induction is not elicited by a cellular response to oxidative stress and involves another mechanism. The most plausible explanation is that some of the rate limiting enzymes in CoQ biosynthesis is encoded by genes that have PPRE in their promoter regions. Nevertheless, the promoter regions are not identified yet, and a definite mechanism cannot therefore be assigned.

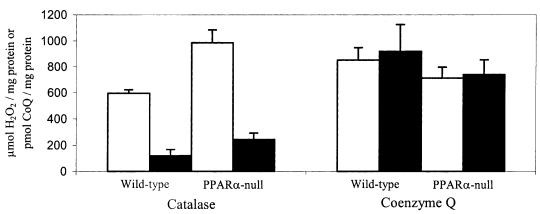

FIGURE 5 Inhibition of catalase activity in wild type and PPARα-null mice. Open column = control, filled column = mice treated with a 1% aminotriazole-containing diet for 3 weeks. CoQ was determined in liver homogenates. Data taken from Ref. [20].

The degree of CoQ induction by peroxisomal inducers is dependent on the PPARα amount in the individual tissues. This correlation, however, is modified during aging.[21] In 1–2 month old rats, peroxisomal β-oxidation activity is increased 14 times upon dietary administration of DEHP and the amount of CoQ is elevated three-fold. While treatment of 18 month old rats with DEHP increased the β-oxidation activity 30 times, CoQ amount was not induced and remained at the same level. It appears that the induction of CoQ by peroxisomal proliferators is dependent on other mediators that change during aging. Such permissive factors are common in gene activation and could for instance be a hormone. It is well known that for example, thyroxin, growth hormone and DHEA decrease in older animals.

It is not known how peroxisomal inducers affect CoQ biosynthesis in humans. Many of these agents, such as clofibrate and acetylsalicylic acid, are used as drugs and it seems therefore feasible to design drugs that would up-regulate CoQ synthesis selectively. Clofibrate in rodents not only increases CoQ but also decreases blood cholesterol. These two effects could be advantageous in treatment of arteriosclerosis. Up-regulation of CoQ biosynthesis is followed by a distribution of the newly synthesized lipid to all membranes with the right intramembranous localization. The elevation of CoQ by peroxisomal inducers may be more efficient that the dietary

CoQ supply since the latter may not reach appropriate compartments.

UPTAKE OF DIETARY CoQ

Uptake of dietary CoQ from the gastrointestinal system to blood and various organs in both experimental and human systems is limited. Uptake of CoQ have been described into the blood, liver and spleen but were not found in other organs.[22–26] In other investigations some uptake were observed in mouse kidney mitochondria and rat brain.[27,28] In genetic disturbances, when children are born with extensive CoQ deficiency as a result of enzyme defects, the situation is different.[3] In these cases muscular and organ functions are drastically improved by dietary administration of the lipid, indicating an effective uptake. It is reasonable to suppose that the uptake is correlated with the degree of deficiency. This is not unexpected since there is a strict limitation to the amount of polyisoprenoid compounds that can be incorporated into the central hydrophobic region of the membrane. On the other hand, it is well documented that CoQ has beneficial effects and quantitatively improves organ function in many conditions.[29] These positive effects may only partially be explained by the direct uptake of the lipid (Table II). It is well known that many substances, such as neurotransmitters and some hormones, do not enter into the cell but activate signal transduction systems at the plasma membrane level. Thus, CoQ may modulate receptors at the plasma membrane and exert an effect without entering into the cell. Systemic effects could also be mediated by the increase of CoQ in blood. Enrichment of white blood cells with CoQ may modify the functional activity of monocytes, lymphocytes and granulocytes by influencing inflammation, immune reactions and arteriosclerosis. The gastrointestinal system is a favorable place for oxidation reactions and CoQ in the food may serve as an antioxidant. The metabolism of dietary CoQ may generate several lipid metabolites that could have pronounced effects on cellular metabolism. Candidates for such metabolites are those produced during physiological breakdown, upon ultraviolet irradiation or those appearing during oxidative breakdown of oxidized CoQ. Taking into consideration the effects of other mevalonate pathway products, such as farnesol and oxysterols, the metabolites of CoQ should render further investigation.

AGING AND DISEASES

There are a number of conditions where CoQ tissue concentrations are modified with functional consequences. The behavior of the lipid during aging both in experimental and human systems is very characteristic. In rat the highest concentration in various tissues was found around the age of 30 days, followed by a decrease during aging.[15,30,31] In other studies, 6 months old rats and mice were compared with older rodents and a decrease of CoQ was found in liver and skeletal muscle, but not in other organs.[25,32] In humans the lipid concentration increases substantially up to 20–30 years, followed by a successive decrease.[15] At the age of 80 the level equals that found at birth. In many age-related diseases oxidative damage of lipids and proteins is believed to be major etiological factor and the low level of the endogenous antioxidant CoQ could accentuate this process. However, this question has not been investigated in sufficient detail since it is important to know whether the cellular deficiency is general or affecting certain organelles.

During carcinogenesis lipid modifications are integral part of the process.[33,34] In preneoplastic noduli of rat liver induced by 2-acetylaminoflourene treatment, CoQ concentration is doubled (Table III). Most characteristically, mitochondria are not affected and the changes are found only in extra-mitochondrial compartments such as microsomes and lysosomes. In the carcinogenic process reactive oxygen species are produced and the increased synthesis of CoQ can be considered as an antioxidant response of the cell. Mitochondrial respiration and coupled phosphorylation are unaffected and an adjustment of the redox lipid in this compartment is therefore not required. At the end stage, when the liver cancer is fully developed, CoQ amount is substantially decreased both in rat and humans.

Though the etiology of Alzheimer's and prion diseases differs, they share several characteristics. A

TABLE II Possible mechanism of dietary CoQ administration on organ function

1.	Direct CoQ organ uptake
2.	Modulation of signal transduction systems
3.	Influence on organ circulation/vasculature
4.	Antioxidant effect in the gastrointestinal system
5.	Effects of CoQ metabolites

TABLE III CoQ in preneoplastic noduli and hepatic cancer

	Control (μg/mg protein)	Pathological tissue (μg/mg protein)
Noduli, rat	0.25	0.49
Noduli		
Mitochondria	2.71	2.82
Microsomes	0.15	1.04
Lysosomes	3.73	9.76
Cancer, rat	0.25	0.15
Cancer, human	0.58	0.23

Data taken from Refs. [33,34].

probable reason for this similarity is the involvement of oxidative damage in both diseases. Both conditions are characterized by increased CoQ, α-tocopherol and dolichyl-P levels, while dolichol decreases and cholesterol remains unchanged.[35] The long duration of these diseases, as well as the lack of experimental models for Alzheimer's disease, has made it difficult to investigate the involvement of lipid and protein oxidation. CoQ has multiple functions in the cell and it may be difficult to evaluate the influence of a concentration change without knowing which compartment is affected. Small modifications are sufficient to cause profound changes in electron transport and related reactions as well as in antioxidant defense. Further studies of CoQ metabolism are required in order to introduce steps to reestablish optimal distribution and concentrations.

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