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Discovery of ubiquinone (coenzyme Q) and an overview of function

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Abstract

Details of the discovery of ubiquinone (coenzyme Q) are described in the context of research on mitochondria in the early 1950s. The importance of the research environment created by David E. Green to the recognition of the compound and its role in mitochondria is emphasized as well as the dedicated work of Karl Folkers to find the medical and nutritional significance. The development of diverse functions of the quinone from electron carrier and proton carrier in mitochondria to proton transport in other membranes and uncoupling protein control as well as antioxidant and prooxidant functions is introduced. The successful application in medicine points the way for future development.

Keywords: Bioenergetics; Uncoupling protein; Antioxidant; Oxygen radical; Therapeutic; Nutrition

The discovery of coenzyme Q was not a simple accident as sometimes mentioned. It was the result of a long train of investigation into the mechanism of, and compounds involved in biological energy conversion. Its origin can be traced back to the early studies of biological oxidation especially those of Warburg and Keilin which introduced a chain of cytochromes as electron carriers to oxygen. These studies were extended by Chance (1954) with the development of the rapid flow-dual beam spectrophotometer. With this instrument the rate of reduction of the component flavins and cytochromes could be measured which led to definition of an electron transport chain from NADH or succinate through flavin, cytochrome *b*, cytochrome *a*, cytochrome *c*, cytochrome *a* and a_3 to oxygen.

The next question was how these cytochromes were associated and how they drove the formation of ATP.

In the early 1950s good biochemistry required the purification of enzymes for proper definition of their catalytic properties. When David Green proposed that the citric cycle and oxidative phosphorylation was contained in an organized complex which he called cyclophorase it was met by extreme skepticism (Green et al., 1948). The development of microscopic staining and ultracentrifuge techniques to identify the respiratory particles as mitochondria has been reviewed by Lehninger (1964). In 1950 Green at the Enzyme Institute, University of Wisconsin then embarked on a major program to determine how the enzymes of the fatty acid oxidation and citric cycle oxidation were organized and how this contributed to energy coupling in oxidative phosphorylation. A unique and crucial component of this program was isolation of large amounts of mitochondria. Most laboratories involved in these studies used small amounts of rat liver or pigeon breast muscle mitochondria which gave good ratios of ATP formed to oxygen consumed (P/O ratios) approaching 3 but left little to work with in enzyme isolation.

To obtain a large amount of material to work with Green arranged to get up to a dozen beef hearts per day from the Oscar Meyer plant in Madison. These hearts were homogenized in a large blender followed by centrifugation in a large 13 l centrifuge to remove unwanted material such as myosin. The supernatant was then centrifuged in a large industrial size sharples machine to sediment the mitochondria as a brown paste which were suspended in a sucrose phosphate buffer prior to freezing. The production was

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80–100 g of mitochondrial protein per day. To start a study we could just go to the freezer and take out a liter of concentrated mitochondria.

With a good supply of mitochondria available Green instituted a program to systematically separate parts of the electron transport system to see how they interacted and how this interaction was related to ATP formation. By using aqueous extractions it was possible to prepare isolated flavoproteins, succinc dehydrogenase and NADH dehydrogenase, which could react with artificial electron acceptors but not with cytochrome *c*. Further fractionation required the use of detergents. The first success was separation of a succinate cytochrome *c* reductase preparation which contained flavin, cytochrome *b* and cytochrome *c*1 by Green and Burkhard (1961). In the meantime Wainio et al. (1948) using deoxycholate had succeeded in separating a cytochrome *c* oxidase which contained only cytochromes *a* and a_3. This led to studies with cholate detergents which gave other fractions most notably a NADH cytochrome *c* reductase. Further fractionation led to loss of activity. Until the discovery of coenzyme Q made it possible for Hatefi et al. (1962) to reconstruct the complete electron transport system. During these fractionation studies it became clear that the lipid in the membrane was closely associated with the cytochromes and flavine. According to theories of membrane structure at that time (late 1950s) the components of the electron transport would be bound to the surfaces of the mitochondrial lipid bilayer. Since the products of fractionation all retained lipid it became apparent that the association of the carrier protein and lipid was very strong. This led to a consideration of the possible functional role of lipid. At this point I felt that detergent based fractionation of the mitochondrial membranes had been exploited as much as possible so Carl Widmer and I started a study of the lipids associated with the various fractions. At about this time (1955) Nason and coworkers (Donaldson et al., 1958) reported inducing a requirement for α-tocopherol in mitochondrial electron transport by isooctane extraction. I tried the effect of isooctane on mitochondrial electron transport and found isooctane induced inhibition could be reversed by α-tocopherol but that the reversal could also be achieved with beef serum albumin. I wrote to Nason and he agreed that serum albumin had something that reversed the isooctane inhibition. These experiments led to two considerations: first that the electron transport proteins were remarkably resistant to denaturation by hydrocarbon solvents which laid the ground work for the use of these solvents to extract coenzyme Q in studies of its activity. Second it led me to consider if any other vitamin might be needed in the electron transport, loss of which might account for fractions where activity could not be restored. To see what vitamins might be involved I sent a liter of mitochondria to the Wisconsin Alumni Research Laboratory for vitamin analysis. Several B vitamins were found in the beef heart mitochondria preparation, but no niacin. A significant amount of α-tocopherol was present. In separate assays I found no vitamin K. The research laboratory did not do vitamin A analysis so I set out to do that. Because of my plant physiology background I was interested in plant mitochondria. Since the Enzyme Institute was uniquely equipped for study of mitochondria I took advantage of the facilities to make cauliflower mitochondria on the weekends when the laboratory was essentially empty (Crane, 1957). Surprisingly the cauliflower mitochondria were yellow, not brown like animal mitochondria. So the thought occurred to me that the cauliflower mitochondria might contain carotenoids and that beef heart mitochondria might have carotenoids hidden under the brown pigments. I figured that many compounds with absorption spectra in the visible range had loose electrons and could act as electron carriers in oxidation reduction reactions so carotenoids were possible carriers. It turned out that beef heart mitochondria have carotenoids but no vitamin A. If the amount of carotenoids is estimated as β carotene by spectral absorption of unsaponifiable lipid at 448 nm the 9 nmole/mg protein found is higher than the concentration of cytochromes (0.8–0.4 nmole/mg protein) so it would be sufficient to function in electron transport. The lack of vitamin A was confirmed by a negative Carr–Price reaction. When the non-saponifiable lipid was chromatographed on an alumina or Decalso column three carotenoid bands were eluted with heptane. Following the carotenoids was a broad yellow band which eluted off the column with 2% ethyl ether in heptane. This compound had a broad absorption peak around 400 nm and was first observed December 3, 1956. Later it was found to have a strong peak at 275 nm. To guard against saponification artifacts we prepared the "400" compound from a petroleum ether–ethanol extract of mitochondria. Removal of the solvent from the "400" fraction eluate left a yellow oil. When the oil was dissolved in ethanol and put in the refrigerator for 2 days long needle like yellow crystals formed which could be filtered off. These were recrystalized until a constant melting point of 48–49 °C was maintained (Crane et al., 1957). The next question was what was this strange compound and could it have a role in electron transport? We knew that it was probably not a short chain carotenoid (like colorless vitamin A) or a long chain carotenoid (like β carotene) because of lack of multiple peaks in the visible spectra (400 nm) and lack of Carr Price reaction (40 carbon poly unsaturated carotenes like β carotene show Carr Price peaks in the infrared region ~ 1000 nm). In the organic chemistry course at the University of Michigan Prof Bachman taught organic chromophore which included quinones. As a graduate student in plant physiology I was exposed to discussion of possible roles of quinones in plant respiration which was not expected in animals because benzoquinones were reported to be rare in animals (Thomson, 1957). Bob Lester and I discussed the idea that the 400 compound might be a quinone. We dug a small book by Morton on organic spectra out of the library and found the spectrum of benzoquinone with an oxidized peak at 254 nm and a smaller peak in the

reduced state at 290 nm. When we refluxed the 400 compound with ascorbic acid and HCl the 275 band shifted to a smaller peak at 290 nm which was consistent with formation of a hydroquinone. Joe Hatefi suggested using borohydride as an easier reducing agent for direct reduction in ethanol. The evidence that the 400–275 compound was a quinone led to consideration of substitutions on the ring to modify the quinone spectra to shift the peak to 275 nm. Since it appeared to be a quinone with an absorption peak at 275 nm we started to call it Q275.

Further analysis found two methoxy groups and isoprene units on the quinone. Molecular weight determination by boiling point depression gave variable results but redox titration of the reduced quinone gave a molecular weight between 797 and 920. Subsequent molecular weight determination by X-ray diffraction gave 849 (Lester et al., 1959). We also developed an assay for Q275 function in succinoxidase by extraction of beef heart mitochondria with heptane to remove some of the coenzyme Q. This extraction decreased succinate oxidase activity which could be restored by adding back Q275. The carotenoids from mitochondria, vitamin A, α-tocopherol and α-tocopherol quinone did not restore activity after heptane extraction but surprisingly cytochrome *c* did. Later studies using other solvents for extraction showed a requirement for Q275 for cytochrome *c* reduction and both Q275 and cytochrome *c* for succinic oxidase (Green, 1961). We also found that Q275 was reduced when incubated with mitochondria and that the quinol was oxidized by mitochondria. These oxidation and reduction changes were inhibited by specific mitochondrial inhibitors. The evidence clearly indicated that Q275 could be a component in the mitochondrial electron transport. In April 1957, we sent a short note for publication in BBA (Crane et al., 1957) outlining our evidence for the role of the quinone in mitochondria. Following the publication Karl Folkers at Merck, Sharpe, and Dohm called Green to arrange a collaboration in the study of quinone. Folkers felt that if the quinone was essential for mitochondrial electron transport it was likely that in some people deficiencies could occur which would mean that the quinone could be a vitamin. Since there was no vitamin Q at that time Folkers thought that a functional designation, coenzyme Q, would be a good tentative name until a vitamin Q function could be established. This was the beginning of a dedicated 10 year search by Folkers for nutritional significance culminated by Yamamura's use in the treatment of heart failure in 1967 (Yamamura, 1977). Folkers's efforts resulted in the organization and publication of a series of symposia on clinical and medical applications of coenzyme Q (Folkers and Yamamura, 1981, 1984, 1986; Yamamura et al., 1980; Folkers et al., 1991; Littarru et al., 1994, 1997). These symposia have been continued by the International Coenzyme Q10 Association (Biofactors, 1999, 2003).

To determine the specificity of mitochondrial electron transport for coenzyme Q the Merck group synthesized all combinations of dimethoxy benzoquinones and we found that only the 2,3 dimethoxy quinone analog could restore succinoxidase after extraction of coenzyme Q.

The essential role of coenzyme Q in mitochondrial electron transport was questioned on the basis that the rate of oxidation reduction was slower than the other electron carriers such as cytochrome (Redfearn, 1961). This problem was solved by Klingenberg's (1968) consideration that there was 10 times as much coenzyme Q as other carriers. Therefore reduction of each molecule of Q would be slower than the less abundant carriers.

The groundwork for broader functions of coenzyme Q in membranes other than mitochondria was laid at this time when Ramasarma and coworkers (Sastry et al., 1961) showed that coenzyme Q was in other cellular membranes. This observation has led to consideration of coenzyme Q as an antioxidant and as a carrier for proton transfer across other membranes.

At the same time that we were looking for vitamin A in mitochondria and finding Q275 Morton's laboratory in Liverpool were studying a compound (SA) which increased in vitamin A deficient rat liver. They were interested in the possible relation between sterols and vitamin A so they first considered SA to be an ene dione steroid. When we found the spectrum they published for SA was the same as for Q275 Bob Lester and I wrote to Morton to say we thought it was a quinone. It was nice to find out that they agreed with us. This indicates how the framework of the research determines the interpretation of the observation. The work on SA has been discussed by Morton (1961).

By investigating other plant and animal material we supported an almost universal role of coenzyme Q. A similar conclusion was reached by Morton's group which led to the name ubiquinone. Variation was found in the length of the isoprenoid side chain which ranged from 10 to 6 isoprenoid groups. In addition, we found in green plants and chloroplasts a similar quinone with absorption maximum at 254 nm which we named plastoquinone. It later was shown to be essential for photosynthesis with a role in chloroplasts like coenzyme Q in mitochondria (Bishop, 1961).

The finding of an essential quinone in mitochondria naturally led to consideration of a quinone derivative as an intermediate in oxidative phosphorylation. It was generally considered that a phosphorylated intermediate would be activated by oxidation to phosphorylate ADP to make ATP. Various quinone derivatives, especially chromanols, were tested without success. It took a different frame of reference introduced by Peter Mitchell to find how coenzyme Q contributed to ATP synthesis (Mitchell, 1975). Mitchell had been considering formation of a membrane potential as a driving force for ATP synthesis. If the oxidation and reduction of coenzyme was oriented across the membrane it would provide a way to generate a membrane potential by proton gradient generation across the membrane. When coenzyme Q is reduced it takes up two protons which are released when it is oxidized. Thus the energy conversion role of coenzyme Q was in the protonation and not in the electron transport function. Protons are taken up inside

the mitochondrial membrane and released outside as the quinone oscillates back and forth. Thus the unique role for coenzyme Q in energy conversion was discovered.

Folkers search for a coenzyme Q deficiency condition ranged from tests on kwashiorkor to dystrophy. These early investigations were hampered initially by supply of sufficient coenzyme Q for large scale testing and poor uptake when administered in crystalline form. In early studies analogs which were easier to synthesize such as coenzyme Q_7 and hexahydro Q_4 were tested without great success. The supply problem was solved by production through yeast fermentation by Kanegafuchi Chemical Co and by chemical synthesis by Nisshin Chemicals Co. Pharmaceutical preparations were made available by Eisai Co in 1974 (Folkers, 1985).

It took some time before poor absorption of orally administered coenzyme Q was measured. It was found that only 2–3% of crystalline coenzyme Q was taken up in the blood. In hindsight it is clear that a combination of low dosage, 30–60 mg per day, and poor absorption was unlikely to be very effective in treatment of any deficiency. The first break came with the demonstration that absorption was remarkably improved by taking coenzyme Q mixed with peanut butter. Further study of absorption led to development of gel capsules which gave a high percentage of uptake and led to significant increase in coenzyme Q in the blood (Bhagavan and Chopra, 2006). There still remains a question of what controls uptake into various tissues. Further study of control of breakdown and excretion is needed. For many years the focus of coenzyme Q research was on its role in energy transduction in mitochondria. It gradually became recognized that it was widely distributed in cell membranes and could play a role in antioxidant function and proton transport in other membranes. Early study by Ramasarma and coworkers (Sastry et al., 1961) found coenzyme Q in microsomes as well as mitochondria. Later we (Crane and Morre, 1977) found a high concentration of coenzyme Q in Golgi membranes and found that it functioned in a non-mitochondrial electron transport. Further study by Dallners group (Ernster and Dallner, 1995) showed coenzyme Q in all endomembranes. The finding of coenzyme Q in all membranes brought on a concept of coenzyme Q as an important antioxidant (Kagan et al., 1990). Early studies had shown that coenzyme Q hydroquinone is an excellent free radical scavenging antioxidant but its role was restricted to mitochondria until a general membrane distribution was shown. Even greater significance was apparent when it was shown that reduced coenzyme Q could restore antioxidant function to oxidized tocopherol. This is important because endomembranes have enzymes that can reduce coenzyme Q but none for reduction of oxidized tocopherol directly. On the other hand a role of hydroquinone as an oxygen radical generator is being explored (Crane, 2000). The formation of a semiquinone radical during the oxidation–reduction in mitochondria was observed soon after discovery of coenzyme Q and has been indicated as a basis for part of the peroxide production in mitochondria when ADP is not available for phosphorylation or inhibition of Q oxidation are present (antimycin) (Ozawa, 1985). During oxidoreduction in other membranes coenzyme Q may form a partially reduced semiquinone radical. If the semiquinone reacts with oxygen the superoxide radical can be formed which can be converted to hydrogen peroxide. Thus coenzyme Q could contribute to the generation of reactive oxygen radicals which might contribute to destruction of membrane lipids or be responsible for hydrogen peroxide signaling (Rhee, 2006). Further significance of the presence of coenzyme Q in endomembranes comes from the evidence that it functions as a proton transferring redox agent in acidification of lysosomes. This is an area which needs further study because it may relate to proton transfer across the plasma membrane also (Crane, 2000). Other effects of coenzyme Q which have not been fully examined are effects on membrane fluidity (Turunen et al., 2004) and on phospholipid metabolism. The recent finding that coenzyme Q is required for the protonophoric mitochondrial uncoupling protein indicates further unknown role in control of cell metabolism (Echtay et al., 2000). Thus the all out attack which Green developed on mitochondrial electron transport led to an unexpected molecule with diverse biochemical significance. The full extent of its diversity remains to be explored. One can speculate that Morton in his study of vitamin A relation to ubiquinone would have developed the antioxidant approach which would have led back to mitochondria as a prime basis of superoxide removal or production. The later years of coenzyme Q history revolve around Karl Folkers and his search for a vitamin-like requirement for coenzyme Q which led to therapeutic approaches. For 40 years from 1958 to 2000 he organized an unrelenting campaign to find nutritional and therapeutic significance for coenzyme Q. After determining the structure by synthesis of coenzyme Q he was instrumental in organizing the CIBA Symposium on Quinones in Electron Transport which brought up the general role of lipophilic quinones in biological electron transport in mitochondria, chloroplasts, and bacteria. Folkers then did pioneering studies to try and ameloriate diseases such as kwashiorkor and dystrophy without much success. He also organized a series of six synopsia on coenzyme Q from 1977 to 1990 which brought together workers in both basic biochemistry and medical applications. The first successful application of coenzyme Q to a medical problem was in Yamamura's treatment of congestive heart failure. The search for medical or nutritional application continues and the coenzyme Q synopsia continue under the International Coenzyme Q association. The medical conditions which have shown some response to coenzyme Q (Ebadi et al., 2001) now include congestive heart failure (Langsjoen and Langsjoen, 1998), Immune deficiency (Bliznakov and Hunt, 1987), Encephalomyopathy or ataxia (Quinzii et al., 2006), Parkinsonism and Huntingtons disease (Shults, 2003; Beal, 2004; Ryu and Ferrante, 2005), and Cancer (Hodges et al., 1999; Brea-Calvo et al., 2006).

Indication of therapeutic effects in diabetes (Hodgson et al., 2002) and relief of statin side effects (Littarru and Tiano, 2005) have also been reported. Thus Folkers long search has been more productive than expected and has developed from more functions of coenzyme Q than simple protonophoric electron transport. The biochemical pathways for coenzyme Q synthesis were investigated soon after the discovery (Clarke, 2000). In general all animals, plants, and bacteria synthesize their own coenzyme Q so a typical vitamin deficiency was not found until recently. Now several instances of mitochondrial deficiency disease have been related to coenzyme Q (Di Mauro, 2004). Knowledge of the biochemical synthesis now permits a molecular biology approach to deficiency in synthesis. A mutation in a gene necessary for coenzyme Q synthesis has recently been found to explain a deficiency (Quinzii et al., 2006).

In contrast to its functions as an electron transport protonophore and antioxidant there are conditions under which quinol can generate superoxide as an oxygen radical. Under conditions which lead to increased coenzyme Q reduction in mitochondria it is possible to show increased oxygen radical generation (Nohl et al., 1996). Since reduced Q is also found in other membranes and especially in blood plasma it may be involved in oxygen radical generation at these sites also. The generation of superoxide and hydrogen peroxide may also be a basis for activation of defensive genes to protect against free radical damage and aging (Linnane and Eastwood, 2004).

True there are many questions about coenzyme Q in medicine, nutrition, and basic biochemistry which remain to be investigated (Dhanasekaren and Ren, 2005). Although the role in electron transport and proton transport for energy conversion are quite well understood more study is needed about antioxidant–prooxidant balance, mechanism of uncoupled protein action, and control of membrane fluidity (Fato et al., 1984).

To gain a basis for understanding requirements for coenzyme Q a better understanding of genetic and nutritional control of serum and tissue levels of coenzyme Q and excretion of coenzyme Q is needed. To further the understanding of requirements for coenzyme Q a more readily available clinical assay of coenzyme Q would be desirable since the extent and basis for variation in serum and tissue levels is not known.

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