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Cellular redox poise modulation; the role of coenzyme Q_{10}, gene and metabolic regulation

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Abstract

In this communication, the concept is developed that coenzyme Q_{10} has a toti-potent role in the regulation of cellular metabolism. The redox function of coenzyme Q_{10} leads to a number of outcomes with major impacts on sub-cellular metabolism and gene regulation. Coenzyme Q_{10}'s regulatory activities are achieved in part, through the agency of its localization in the various sub-cellular membrane compartments. Its fluctuating redox poise within these membranes reflects the cell's metabolic micro-environments. As an integral part of this process, H_2O_2 is generated as a product of the normal electron transport systems to function as a mitogenic second messenger informing the nuclear and mitochondrial (chloroplast) genomes on a real-time basis of the status of the sub-cellular metabolic micro-environments and the needs of that cell. Coenzyme Q_{10} plays a major role both in energy conservation, and energy dissipation as a component of the uncoupler protein family. Coenzyme Q_{10} is both an anti-oxidant and a pro-oxidant and of the two the latter is proposed as its more important cellular function. Coenzyme Q_{10} has been reported, to be of therapeutic benefit in the treatment of a wide range of age related degenerative systemic diseases and mitochondrial disease. Our over-arching hypotheses on the central role played by coenzyme Q_{10} in redox poise changes, the generation of H_2O_2, consequent gene regulation and metabolic flux control may account for the wide ranging therapeutic benefits attributed to coenzyme Q_{10}.

Keywords: Coenzyme Q_{10}; Redox poise; Gene regulation; Metabolic regulation; Hydrogen peroxide; Pro-oxidants; Anti-oxidants

1. Introduction

Some years ago, we proposed that mitochondrial DNA mutations are important contributors to the ageing process and degenerative diseases (Linnane et al., 1989). Further, that such conditions could be ameliorated by redox compounds, notably coenzyme Q_{10}, acting to re-energize tissues and as an anti-oxidant. The basic tenets of the hypothesis have since been confirmed by our laboratory and many others [for review, Linnane (2000); Kopsidas et al. (2000)].

The purpose of this short essay, is to continue to extend and make some modifications to the original hypothesis with the proposal that coenzyme Q_{10} plays a totipotent role in the regulation of sub-cellular metabolism. Our hypothesis integrates several known

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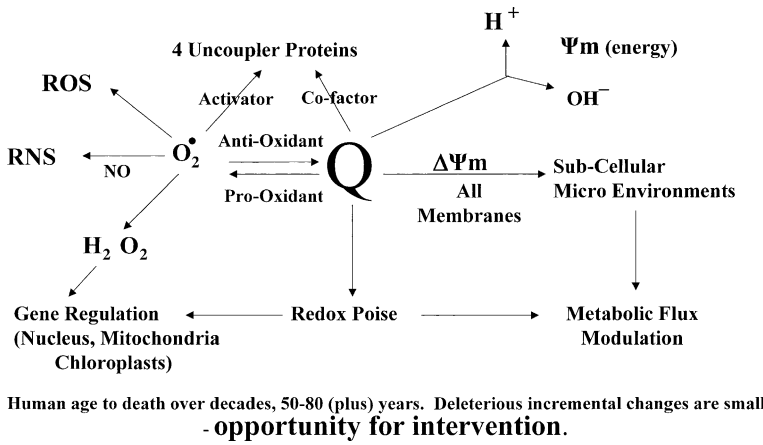

Fig. 1. Coenzyme Q_{10}: the orchestra leader, energy generation, metabolic flux modulation, gene regulation.

and new aspects of coenzyme Q_{10} molecular biology to provide a basis upon which the multitude of its claimed biological/clinical effects may be considered. Coenzyme Q_{10} is known to occur in all sub-cellular membranes and has a functional role in many known membrane oxido-reductase systems therein; mitochondria, lysosomes, plasmalemma, Golgi apparatus. We propose that, in essence, it is coenzyme Q_{10}'s particular sub-cellular redox poise (ratio of reduced to oxidized form) changes that determines its key metabolic control function. The redox poise of coenzyme Q_{10} in the various membranes, will fluctuate continuously as an expression of the metabolic processes being carried out at any given time, within the various sub-cellular compartments, to produce a particular localized redox poise, resulting in a signaling process. This process together with coenzyme Q_{10} acting as a pro-oxidant will produce superoxide anion and the known mitogen H_2O_2; which then functions, as a second messenger to inform the nucleus, and mitochondria (chloroplasts) of the need for appropriate gene expression/regulation. The pro-oxidant role of coenzyme Q_{10} is envisaged as critical to healthy cell function. The biological role of coenzyme Q_{10} is thus complex; the effects of coenzyme Q_{10} administration and function will not be limited to a small number of pathways but influence the over-all metabolism of the cell through small localized sub-cellular metabolic perturbations. Coenzyme Q_{10} also plays a role in energy dissipation by the uncoupler proteins, both as a co-factor proton carrier and by the generation of superoxide, which activates the system. It can be readily envisioned that coenzyme Q_{10} will play an embracing role in modulating cellular well being and cellular pathology. Fig. 1 outlines the global functions of coenzyme Q_{10} in relation to sub-cellular bioenergy systems, redox poise, metabolic flux modulation, gene regulation and oxygen radical formation.

One of the main sources of evidence for our hypothesis is a human clinical trial we conducted investigating the effects of coenzyme Q_{10} on vastus lateralis muscle of aged (50–80 years) subjects scheduled to undergo hip replacement surgery (Linnane et al., 2002a,b). The human trial subjects received either 300 mg coenzyme Q_{10} or placebo per day for 25–30 days before surgery. At the time of surgery, a corresponding sample of the vastus lateralis muscle was taken for analysis from each of the subject cohorts. The impact of the coenzyme Q_{10} compared with placebo material on the molecular profile of the tissue, was surveyed using gene array and gene display technologies as well as protein expression patterns. In addition, the muscle tissue samples were assessed in regards to their muscle fibre type composition. It was appreciated that the analytical tools employed would yield results bearing only on a limited number of genes and proteins, but sufficient (several thousand) to answer the question as to whether coenzyme Q_{10} had a wide-ranging major effect on the muscle metabolic profile of aged subjects.

Table 1
Genomic expression and proteome analysis comparing placebo and coenzyme Q_{10} patient vastus lateralis specimens

Gene expression	
Microarray	115 genes regulated by coenzyme Q_{10} (47 up regulated, 68 down regulated)
Differential display	15 genes strongly regulated by coenzyme Q_{10} (12 up regulated, 3 down regulated)
Protein changes	Of the high abundance proteome, 229 proteins induced by coenzyme Q_{10}, 236 repressed by coenzyme Q_{10}

The gene expression changes detected by gene microarray technology, refers to gene expression being up or down regulated by a minimum factor of 1.8, compared to placebo muscle samples. Gene expression changes detected by differential display refers to up or down regulation by a minimum factor of 3.0. The protein numbers changes observed in proteome display analyses of muscle extracts refer to newly detected proteins (induced) or protein spots no longer detected in coenzyme Q_{10} specimens (repressed) but present in the placebo samples. Data summarized from Linnane et al. (2002a,b).

1.1. Effect of coenzyme Q_{10} on skeletal muscle gene expression

The gene expression profiles of human vastus lateralis samples taken from subjects receiving coenzyme Q_{10} or placebo were compared using Microarray and Differential Gene Display technologies. The overall results are summarized in Table 1 (data from Linnane et al., 2002a,b).

The Affymetrix U95A oligonucleotide array, which contains 12,000 annotated human genes, was used in the Microarray studies; many of the sequences belong to no known protein product. This survey showed that following 25–30 days of coenzyme Q_{10} administration, the change in expression of most detected transcripts compared to the placebo muscle samples were probably not significant. However, the expression of 115 gene transcripts underwent significant change (defined as up or down regulated by a factor of 1.8), compared to the placebo; of these, 47 were up-regulated and 68 down-regulated. While many of the coenzyme Q_{10} regulated genes were of unknown function, they did include; Glutamate Receptor Protein (GluR5), Fibroblast growth factor receptor (N-SAM), Protein kinase C-epsilon, Guanylyl cyclase, TTF-1 interacting peptide 20 (TIP-20), TR3 orphan receptor and HZF Helicase, among others. A cursory analysis demonstrates that a wide range of cellular functions have been influenced by coenzyme Q_{10} administration; some direct, others presumably a reflection of an induced metabolic flux. Further detailed studies are required to identify the individual components of skeletal muscle affected by whole body administration of coenzyme Q_{10}. For the present, such studies will be limited by the lack of gene array chips, which constitute a complete skeletal muscle gene atlas. However, our hypothesis at this time, only requires a demonstration of a global effect of coenzyme Q_{10} on tissue metabolism, which our muscle results support.

Differential Gene Display analyses were directed towards investigating myosin heavy chain expression having regard to the well known age associated muscle fibre type compositional changes. The Myosin Heavy chain type IIa and IIb were both up-regulated consistent with the observed histochemical results (see later). In addition, in this limited focused study, the analyses revealed that 15 genes appeared to be strongly influenced by coenzyme Q_{10} administration (12 up-regulated and 3 down-regulated); the expression of Adenylate cyclase 9, DNA ploymerase epsilon subunit, heat shock protein (HSP70) most notably, among others, were up-regulated, while the amounts of Telomerase, RNA I helicase and Glial fibrillary acidic protein were down-regulated. The Differential Gene Display result complemented the Microarray study in that both indicated that a complex mix of cellular functions appear to share an element of coenzyme Q_{10} regulation.

1.2. Effect of coenzyme Q_{10} on skeletal muscle protein expression

Microarrays containing the complete human genome are unavailable and more particularly skeletal muscle gene atlases do not exist at this time. Gene expression results are less informative relative to cellular protein compositional profiles which more directly reflect the cell's metabolic state. Furthermore, proteins are subject to post-transcriptional mechanisms that regulate their functional half-life and synthesis (Varshavsky, 1996) which can lead to a non-linear relationship between mRNA and protein levels, which

brings into question the current value of gene array analyses, as a reflection of intermediary metabolism activity. Thus, invariant steady-state levels of some cellular proteins have been observed while their respective mRNA transcript levels varied by as much as 30-fold (Gygi et al., 1999).

The muscle proteome analyses of placebo and coenzyme Q_{10} samples were compared to determine coenzyme Q_{10} regulated proteins; about 2000–2200 high abundance proteins can be visualized by two-dimensional PAGE analyses. The vastus lateralis muscle protein profile of the placebo versus coenzyme Q_{10} treated subjects were clearly very different; 229 protein spots were up-regulated (induced) and 236 were repressed (decreased) in the muscle protein samples from coenzyme Q_{10} treated subjects compared with the placebos (Table 1). As would be expected, the majority of proteins in the samples were unaffected or little changed. While these analyses deal only with high expression proteins of the muscle (an additional 4–6000 probably make up the total muscle proteome), nonetheless a major impact is made by coenzyme Q_{10} on the metabolic profile of human vastus lateralis muscle of aged subjects. Maldi-TOF mass spectrometer technology could be used to characterize the different proteins modulated by coenzyme Q_{10} action.

1.3. Effect of coenzyme Q_{10} on skeletal muscle fibre type expression

It is well known that with increasing age, there is a change in the fibre type composition of skeletal muscle. In particular, the percentage of fast-twich fibres (Type II fibres) decrease relative to the slow twitch Type I fibres. The preferred energy systems of the three main muscle fibre types are; Type 1 mitochondrial, Type IIa balance between mitochondrial and glycolytic activity, and Type IIb obtain their energy mainly by glycolysis. The histochemical analyses data summarized in Fig. 2 (Linnane et al., 2002a,b) illustrate the effect of coenzyme Q_{10} administration to subjects on their muscle. Most strikingly, coenzyme Q_{10} appears to induce a change towards a younger muscle fibre composition profile. An increase in the percentage of fast twitch type II fibres relative to type I fibres was observed. Muscle weakness is a major feature of the aging process resulting in a decrease in mobility and loss of

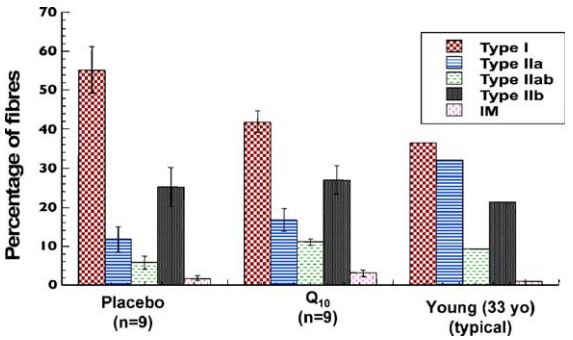

Fig. 2. Fibre type composition of vastus lateralis muscle sample from placebo and coenzyme Q_{10} patients. Average aged skeletal muscle (vastus lateralis) fibre type composition of 9 placebo and 9 coenzyme Q_{10} treated male patients and vastus lateralis composition of a young male 33-year-old subject sample.

coordination, which impinges greatly on the elderly population. Coenzyme Q_{10} administration has a profound effect on human vastus lateralis skeletal muscle as demonstrated by its effect on gene activity, proteome changes and most significantly, on alteration in the physiological function of the muscle, albeit inferred from muscle fibre myosin type changes. Redox therapy by coenzyme Q_{10} in ameliorating muscle weakness could make a meaningful contribution to the improvement in the quality of life of the aged.

2. Cellular functions of coenzyme Q_{10}

The diversity of cellular functions which significantly involve coenzyme Q_{10} are summarized in Table 2, and discussed below.

2.1. Significance of sub-cellular membrane localisation of coenzyme Q_{10}.

Mitchell's (1974) revolutionary work concerning the mechanism of conservation of (mitochondrial) redox potential energy, overturning a 25 year phosphorylated intermediate hypothesis, owed much to his formulation of the Q cycle hypothesis (Mitchell, 1975). A critical early aspect of the Q cycle hypothesis, was the demonstration of a proton motive force generated by vectorial separation of protons across impermeable biomembranes, with coenzyme

Table 2
Cellular functions of coenzyme Q_{10}

Coenzyme Q_{10}/electron transport/energy systems mitochondria/plasma membrane/golgi/lysosomes/chloroplasts (plastoquinone)
Coenzyme Q_{10} occurs in all cellular membranes, its redox poise influences membrane potential Ψm values
Plastoquinone (coenzyme Q_{10} analogue) redox poise regulates chloroplast and nuclear gene transcription
Coenzyme Q_{10} is both an anti-oxidant scavenging ROS and acting as a pro-oxidant, to generate superoxide and H_2O_2. There is an essential cellular requirement for H_2O_2 formation
Coenzyme Q_{10} acts as a gene regulator with (H_2O_2, acting as a second messenger)
Uncoupler Proteins1,2,3 (4) Ψm↓m are proton translocators, requiring fatty acids and coenzyme Q_{10} as cp-factor. Superoxide is an activator of the uncoupler protein family
Coenzyme Q_{10} is a co-factor required for protein SH↓S-S interconversions cell compartments: cytosol-SH. Other-S-S-

References in text. Redox poise, ratio of oxidized to reduced form at any instant in time.

Q_{10} playing a key role. It has long been established that a wide range of biomembrane systems are energized via a redox process which create transient localized bio-capacitors. This energy is utilized, apart from ATP synthesis, for such processes, among others, of nerve conduction, metabolite translocations and reversed mitochondrial electron transport. It is to be emphasized that coenzyme Q_{10} occurs in all cellular membranes and coenzyme Q_{10} based electron transport systems are being progressively identified in these different sub-cellular membrane compartments; specifically to date, in the mitochondria, plasma membrane, Golgi apparatus and lysosomes (Crane et al., 1957, 1994a,b; Gille and Nohl, 2000a). (We would suggest, the likelihood, that additional sub-cellular membrane located oxido-reductase systems will be discovered, which include coenzyme Q_{10}).

These redox systems participate in the generation of a range of localized sub-cellular membrane potentials, which are in a continual state of flux, thereby influencing localized membrane ingress and egress of all manner of metabolites. Embodied in this concept, is that coenzyme Q_{10} has a universal role in the cell, whereby its redox poise in the different sub-cellular compartments acts as a redox sensing, signaling mechanism affecting gene expression and proteome composition for the maintenance of optimum sub-cellular regional metabolism.

2.2. Plant chloroplast redox poise signaling systems

Our consideration of an all encompassing role for coenzyme Q_{10} is consistent with the earlier work of Maxwell et al. (1995); Escoubas et al. (1995) on the algal *Dunaliella* species. Specifically these two groups independently reported that changes in the redox state/poise of chloroplast plastoquinone, regulates the mRNA abundance of the nuclear gene, *cab*, which is reflected in the amount of this light harvesting protein synthesized. Communication from chloroplast to nucleus was suggested by Escoubas and colleagues to be mediated via a phosphorylated factor coupled to the redox state of plastoquinone through the action of a chloroplast protein kinase.

Subsequently Pfannschmidt et al. (1999) demonstrated that the redox state of plastoquinone controls the rate of transcription of chloroplast DNA encoding reaction-centre apoproteins of photosystems I and II. The occurrence of plastoquinone is limited to the chloroplast, but taken together with our results it may be suggested that redox poise/gene regulation is a universal phenomenon and that coenzyme Q_{10} and its analogues are the orchestra leaders in most cells.

2.3. Coenzyme Q_{10} anti-oxidant, pro-oxidant and hydrogen peroxide formation: a re-evaluation

Coenzyme Q_{10} is both an anti-oxidant and pro-oxidant. There is an exhaustive literature on its anti-oxidant role which does not warrant re-visiting here. Our attention herein is focussed on its pro-oxidant function; during the redox process associated with coenzyme Q_{10} semiquinone formation, superoxide radicals are generated, which are in part, converted to hydrogen peroxide by superoxide dismutase (Fig. 1). We suggest that the significance of coenzyme Q_{10} mediated hydrogen peroxide formation has been largely over-looked and misinterpreted. Most earlier studies have concentrated on the potential toxicity of superoxide and hydrogen peroxide at concentrations grossly in excess of those generated at physiological

levels. Hydrogen peroxide at physiological concentrations is essentially a benign substance. Early mitochondrial studies for the most part, consisted of in vitro experiments designed (e.g. using inside out membrane sub-mitochondrial particles) to demonstrate excessive H_2O_2 formation derived from coenzyme Q_{10} semiquinone reaction generating ROS. The results have been interpreted by some as having physiological significance, thereby purporting to demonstrate the serious deleterious pro-oxidant role of coenzyme Q_{10}. The more carefully controlled studies of Gille and Nohl (2000a,b) have emphasized that intact mitochondria, produce only small amounts of H_2O_2. St-Pierre et al. (2002) concur, and have reported H_2O_2 generated by well prepared mitochondria is barely detectable, and that earlier studies had over-estimated the levels of H_2O_2 produced by up to two orders of magnitude. Nonetheless, we would suggest that the very low levels of H_2O_2 formed are crucial to cell function and that such low levels may be expected for a second messenger molecule. Hydrogen peroxide is now widely recognized as a mitogen (for review Rhee, 1999); among the many studies of interest, Rusnak and Reiter (2000) have indicated how H_2O_2 can function to induce phosphatase cascades, which lead to altered nuclear gene transcription. Smith et al. (2000) have recently reported that the differentiation of the glial precursor cells is subject to redox control, such cells being manipulated by their redox state to self-propagation or cell type differentiation. Small charges in intracellular redox state can lead to strikingly different differentiation and metabolic outcomes. Superoxide anions and H_2O_2 generated outside the mitochondrian are now clearly demonstrated to function as intracellular second messengers (for review Finkel, 1998). No attempt is made here, to integrate those studies with the mitochondrial functions presented herein but clearly in a consideration of overall cell function they are relevant and important; coenzyme Q_{10} we hypothesize would play an important role in plasma membrane (among others) transduction signalling. All biological systems are in dynamic equilibrium and activation must be appropriately accompanied by de-activation. NO is an important transient messenger in signal transduction whose activity is terminated by reaction with superoxide: another participating role for coenzyme Q_{10} (Fig. 1).

Coenzyme Q_{10} pro-oxidant and anti-oxidant roles are not mutually exclusive, rather both functions are essential to cells. The pro-oxidant action of coenzyme Q_{10} leads to the cellular bioenergy modulation through superoxide formation and the synthesis of the mitogen H_2O_2, which is accompanied by ROS formation and some lipid, protein and DNA damage. This is the price paid for aspects of superoxide and H_2O_2 formation; also importantly, in the early years, oxidative damage is essentially completely repaired. However, over the decades from about 50 years of age, this damage/repair process begins to move out of equilibrium and the damage increasingly contributes to the inevitable age associated decrease in cell function and eventually, cell death and loss. As an anti-oxidant, coenzyme Q_{10} quinol contributes to the amelioration of the ROS damage.

2.4. The role of metallo cytosolic and mitochondrial superoxide dismutases (SOD)

All biological systems are in a dynamic equilibrium and activation must be appropriately accompanied by de-activation. Studies of knock out mice provide insight on the role played by superoxide. Mn SOD is localized in the mitochondrial matrix and it has been demonstrated that transgenic mice heterozygous for Mn SOD (+/−) had about half the Mn SOD activity of wild type (+/+) but there is no effect on longevity, the animals apparently suffering no ill-effects from the activity decrease. On the contrary construction of homozygous transgenic mice, null (−/−), for Mn SOD resulted in animals being severely affected. Such animals as were born, died within a few days of birth as a result of severe cardiopathy and other pathological charges (Melov et al., 1998). However, the interesting finding with this mouse model was that apparently only nuclear encoded proteins imported from the cytosol were severely oxidatively damaged, as exemplified particularly by the Fe-S centre enzyme aconitase and complex II activity of the electron transport chain. There was little effect on complex I, III and IV activities. In studies reported by Jaarsma et al. (2000) transgenic mice constructed to over-express cytosolic Cu/Zn metallo SOD were severely affected. The mice developed an array of neurodegenerative changes although their life span was not greatly shortened.

Consideration of the results reported for animals with changed Mn SOD and Cu/Zn SOD, activities have lead us to consider that there may be a an ordered functional vectorial formation of mitochondrial H_2O_2 as the results of St-Pierre et al. (2002) may be interpreted to strongly suggest. In this scenario, of the synthesized H_2O_2, a portion of it targets the mitochondrial matrix and the remainder is destined for the cytosol. It is envisaged that the mitochondrial matrix H_2O_2 can act as a mitochondrial gene regulator but the amounts must be controlled, hence Mn SOD null transgenic mice have no real survival value. The cytoslic destined H_2O_2 acts as a nuclear mitogen and again the total amounts of H_2O_2 must be regulated by Cu/Zn SOD together with other appropriate systems such as catalase and the glutathione peroxidase. Indeed transgenic mice null (−/−) for Cu/ZN SOD apparently develop normally showing no effects as reported up to 6 months of age. The enzyme is not required for normal motor neuron function but the animals are vulnerable to motor neuron loss when subjected to the stress of induced axonal injury (Reaume et al. 1996). However we interpret the over-expression of cytosolic Cu/Zn SOD with consequential neurogenerative changes and motor abnormalities, as highlighting the essential metabolic regulatory role played by H_2O_2. Thus there is an essential H_2O_2 requirement for normal physiological function and that excessive depletion of cytosolic H_2O_2 by over-expression of Cu/Zn SOD is detrimental to cell function.

The concepts developed in this communication place considerable weight upon compartmentalization of enzyme systems and sub-cellular metabolic micro-environments. There are regulatory systems, geared to the production of H_2O_2 functioning as a redox state messenger and also others geared to the removal of H_2O_2 both systems acting in an appropriate temporal frame work and strategically geographically located.

It must be recognized that administered anti-oxidants distribute unevenly among tissues and there has been a tendency in the literature to ignore the significance of this phenomenon. The human vitamin and anti-oxidant ascorbic acid is a case in point; thus ascorbate levels in different tissues vary over a wide range, tissues such as the adrenal and pituitary glands contain very high levels of ascorbate while lung, testes, thyroid, heart and skeletal muscle contain comparatively very low levels. (Table 3, after Hornig, 1975). It is of note that the rat for which ascorbate is not a vitamin, has much higher levels of ascorbate in its various tissues compared with humans, although the relative concentrations in each tissue are reasonably similar. There is a need for tissue specific anti-oxidants required for the treatment of the individual systemic diseases which develop in different tissues during the ageing process.

Table 3
Ascorbic acid content of human and rat tissues

Tissue	Human	Rat
Adrena glands	35	340
Pituitary gland	45	115
Liver	13	32
Spleen	12	45
Lungs	7	30
Kidneys	10	17
Testes	3	27
Thyroid	2	22
Heart muscle	10	7
Skeletal muscle	4	5
Brain	14	37
Eye lens	27	9
Plasma	0.8	2

Ascorbic acid (mg/100 g tissue). Modified, after Hornig (1975).

Recent studies of Murphy and colleagues have been addressing the sub-cellular targeting of anti-oxidants; in particular the use of a triphenylphosphonium coenzyme Q_{10} derivative (among others) which specifically accumulates in the mitochondrial matrix and function therein (for review Smith et al., 2003). These studies illuminate one way forward, towards a more sophisticated approach to intervention in the control of excessive localized ROS formation. Parenthetically it may be added that insufficient attention has been directed towards potential ROS damage arising from the cytochrome oxidase complex. It is notable that cytochrome oxidase activity decline is used as the exemplifier of the decline in cellular bioenergy capacity with age.

2.5. Coenzyme Q_{10} plays a key role both in increasing and decreasing membrane potential

The role of coenzyme Q_{10} in contributing to the generation of membrane potential and bioenergy

capacity has been discussed. However, recently, Klingenberg (1999) and colleagues (Echtay et al., 2000) have reported that coenzyme Q_{10} is a co-factor required by the uncoupler protein family. These proteins function by translocating protons across membranes in the reverse direction required for energy generation and thus collapse or modulate membrane potential and bioenergy which is dissipated as heat (Echtay et al., 2001). Again the coenzyme Q_{10} redox poise value will be reflected in the activity of the uncoupler protein family. Further, more recently it has been reported that the proton translocation uncoupler protein family requires activation by superoxide (Echtay et al., 2002). Coenzyme Q_{10} has the dual role in this uncoupler protein system of being both a proton carrier co-factor as well as a key component in the generation of superoxide (Fig. 1).

2.6. Cytosol redox state: the role of coenzyme Q_{10}

Many of the proteins of the cytosol are characterized by the presence of active cysteine residues, the cytosol is more electronegative than the cellular membrane compartments. Within membrane compartments of the cell, the cysteines exist in the cystine configuration. Bader et al. (2000) have reported extensively on the enzyme complexes responsible for the interconversion for protein sulphydryl/disulphide formation and the requirement for coenzyme Q_{10} as an essential co-factor.

3. A clinical role for coenzyme Q_{10}

It was not for about some 20 years after its discovery that a possible role for coenzyme Q_{10} as a therapeutic substance, began to emerge; many of the claims and assertions have recently been comprehensively reviewed (Ebadi et al., 2001). However, even to the present time, most of the therapeutic benefits claimed are essentially anecdotal and have accordingly not been accepted by the wider medical community. A selection of some of the wide-ranging claims for a beneficial clinical effect attributed to coenzyme Q_{10} are listed in Table 4. A number of the claims attribute coenzyme Q_{10}'s therapeutic benefit to its anti-oxidant properties as well as its enhancement of cellular bioenergy capacity. The best accredited use for coenzyme Q_{10}, is in the notable amelioration of the symptoms of those diseases arising from mt. DNA point mutations and deletions with resultant disruption of the electron transport system; most commonly, they phenotypically present as neuromuscular diseases. These conditions are progressive and commonly lead to early age severe incapacity and middle age death. Coenzyme Q_{10} is now widely used to ameliorate the consequences of mitochondrial disease particularly the encephalomyopathies. Parkinson's disease is an idopathetic condition, probably multi-system and has been reported to be associated with mitochondrial dysfunction in a range of central nervous system tissues (notably the substantial nigra), Gu et al. (2002) as well as in the platelets (Haas et al., 1995). Current promising clinical trials are in progress treating early Parkinson's disease patients with large doses of coenzyme Q_{10} and an ameliorating effect has been reported (Shults et al., 2002).

Table 4
Pathologies with anecdotal coenzyme Q_{10} therapeutic benefit

Mitochondrial neuromuscular diseases
Neurodegenerative diseases (Parkinson's disease, dementias, others)
Congestive heart failure-prevention/support therapy
Muscle weakness
Chronic fatigue syndrome
Cancer-breast treatment
Chemotherapy amelioration, support for AZT/AIDS treatment
Vascular disease, diabetes mellitus
Sports medicine. Performance enhancement (not a pathology)

Consult Ebadi et al. (2001) and references in the text.

There is a substantial anecdotal literature on the benefits of coenzyme Q_{10} as a complementary medicine in the treatment of ischemic heart disease and these claims warrant serious consideration (Langsjoen et al., 1994). They have been made by a number of unrelated groups and coenzyme Q_{10} is slowly finding its way into the cardiologist's armourment. However, there are few trials conducted with adequate patient numbers including placebo controls.

Claims for coenzyme Q_{10} therapy alleviating muscle fatigue and weakness have been made by a number of laboratories, including our own, based on data related to the re-energisation of cells/tissues of aged subjects (see earlier text).

There are a number of reports on the use of coenzyme Q_{10} in the treatment of cancer, notably breast. (Lockwood et al., 1994, 1995).

AZT which is used for the treatment of AIDS patients, has the severe side-effect of inhibiting mitochondrial DNA polymerase, which results in the disruption of the electron transport system. Coenzyme Q_{10} and its analogues, have been proposed as amelioration therapy based on rat studies (Linnane et al., 1995).

It may be readily appreciated that coenzyme Q_{10} could play a role in sports performance enhancement but there are apparently no definitive placebo controlled trials. If successful, it might become a banned substance for athletes!

How can the proposed therapeutic benefits of coenzyme Q_{10} in the treatment of a spectrum of degenerative diseases be reconciled?

Recall:

- There is a universal age related decline in the bioenergetic capacity of tissues, attributable to mt. DNA changes and mitochondrial dysfunction.
- ROS species are continually being produced by the endoplasmic reticulum and mitochondria (mainly through the agency of coenzyme Q_{10} semiquinone) and H_2O_2 is formed and some protein, lipid DNA damage occurs.
- Coenzyme Q_{10} tissue levels decline with age, and cellular membranes will be damaged by ROS, including their redox systems.
- Ageing is a slow process, occurring over the decades, beginning to be deleteriously expressed at about 50 years of age. Cardiovascular disease, cancers, neurological dysfunctions (cognitive decline, dementia, strokes), muscle weakness and others are the end result of small, incrementing changes, leading to pathogenesis.
- Coenzyme Q_{10} supplementation enhances cellular compartment bioenergy capacity rescuing cells from bioenergy degradation.
- Coenzyme Q_{10} occurs in all membranes and redox poise regulation signaling, particularly through the agency of H_2O_2, is now recognized as relatively common place, having a major influence on sub-cellular localized metabolic fluxes and cell differentiation pathways.

Our proposal is that this data may constitute a coherent whole, and that as coenzyme Q_{10} has an over-arching role in the maintenance of appropriate cell function, such function as we have outlined, may be sufficient to reconcile the range of claims for the successful treatment of systemic degenerative diseases by coenzyme Q_{10} administration.

Redox poise changes and any proposed deleterious fluxes in sub-cellular metabolic activity are envisaged to be small over time. However, these small undesirable changes act to produce a continuing low load metabolic stress that results in the gradual decline of the cell's ability to maintain optimum function and the eventual emergence over decades of systemic diseases. Clinically, these changes are ameliorated by the administration of coenzyme Q_{10} to readdress some of the developing imbalances associated with ageing. Finally, it may be added that each individual's gene pool, nutrition and environment will determine the development of systemic disease specific to that individual always recalling that the ageing process is stochastic. In any event the data summarized herein serves to emphasize the over-arching role coenzyme Q_{10} plays in cellular metabolism.

Finally it may be remarked that mitochondrial dysfunction associated with the systemic diseases of ageing and overt mitochondrial disease will also adversely affect a number of non-mitochondrial metabolic pathways requiring, for example, a need for UMP. Specifically we suggest that orotic acid supplementation together with coenzyme Q_{10} to promote UMP synthesis may assist mitochondrial disease patients. UMP synthesis is dependent upon a functional mitochondrial electron transport chain whose function declines with age and disease.

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