Have No Fear, MitoQ\textsubscript{10} Is Here

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The physical manifestation of a trait is a constant interplay between one’s genetic makeup and environmental factors. This notion has been substantiated by nutrigenomic studies demonstrating the benefits of nutritional supplements along the continuum between health and disease. More importantly, these studies have revealed the plasticity by which the genetic substrate can interact with various environmental components to either exacerbate or mitigate the manifestation of a disease process in those genetically predisposed.

Focusing on cardiovascular disease, a vast literature has demonstrated that this disease process is associated with impaired energy production, increased oxidative stress, and cell calcium overload. To these ends, both clinical and animal studies have demonstrated nutrient deficiencies, integral to these processes, to be associated with cardiovascular disease and that these deficiencies represent independent predictors of increased morbidity and mortality. One cellular component that has received considerable attention regarding function and nutrient supplementation is the mitochondria.

Mitochondria are responsible for cellular bioenergetics via oxidative phosphorylation. However, the perpetual transfer of electrons from one molecule to another within the mitochondria renders this organelle a major site for the genesis of reactive oxygen species (ROS). Although the mitochondria have antioxidant defenses, the disequilibrium between ROS production and ROS neutralization paves the way for disease manifestation.

ROS damage to mitochondrial proteins, lipids, and DNA poses a serious detriment to the mitochondria. In particular, knockout experiments of key mitochondrial oxidative defenses are associated with the onset of cardiovascular disease, whereas their overexpression is capable of forestalling the onset of disease. Conversely, supplementation of specific antioxidants has been shown to mitigate the disease state in animal models. However, it is difficult to determine with alacrity the contribution that mitochondrial-derived ROS may have on cardiovascular disease. To this end, the work by Graham et al published in this issue of *Hypertension* demonstrated the enhanced delivery of CoQ\textsubscript{10} to a specific target. In addition, this study reinforced the importance of CoQ\textsubscript{10} supplementation. However, at the same time, these findings have raised some important questions regarding CoQ\textsubscript{10}.

Although coenzyme Q\textsubscript{10} is an essential component of the respiratory chain and protects the mitochondrial and cell membranes from lipid oxidation, it also functions as a cofactor for uncoupling proteins (Figure, (c)). Uncoupling proteins are, in essence, the molecular switch that change the end product of the respiratory chain from an ATP producer to that of heat generator. Several studies have demonstrated that uncoupling proteins reduce ROS and that CoQ\textsubscript{10} is an essential cofactor for these uncoupling proteins. Therefore, CoQ\textsubscript{10}, along with uncoupling proteins, may play a role in ROS-dependent signaling pathways, and the ratio of oxidized:reduced CoQ\textsubscript{10} may also play an important signaling role. This notion is of particular interest, because CoQ\textsubscript{10} has been shown to be a potent gene regulator. Specifically, CoQ\textsubscript{10} caused an increased expression of hundreds of genes in human cell lines. Although the molecular mechanisms whereby CoQ\textsubscript{10} is imparting these pleiotropic effects has yet to be discerned, CoQ\textsubscript{10} may have a more far-reaching action than simply as an antioxidant.

Another important question raised by the study by Graham et al relates to who can benefit from this formulation of CoQ\textsubscript{10} and what other circumstances would warrant its administration. By demonstrating the salutary actions of MitoQ\textsubscript{10} in stroke-prone spontaneously hypertensive rats, Graham et al demonstrated the beneficial role of CoQ\textsubscript{10} supplementation in a...
model genetically predisposed to cardiovascular disease and, thus, mitigated the cardiovascular sequelae associated with this particular rodent strain. Therefore, we are only left to speculate as to the immense impact that this compound could have in medicine. One specific and sometimes controversial area that first comes to mind is the adverse effects of certain cholesterol-lowering medication and its action on endogenous CoQ10 production. Endogenous production of CoQ10 occurs via a shared pathway, which uses 3-hydroxy-3-methyl-glutaryl-CoA reductase, the rate-limiting reaction of the mevalonate pathway (see the Figure). This metabolic pathway produces cholesterol and other isoprenoids, the later of which are required by CoQ10 to anchor it in the inner membrane of the mitochondria. Therefore, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductases decrease the endogenous pool of CoQ10. Thus, formulations like MitoQ10 could be beneficial to those patients taking cholesterol-lowering drugs. On the basis of this notion, the work by Graham et al has demonstrated that CoQ10 supplementation represents a novel adjunct to conventional therapeutic modalities and may become an essential component for disease prevention to reduce the incidences of cardiovascular disease.

Disclosures

None.

References


Figure. Mitochondrial schematic illustrating a possible role of MitoQ10 when endogenous levels of CoQ10 are low or insufficient for use in mitochondrial functions. Sequence (a) depicts a role in the respiratory chain (RC), (b) depicts MitoQ10 as an antioxidant to protect mitochondrial DNA and lipid membranes, and (c) depicts a cofactor for uncoupling proteins (UnP). AS indicates ATP synthase; HMGCoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase.
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