Review Article

Coenzyme Q and its role in glaucoma

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Quick Response Code:

Website: www.saudijophthalmol.org

DOI: 10.4103/1319-4534.301299

Abstract:

Presently the management of glaucoma is limited to lowering of intra-ocular pressure (IOP). Since this modality does not appear to be successful in all cases there is increasing focus on non-IOP lowering medications. Coenzyme Q is a naturally occurring compound similar to vitamins. There are a few reports suggesting the neuroprotective efficacy of this agent in glaucoma models. The present systematic review was undertaken to study the pharmacology, physiology, metabolism and role of Coenzyme Q in glaucoma. An English-language search for relevant items was undertaken using PubMed, Google Scholar, Scopus and other databases. The present review found a positive outcome of Coenzyme Q as a neuroprotectant being reported in all studies. However, the review also found that the majority of studies on Coenzyme Q have been reported by a single group of researchers. In order to have a more wide-ranging impact regarding the efficacy of Coenzyme Q in glaucoma, it would be useful to undertake further multi- center trials.

Keywords:

Coenzyme Q10, glaucoma, mitochondria, neuroprotectants, retinal ganglion cells

Introduction

It has been reported that despite adequate lowering of intraocular pressure (IOP), nearly 42% patients suffering from glaucoma become blind in one eye and 16% in both eyes in their lifetime.[1] Yet, even now, IOP remains the only modifiable risk factor for the pathogenesis of glaucoma.[2] However, research on other neurodegenerative disorders such as Parkinsonism, Lebers Hereditary Optic Atrophy and Huntington's disease is giving hope that neuromodulation could one day become part of our armamentarium in the management of glaucoma.[3] As focus shifts to non-IOP lowering modalities, newer agents are being studied for their role in this disease process. In this context, the present review focuses on a naturally occurring compound in nature, known as Coenzyme Q (CoQ), which could act as a neuroprotectant in glaucoma patients.

The exact mechanism of glaucoma is still unknown. There are a number of theories regarding the etiopathogenesis of glaucomatous optic nerve degeneration (GOND). Some of the known theories regarding GOND include the mechanical, vascular, biochemical, genetic, lymphatic and intra-cranial pressure mechanisms. One significant process in the development of glaucomatous degeneration of retinal ganglion cells (RGCs) and optic nerve axons is impaired mitochondrial oxidative-phosphorylation (OXPHOS).[4-8]

Mitochondrial dysfunction leads to formation of reactive oxygen species (ROS), triggering oxidative stress and affecting calcium (Ca^{++}) hemostasis in the ocular structures. The excessive ROS generated as a result of mitochondrial dysfunction, in turn, leads to further mitochondrial damage, activating a vicious cycle of tissue injury in the optic nerve head (ONH) astrocytes. A number of studies have shown that oxidative stress, mitochondrial dysfunction and Ca^{++} overload are commonly occurring biochemical events in the lamina cribrosa cells of glaucomatous human eyes. These processes are vital for the damage seen during development of GOND.[2,9-11]

Normal cellular metabolism is the engine which constantly produces ROS in the body. These unstable compounds damage biological systems and are responsible for ischemia-reperfusion-injury (IRI) in neural cells. ROS mediate IRI by reacting with lipids, nucleic acids and

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Submitted: 26-Jan-2019
Accepted: 26-Apr-2020
Published: 22-Nov-2020

How to cite this article: Ahmad SS. Coenzyme Q and its role in glaucoma. Saudi J Ophthalmol 2020;34:45-9.

proteins. Another pathway for ROS production is through intracellular Ca^{++}, by activation of phospholipids which catalyze arachidonic acid oxidation and ROS production. Ca^{++} may also activate xanthine dehydrogenase to xanthine oxidase, resulting in the formation of uric acid and superoxide radical which is deleterious to the surrounding tissues.[5]

In healthy populations, ROS are removed from biological systems through two mechanisms: Firstly, through antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase and secondly, by the action of free radical scavengers such as glutathione, alpha-tocopherol (Vitamin E) and beta-carotene. However, in susceptible populations oxidative stress causes RGC apoptosis by inducing mitochondrial deoxyribonucleic acid (DNA) mutations. Over time, these mutations may accumulate and manifest in the form of age-related decrease in adenosine triphosphate (ATP) synthesis and tissue degeneration.[5,9]

Mitochondrial dysfunction is a fundamental pathology affecting ATP synthesis and subsequent development of glaucoma. CoQ has a vital role in cellular bioenergetics as a cofactor in the mitochondrial transport chain (respiratory chain) and is essential for the production of ATP. With aging a 40% decline in CoQ may occur, contributing to GOND.[9,11] Thus, supplemental CoQ could play a role in modulating GOND. This review focuses on the pharmaco-physiology of CoQ and its association with glaucoma.

Pharmacology

Coenzyme Q is also called ubiquinone, ubidecarenone or coenzyme Q10. It is abbreviated to CoQ, CoQ10 or Q10. This coenzyme is widely present in nearly all eukaryotic cells, hence the term "ubiquinone" (ubiquitous = very common). CoQ is a 1,4-benzoquinone. It belongs to a homologous series of compounds that share a common benzoquinone ring structure, but differ with regards to the length of the isoprenoid side chain. The "Q" in the name refers to the quinone chemical group and the "10" denotes the number of isoprene subunits in its tail. The isoprene units contain 5 carbons each, for a total of 10 carbons. CoQ is quite similar to Vitamin K in its chemical structure but is not considered a vitamin since it cannot be synthesized in the body.[12,13]

Physiology

Coenzyme Q is distributed along the cell and organelle membranes. A major portion of the coenzyme is present within the mitochondria. It is also found in peroxisomes, lysosomes, golgi membranes and endoplasmic reticulum. A minor amount is found floating in the phospho-lipid bilayer of the membranes. The isoprenoid side chain presumably helps in stabilizing the lipid bilayer and is responsible for the affinity of the coenzyme to the interior of the cell membranes. The quinone head group occurs either in an oxidized (quinone) or reduced (quinol) form. The quinol form may occur in serum or various membranes to the extent of 30–90% of the total CoQ in the body. The quinol form is more hydrophilic, so the quinone head group could come to lay closure to the surface of the cell membrane. The change in the oxidation-reduction states of CoQ, in turn, leads to a modification in the structural or enzymatic properties of the membrane.[9,13]

In the mitochondria, CoQ plays a crucial role in ATP production. Most of the ATP is produced in the inner wall of mitochondria where CoQ is located. CoQ transfers electrons from the primary substrates to the oxidase system and simultaneously transfers protons to the outside of the mitochondrial membrane. This leads to a proton gradient across the membrane. Finally, the protons return back to the interior through an enzymatic process, which drives the formation of ATP.[13]

CoQ also participates in a number of oxidation-reduction reactions which control signal origin and transmission in cells. Electron transport activity in various cellular membranes is associated with auto-oxidation of semi-quinone. This process contributes to the formation of hydrogen peroxide (H2O2). In turn, H2O2 activates transcription factors such as Nuclear Factor kappa-light-chain-enhancer of activated B cells (NFkB) which induce gene expression. As an important cellular cofactor CoQ modulates the expression of genes involved in human cell signaling, metabolism and transport.[9,13]

Metabolism

The recommended daily requirement of CoQ is around 3–6 mg/day. Naturally occurring CoQ is found in diverse plant and animal sources. The richest dietary sources are beef, pork, chicken heart and liver. Vegetable oils, parsley, perilla and avocados are plant sources rich in CoQ.[14]

CoQ is a lipophilic substance with an absorption pattern similar to lipids and Vitamin E, another lipid soluble substance. The absorption of CoQ is further enhanced in the presence of other lipids, such as those provided in fatty foods. Most of the CoQ is absorbed in the small intestine. It is reduced to ubiquinol either during the absorption in the small intestine or subsequently. However, ubiquinol first appears in the form of mesenteric triacylglycerol-rich lipoproteins. Subsequently, these lipoproteins are converted to chylomicron remnants in circulation by the action of lipoprotein lipase. The particles are rapidly taken up by the liver where CoQ is repackaged mostly into very low density lipoprotein (VLDL)/ low density lipoprotein (LDL) particles, which are released into circulation. A small amount is also present in High Density Lipoprotein (HDL). In humans and animals, CoQ is present in all tissues in varying amounts.[12]

Coenzyme Q and Glaucoma

Glaucoma is a neurodegenerative disorder affecting the RGCs and their axons. A number of processes, as mentioned previously, have been presented to elucidate the mechanisms responsible for GOND. In the context of the present review, biochemical mechanisms form an important aspect in the development of glaucomatous optic atrophy.

Oxidative stress, such as exposure to H2O2 and kainate, is linked to increased Glial Fibrillary Acidic Protein (GFAP) expression in ONH astrocytes. GFAP is an intermediate-filament-III (IF-III) protein expressed by a number of cell types in the central nervous system (CNS) including astrocytes. GFAP provides mechanical strength and support to these cells. It is also involved in numerous vital processes in the CNS, including cell communication and functioning of the blood-brain barrier.[15] A study reported GFAP to increase by 1.23 ± 0.10 folds as a consequence of oxidative stress. In contrast, treatment with CoQ was associated with reduction in GFAP expression by 0.98 ± 0.08 fold. CoQ probably inhibits apoptosis by thiol redox control, membrane channel control or modification of phospholipids through inhibition of ceramide formation.[7,11,13]

Oxidative stress triggers the upregulation of Superoxide dismutase-2 (SOD2) and Heme Oxygenase-1 (HO-1) protein expression in ONH astrocytes. SOD2 actively stabilizes mitochondrial transmembrane potential and calcium buffering activity. Thus, upregulation of SOD2 and other anti-oxidative enzymes promotes stronger endogenous compensatory mechanisms to oxidative stress in the astrocytes. Cells treated with CoQ prior to the oxidative stress were found to have even higher resistance to oxidative stress. Studies report a 0.63+/-11 and 0.63+/-0.07 folds reduced SOD2 and HO-1 expression respectively in ONH astrocytes pre-treated with CoQ. Therefore, CoQ could prove to be a vital antioxidant to protect against oxidative stress mediated dysfunction in ONH astrocytes.[7,11,16]

Studies have shown that ONH astrocytes exposed to H2O2 demonstrate dysfunctional small, rounded mitochondria. On the other hand, astrocytes treated with CoQ prior to the oxidative insult showed partial preservation of mitochondrial morphology, increased mitochondrial numbers and mitochondrial volume density. This is attributed to triggering of nascent mitochondrial biogenesis.[11]

The mitochondrial inner membrane protein, mitofilin, which plays a vital role in maintenance of mitochondrial cristae morphology, is found to reduce following oxidative stress. Mitofilin depletion decreases cellular proliferation, increases apoptosis and triggers structural and functional abnormalities in mitochondria. Studies report CoQ to significantly promote mitofilin protein expression, provide protection to the mitochondria and ultimately OXPHOS capacity against oxidative stress.[11]

Peroxisome-proliferator-activated-receptor-γ-coactivator-1 (PGC-1α) is a transcriptional coactivator. It mediates mitochondrial biogenesis and oxidative metabolism, as well as, regulates transcription target proteins such as nuclear-encoded respiratory chain proteins and mitochondrial transcription Factor A (Tfam). This factor plays a fundamental role in mitochondrial gene expression and mitochondrial DNA maintenance. It is also critical in OXPHOS-mediated ATP synthesis. Oxidative stress is found to trigger compensatory upregulation of PGC-1α in ONH astrocytes as a protective response. However, astrocytes pretreated with CoQ reportedly have an even greater increase in PGC-1α, to the extent of 1.74+/-0.40 folds, in response to oxidative stress.[7,11]

Oxidative stress also increases OXPHOS respiratory chain (Cx I, II and V) protein expression. This reduces ATP production and increases ROS generation, which increases oxidative stress and triggers a vicious cycle. ROS cause mitochondrial bioenergetic dysfunction as well. These mechanisms affect the cell viability in ONH astrocytes. However, pretreatment with CoQ preserves the expression of these proteins in ONH astrocytes on exposure to oxidative stress. Pretreatment with CoQ also restores the cellular ATP levels in ONH astrocytes exposed to H2O2. Thus, CoQ possibly restores the bioenergetic parameters in ONH astrocytes such as oxygen consumption rate, mitochondrial transmembrane potential and ATP synthesis, to counter oxidative stress.[11]

Apoptosis of RGCs also involves the Bcl-2 gene family. Cellular suicide or apoptosis is initiated by Bax/Bak with the formation of the "mitochondrial permeability transition pore" (mPTP) and "mitochondrial apoptosis-induced channel" (MAC) in the mitochondrial outer membrane.[17] This allows cytochrome c to escape into the cytoplasm and activate the pro-apoptotic caspase cascade pathway. Bcl-2 and Bcl-xL proteins inhibit the release of cytochrome c and the subsequent caspase cascade activation, thus, acting as anti-apoptotic proteins. Bcl-2-associated death promoter (BAD) protein is a pro-apoptotic member of the Bcl gene family. On activation, BAD forms a heterodimer with Bcl-2 and Bcl-xL, inactivating them and thereby allowing Bax/Bak-triggered apoptosis of the RGCs. CoQ has been found to decrease Caspase-3 protein expression and Bax protein expressions, as well as increase in pBAD protein expression in ischemic retinas. Papucci *et al.* reported CoQ to dramatically reduce apoptotic cell death, attenuate ATP decrease and hinder DNA fragmentation in the presence of apoptotic stimuli. They also reported inhibition of mitochondrial depolarization, cytochrome c release and caspase-9 activation in presence of CoQ. Thus, CoQ protects the RGCs against oxidative stress by modulating the Bax/Bad-mediated mitochondrial pathway.[7,18,19]

CoQ has also been found to be protective for RGCs independently of its antioxidant function. It increases RGC viability and inhibits apoptosis in response to a number of apoptotic stimuli such as glutamate, chemical hypoxia and serum withdrawal by preventing mitochondrial depolarization. The mechanism of CoQ as a neuroprotective agent is attributed to its anti-oxidant activity; mechanical stabilization of membrane structure; reduced mitochondrial depolarization; Ca++ buffering activity; Glutamate inhibitory effect; inhibition of astroglial activation via mitochondrial-mediated effects, as well as, direct action on retinal glia.[20] This unique property of CoQ can have far reaching clinical implications in our search for neuroprotection.

Coenzyme Q Administration

Topical CoQ has poor intraocular penetration and bioavailability. This characteristic is attributed to the large molecular weight and hydrophobicity of the CoQ molecule.[12] CoQ also interacts with the P-glycoprotein (P-gp) efflux pump expressed on the corneal epithelial cells and the RGCs.[20] This pump extrudes CoQ out of the cells, lowering the bioavailability of CoQ in tissues. Different formulations and forms of supplemental CoQ have been developed and tested on animals and humans. Solubilized CoQ has better absorption, higher plasma concentration and better bioavailability compared to powdered forms. Therapy with solubilized CoQ was found to have a 3–6 times higher bioavailability compared to the CoQ in powdered form.[21] Nanoparticles have also been investigated as a delivery system to improve the oral bioavailability of drugs with poor absorption characteristics. An emulsion of CoQ in soybean oil and other oil-based formulations have been found to improve bioavailability. There are also reports of liposomes and dendrimers being investigated for this purpose. Side effects occur in 1% of the individuals on oral CoQ. These include nausea, vomiting, diarrhea, appetite reduction and heartburn. Drug interactions may occur in patients on antihypertensive treatment, causing an additive effect. CoQ also has the potential to reduce the effectiveness of warfarin. However, in view of the overall safety profile of CoQ, this agent could provide an alternate route for administering anti-glaucoma medications and reduce the side effects of topical drugs.[14,22]

Topical administration of CoQ in a rat ischemic model was studied by Nucci *et al* and also Russo *et al*. Retinal ischemia in male Wistar rats was induced by cannulation of the anterior chamber and infusion of sterile solution to achieve an IOP of 120 mmHg for 45 min. The study group was treated with intravitreal or topical CoQ solution 30 minutes prior to ischemia. CoQ treated rats were observed to have lower levels of extracellular glutamate levels. CoQ also minimized retinal damage and cell death from apoptosis.[23,24]

Topical CoQ is usually used in combination with Vitamin E. α-Tocopherol, a form of Vitamin E, is well known to inhibit P-gp activity and thus, improve bioavailability of CoQ. The fixed dose combination marketed as Coqun eyedrops contains CoQ 100 mg; Vitamin E derivative: D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) 500 mg and physiological solution at 100 mL. In a study conducted on open-angle glaucoma patients, the medication was instilled twice daily. When followed up over 12 months, 60% patients showed an improvement of retinal biometric responses, as suggested by the increase in PERG amplitudes and reduction in implicit times. 50% patients also had improvement in bioelectric cortical responses, as suggested by an increase in VEP amplitudes and shortening of VEP implicit times. Incidentally, VEP enhancement was seen only in those patients who had concomitant improvement in PERG responses.[25]

Clinically satisfactory corneal penetration and intraocular absorption of Coqun eyedrops has been shown in a study in which the eyedrops were administered 1 hour prior to vitreo-retinal surgery. Intraoperative vitreous samples were studied for CoQ with High Performance Liquid Chromatography (HPLC) and found to have significantly high concentration of the drug.[26]

Davis and colleagues have reported their laboratory study in which a surgically induced rat model of ocular hypertension was use. The rats were topically treated with either CoQ/alpha-tocopherol polyethylene glycol succinate (TPGS) micelles or TPGS vehicle twice daily for 3 weeks. Subsequently, retinal cell health was assessed in vivo using Detection of Apoptotic Retinal Cells (DARC). Post-mortem Brn3 histological study of whole retinal mounts was performed. The study reported significant neuroprotective efficacy of the CoQ/TPGS treated rats compared to controls.[20]

Most of these reports are animal based studies where CoQ was administered prior to the acute ischemic event. The studies are also limited by the short duration of exposure to CoQ. Long-term trials regarding the continued efficacy of CoQ and side-effects have not been performed. Finally, the efficacy of CoQ based on its activity on biochemical factors responsible for glaucoma, such as glutamate excitotoxicity, does not explain its role in light of the multifactorial etiology of glaucoma.

Conclusion

Glaucoma is a multifactorial neurodegenerative disorder. Among other causative factors, impaired mitochondrial OXPHOS plays an important role in the development of GOND. CoQ has a vital role in cellular bioenergetics. Age-related decline in this co-factor probably contributes to GOND. Treatment of cells prior to oxidative stress is associated with increased resistance to oxidative stress, better mitochondrial preservation and reduced apoptosis. CoQ has also been found to be neuroprotective independent of its antioxidant property. These findings suggest CoQ could prove to be a missing piece in the puzzle to treat glaucoma.

Acknowledgment

Author(s) would like to thank Ms Emmeline Stanislaus for her help in editing this article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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